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ORIGINAL ARTICLE

A new population pharmacokinetic model for recombinant factor IX-Fc fusion concentrate including young children with haemophilia B

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Abstract

Aims: Recombinant factor IX Fc fusion protein (rFIX-Fc) is an extended half-life factor concentrate administered to haemophilia B patients. So far, a population pharmacokinetic (PK) model has only been published for patients aged ≥12 years. The aim was to externally evaluate the predictive performance of the published rFIX-Fc population PK model for patients of all ages and develop a model that describes rFIX-Fc PK using real-world data.

Methods: We collected prospective and retrospective data from patients with haemophilia B treated with rFIX-Fc and included in the OPTI-CLOT TARGET study (NTR7523) or United Kindom (UK)-EHL Outcomes Registry (NCT02938156). Predictive performance was assessed by comparing predicted with observed FIX

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activity levels. A new population PK model was constructed using nonlinear mixed-effects modelling.

Results: Real-world data were obtained from 37 patients (median age: 16 years, range 2–71) of whom 14 were aged <12 years. Observed FIX activity levels were significantly higher than levels predicted using the published model, with a median prediction error of −48.8%. The new model showed a lower median prediction error (3.4%) and better described rFIX-Fc PK, especially for children aged <12 years. In the new model, an increase in age was correlated with a decrease in clearance ($P < .01$).

Conclusions: The published population PK model significantly underpredicted FIX activity levels. The new model better describes rFIX-Fc PK, especially for children aged <12 years. This study underlines the necessity to strive for representative population PK models, thereby avoiding extrapolation outside the studied population.

KEYWORDS
extended half-life, factor IX, haemophilia B, pharmacokinetics

1 | INTRODUCTION

Haemophilia B is an inherited bleeding disorder caused by mutations in the *F9*-gene on the X-chromosome.[1] These mutations result in a coagulation factor IX (FIX) deficiency, leading to impaired haemostasis. Severely and moderately affected haemophilia B patients suffer from spontaneous bleeding or bleeding after minor trauma, especially into joints and muscles. When left untreated, these bleeds may be life-threatening or lead to arthropathy with ultimately long-term disability.[2] FIX replacement therapy—both prophylactically and on demand—is mainstay of treatment, leading to a normal life expectancy with good quality of life.[3] Extended half-life (EHL) FIX concentrates have further ameliorated the burden of disease by substantially decreasing the frequency of intravenous FIX concentrate administration to on average once every week.[4]

Recombinant factor IX Fc fusion protein (rFIX-Fc) is an EHL-FIX concentrate that consists of a single recombinant FIX molecule fused to the dimeric Fc domain of human immunoglobulin G1.[5] This fusion delays the lysosomal degradation by recycling rFIX-Fc back into circulation. As a result, half-life is prolonged from 17 h for rFIX to 82 h for rFIX-Fc in patients aged ≥12 years.[4] The pharmacokinetics (PK) of FIX concentrates are complex and demonstrate a moderate level of interindividual variability (IIV).[6–9] As a result, FIX activity levels vary between patients.[10–12] The variability in PK parameters of individual subjects entails individual adjustments for administration of FIX replacement therapy by application of Bayesian forecasting. This application using population PK models has been shown to be successful to individualize factor concentrate dosing in haemophilia treatment.[13,14] Furthermore, Bayesian forecasting methodology allows for limited sampling in contrast to traditional modelling methods.[15]

To establish the PK characteristics of rFIX-Fc and identify covariates, Diao *et al*. developed an rFIX-Fc 3-compartment population PK model[16] using data from several clinical trials. To our knowledge, this is the only population PK model currently published for this EHL factor concentrate. Importantly, this model has not been externally evaluated. Moreover, this model was constructed using data of 11 children, all aged ≥12 and <18 years. Therefore, the accuracy of this model in children aged <12 years may be limited. The aim of this study is to externally evaluate and assess the predictive performance of the published rFIX-Fc model using new independent real-world patient data. Sequentially, this study aims to develop a new population PK model describing the PK in a more extended age range, including children aged <12 years, and to compare doses calculated by the 2 models.

2 | METHODS

2.1 | Data collection

We collected data from haemophilia B patients treated prophylactically with rFIX-Fc (eftrenonacog alfa, Alprolix, **GtoPdb Ligand ID 7373**[17]) included in the OPTI-CLOT TARGET study[18] or UK-EHL Outcomes Registry (NCT02938156). Ethical approval and written informed consent were obtained. Briefly, haemophilia patients in the OPTI-CLOT TARGET study received 9 months of PK-guided dosing to investigate the reliability and feasibility of the Bayesian forecasting procedure. FIX samples for PK profiling were obtained pre-infusion and approximately 15–30 min, 4, 24, 72–120 and 168 h after infusion. During PK-guidance, a minimum of 4 FIX activity (at nonspecific time points after infusion) levels per patient was collected in a minimum of 2 visits to evaluate predicted FIX. The UK-EHL Outcomes Registry contains patient characteristics and treatment information, including FIX infusions (timing and doses) and FIX activity level measurements. During PK profiling, FIX activity levels were measured at pre-infusion and approximately 15 min, 24, 72, 120 and 168 h after infusion. Additional FIX activity levels were sampled during visits at

10 days, 3, 6, 12 and 18 months after initiation of rFIX-Fc treatment. In both studies, no wash-out was required during PK profiling if 3 prior infusions were documented. Informed consent was obtained from all patients and/or caregivers.

