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Population pharmacokinetics of a new long-acting recombinant coagulation factor IX albumin fusion protein for patients with severe hemophilia B

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Running head: Population pharmacokinetics of rIX-FP

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Essentials

- The new recombinant factor IX (FIX) albumin fusion protein (rIX-FP) has a prolonged half-life.
- A population pharmacokinetic (PK) model was based on FIX activity levels of hemophilia B patients.
- The model was used to simulate different dosing scenarios of rIX-FP to help guide dosing.
- The population PK model supported prolonged dosing of rIX-FP with intervals of up to 2 weeks.

Summary. *Background:* The recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP; Idelvion[®]) exhibits a longer half-life than plasma-derived factor IX (FIX) and the commercially available recombinant FIX products.

Objectives: (i) characterize the population pharmacokinetics (PK) of rIX-FP in hemophilia B patients, (ii) identify covariates that are potential determinants of rIX-FP PK variability, and (iii) simulate different dosing scenarios of rIX-FP following single and steady-state dosing.

Patients/Methods: A population PK model was developed based on FIX activity levels of 104 patients who had received treatment with rIX-FP. Patients were aged 1–65 years with FIX activity ≤ 2 IU dL⁻¹. PK sampling was performed up to 14 days (336 hours). *Results:*

Simulation of a single intravenous infusion of rIX-FP (25–75 IU kg⁻¹) predicted the median trough exogenous FIX activity levels would remain >5 IU dL⁻¹ of normal for up to 16 days in adolescents/adults aged ≥ 12 years, up to 12 days in children aged 6 to <12 years, and up to 9.5 days in children aged <6 years. For steady-state dosing, the median trough exogenous FIX activity levels were maintained >5 IU dL⁻¹ for the duration of the dosing interval for the 25, 35 and 40 IU kg⁻¹ weekly regimens and for 75 IU kg⁻¹ every 14 days in

adolescents/adults, and for the 35 and 40 IU kg⁻¹ weekly regimens in children. *Conclusion:*

The population PK model developed here correlates well with observed clinical data and supports prolonged dosing of rIX-FP with intervals of up to 2 weeks.

Keywords: factor IX, hemophilia B, children, pharmacokinetics, recombinant proteins.

Introduction

Hemophilia B is a rare bleeding disorder caused by a deficiency in coagulation factor IX (FIX), a vital component of the coagulation cascade and hemostatic response to injury [1].

Over 2100 possible FIX gene mutations have been identified in the long arm of the X chromosome, resulting in different levels of disease severity ranging from mild (>5–40 IU dL⁻¹ of normal FIX concentration; with no spontaneous bleeding, but bleeding after surgery/trauma) to moderate (1–5 IU dL⁻¹ of normal; bleeding into joints after minor injuries) to severe (<1 IU dL⁻¹ of normal; repeated spontaneous joint and muscle bleeding) [1,2].

Factor IX (FIX) replacement therapy using either plasma-derived FIX (pdFIX) or recombinant FIX (rFIX) products is the current standard of care for patients with hemophilia B [3]. However, the first available rFIX products had a relatively short mean elimination half-life of approximately 18–26 hours [4,5], resulting in the requirement for twice-weekly administration in prophylaxis [5,6], and multiple infusions to manage some bleeds [7–9]. Therefore, extending the half-life of exogenous FIX therapies offers an opportunity to improve treatment outcomes for patients with hemophilia B by reducing dose frequency and extending bleeding-free intervals. Indeed, several technologies have been developed to prolong the half-life of FIX. Preclinical studies have demonstrated that the pharmacokinetic (PK) properties of rFIX can be enhanced by fusing it to either a constant region of

immunoglobulin G domain peptide [10], or to the human carrier protein, albumin, which has a naturally long half-life of approximately 20 days [11].

The recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP; Idelvion[®]) is a purified fusion protein comprised of recombinant human FIX and recombinant albumin connected by a short linker peptide derived from the human FIX sequence [11]. It was developed to prolong the half-life of the coagulation factor, with the aim of improving patient care. Indeed, data from the pivotal phase III clinical program confirm prophylaxis treatment once every 7, 10 and 14 days [12–15].

