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ORIGINAL ARTICLE

Pharmacokinetic modeling and simulation support for age- and weight-adjusted dosing of dabigatran etexilate in children with venous thromboembolism

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Abstract

Background: Dabigatran etexilate (DE), a direct oral thrombin inhibitor, has been evaluated in children with venous thromboembolism (VTE) using oral solution, pellets, or capsules.

Objectives: This study evaluated DE pharmacokinetics (PK) in children with VTE and the appropriateness of a DE pediatric age- and weight-based dosing algorithm.

Patients/Methods: A population PK model was fitted to data from four single-arm and one randomized, comparative pediatric VTE studies (358 children aged birth to <18 years; 2748 PK observations) and one healthy-adult study (32 males aged <40 years; 1523 PK observations) using nonlinear mixed-effects modeling. A stepwise, covariate, model-building procedure evaluated the influence of covariates (e.g., age,

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body weight, body surface area [BSA]-normalized renal function, and sex). The final model was used to evaluate the pediatric dosing algorithm, with simulations comparing pediatric trough exposure with reference exposure defined for the pediatric studies.

Results: The population PK of dabigatran was adequately described by a two-compartment model with first-order elimination and absorption. Age, weight, BSA-normalized renal function, and sex were statistically significant covariates (all $P < .05$). Apparent clearance increased with age (independently of body weight), diminished with decreasing BSA-normalized renal function, and was lower in females than males. All disposition parameters increased with body weight escalation (allometric scaling). Simulations confirmed that for all DE formulations, the final pediatric dosing algorithms achieved reference exposure without dose adjustment.

Conclusions: Using a population PK model of DE for children with VTE, simulations showed that the final dosing algorithms were appropriate for all DE formulations; no dose titration was needed.

KEYWORDS
algorithms, children, dabigatran, pharmacokinetics, venous thromboembolism

ESSENTIALS

- Responses to standard of care anticoagulation treatment may differ as children age.
- We evaluated dabigatran etexilate (DE) pharmacokinetics (PK) in children with venous thromboembolism (VTE).
- Our PK and simulation model supports the age- and weight-based dosing algorithm used in the two pediatric clinical trials, suggesting it to be appropriate for DE with minimal/no dose adjustments required.
- On clinical confirmation, these findings would significantly simplify the treatment of children with VTE.

1 | INTRODUCTION

The incidence of venous thromboembolism (VTE) in children, a condition associated with considerable morbidity and mortality, has risen over the past 20 years.[1-3] Standard of care (SOC) treatment for VTE in children is based upon data from clinical studies in adults with VTE, and comprises unfractionated heparin (UFH), low molecular weight heparin (LMWH), or vitamin K antagonists such as warfarin.[4] However, each SOC treatment has its own limitations; for example, all require frequent monitoring, and neither UFH nor LMWH are available as oral formulations.[2,4] The treatment of VTE in children is challenging for physicians as they need to consider the differing responses to SOC as children age and their hemostatic and coagulation systems mature.[5-7]

Direct oral anticoagulants (DOACs) could be an alternative to SOC in treating VTE in children, and may overcome some of the limitations associated with SOC. Indeed, initial clinical study data support the use of DOACs in treating acute VTE[8] and in preventing VTE recurrence, as a viable alternative in children.[9] One such DOAC is dabigatran etexilate, a direct oral thrombin inhibitor, which is approved for the treatment of VTE and the prevention of recurrent VTE in adults based upon efficacy and safety data from the phase 3 RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE studies.[10-12] Dabigatran etexilate capsules are available for children aged ≥8 years, although those aged ≥8 to 12 years who cannot take capsules can be given pellets (coated granules in sachets). Pellets are available for children aged <8 years, and oral solution is available for infants aged <12 months who cannot swallow the pellets. Five pediatric studies have evaluated different formulations of dabigatran etexilate in children aged from birth to <18 years with VTE,[9,13-16] with the dosage adjusted according to the age and/or weight of each child. The majority of children were dosed according to an age- and weight-based dosing algorithm derived from estimated renal function,[17] using adult doses as a reference.

We have developed a population pharmacokinetic (PK) model to describe the PK characteristics of dabigatran and to quantify covariate–parameter relationships in children. Simulations based upon the population PK model have been used to evaluate the appropriateness of the dabigatran etexilate pediatric dosing algorithm for use in clinical practice.

2 | METHODS

2.1 | Clinical data sources

Data were included from five studies in children aged from birth (neonates had to be full term [≥37 weeks of gestation] for inclusion) to <18 years with VTE; three were phase 2a studies (NCT02223260, NCT01083732, and NCT00844415) and two were phase 2b/3 studies (DIVERSITY [NCT01895777] and NCT02197416).[9,13-16] One study (NCT00844415) in children aged 12 to <18 years dosed dabigatran etexilate (given as capsules) by adjusting for the patient's weight.[14] The remaining four studies evaluated dabigatran etexilate given as oral solution, pellets, or capsules when dosed using an age- and weight-based algorithm.[9,13,15,16] The studies were single-arm except for DIVERSITY, which was an open-label, randomized, non-inferiority study. Phase 1 data from healthy adult males treated with dabigatran etexilate 150 mg twice daily, given as oral solution, pellets, or capsules (NCT02044367[18]), were included in order to stabilize the model and to further inform on potential differences among the three different formulations used in the pediatric studies. The studies were conducted between August 2009 and November 2019. Exploratory graphical analyses of the administered dose of dabigatran etexilate by age and weight, stratified by study and formulation, are shown in Figure S1 in supporting information.