2.2 | Patient data handling

In both cohorts, FIX activity was measured using the 1-stage assay (OSA) according to local protocol. Laboratory specifications of all participating sites are shown in Table S1. All FIX activity levels measured during bleeding episodes or surgeries[19] were excluded from this analysis.

Since the OSA does not distinguish FIX activity from the endogenous baseline FIX activity or respective FIX concentrates (e.g. residual FIX activity levels from the previous FIX dose or currently present FIX concentrate), it is required to correct for the endogenous baseline and previously administered factor concentrates. To do so, we performed the following corrections in line with Diao *et al.*[16] and previously reported PK analyses with FIX concentrates[7,10,20,21]:

$$\textit{Residual decay correction} = (\textit{Predose activity} - \textit{baseline}) * e^{-kt} \quad (1)$$

$$\textit{Corrected FIX activity} = \textit{Measured FIX activity} - \textit{baseline} - \textit{residual decay correction} \quad (2)$$

$$k = \frac{\ln(2)}{t_{1/2}}; \quad (3)$$

in which k represents the elimination rate constant of the previously used concentrate for rFIX-Fc (Alprolix), rFIX (Benefix) or rIX-FP (Idelvion) calculated for each age group (<6, ≥6–12, ≥12–18 and ≥18 years). For these calculations, we used typical half-lives ($t_{1/2}$) of each age group as reported by the respective European Public Assessment Report (EPAR).[22–24] Other patient characteristics collected were age, height, body weight, lean body weight (LBW) and fat-free mass (FFM). Occasions were defined as a visit with PK assessment, as described in literature.[25]

2.3 | Evaluation of published population PK model

The predictive performance of the published rFIX-Fc population PK model by Diao *et al.*[16] was assessed with our data using NONMEM software (v7.4.1, Icon Development Solutions, Gaithersburg, MD, USA).[26] Data visualization and evaluation were performed in R (version 4.1.1), Pirana (version 2.9.8) and PsN (version 4.8.1). Predictive performance was visualized in goodness of fit (GOF) plots showing predicted *vs.* observed FIX activity levels. A priori population predicted (PRED) activity was obtained using typical PK parameters which can be calculated on basis of patient characteristics (e.g. body weight). Individual PK parameters were obtained after Bayesian estimation providing a posteriori individual predicted activity (IPRED). Next, predictive performance was evaluated by comparing predicted *vs.* observed FIX activity levels. The prediction error (PE, Equation 4) was determined to assess bias. The root mean squared error (RMSE, Equation 5) was determined to elaborate on differences between individual predictions of the published and new model.

$$\text{PE} = \left(\frac{C_{pred} - C_{obs}}{C_{obs}}\right) * 100\% \quad (4)$$

$$\text{RMSE} = \sqrt{\frac{\sum_{j=1}^{n} \left(C_{ipred} - C_{obs}\right)^2}{n}} \quad (5)$$

Cpred represents the population predicted and *Cipred* the individually predicted FIX activity level of measurement *j*. *Cobs* represents the observed FIX activity level. The total number of measurements is denoted by *n*. A negative or positive PE indicates a systematic under- or overestimation of population predicted FIX activity levels. A median PE between −5% and 5% is deemed as not biased. RMSE was determined for peak (time after dose 0–2 h), mid (time after dose 2–120 h) and trough (time after dose 120–300 h) FIX activity levels separately.

Furthermore, for patients aged <12 years, we investigated potential bias due to possible relationships between covariates and population PK parameters volume of central compartment (V1), volume of peripheral compartment (V2), clearance (CL) and intercompartmental clearance (Q). Therefore, we plotted interindividual variability (η) in these PK parameters against the patient characteristics age and body weight. Plots of an unbiased model should not show trends, indicating that η in these PK parameters are divided randomly over patient characteristics.

Finally, terminal elimination half-lives ($t_{1/2}$) were determined by *posthoc* calculation for patients aged <12 years, patients aged ≥12 and <18 years and adults. Results were compared with results from the new model (see below). As the $t_{1/2}$ estimates are influenced by the number of compartments,[27] the respective compartments of both models were taken into account.

2.4 | Development of a new population PK model

When the predictive performance of the published model was inadequate, an alternative population PK model was constructed. During construction, the number of compartments was evaluated. In this study, the initial visit with PK profiling was considered as the first occasion. Subsequent occasions were defined as a visit with a PK assessment. PK parameters were expressed by CL, Q and V; IIV and interoccasional variability (IOV) of these parameters was estimated. Residual error is described with a combined additive and proportional model. We evaluated candidate models by examination of PK parameter estimates, their respective residual standard errors, objective function value (OFV), GOF plots and visual predictive checks.