This study aimed primarily to use individual PK data from four clinical trials to develop a model to characterize population PK of rIX-FP in adolescents/adults and children with severe or moderately severe hemophilia B and to identify potential determinants (demographic and clinical covariates) of inter-individual rIX-FP PK variability. Additionally, the population PK model was used to simulate different dosing scenarios of rIX-FP to help guide dosing of rIX-FP for routine prophylaxis of patients with hemophilia B.

Materials and methods

Study population

A PK model was developed based on the levels of FIX activity obtained from four clinical trials: Study CSL654_2001 (Phase I), Study CSL654_2004 (Phase I/II), Study CSL654_3001 (Phase II/III) and Study CSL654_3002 (Phase III) (See also Supplementary Table 1) [13,14,16,17]. These trials included 132 children (aged <12 years) and adolescents/adults (aged 12–65 years) with severe or moderately severe hemophilia B (FIX activity ≤ 2 IU dL⁻¹ of normal) who had received treatment with rIX-FP (CSL Behring, Marburg, Germany). Patients had no detectable FIX inhibitors (neutralizing antibodies) at screening and no

personal history of FIX inhibitors. All patients had not received FIX therapy for at least 4 days prior to being administered rIX-FP.

Pharmacokinetic sampling and bioanalytical methods

Pharmacokinetic sampling (during the PK assessment) was performed up to 14 days (336 hours) in all four clinical trials. Additional FIX activity levels from patients were collected during routine prophylaxis up to 16 weeks in the phase I/II trial, at monthly intervals up to 60 weeks in the phase II/III trial of adolescents/adults aged ≥ 12 years, and at weeks 4, 12, 24 and 36 in the phase III trial of children aged < 12 years.

The FIX activities of rIX-FP were measured using a validated 1-stage clotting method, as previously described by Santagostino *et al.* [16], by determining the activated partial thromboplastin time *in vitro* and comparing it against a reference curve prepared from standard human plasma calibrated against the World Health Organization standard for FIX. Plasma samples of FIX were measured using the Behring Coagulation System (Siemens Healthcare Diagnostics, Marburg, Germany).

Population PK model development

The population PK model was built in a stepwise fashion: the structural (compartmental PK) model was developed first, followed by the addition of the pharmacostatistical model (comprised of the inter-individual variability and residual error models), and finally the covariate model.

Structural model The structural model describes the disposition of the drug following intravenous administration and also represents the best description of the data without considering between-patient variability. Model appropriateness was evaluated using one-,

two- and three-compartment PK models, and the best model was selected based on goodness of fit (GoF) and objective function value. Modeling was performed using the nonlinear mixed-effect modeling software package NONMEM® 7.3 (ICON Development Solutions, Ellicott City, Maryland, USA). R programming version 3.1.2 (The R Foundation, Vienna, Austria) was used to generate the diagnostic plots.

For the FIX activity PK models, the endogenous FIX activity levels were assumed not to be $>2 \text{ IU dL}^{-1}$ (2 IU dL^{-1} of normal), to be consistent with the study inclusion criteria of FIX activity $\leq 2 \text{ IU dL}^{-1}$. Thus, where patients had an observed FIX activity $>2 \text{ IU dL}^{-1}$ prior to receiving the first dose of rIX-FP, it was assumed that this represented a combination of endogenous FIX activity plus any residual activity associated with previously administered FIX products. However, if a patient's pre-dose FIX activity levels were $\leq 2 \text{ IU dL}^{-1}$ of normal, it was considered to be endogenous activity only. Thus, endogenous FIX activity and residual contributions from previous FIX products to overall FIX activity were estimated separately.

Missing drug concentrations were not imputed or accounted for in the model. All samples with FIX activity below the quantifiable limit or not quantifiable were excluded from the analysis.

Pharmacostatistical model The pharmacostatistical model was comprised of two components: the inter-individual variability model and the residual error model. The inter-individual variability model describes the unexplained random variability in individual values of the structural model parameters. It was assumed that the inter-individual variability of the PK parameters was log-normally distributed. The relationship between a PK parameter and its variance was therefore described using an exponential function. The inter-individual

variability was estimated on clearance, central volume and the estimated endogenous FIX activity.

The residual error model describes the residual variability between the observed response and that predicted by the model. The residual error model was described by a combined additive and proportional error model.