2.2 | Population PK model development

A previous pediatric-population, two-compartment, PK model (based upon three of the pediatric studies: NCT02223260, NCT01083732, and NCT00844415),[19] and a previously published adult PK model (based upon RE-LY study data),[20] were updated using final data from the two pediatric phase 2b/3 studies (NCT01895777 and NCT02197416).[9,13] A population PK model was fitted to the dabigatran PK data using nonlinear mixed-effects modeling. Model refinement considered modification of the absorption model; the disposition model; and aspects concerning the relationship between model parameters and body weight, age, renal function normalized to body surface area (BSA-normalized renal function), and drug formulation.[21] A priori structural covariates were age (in the model, postmenstrual age [defined as postnatal age plus 40 weeks] was used primarily, as renal function starts to develop prior to birth; however, only postnatal age is reported, as all children included were full-term gestation of ≥37 weeks) and body weight for disposition parameters, and the impact of the type of formulation (oral solution, pellets, and capsules) for absorption parameters. Covariate–parameter relationships of the final dabigatran model are shown in Figure S2 in supporting information, and parameter estimates of the final model are shown in Table S1 in supporting information. The potential influence of baseline covariates (sex, age, race, hemoglobin, BSA-normalized renal function [estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) using the Schwartz formula[22] for both children and adults], and concomitant medication with proton pump inhibitors [PPIs, often co-administered because of the adverse effects of dabigatran etexilate on the gastrointestinal tract]) was evaluated using a stepwise covariate model--building procedure.

2.3 | Population PK simulation

For each evaluated dosing strategy (oral solution, pellets, and capsules), dabigatran exposure was simulated in a pediatric VTE population with 500 patients (approximately 50% girls and 50% boys) in each studied age category, according to the age categories of the proposed dosing algorithm. A realistic distribution between age and body weight was obtained by sampling demographic data from 13,522 subjects aged 0 to <18 years entered into the National Health and Nutrition Examination Survey (NHANES) III database between 1999 and 2006,[23] and trimming to exclude those with a body weight outside the 3rd and 97th percentiles.

The final population PK model was used for evaluating the performance of the dabigatran etexilate pediatric dosing algorithm by comparing the simulated pediatric trough exposure with a reference exposure range of 26 to 250 ng/ml, which was defined for the conduct of the pediatric studies; 26 ng/ml is the 10th percentile of the trough dabigatran concentration range found in the RE-COVER trial of patients with VTE[11] and 250 ng/ml represents a conservative upper boundary based on risk of bleeding events (e.g., in RE-COVER, the rate of major bleeding events showed a steeper increase above trough dabigatran concentrations of 250 ng/ml). The main assumptions used in the simulations are shown in the supporting information. Two different age- and weight-based dosing algorithms were compared; the dosing algorithm used in the clinical studies (which allowed for one dosing adjustment), and a final, updated and smoothed dosing algorithm that did not have any dose adjustments (up- or down-titration of dabigatran etexilate dose). Simulation results were summarized for the various dosing strategies and stratified by the type of dabigatran etexilate formulation. These included: (1) a prediction interval for the full concentration–time profiles after the first dose and at steady state, with and without dose adjustments for algorithm-based dosing; (2) dabigatran minimum concentration at steady state ($C_{ss,min}$) by age categories and across the applicable weight range; and (3) the proportion of children by age outside the $C_{ss,min}$ reference range derived from adult studies.

2.4 | Analyses

Both the PK model and the population PK simulation analysis were performed using NONMEM version 7.3.0 (Icon Development Solutions). Data management and further processing of NONMEM outputs were performed using the R statistical environment version 3.3.3 (R Foundation for Statistical Computing). PK model visual predictive checks and log-likelihood profiling were run using Perl-speaks-NONMEM version 4.4.8.[24,25]

TABLE 1 Population PK model baseline continuous and categorical covariate statistics stratified by study (analysis data set)