Stepwise covariate modelling was used to perform covariate analysis applying the generalized additive models approach.[28,29] This approach allows to test if potential patient characteristics are able to explain IIV and IOV in PK parameters. We applied a forward inclusion and backward elimination process. Age, height, body weight, LBW, FFM, body mass index (BMI) and centre of inclusion were available and explored as covariates. Allometric scaling was applied with fixed exponents of 0.75 for CL and 1.00 for V.[30,31] As height was not available in 2 patients, their height was fitted by a linear regression model based on available height and age of other patients, and used to calculate BMI. Consecutively, BMI was used in the calculation of LBW and FFM in accordance with Janmahasatian *et al.*[32] and Al-Sallami *et al.*,[33] respectively. We explored the impact of the centre on FIX predictions as haemophilia treatment centres used different laboratory specifications according to local protocol. This was tested by incorporating a residual error per centre.

In the stepwise covariate modelling, covariates were screened for relevance by univariate analysis. Improvement of the model was deemed significant if addition of a covariate to the model decreased the OFV (ΔOFV) with 3.84 ($P < .05$, χ^2 distribution, 1 *df*). When 2 parameters were added simultaneously, e.g. during expansion of a 2-compartment model to a 3-compartment model, a ΔOFV of −5.99 ($P < .05$, χ^2 distribution, 2 *df*) was warranted. Subsequently, all significant covariates were simultaneously added to the model, followed by backward elimination. Elimination of a covariate that resulted in an OFV increase of >6.64 ($P < .01$, χ^2 distribution, 1 *df*) was regarded as a significant improvement to the model.

The new population PK model was internally evaluated with a visual predictive check to compare the distribution of the observations with the distribution of the predictions. The robustness of the parameter estimates was assessed by bootstrap analysis. Bias of the new population PK model were assessed throughout the PE (Equation 4).

2.5 | Individual dosing advice

To evaluate the clinical impact of the choice of model on dosing regimens, we compared the dose (IU) for each individual with a PK profile assessment of rFIX-Fc ($n = 36$) as calculated by application of (*posthoc*) Bayesian forecasting using both the published and the developed new model. Individual PK parameters were calculated for a situation in which 3 FIX activity levels (peak, trough and random mid) were considered available, to mimic clinical circumstances. Doses were targeted at maintaining a FIX level >3 IU/dL at 168 h after infusion of rFIX-Fc during steady-state ($Dose_{3\%}$). We wanted to perform Bayesian forecasting on data that was not included in the development of the model. Hence, an adjusted jackknife method was performed.[34,35] Based on our original dataset of 36 patients, we created 5 separate datasets including 29–30 patients on which population PK parameters were estimated. These parameter estimates were used for Bayesian forecasting of the remaining 6–7 patients—that were not included in the dataset—using their (3) considered available FIX activity levels. Differences in calculated doses between the 2 models were explored by the permutation test, as the doses were not normally distributed and contained too many ties to perform a Wilcoxon signed rank test. This analysis was also performed separately for children aged <12 years, since the previously published model did not include children aged <12 years, whereas the newly developed model did.

3 | RESULTS

3.1 | Patient characteristics and PK profiling

Real-world data from 35 severe and 2 moderately severe haemophilia B patients were available for assessment of the predictive performance of the published rFIX-Fc population PK model (Table 1). Median age was 15.8 years (range 2.3–71.0), and 14 patients were younger than 12 years. Patients received a median dose of 36 IU/kg rFIX-Fc concentrate (range 10–132 IU/kg). In total, 287 FIX activity levels measured by OSA were available for analysis. Three FIX activity levels (1% of the data) were below lower limit of quantitation and therefore excluded from the analysis.[31,36] During PK profiling, a median of 5 FIX activity levels (range 3–7) in adolescent and adult patients (aged ≥12 years) and 4 FIX activity levels (range 3–7, mean 4.5) in children (aged <12 years) were sampled. PK data was obtained during a median of 2 occasions per individual (range 1–9).

3.2 | Predictive performance of the published model

Figure 1A,B present the population predictions GOF plots for all patients and children aged <12 years separately. Observed FIX activity levels are higher than their respective predictions (Figure 1A,B) and a clear deviation of trend lines from identity lines can be seen in all patients (Figure 1A), but especially in children aged <12 years (Figure 1B). These observations indicate structural bias (underprediction) of the published model. This is also illustrated by the median PE of −48.8% (interquartile range [IQR]: −29.9 to −63.9) for all patients and −54.1% (IQR: −43.3 to −65.8) for children aged <12 years (Table S2A). The RMSE is shown in Table S2B.

Furthermore, deviations were observed in plots of conditional weighted residuals (CWRES) *vs.* population predictions (PRED, Figure S1A) and time after dose (TAD, Figure S1B).

For children aged <12 years, Figure 2A,B show the deviation from the individual PK estimate from the typical population value over the weight range. For the evaluation of these graphs, it is important to realize that an adequate population model would have random interpatient variability with an average of zero and no trend with weight. Figure 2A,B clearly demonstrate that children's CL and V1 are lower than would typically be expected over the studied weight range and advocate the development of a new model.

TABLE 1 Patient characteristics at baseline.