Covariate model Following the development of the base model, the final model was built by evaluating the effect of covariates on the PK parameter estimates. Two types of covariates were planned for analysis: continuous covariates (dose, body weight, age, body mass index, aspartate transaminase levels, alanine transaminase levels and creatinine clearance), and categorical covariates (hepatitis status, presence/absence of antidrug antibody and geographical region). The continuous covariates were assumed to be normally distributed.

Plots of inter-individual variability versus potential covariates were used to identify possible correlations. The covariate was retained in the model if it significantly reduced the objective function value (OFV) (i.e. difference between the two OFVs <10.83 points; $P < 0.001$, 1 degree of freedom) and if the 95% confidence interval (CI) did not include zero.

Model evaluation

To evaluate the performance of the final population PK model, a prediction-corrected visual predictive check (pcVPC) [18] was performed. The pcVPC assesses graphically whether simulations from a model can reproduce the observed data. The median and the 5th and 95th percentiles of the concentration-time curves following 1000 simulations were superimposed with the observed data.

Simulations

The final FIX activity population PK model was used to simulate FIX activity–time profiles in patients administered single doses of 25, 35, 40, 50 or 75 IU kg⁻¹ of rIX-FP and at steady-state following repeated doses of 25, 35 or 40 IU kg⁻¹ weekly, 50 or 75 IU kg⁻¹ every 14 days, and 75 IU kg⁻¹ every 21 days. The original dataset was used to create the simulations, with a 10-minute infusion time assumed. One thousand replicates of each simulation scenario were performed. The median and 90% CIs of the simulated FIX activity-time profiles were calculated and constructed graphically for different dosing regimens.

The output reported both single-dose and multiple-dose/steady-state simulations. For the single-dose simulations, the duration for which the baseline-corrected FIX activity was maintained above 1 IU dL⁻¹, 3 IU dL⁻¹ and 5 IU dL⁻¹ of normal was estimated. These plasma levels of 1 IU dL⁻¹, 3 IU dL⁻¹ and 5 IU dL⁻¹ are representative of total baseline uncorrected FIX activity levels that characterize disease severity for patients with severe, moderate and mild hemophilia B, respectively. For the steady-state simulations, baseline-corrected trough FIX activity was calculated.

Results

Patient demographics and clinical dataset

A total of 126 individual assessments were available for analysis from 104 male patients with hemophilia B, including 22 patients who participated in more than one study, as shown in Table 1. The sample population was geographically diverse, had a median age of 26 years, a body mass index of 21.8 kg m⁻², and median pre-dose FIX activity of 1.6 IU dL⁻¹. Twenty-seven patients were aged <12 years, of whom 12 were <6 years of age and five were ≤2 years of age.

Of the 2752 blood samples collected, 197 samples were excluded due to treatment with FIX products other than rIX-FP or sample collection/quality issues. Therefore, the population-based PK model was developed using FIX activity data from a total of 2555 quantifiable samples from 104 individuals.

Pharmacokinetic model development

Based on the exploration and comparison, a two-compartment model provided a good description of FIX activity and was used for the current analysis. Furthermore, FIX activity data were log-transformed prior to developing the PK model due to the variability and right skew observed in the data.

The base two-compartment model included structural parameters for clearance (CL), central volume of distribution (V1), inter-compartmental clearance (Q), peripheral volume of distribution (V2), as well as estimated endogenous FIX activity (BASE) and residual contributions from previously administered FIX products. Inter-individual variability was estimated for CL, V1 and BASE, but not for Q or V2, as these did not improve the model fit. Only body weight (on V1, V2 and CL) and weight-adjusted dose (on V1) were significant covariates and were therefore incorporated into the model. Allometric scaling for patient body weight was applied to the clearance terms of the final model.

Pharmacokinetic model parameters

The parameters of the final PK model are shown in Table 2. The typical parameter estimates were 0.57 dL h⁻¹, 64.8 dL, 0.29 dL h⁻¹ and 15.8 dL for CL, V1, Q and V2, respectively. Endogenous FIX activity was estimated to be 1.06 IU dL⁻¹, with individual estimates being ≤ 2 IU dL⁻¹ in all but one patient (BASE = 2.50 IU dL⁻¹). All parameters were estimated with reasonable precision (% relative standard error of the estimate <37%). Inter-individual

variability was applied on CL, V1 and BASE. Combined additive and proportional residual errors were estimated separately for Study CSL654_2001/2004 and CSL654_3001/3002 (Table 2). The initial and elimination phase half-lives of rIX-FP were calculated using a post hoc method. The median of the initial phase half-life was 23.7 hours (95% CI 8.3 to 33.8 hours), and the median elimination phase half-life was 96.4 hours (95% CI 66.8 to 137.3 hours).