	NCT02223260 Aged <1 y	NCT01083732 Aged 1 to <12 y	NCT00844415 Aged 12 to <18 y	DIVERSITY (NCT01895777) Aged birth to <18 y	NCT02197416[a] Aged 3 m to <18 y	NCT02044367 Aged 18–40 y
Children, *N*	8	18	9	173	210	–
Subjects, *N*	–	–	–	–	–	32
PK observations, *N*	16	82	33	1092	1525	1523
Continuous covariates						
N	8	18	9	173	150	32
Age, y						
Median (range)	0.2 (0.1–0.5)	4.1 (1.2–11.8)	16.0 (13.8–18.0)	14.3 (0.1–18.1)	14.6 (0.5–18.0)	27.7 (20.6–39.8)
Body weight, kg						
Median (range)	4.2 (3.8–7.1)	16.0 (9.0–43.0)	54.0 (47.0–84.0)	52.7 (3.7–131.0)	60.6 (6.0–132.0)	83.0 (70.0–97.0)
Height, cm						
Median (range)	55.5 (48.0–62.0)	102.0 (74.0–137.0)	167.0 (155.0–189.0)	160.0 (51.0–192.0)	165.0 (64.0–195.0)	180.0 (166.0–190.0)
SCR, mg/dl						
Median (range)	0.2 (0.2–0.5)	0.3 (0.2–0.7)	0.6 (0.5–0.9)	0.6 (0.2–1.1)	0.7 (0.1–1.2)	0.9 (0.7–1.1)
eGFR, ml/min/1.73 m^2						
Median (range)	92.5 (48.3–138.0)	130.0 (78.5–174.0)	106.0 (81.8–127.0)	107.0 (52.4–248.0)	105.0 (60.0–466.0)	85.0 (70.8–102.0)
Hb, g/dl						
Median (range)	10.4 (9.2–14.5)	12.0 (10.6–12.9)	13.2 (10.5–16.1)	12.5 (7.0–16.9)	13.5 (8.4–17.6)	15.6 (14.2–17.7)
Categorical covariates						
Sex, *n* (%)						
Male	3 (37.5)	11 (61.1)	3 (33.3)	79 (45.7)	85 (56.7)	32 (100.0)
Female	5 (62.5)	7 (38.9)	6 (66.7)	94 (54.3)	65 (43.3)	0
Race, *n* (%)						
White	7 (87.5)	14 (77.8)	9 (100.0)	160 (92.5)	139 (92.7)	32 (100.0)
Black	1 (12.5)	0	0	1 (0.6)	5 (3.3)	0
Asian	0	4 (22.2)	0	10 (5.8)	4 (2.7)	0
Multiple	0	0	0	2 (1.2)	2 (1.3)	0
Formulation, *n* (%)						
Oral solution	8 (100.0)	18 (100.0)	0	13 (7.5)	0	10 (31.2)
Pellets	0	0	0	41 (23.7)	24 (16.0)	11 (34.4)
Capsules	0	0	9 (100.0)	119 (68.8)	126 (84.0)	11 (34.4)

Abbreviations: eGFR, estimated glomerular filtration rate using the Schwartz formula; Hb, hemoglobin; m, month; PK, pharmacokinetics; SCR, serum creatinine; y, year.

[a]61 patients treated with dabigatran in the DIVERSITY study were rolled over to the NCT02197416 study (60 of these patients have included PK observations in the NCT02197416 study); to avoid counting the same patient twice, the statistics shown do not include these patients.

3 | RESULTS

The analysis data set comprised 358 children with a total of 2748 PK observations, and 32 healthy adult males with 1523 PK observations (Table 1). Baseline continuous and categorical covariates across the studies included in the analysis are shown in Table 1. As age- and weight-based dosing was applied in the pediatric studies, a large number of dose levels (12.5–330 mg) were studied in children (Figure S1), with the baseline age ranging between 0.1 and 39.8 years, and body weight ranging between 3.7 and 132.0 kg (Table 1).

3.1 | Population PK model

The population PK of dabigatran was adequately described by a two-compartment model with first-order elimination and absorption, and a lag time describing delayed absorption. The visual predictive check for the final population PK model adequately described dabigatran data across all age and body weight ranges (Figure S3 in supporting information), as well as the different formulations, during the whole study period for all studies (data not shown).

Age, weight, BSA-normalized renal function, and sex were identified as statistically significant covariates ($P < .05$ for all), with all subgroup effects independent of each other (data not shown). Typical apparent clearance increased with rising age (independent of body weight), with 90% of the full-maturation drug-eliminating organ function occurring at a postnatal age of 20 months. All the disposition parameters increased with increasing body weight, in accordance with allometric scaling (exponents of 0.75 for clearances and 1 for volumes of distribution), and the typical apparent clearance in a typical patient with body weight of 10 kg versus 70 kg was 25.6 L/h versus 110 L/h. As BSA-normalized renal function decreased, so did the typical apparent clearance, which was 15% lower in a patient with an eGFR of 50 ml/min/1.73 m^2 versus a reference patient with a median eGFR of 104 ml/min/1.73 m^2. In children, the lowest eGFR value was 48 ml/min/1.73 m^2, and no additional dose adjustment appeared to be warranted in patients with eGFR >50 ml/min/1.73 m^2. In females, apparent clearance was on average 10% lower than in males, independent of the formulation. This difference between females and males was similar to data from the adult population PK model,[20] and was not considered to be clinically relevant; as such, no additional dose adjustment seemed to be warranted. Race, hemoglobin, and PPIs ($n = 21$) were not identified as statistically significant covariates, and race did not have any statistically significant influence on the PK parameters, although there were few Black ($n = 7$) or Asian ($n = 18$) patients.