	Number (*n*)	% or median [IQR] (range)	
Patients in total			
Number	37		
Severe haemophilia (FIX<1 IU/dL)	35	(95%)	
Baseline FIX non-severe patients (IU/dL)	1.00		(1–1)
Age (years)	15	[11–30]	(2–71)
Body weight (kg)	65.4	[33–77]	(12–103)
Height* (cm)	169	[140–180]	(85–192)
BMI* (kg/m^2)	22.0	[18–25]	(13–32)
Lean body mass (kg)	51.7	[30–59]	(11–74)
Fat-free mass (kg)	51.1	[26–59]	(10–74)
Paediatric patients			
Number of paediatric patients[a]			
<18 years (% of total patients)	19	(51%)	
<12 years	14	(38%)	
<6 years	7	(19%)	
Age (years)	11	[4–12]	(2–16)
Body weight (kg)	32.8	[16–32]	(12–52)
Lean body mass (kg)	29.5	[15–44]	(11–52)
Fat-free mass (kg)	26.3	[13–41]	(10–51)
Treatment			
Dose (IU/kg)	36	(10–132)	
Blood samples at PK profiling[b]	5	(3–7)	

[a]Percentages reflect proportions of the total population ($n = 37$).
[b]No first PK profile assessment in 1 patient.
*No data available in 2 patients.
BMI, body mass index; FIX, factor IX.

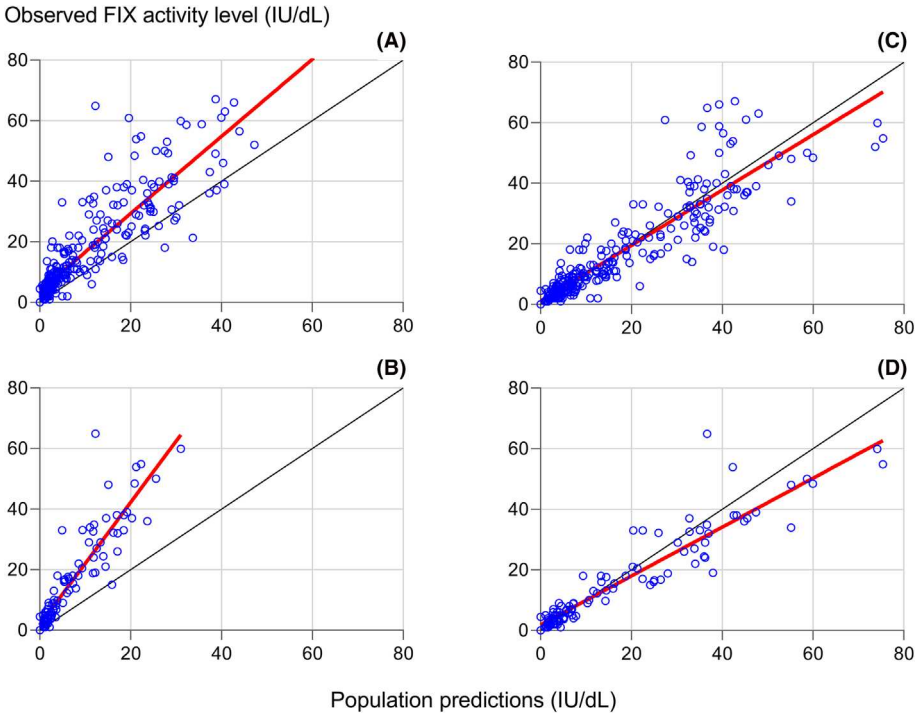

FIGURE 1 Population goodness of fit (GOF) plots of both the published model (A,B) and new model (C,D) using real-world clinical data, including children aged <12 years. Observed factor IX (FIX) activity levels are plotted against the predicted factor IX activity levels for all patients (A,C) and children aged <12 years (B,D). The trend line (red line) combines all individual data points (blue circles) and should approximate the line of identity (black line). The new model shows an improved fit compared to the published model for all patients—but especially for children <12 years—as the trend lines better approximate the line of identity.