Model validation

A pcVPC confirmed that the final FIX activity population PK model provided a good description of the data. Observed median FIX activity concentrations, as well as the observed 5th and 95th percentiles, were consistently within the 90% prediction intervals for each parameter derived from the PK model (Fig. 1). Thus, there was good agreement between the model predictions and the observed FIX activity levels, demonstrating the suitability of the model for PK predictions. In addition, the GoF plots described the data well (Supplementary Fig. 1).

Pharmacokinetic simulations

The final population PK model was used to determine the probability of reaching a target level of FIX activity. The simulation was conducted to investigate the effect of age and this was evaluated separately for the four different age groups. However, owing to the similar PK between adolescents and adults, data for these two groups were combined.

Single-dose simulations For adolescent/adult patients, simulation of a single intravenous infusion of rIX-FP at 25, 35, 40, 50 and 75 IU kg⁻¹ predicted that median exogenous FIX activity levels would remain above 5 IU dL⁻¹ of normal for 7, 9.5, 10.5, 12.5 and 16 days,

respectively (Table 3). For children aged 6 to <12 years, the corresponding values were 5, 7, 7.5, 9 and 12 days, respectively, and for children aged <6 years, the values were 4, 5.5, 6, 7 and 9.5 days, respectively (Table 3).

Multiple-dose/steady-state simulations Multiple-dose/steady-state PK simulations were also performed to explore the effect of reduced dosing frequency in all age groups (Table 4). The median trough exogenous FIX activity levels were maintained above 5 IU dL⁻¹ for the duration of the dosing interval for the 25, 35 and 40 IU kg⁻¹ weekly regimens and 75 IU kg⁻¹ every 14 days in adolescents/adults, and for the 35 and 40 IU kg⁻¹ weekly regimens in children.

The predicted steady-state profiles of different dosing scenarios for adolescents/adults are shown in Fig. 2 (25 IU kg⁻¹ weekly, 50 IU kg⁻¹ every 14 days, and 75 IU kg⁻¹ every 21 days) and Fig. 3 (40 IU kg⁻¹ weekly, 75 IU kg⁻¹ every 14 days, and 100 IU kg⁻¹ every 21 days). Figure 4 shows the predicted steady-state profiles of 40 IU kg⁻¹ weekly and 75 IU kg⁻¹ every 14 days for children.

Discussion

The improved PK parameters of rIX-FP suggest that extended dosing intervals of 7 or more days are feasible for patients with hemophilia B. In the current study, a population PK model has been developed to further describe such extended rIX-FP dosing intervals and the PK parameters that may influence dose management.

The two-compartment model for intravenous dosing of rIX-FP in patients with hemophilia B described here was derived from pooled data from four clinical PK studies comprising children and adolescent/adult patients with hemophilia B. All PK parameters for rIX-FP were estimated with reasonable precision and were consistent with the observed

clinical data. Furthermore, predicted steady-state FIX activity levels for patients administered rIX-FP at a range of doses and dosing intervals suggest that dosing intervals of 7 or more days are feasible, which compares favorably with published clinical data [14].

After developing a basic and pharmacostatistical model, a final covariate model was built to determine the effect of several continuous and categorical between-patient covariates on PK parameters. Of the covariates tested, only body weight and the related weight-adjusted dose were found to significantly contribute to variability in FIX PK. Body weight was a significant covariate for V1, V2 and CL, with weight-adjusted dose only contributing to the variability in V1. This finding correlates with previous findings of a relationship between patient body weight, volume of distribution, and clearance of FIX in a computer model investigating the effects of age on the PK parameters of unconjugated rFIX [19]. These data also confirm that calculating rIX-FP dosing on the basis of age/weight is appropriate for all of the age groups. Overall, the PK model was validated and assessed using VPC and GoF plots, as outlined by the European Medicines Agency's guideline on reporting the results of population PK analyses [20].