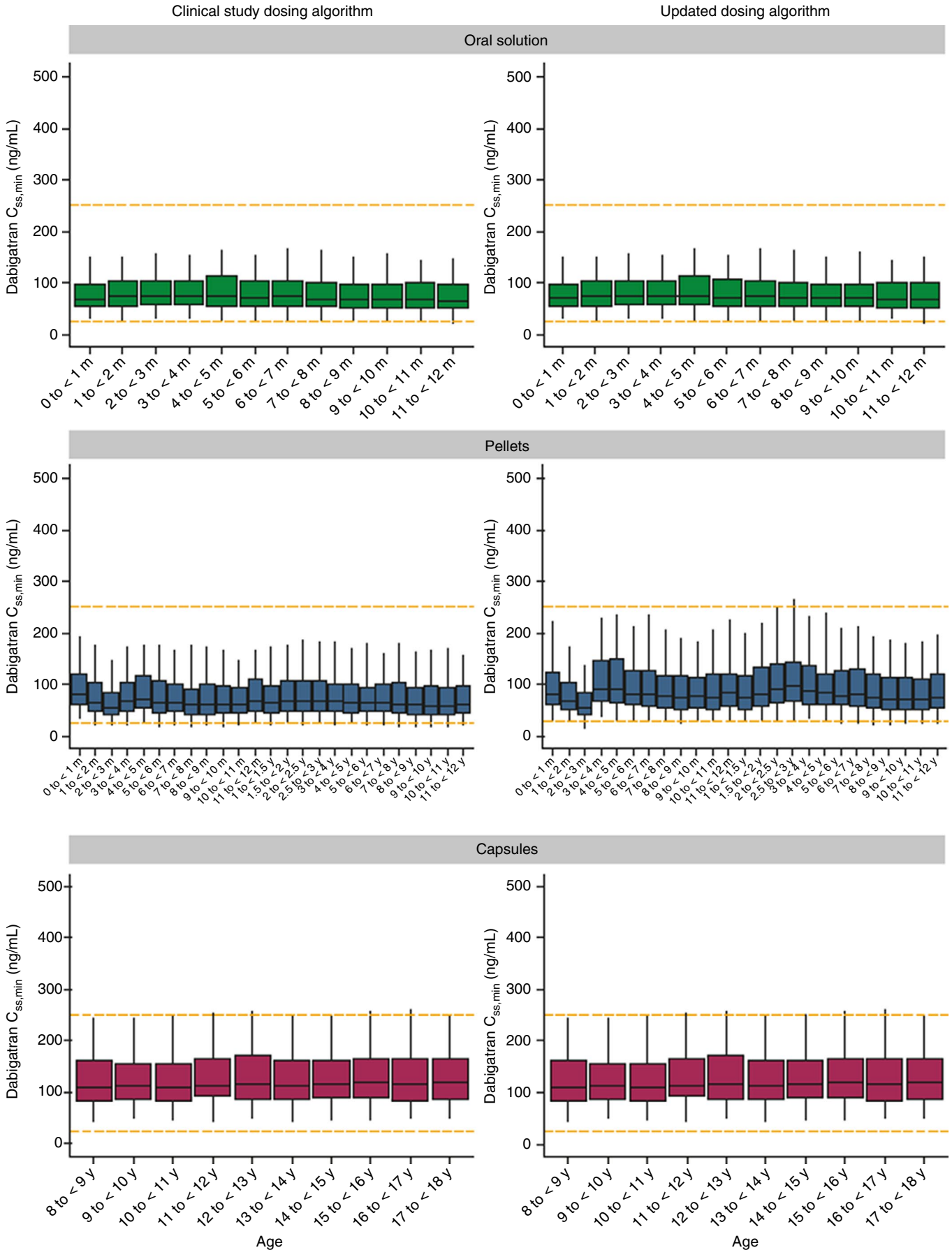
Covariate–parameter relationships of the final dabigatran model are shown in Figure S4 in supporting information and Table S1. The apparent relative bioavailability of dabigatran was approximately 30% and 40% lower in children receiving oral solution and pellets, respectively, compared to those receiving capsules (0.69 and 0.62 times the bioavailability of capsules, respectively). In contrast, the apparent relative bioavailability of dabigatran in healthy adults receiving oral solution and pellets was 1.16 and 1.25 times greater than that for capsules, respectively. In both children and adults, the first-order absorption rate constant (k_a) was higher after dabigatran etexilate administration as either oral solution (k_a 1.84 h^{-1}) or pellets (k_a 1.56 h^{-1}), compared to capsules (k_a 0.939 h^{-1}), while the absorption lag time was largely similar across formulations (0.300 hours for oral solution, 0.408 hours for pellets, and 0.431 hours for capsules). Model diagnostics for the final population PK model supported its usability for simulations to explore various dosing strategies and justify suitable doses for children with VTE.

3.2 | PK simulation

A simulation of the clinical study dosing algorithm dabigatran concentration–time profiles after the first dose and at steady state, with and without dose adjustments (only one dose adjustment was allowed with the clinical study dosing algorithm), showed minimal changes in simulated dabigatran levels following dose adjustment across all dabigatran formulations.

Simulation of $C_{ss,min}$ 12 hours after dabigatran etexilate dosing (at steady state and without any dose adjustment), based upon reference ranges derived from the adult dabigatran clinical study program (26–250 ng/ml), is shown in Figure 1. Exposure for most of the younger children given oral solution was within the reference range, with only a few children having exposure <26 ng/ml or >250 ng/ml (<5% and <1%, respectively). Furthermore, in younger children given pellets, exposure tended to be toward the lower end of the reference range across several age categories; >10% of children had exposure <26 ng/ml, with few (<2%) having exposure >250 ng/ml. For capsules, given to older children/adolescents, exposure was within the reference range for most patients.