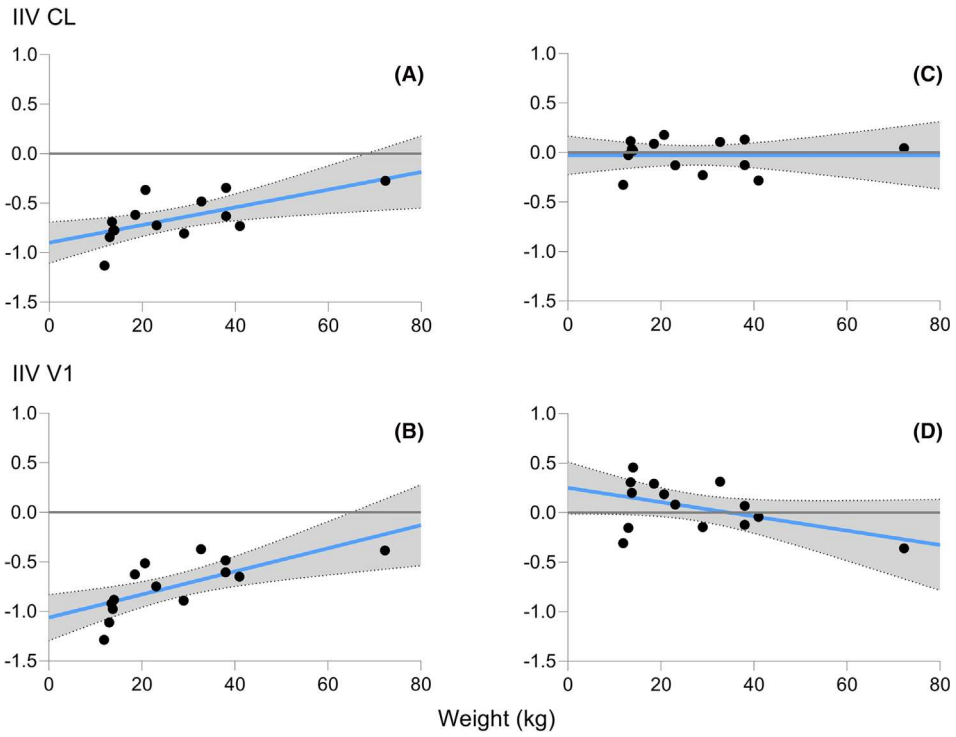

FIGURE 2 Interindividual variability (IIV) of clearance (CL) and volume of central compartment (V1) for the published (A,B) and new (C,D) model exclusively for children aged <12 years. Individual data (black dots) is visualized as a trend line (blue line) approximating the line of identity (grey line). For an adequate population model, interindividual variability should be randomly distributed around the axis y = 0 with no apparent trend. The new model shows an improved fit compared to the published model for the IIV of CL, as the trend line is closer to the line of identity.

3.3 | Development of the new model

3.3.1 | Structural model

A new rFIX-Fc population PK model using clinical data including children aged <12 years was developed (Table 2). A 2-compartment model with a central and a peripheral compartment adequately described our data. Addition of a second peripheral compartment did not improve the fit of the model to the data. All PK parameters were allometrically scaled. With allometric scaling, body weight is included in the structural model. IIV could be estimated for CL, V1 and V2, with a correlation between CL and V1. The clinical data supported the estimation of IOV on CL.

3.3.2 | Covariate analysis

Age, height, LBW, FFM, BMI and centre of inclusion were explored as covariates. In univariate analysis—using the structural model without application of allometric scaling – the separately weight-related covariates body weight, FFM and LBW were significantly related to CL and V1. We chose, however, to allometrically scale these parameters with body weight as it is easy and routinely measured, as opposed to LBW and FFM. Incorporation of a separate residual error for 1 haemophilia treatment centre improved the model ($P < .05$), but was not significant after the backward selection reprocess ($P < .01$). Therefore, all centres were described by the same residual error model. CL decreased with age; the latter was the only covariate that improved the fit of the model to the data. On basis of this relationship, typical clearance of a 73-kg patient would decrease from 1.89 dL/h at age 20 years to 1.36 dL/h at 70 years.

3.3.3 | Diagnostics of the new model

The internal validity throughout the visual predictive check (Figure 3) shows observed FIX activity levels being adequately predicted by the new model. Bootstrap results are presented in Table 2. The trend lines in the GOF plots are close to the line of identity for both all patients (Figure 1C) and children aged <12 years (Figure 1D). The trend line in children aged <12 years (Figure 1D) shows a slight deviation at high FIX activity levels, but this may be caused by the sparse number of samples in this range. A slight bias was detected for the new model, as the median PE was 3.4% (IQR −22.2–25.8) for all patients and 4.9% (IQR −20.8–27.5) for children aged <12 years (Table S2A).

CWRES plots (Figure S1C,D) show an improved fit compared to the published model (Figure S1A,B). In addition, the vast majority of values in the new model is within the warranted −2 to 2 range,[37] in contrast to the values of the published model.

Typical parameter values (Table 2) differed between the published and new model. For a typical 16-year-old 73-kg patient (the typical patient in the published model), CL was 1.41 dL/h and lower than the value of the published model (2.39 dL/h). In addition, distribution volume at steady-state was also lower with respective values of 153 and 198 dL. Likewise, terminal $t_{1/2}$ was lower in the new model compared to the published model for children aged <12 years (70 *vs.* 88 h), adolescents aged ≥12 and <18 years (76 *vs.* 99 h) and adults (88 *vs.* 101 h; Table S3).

TABLE 2 Recombinant factor IX Fc fusion protein population pharmacokinetic (PK) parameters from the published and new model.

Population PK model Parameters	Published Estimate	New Estimate (RSE %) [Shr.]			Bootstrap estimate (95% CI*)	
CL (dL/h)	2.39	1.41	(5)		1.41	(1.3–1.6)
Bodyweight exponent on CL	0.436	0.75				
Age exponent on CL		0.0047	(11)		0.0050	(0.001–0.010)
V1 (dL)	71.4	73.1	(5)		72.5	(65–80)
Bodyweight exponent on V1	0.396	1.00				
Q2 (dL/h)	1.67	2.77	(14)		2.87	(2.1–6.2)
Bodyweight exponent on Q2		0.75				
V2 (dL)	87.0	80.1	(11)		80.6	(66–100)
Bodyweight exponent on V2		1.00				
Q3 (dL/h)	39.3					
V3 (dL)	39.9					
Interindividual variability (IIV)						
IIV[a] on CL (%)	17.7	23.6	(20)	[14]	22.0	(14–32)
IIV on V1 (%)	21.7	31.6	(16)	[8]	29.8	(21–40)
Correlation[b] IIV CL and V1 (%)	75.6	44.0	(17)		42.0	(−9–62)
IIV on Q2 (%)	35.8					
IIV on V2 (%)	46.2	41.2	(17)	[39]	38.1	(19–53)
IIV on V3 (%)	37.7					
Interoccasion variability (IOV)						
IOV[a] on CL (%)	15.1	19.8	(22)	[36]	19.8	(8–27)
IOV on V1 (%)	17.4					
Residual variability						
Proportional error (%)	10.6	16.3	(14)		15.7	(9–22)
Additive error (IU/dL)	0.24	1.04	(21)		1.08	(0.3–1.5)