A key clinical target for patients with hemophilia B receiving prophylactic treatment is maintaining trough FIX activity levels above 5 IU dL^{-1} because symptoms of the condition are generally classified as 'mild' under these circumstances [2,21,22]. Both the modeled and observed clinical data show that rIX-FP has an improved PK profile and extended half-life compared with standard FIX products, allowing trough FIX activity to be maintained above 5 IU dL^{-1} when intervals of more than a few days between rIX-FP doses occur. For example, the model presented here predicts that a single 75 IU kg^{-1} dose of rIX-FP would maintain FIX activity levels above the clinical target of 5 IU dL^{-1} for up to 16 days in adolescent/adult patients. This finding compares favorably with the observed clinical trial data in which a regimen of 75 IU kg^{-1} once every 14 days achieved a mean trough level of 12.4 IU dL^{-1} ,

based on a subset of patients in the phase II/III trial (Study CSL654_3001) [14]. Of note, the population PK model estimated a lower median trough level of 8.0 IU dL⁻¹. This slightly lower value is not unexpected, as the PK model defines the exogenous component of the observed activity and also represents patient PK data obtained from several trials. Similarly, with 40 IU dL⁻¹ once weekly, for example, the observed (exogenous plus endogenous) mean trough level was 20.0 IU dL⁻¹ [14] whereas the simulated (exogenous) median trough level was slightly lower at 13.6 IU dL⁻¹.

Furthermore, our steady-state simulations following dosing intervals of up to 2 weeks in adolescent/adult patients administered rIX-FP at 25–75 IU kg⁻¹ indicated that trough FIX activity was also maintained around the 5 IU dL⁻¹ target (Table 4). The predictions derived from the population model for both single-dose and multiple-dosing regimens are consistent with the observed PK data from phase I/II and phase III studies of rIX-FP that investigated the efficacy of a 7-day dosing interval [17,23] and of 10- to 14-day dosing intervals for rIX-FP [14]. Notably, even weekly administration of the lowest dose (25 IU kg⁻¹) maintained trough FIX activity levels above 5 IU dL⁻¹ in the current model.

By comparison, a previous study that modeled dosing with 40 IU kg⁻¹ of glycoPEGylated rFIX (nonacog beta pegol) every second week predicted mean trough FIX activity levels of 4 IU dL⁻¹ [24]. The current model also revealed that extended dosing regimens of rIX-FP with doses as far apart as 3 weeks were able to maintain FIX activity levels at 1–3 IU dL⁻¹. In contrast, standard rFIX products, such as BAX326 (Rixubis) and nonacog alfa (Benefix), require twice-weekly dosing [5,6]. For example, the study of nonacog alfa by Powell *et al.* [6] reported that the time to reach a FIX activity level of 1 IU dL⁻¹ was 5.1 days with a dose of 50 IU kg⁻¹. Likewise, simulated data obtained from a previously published population PK model demonstrated that prophylaxis with nonacog alfa 100 IU kg⁻¹ once weekly did not maintain trough levels above 1 IU dL⁻¹ throughout the

dosing interval [25]. However, in our study, rIX-FP 100 IU kg⁻¹ dosed once every 3 weeks, and even lower doses such as 25 IU/kg once weekly, were able to maintain trough FIX activity levels above 1 IU dL⁻¹ throughout the dosing interval.

The current study demonstrated differences in the duration of time spent above 1 IU dL⁻¹, 3 IU dL⁻¹ or 5 IU dL⁻¹ for the different age groups. This finding may reflect age-related changes in the clearance of FIX; a finding which we observed in our current study (see Supplementary Fig. 2) and which has been reported previously [19]. For example, a dose of 50 IU kg⁻¹ will maintain FIX activity levels >1 IU dL⁻¹ for 14 days for even the youngest children, and up to 23 days for adults (Table 3). However, if routine prophylaxis with a higher trough is desired for patients such as children, or those with a severe bleeding phenotype, with target joints, other comorbidities, or an active lifestyle, then a higher dose or a weekly treatment interval can attain these higher trough levels (Table 4). The enhanced PK profile of rIX-FP will allow physicians to adjust the dose and/or treatment interval to select the desired trough and therefore optimize treatment to the individual patient.