Simulations of $C_{ss,min}$ 12 hours after dabigatran etexilate dosing using the updated dosing algorithm appear to indicate that, without any potential dose adjustment, exposure for all formulations was within the reference range derived from adult studies for the majority of children across all age categories (Figure 1). The simulated proportions of children by age who would be within (26 to <250 ng/ml) or outside the $C_{ss,min}$ reference range using the updated dosing algorithm are shown in Table 2. For children aged <12 months given oral solution, >94.0% would be within the reference range, with <6.0% and 1.0% having $C_{ss,min}$ exposure <26 and ≥250 ng/ml, respectively. More than 89.0% of children aged <12 years treated with pellets would be within $C_{ss,min}$ exposure 26 to <250 ng/ml, with <9.4% and <4.1% having $C_{ss,min}$ exposure <26 and ≥250 ng/ml, respectively. For children aged 8 to <18 years treated with capsules, >92.8% would be within $C_{ss,min}$ exposure 26 to <250 ng/ml, with <1.8% and <6.2% having $C_{ss,min}$ exposure <26 and ≥250 ng/ml, respectively.


Clinical study dosing algorithm
Updated dosing algorithm
Oral solution
Pellets
Capsules
Dabigatran $C_{ss,min}$ (ng/mL)
0
100
200
300
400
500
0 to < 1 m
1 to < 2 m
2 to < 3 m
3 to < 4 m
4 to < 5 m
5 to < 6 m
6 to < 7 m
7 to < 8 m
8 to < 9 m
9 to < 10 m
10 to < 11 m
11 to < 12 m
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1.5 to < 2 y
2 to < 2.5 y
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12 to < 13 y
13 to < 14 y
14 to < 15 y
15 to < 16 y
16 to < 17 y
17 to < 18 y
Age

FIGURE 1 Simulated dabigatran $C_{ss,min}$ by age, without dose adjustment, following dosing using the clinical study and the updated algorithms. The horizontal line in the middle of the boxes is the geometric mean. Boxes indicate the 25th and 75th percentiles, with whiskers extending between the 5th and 95th percentiles. Dashed lines represent the reference range (26–250 ng/ml) derived from adult studies. $C_{ss,min}$, minimum concentration at steady state; m, month; y, year

TABLE 2 The simulated proportion of children inside and outside the target $C_{ss,min}$ reference range using the final dabigatran etexilate dosing algorithm, by age category and dabigatran formulation

	Oral solution			Pellets			Capsules		
	% of children with $C_{ss,min}$			% of children with $C_{ss,min}$			% of children with $C_{ss,min}$		
Age	<26 ng/ml	26 to <250 ng/ml	≥250 ng/ml	<26 ng/ml	26 to <250 ng/ml	≥250 ng/ml	<26 ng/ml	26 to <250 ng/ml	≥250 ng/ml
0 to <1 m	4.23	95.59	0.20	4.43[a]	92.41[a]	3.16	–	–	–
1 to <2 m	3.94	95.84	0.22	5.01 [a]	94.08[a]	0.91	–	–	–
2 to <3 m	3.85	95.13	1.03	9.42[a]	90.31[a]	0.26	–	–	–
3 to <4 m	3.85	96.15	0	3.63[a]	92.54[a]	3.83	–	–	–
4 to <5 m	5.39	94.61	0	4.55[a]	91.30[a]	4.14	–	–	–
5 to <6 m	3.80	95.60	0.60	4.60[a]	92.60[a]	2.80	–	–	–
6 to <7 m	4.30	95.29	0.41	5.00	91.04	3.96	–	–	–
7 to <8 m	4.71	94.26	1.02	4.31	94.66	1.03	–	–	–
8 to <9 m	4.84	94.76	0.40	6.71	91.87	1.42	–	–	–
9 to <10 m	3.21	96.39	0.40	4.02	93.98	2.01	–	–	–
10 to <11 m	4.01	95.99	0	5.22	92.37	2.41	–	–	–
11 to <12 m	6.00	94.00	0	4.40	92.40	3.20	–	–	–
1 to <1.5 y	–	–	–	5.20	93.00	1.80	–	–	–
1.5 to <2 y	–	–	–	4.20	92.80	3.00	–	–	–
2 to <2.5 y	–	–	–	3.20	91.20	5.60	–	–	–
2.5 to <3 y	–	–	–	3.60	90.20	6.20	–	–	–
3 to <4 y	–	–	–	3.00	93.20	3.80	–	–	–
4 to <5 y	–	–	–	4.00	91.20	4.80	–	–	–
5 to <6 y	–	–	–	6.60	90.20	3.20	–	–	–
6 to <7 y	–	–	–	6.40	90.80	2.80	–	–	–
7 to <8 y	–	–	–	8.20	89.00	2.80	–	–	–
8 to <9 y	–	–	–	8.60	89.20	2.20	1.60	93.60	4.80
9 to <10 y	–	–	–	6.20	92.40	1.40	0.40	95.20	4.40
10 to <11 y	–	–	–	6.80	91.80	1.40	1.80	93.80	4.40
11 to <12 y	–	–	–	6.20	91.60	2.20	1.60	92.80	5.60
12 to <13 y	–	–	–	–	–	–	1.20	92.80	6.00
13 to <14 y	–	–	–	–	–	–	1.40	93.60	5.00
14 to <15 y	–	–	–	–	–	–	0.80	94.00	5.20
15 to <16 y	–	–	–	–	–	–	0.60	93.20	6.20
16 to <17 y	–	–	–	–	–	–	0.60	93.60	5.80
17 to <18 y	–	–	–	–	–	–	1.00	93.40	5.60

Abbreviations: $C_{ss,min}$, minimum concentration at steady state; m, month; y, year.