CL and V1 and V2 were scaled and normalized for an average patient with a body weight of 73 kg.
CL, clearance; Q2, intercompartmental clearance between compartments 1 and 2; Q3, intercompartmental clearance between compartments 1 and 3; RSE, relative standard error; Shr, shrinkageV1, central volume of distribution; V2, volume of compartment 2; V3, Volume of compartment 3.
[a]IIV and IOV coefficient of variation calculated as: √(variance) *100%.
[b]Correlation calculated as: covariance/(√(variance1)* √(variance2)) *100%.
*95% CI, nonparametric 95% confidence interval from bootstrap results with 2000 datasets.

Published model

$$CL = \theta_{CL} * \left(\frac{BW}{73}\right)^{0.436} * e^{\eta_{CL}}$$

$$V1 = \theta_{V1} * \left(\frac{BW}{73}\right)^{0.396} * e^{\eta_{V1}}$$

$$Q2 = \theta_{Q2} * e^{\eta_{Q2}}$$

$$V2 = \theta_{V2} * e^{\eta_{V2}}$$

$$Q3 = \theta_{Q3}$$

$$V3 = \theta_{V3} * e^{\eta_{V3}}$$

New model

$$CL = \theta_{CL} * \left(\frac{BW}{73}\right)^{0.75} * (1 - 0.0047 * (AGE - 15.8)) * e^{\eta_{CL}}$$

$$V1 = \theta_{V1} * \left(\frac{BW}{73}\right)^{1.00} * e^{\eta_{V1}}$$

$$Q = \theta_{Q} * \left(\frac{BW}{73}\right)^{0.75}$$

$$V2 = \theta_{V2} * \left(\frac{BW}{73}\right)^{1.00} * e^{\eta_{V2}}$$

Lastly, the validity of the model for children aged <12 years is illustrated in Figure 2C,D. The figure demonstrates random variability of CL and V with an average not different from zero. Of note, an adequate covariate model shows no trend and deviations from zero in the IIV.

3.4 | Individual dosing advice

To maintain a FIX level >3 IU/dL 168 h after rFIX-Fc infusion, individual doses were calculated by application of Bayesian forecasting using the published and the new model by taking 3 clinically

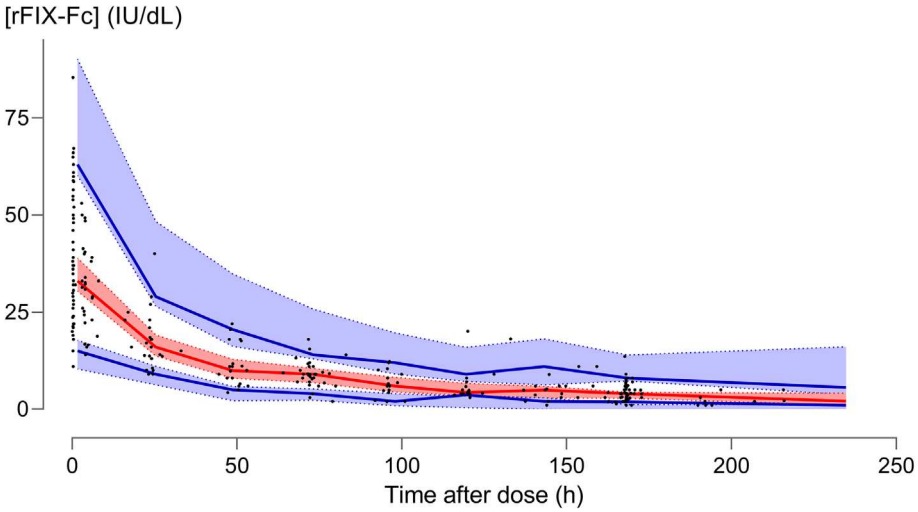

FIGURE 3 Visual predictive check of the new recombinant factor IX Fc fusion protein (rFIX-Fc) model. The median (red line) and 95% confidence interval (blue lines) of the observed data (black dots) are plotted against the simulated data ($n = 1000$) indicated as highlighted areas: the red area represents the median and the blue area the 90% prediction interval. A model predicts the factor concentrations adequately when the red and blue lines run through the corresponding areas.