A potential limitation of the current study is that the dose regimens used in the simulations were not identical to those used in the clinical trial; in the simulations, a maximum dose of 100 IU kg⁻¹ every 21 days was used compared with 75 IU kg⁻¹ every 14 days derived from the clinical trial. Although the validated model can fit the observations from 25–75 IU kg⁻¹ dose levels very well and has the potential to help guide the selection of dosing, the simulation using 100 IU kg⁻¹ for 21 days cannot be compared directly with observed clinical data at the present time.

In conclusion, a population PK model for rIX-FP has been developed and validated in adolescents/adults and children with severe hemophilia B. The PK parameters estimated by the model correlated well with observed clinical data (observed factor activity and clinical efficacy), indicating that this model is suitable for predicting trough FIX activity levels in

patients treated with rIX-FP. Variability in FIX activity was not significantly associated with any demographic or clinical covariates apart from body weight, indicating that a single weight-based dosing model for rIX-FP can be broadly applied across the hemophilia B patient population. This model also supports prolonged dosing intervals with aimed FIX activity troughs $>3 \text{ IU dL}^{-1}$, $>5 \text{ IU dL}^{-1}$ or even $>10 \text{ IU dL}^{-1}$ for up to 2 weeks in patients with hemophilia B treated with rIX-FP, representing a considerable advantage over current rFIX therapies.

Addendum

D. Bensen-Kennedy, I. Jacobs and C. Voigt contributed to the concept and design of the study. Y. Zhang, J. Roberts, A. Feussner and J. Sidhu analyzed and interpreted the data. Y. Zhang and J. Roberts wrote the paper. I. Jacobs, E. Santagostino, C. Voigt, A. Feussner, M. Morfini and J. Sidhu revised the intellectual content and all authors approved the final version.

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Disclosure of Conflicts of Interests

E. Santagostino received honoraria for speaking and/or for consulting from CSL Behring, Bayer, Baxter/Baxalta, Pfizer, NovoNordisk, Roche, Sobi/Biogen Idec, Biotest, Kedrion, Octapharma and Grifols, and received unrestricted research grants from NovoNordisk and Pfizer. M. Morfini received research support from CSL Behring to conduct the study, lecture

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Legends to Figures and Tables

Fig. 1. Prediction performance of the final population pharmacokinetic model. A prediction-corrected visual predictive check comparing observed factor IX activity (open circles, individual observations; solid line, median observed concentrations; dashed lines, 5th and 95th percentile of observed concentrations) versus predicted factor IX activity derived from the final model (red shaded region, 90% prediction interval for median predicted concentrations; purple shaded regions, 90% prediction intervals for the 5th and 95th percentiles of predicted concentrations).

Fig. 2. Predicted steady-state factor IX activity profiles of intravenous rIX-FP at three different dosing schedules for adolescents/adults. The dose regimens modeled are 25 IU kg⁻¹ weekly (green), 50 IU kg⁻¹ every 14 days (blue) and 75 IU kg⁻¹ every 21 days (red). Dashed lines represent median predicted values and shaded regions represent 90% confidence intervals. The red horizontal dashed lines represent the equivalent of 1 IU dL⁻¹, 3 IU dL⁻¹ and 5 IU dL⁻¹ of normal factor IX activity.

Fig. 3. Predicted steady-state factor IX activity profiles of intravenous rIX-FP at three different dosing schedules in children aged <6 years. The dose regimens modeled are 40 IU kg⁻¹ weekly (green), 75 IU kg⁻¹ every 14 days (blue) and 100 IU kg⁻¹ every 21 days (red). Dashed lines represent median predicted values and shaded regions represent 90% confidence intervals. The red horizontal dashed lines represent the equivalent of 1 IU dL⁻¹, 3 IU dL⁻¹ and 5 IU dL⁻¹ of normal factor IX activity.

Fig. 4. Predicted steady-state factor IX activity profiles of intravenous rIX-FP at two different dosing schedules in children aged <12 years. The dose regimens modeled are 40 IU kg⁻¹ weekly (red) and 75 IU kg⁻¹ every 14 days (blue). Dashed lines represent median predicted values and shaded regions represent 90% confidence intervals. The red horizontal dashed lines represent the equivalent of 1 IU dL⁻¹, 3 IU dL⁻¹ and 5 IU dL⁻¹ of normal factor IX activity.