[a]While the two phase 2b/3 pediatric study protocols allowed for children aged <6 months to receive pellets, no children aged <6 months were administered pellets in either phase 2b/3 study.

Analysis of $C_{ss,min}$ 12 hours after dabigatran etexilate dosing using the clinical study algorithm showed that, overall, the impact of dose adjustment appeared to be minimal across all weight categories (Figure 2). Dabigatran exposure in some children receiving oral solution and pellets was toward the lower end of the reference range across all weight categories. Exposure appeared to be slightly lower

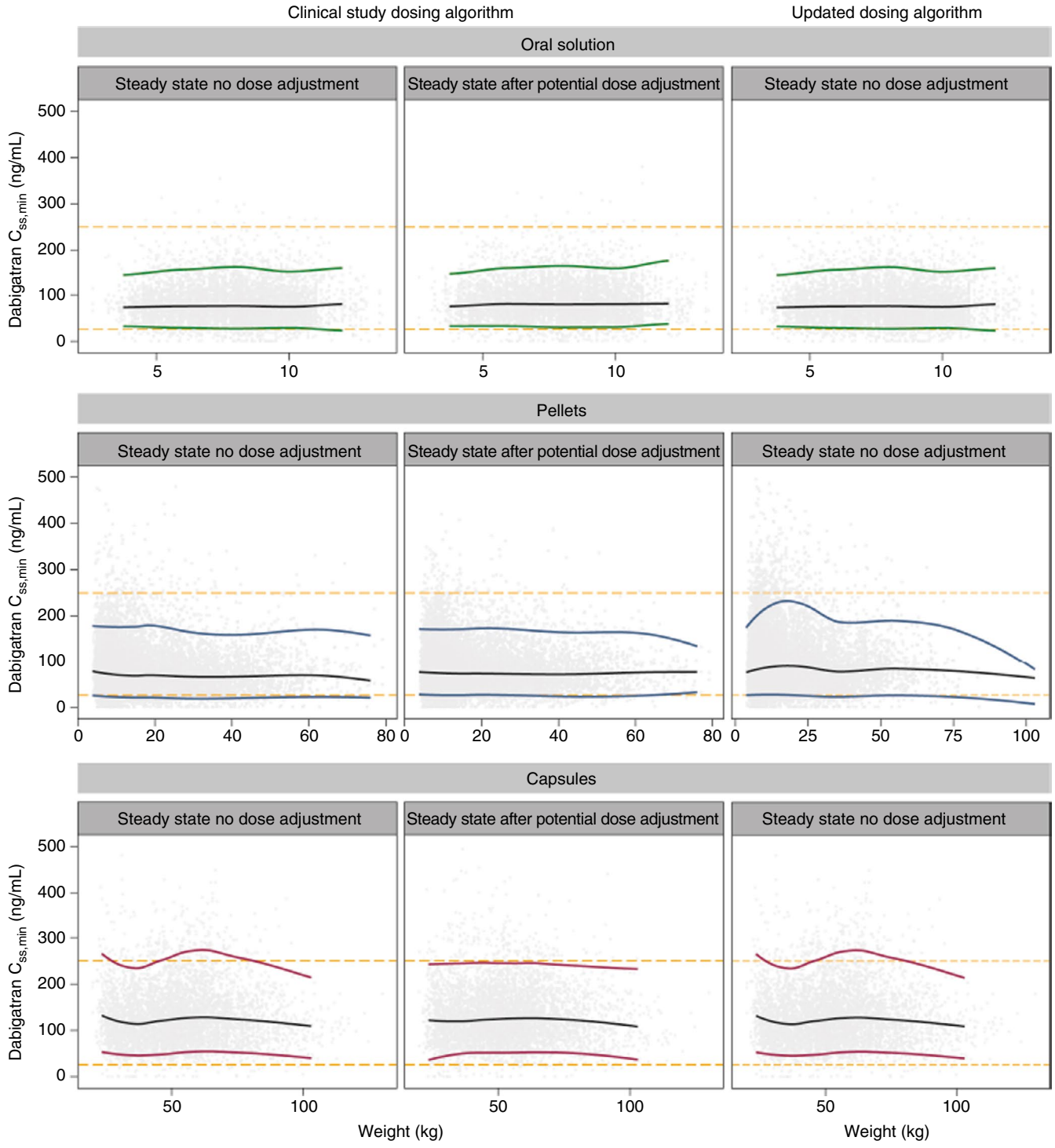

FIGURE 2 Simulated dabigatran $C_{ss,min}$ versus body weight following dosing using the clinical study and the updated algorithms. Black lines: smoothed median concentration. Colored lines: 5th and 95th percentiles. Dashed lines represent the reference range (26–250 ng/ml) derived from adult studies. $C_{ss,min}$, minimum concentration at steady state

for pellets than for the oral solution. For capsules, most children across all weight categories had exposure within the reference range, with some children having exposure slightly above the reference range. Simulations of $C_{ss,min}$ 12 hours after dabigatran etexilate dosing using the updated dosing algorithm indicated that most children across all body weights would achieve adequate exposure without dose adjustment.