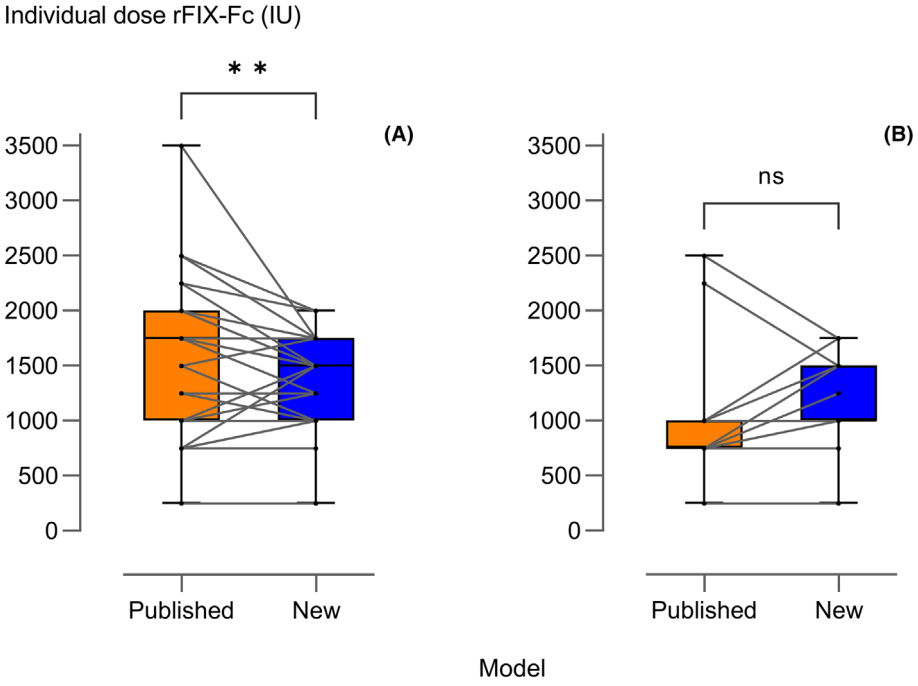

FIGURE 4 Individual dose calculations for both models to maintain a factor IX activity level >3 IU/dL 168 h after infusion of recombinant factor IX Fc fusion protein (rFIX-Fc). Calculations for all patients ($n = 36$; A) and children aged <12 years ($n = 13$; B) are presented separately. Calculations are made based on a situation in which 3 clinically relevant pharmacokinetic profile measurements were used for dose calculation. The boxes of the boxplots present the median (middle line) and interquartile range with whiskers extending to represent the range. The lines represent individual patients. For all patients (A) a significant difference was found ($P < .01$). For children aged <12 years (B), individual dose advices seemed higher with the new model, but no significant differences were found ($P = .63$).

relevant samples into account (Figure 4). The individually predicted $Dose_{3\%}$ was significantly higher ($P < .01$) when predicted by the published model (median 1750 IU [range 250–3500]) than with the new model (median 1500 IU [range 250–2000]) when all patients were considered. Surprisingly, however, when focusing on children <12 years, no significant differences in $Dose_{3\%}$ were found. Median dose was 750 IU (range 250–2500) and 1000 IU (range 250–1750; $P = .63$).

4 | DISCUSSION

In this study, the predictive performance of a published rFIX-Fc population PK model was evaluated using independent real-world data.[16] The published model was based on patients ≥12 years whereas in this study children with age <12 years were included as well. The published model significantly underpredicted the observed FIX activity levels in all patients, especially for children aged <12 years. Consequently, a new population PK model was developed which should preferably be used to perform PK-guided dosing in young children.

Compared to the previously published model, our newly developed model better describes the PK profiles of children aged <12 years that were included. These improvements are not surprising as weight normalized CL and V1 are generally larger in children compared to adults.[10] This phenomenon has also been reported for recombinant factor VIII-Fc fusion protein.[38] For children <12 years specifically, the new model shows adequate characterization of CL and V1 (Figure 2C,D).

Observed interpatient variability of CL and V1, and within-patient variability of CL were somewhat increased in comparison to reported values (Table 2). As real-word data are obtained from a highly heterogenic population, a larger variability is imminent compared to selected clinical study populations. This also explains why the residual proportional error in the new model (16.3%) was slightly higher compared to the published model (10.6%; Table 2). Real-world clinical data may contain more noise due to variability in assay precision, variability in administration and sample times.

Surprisingly, this study found a near 2-fold lower typical clearance than reported by Diao *et al.*[16] (Table 2). A possible explanation for this may be related to the neonatal Fc receptor (FcRn), to which the Fc domain of the immunoglobulin G1 molecule in rFIX-Fc binds. FcRn concentrations are negatively correlated with body weight.[39] Consequently, children have higher concentrations of weight-adjusted FcRn, possibly resulting in lower CL. As half of our population was paediatric (<18 years) and 38% were aged <12 years, the age-related effect on FcRn may have influenced CL estimation. However, this is in contrast to the higher FIX CL in children with decreasing age as reported in the Alprolix EPAR.