4 | DISCUSSION

The objectives of this study were to develop a population PK model that would describe the PK characteristics of dabigatran and quantify covariate–parameter relationships, and to then use this model in population PK simulations to evaluate the appropriateness of the dabigatran etexilate pediatric dosing algorithm. The previous pediatric

population PK model was based on a limited number of pediatric patients, most of whom were exposed to a single dose of dabigatran. The updated model is enriched with data from phase 2b/3 studies in children. The population PK of dabigatran was adequately described by a two-compartment disposition model, and model diagnostics supported the usability of the population PK model for PK simulation. The original pediatric dabigatran etexilate age- and weight-based dosing algorithms used in the clinical studies were confirmed by PK simulations, with and without dose adjustment. Using the final, updated dosing algorithms, PK simulation found that no dose adjustment was needed when dabigatran was administered to pediatric patients as oral solution, pellets, or capsules. In the five pediatric studies,[9,13-16] there were too few pediatric patients with outcome events to be able to directly explore PK and outcomes in dabigatran-treated children. However, the evaluation of pediatric dosing in our analysis was based on the dabigatran target exposure range applied in the pediatric studies (26–250 ng/ml), an exposure range that corresponds with efficacy in the adult VTE setting.[10-12] This matching exposure approach is adequate if PK/pharmacodynamic (PD) parameters are similar between the populations, and a separate PK/PD analysis shows that this is the case.[26]

The population PK model showed that age (<2 years) and body weight were key covariate factors impacting dabigatran exposure, justifying the age- and weight-based dosing algorithm. Apparent clearance increased with age (independent of body weight) and with increasing body weight (in accordance with allometric scaling). Overall, as children aged, increases in apparent clearance could be estimated by the final PK model with precision, and no additional dose adjustment seemed to be warranted. The impact of age upon dabigatran exposure for younger children is not surprising considering that their hemostatic and coagulation systems are maturing.[5-7] For instance, Ignjatovic et al. reported age-related differences in activated partial thromboplastin time levels that correlated with a therapeutic heparin range of 0.35 to 0.7 anti-factorXa IU/ml, with more pronounced differences in younger children compared to adults (≤5 years, 78–200 s; 6 to ≤16 years, 54–154 s; adults, 55–118 s; younger children vs. adults, $P < .05$).[7] Two additional key covariate factors impacting dabigatran exposure and therapy were BSA-normalized renal function and sex. The identification of BSA-normalized renal function is unsurprising considering that 80% of dabigatran is eliminated via the kidneys,[27] and while there was a small effect of eGFR upon clearance, no additional dose adjustment appeared to be warranted in patients with eGFR >50 ml/min/1.73 m^2. The 10% lower apparent clearance in females versus males was in alignment with the adult dabigatran population PK model based on the RE-LY study,[21] and no additional dose adjustment seemed to be warranted.

Hemoglobin value, race, and concomitant use of PPIs were not identified as statistically significant covariates in children, although there were few Black/Asian children or children taking concomitant PPIs. In contrast, an analysis of 27,706 dabigatran plasma concentrations from 9522 adult patients found that dabigatran PK parameters were impacted by hemoglobin (apparent volume of distribution decreased by 4.0% per 1 g/dl increase above median hemoglobin of 14.3 g/dl), race (apparent clearance decreased by 20.3% in South Asian patients), and PPI co-medication (bioavailability decreased by 12.5%).[20] While in adults the effect of hemoglobin was in addition to that of sex, in children there was no effect of hemoglobin although sex differences were of the same magnitude as adults.

In children, while dabigatran absorption was faster (higher k_a) for oral solution or pellets compared to capsules, the apparent relative bioavailability with oral solution and pellets was lower. This is in contrast to the healthy adult volunteers' data, in which relative bioavailability was found to be lower with capsules than with pellets or oral solution. The lower-than-expected relative bioavailability for pellets in children led to an update of the dabigatran etexilate pediatric dosing algorithm. While the expected relative bioavailability was also lower for the oral solution than for the capsules, this was considered acceptable given the wide target exposure range and did not require an update of the dabigatran etexilate dosing algorithm.

While the population PK analysis was based upon several assumptions, these have been shown to be justified. For example, the assumption that the dabigatran exposure–response relationship would be comparable between children and adults has been supported by similarities in the dabigatran exposure–response relationships for the laboratory coagulation parameters (activated partial thromboplastin time, diluted thrombin time, and ecarin clotting time) between adults and children.[26] In addition, the assumption that the simulated population would have comparable age and weight distribution in children in the NHANES database[23] was justified, as simulation results using the original and final dosing algorithms seemed consistent comparing across age- and body-weight categories.

Model diagnostics of the population PK model supported its usability for population PK simulation, which not only verified the suitability of clinical study dosing algorithms, but also identified areas of refinement. Simulation analyses for the oral solution suggested that the apparent relative bioavailability was lower than expected relative to capsules. However, as the proportion of patients with exposure <26 ng/ml was also lower than for those receiving pellets, no modification of the clinical dosing algorithm was considered necessary. For pellets, simulation analyses showed that the apparent relative bioavailability was lower than expected relative to capsules, leading to more children than expected with exposure <26 ng/ml across most age groups (with the exception of children aged <1 month). Increasing the dose by approximately 20% in the simulations to the nearest available strength compensated for the lower-than-expected apparent relative bioavailability. For capsules, the 50-mg dose is no longer considered necessary, and capping the maximum dose from 330 mg to 300 mg did not negatively influence the proportion of patients with exposure <26 ng/ml. The use of these final dosing algorithms for pellets and capsules should result in a higher proportion of children achieving the targeted $C_{ss,min}$ exposure for dabigatran across both the age- and body-weight categories. Moreover, simulations using the clinical study dosing algorithms clearly showed that dose adjustment resulted in only a marginal reduction of patients outside of the 26 and 250 ng/ml limits across all

age groups. As such, any further dose adjustment provides limited value, with a minimal increase in the proportion of patients within the reference range derived from adult studies. Therefore, dose adjustment based on dabigatran plasma levels is not considered necessary when using the final, updated dosing algorithm.

The treatment of VTE in children has been challenging for physicians, so how might these data overcome some of the challenges? We discuss here the potential clinical implications of our findings. Oral anticoagulants that require neither routine laboratory monitoring nor dose titration will provide a significant advance in the treatment of VTE in children, overcoming several of the limitations associated with SOC. Use of the clinical study dosing algorithms in the phase 2b/3 studies provided comparable efficacy and safety for dabigatran compared to SOC in children with acute VTE, and a favorable safety profile for secondary VTE prevention.[9,13] With the final, updated dabigatran etexilate age- and weight-adjusted dosing algorithms, treatment of children with VTE will be simplified for clinicians, as neither routine laboratory monitoring nor dose titration are required. The observed pediatric data show the efficacy and safety of dabigatran in children with VTE aged from birth (≥37 weeks gestational age) to <18 years of age, who weighed between 3.7 and 132.0 kg. We are unable to provide insight into the management of extremely vulnerable premature infants or those weighing <3.7 or >132.0 kg, as infants with gestational age at birth <37 weeks or with body weight lower than the 3rd percentile (according to the World Health Organization child growth standards) were excluded from the dabigatran pediatric studies. In late 2020, the European Medicines Agency approved pediatric indications for dabigatran etexilate, and the latest dosing information is available in the Summary of Product Characteristics (https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf). At the time of manuscript publication, the recommended dosing in the United States is not yet established as discussions with the Food and Drug Administration are still ongoing.

The only other DOAC to report efficacy in the pediatric VTE setting to date is rivaroxaban,[8] using a dosing strategy based upon body weight (once-daily dosing in children ≥30 kg, twice-daily dosing in those ≥12 to <30 kg, and thrice daily in those <12 kg) to achieve exposure within a reference range obtained from 203 adults with VTE aged <45 years who had received 20 mg rivaroxaban once daily.[28,29] Apixaban is also being investigated in a phase 4 randomized, open-label, active controlled study (NCT02464969) in ~250 children with acute VTE and final data are expected in 2023; preliminary safety data from a pilot study are available from 15 children aged 12 to 21 years (NCT04041843).[30] In addition, an ongoing phase 3 randomized study evaluating edoxaban versus SOC (NCT02798471) in 274 children aged from birth to <18 years is due to complete by the end of 2021.

In summary, a population PK model of dabigatran for pediatric patients with VTE was developed and used in PK simulations, which demonstrated that the final dabigatran etexilate dosing algorithm is appropriate for all dabigatran formulations, has fewer dosing categories, and does not require dose adjustments or routine monitoring of dabigatran levels. This, together with the efficacy and safety of dabigatran in the pediatric VTE setting, validates and supports the use of dabigatran etexilate for the treatment of VTE in children.

DATA SHARING STATEMENT

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfil their role and obligations as authors under the International Committee of Medical Journal Editors criteria. Furthermore, clinical study documents (e.g., study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/.

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical study reports and related clinical documents can be requested via this link: https://trials.boehringer-ingelheim.com/.

All requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a data-sharing agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use https://clinicalstudydatarequest.com to request access to study data.

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CONFLICTS OF INTEREST

DR, MBe, and MMAI are employees of Pharmetheus, contracted as external consultants by Translational Medicine and Clinical

Pharmacology, Boehringer Ingelheim Pharmaceuticals. FH, DJ, IT, SG, PR, and MBr are all employees of Boehringer Ingelheim. MA is a member of a pediatric expert working group for Boehringer Ingelheim and has received advisory board fees from Daiichi Sankyo. LB is a member of a pediatric expert working group for Boehringer Ingelheim, and reports fees to her institution from Janssen Pharmaceuticals. EC is a member of a pediatric expert working group for Boehringer Ingelheim, and reports personal fees from Roche, Sobi, Bristol Myers Squibb, CSL Behring, and Shire/Takeda. ML is a member of a pediatric expert working group for Boehringer Ingelheim. JH is a member of a pediatric expert working group for Boehringer Ingelheim and has received honoraria from Boehringer Ingelheim for congress presentation. LGM is a member of a pediatric expert working group for Boehringer Ingelheim and has received a research grant from Bristol Myers Squibb. LRB is a member of a pediatric expert working group for Boehringer Ingelheim and has received advisory board fees from Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

D. Röshammar, F. Huang, D. Joseph, and L. R. Brandão contributed to the concept, design, and analysis of the data. All authors contributed to critical writing or revising of intellectual content and final approval of the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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