Our real-world clinical data were best described by a 2-compartment model and not by a 3-compartment model as previously constructed by Diao *et al.*[16] This is due to differences in sampling times during PK profiling between both study populations. More specifically, the published model was constructed based on a rich sampling schedule during a 10-day period, whereas the current study used a maximum of 6 FIX activity levels sampled during a 7-day period. In the present study, less FIX activity levels were sampled at early time points. This could explain why we were not able to describe a third compartment that characterizes the rapid distribution phase of rFIX-Fc occurring within 2–3 h after the end of administration.[40] Notwithstanding these limitations, our model adequately described the terminal elimination phase, which determines the trough concentration on which doses are generally adjusted for in clinical practice. The observed difference in terminal $t_{1/2}$ between the models is due to the difference in the estimated PK parameters. Nevertheless, the $t_{1/2}$ of the new model (70, 76 and 88 h for <12 years, ≥12 and <18 years and adults, respectively) are closer to the reported $t_{1/2}$ in the Alprolix EPAR[22] (70, 82 and 82 h) than those calculated for the published model (88, 99 and 101 h).

In this study, we have illustrated the clinical impact of underlying population PK models on dosing advice when personalizing treatment. In general, a population PK model should be applied that is representative for the patients for which individual PK are characterized. In our study, however, we did not observe a difference in dose for patients aged <12 years which could be due to the limited number of patients. When considering data from all patients, a significant dose difference was observed, probably caused by the difference in population PK parameters.

In this context, it is important to realize that individual PK parameters are calculated by combining information from both the population and the individual. When more samples are available (5 or more) per individual, individual PK parameters are mainly determined by information from this individual. In the present study, an intermediate clinically representative (3) number of samples was available, hence individual PK parameters were mostly determined by the individual observations. It should however be realized that large differences in dose predictions may occur when less samples are available for an individual patient.

The strength of the present study is that it contains real-world data reflecting clinical variability. A study limitation is the relatively sparse sampling method with aforementioned consequences at early time points. The impact of FIX extravascular distribution is recognized by a growing body of literature and should be incorporated in future models.[41–43] Investigation of extravascular binding of FIX could be of clinical importance, as studies in mice suggest a haemostatic function of extravascular FIX.[44,45] We, carefully, advocate the use of other techniques, like physiology-based PK models, to investigate an estimation of this extravascular compartment.

5 | CONCLUSION

Population PK parameters derived from our new model differ considerably from those reported previously. The new model better describes the real-world PK as opposed to the published model, underlining the necessity to strive for representative population PK models and avoiding extrapolation when performing PK-guided dosing. In the clinical setting, the new population PK model could be used to apply PK-guided dosing.

AUTHOR CONTRIBUTIONS

Tine M.H.J. Goedhart enrolled patients, performed blood sampling for PK analysis and evaluation of predictive performance and collected in the OPTI-CLOT TARGET study. Patient inclusion in the UK-EHL registry was monitored by Pratima Chowdary, R. Campbell Tait, Catherine N. Bagot, Susie Shapiro, Nicola Curry, Mary Mathias, Michael Makris, Jeanette Payne and Peter W. Collins. Tine M.H.J. Goedhart collected data from the UK-EHL registry and checked all clinical data from the EHL registry. Sjoerd F. Koopman and Ron A.A. Mathôt performed the analysis and developed the population PK model. Sjoerd F. Koopman and Tine M.H.J. Goedhart wrote the manuscript. Laura H. Bukkems, Marjon H. Cnossen and Ron A.A. Mathôt supervised the study. All authors contributed substantially to the critical revision of the manuscript and approved the final draft.

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SYMPHONY consortium: The SYMPHONY consortium which aims to orchestrate personalized treatment in patients with bleeding disorders, is a unique collaboration between patients, health care professionals, and translational and fundamental researchers specialized in inherited bleeding disorders, as well as experts from multiple disciplines. It aims to identify best treatment choice for each individual based on bleeding phenotype. To achieve this goal, workpackages have been organized according to 3 themes e.g. Diagnostics

(workpackages 3 and 4); Treatment (workpackages 5-9) and Fundamental Research (workpackages 10–12). This research receives funding from the Netherlands Organisation for Scientific Research (NWO) in the framework of the NWA-ORC Call grant agreement NWA.1160.18.038. Principal investigator: Dr. M.H. Cnossen. Project coordinator: Dr. S.H. Reitsma.

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OPTI-CLOT study group: OPTI-CLOT/To WiN study group aims to implement personalized treatment by *pharmacometric-guided* dosing of factor concentrates, desmopressin and nonfactor therapies in patients with bleeding disorders.

OPTI-CLOT/To WiN Steering Committee, the Netherlands: M.H. Cnossen (principal Investigator & chair OPTI-CLOT-To WiN) and R.A.A. Mathôt (coinvestigator). F.W.G. Leebeek, Rotterdam;, M. Coppens K. Fijnvandraat, Amsterdam; K. Meijer, Groningen, S.E.M. Schols, Nijmegen; H.C.J. Eikenboom, Leiden; R.E.G. Schutgens, Utrecht; F. Heubel-Moenen, Maastricht; L. Nieuwenhuizen, Veldhoven; P. Ypma, The Hague; M.H.E. Driessens, Nijkerk.

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PhDs ongoing: M.C.H.J. Goedhart, J.M. Heijdra, L. Romano, W. Al Arashi, M.E. Cloesmeijer, A. Janssen, S.F. Koopman, C. Mussert.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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