Table 1 Patient characteristics across the four pharmacokinetic studies and the overall pooled population

Table 2 Parameter estimates of the final factor IX (FIX) activity population pharmacokinetic model

Table 3 Maintenance of median exogenous factor IX activity above 1 IU dL⁻¹, 3 IU dL⁻¹ and 5 IU dL⁻¹ of normal following a simulated single intravenous dose of 25–75 IU kg⁻¹ of rIX-FP

Table 4 Median exogenous factor IX (FIX) activity levels following multiple doses of 25–100 IU kg⁻¹ of rIX-FP

Table 1 Patient characteristics of the overall population pooled from the four pharmacokinetic studies

Patient characteristic	Overall
N	126*
Median weight (range), kg	64.0 (11.0–132.3)
Median age (range), years	26 (1–61)
Median BMI (range), kg m ⁻²	21.8 (12.7–63.1)
Median predose FIX activity (range), IU dL ⁻¹	1.6 (0.1–14.1)
Median baseline AST (range), IU dL ⁻¹	25.0 (9.0–142.0)
Median baseline ALT (range), IU d ⁻¹	21.0 (8.0–154.0)
Median CrCl (range), mg mL ⁻¹	118.5 (56.7–300.5)
Hepatitis positivity, N	
Yes	20
No	106
Non-neutralizing antibody to FIX, N	
Present	1†
Absent	125
Region, N	
North America	7
Europe	81
Middle East	28
Asia Pacific	10

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CrCl, creatine clearance; FIX, factor IX. *22 patients participated in more than one study. †Positive prior to first administration of rIX-FP.

Table 2 Parameter estimates of the final factor IX (FIX) activity population pharmacokinetic model

Parameter	NONMEM estimates		
	Point estimate (95% CI)	% RSE	CV%
Structural model			
Endogenous FIX activity, IU dL ⁻¹	1.06 (0.82–1.30)	11.6	
CL, dL h ⁻¹	0.57 (0.54–0.60)	2.7	
V1, dL	64.8 (60.8–68.8)	3.2	
Q, dL h ⁻¹	0.29 (0.08–0.50)	36.4	
V2, dL	15.8 (12.1–19.5)	12.1	
Weight-adjusted dose on V1	0.38 (0.25–0.50)	16.9	
Body weight on V1 and V2	0.79 (0.69–0.89)	6.6	
Body weight on CL	0.53 (0.44–0.63)	9.3	
Inter-individual variability*			
Endogenous FIX activity, IU dL ⁻¹	0.16 (0.03–0.28)	41.5	39.5
CL, dL h ⁻¹	0.05 (0.03–0.06)	22.0	21.1
V1, dL	0.07 (0.03–0.11)	30.2	25.9
Residual variability†			
Study CSL654_2001/2004 (proportional)	0.18 (0.14–0.22)	11.4	17.7
Study CSL654_2001/2004, IU dL ⁻¹ (additive)	0.66 (0.30–1.02)	27.6	
Study CSL654_3001/3002 (proportional)	0.35 (0.30–0.40)	7.2	35.2
Study CSL654_3001/3002, IU dL ⁻¹ (additive)	1.24 (0.84–1.64)	16.5	

CI, confidence interval; CL, clearance; CV, coefficient of variation of proportional error; NONMEM, non-linear mixed-effect modeling software; Q, inter-compartmental clearance; RSE, relative standard error; V1, volume of central compartment; V2, volume of peripheral compartment. *Values shown represent the variance of random effect. †Values shown represent either the proportional or additive components of the residual error model. The reference population weight for the pharmacokinetic parameters for V1 and V2 is a 70-kg patient. The reference weight-adjusted dose for V1 is 50 IU kg⁻¹.

Table 3 Maintenance of median exogenous factor IX activity above 1 IU dL⁻¹, 3 IU dL⁻¹ and 5 IU dL⁻¹ of normal following a simulated single intravenous dose of 25–75 IU kg⁻¹ of rIX-FP

Simulated single intravenous dose (IU kg ⁻¹)	Age group (years)	Duration >1 IU dL ⁻¹ (days)	Duration >3 IU dL ⁻¹ (days)	Duration >5 IU dL ⁻¹ (days)
25	<6	9.5	6	4
	6 to <12	12	7.5	5
	≥12	16	10	7
35	<6	11.5	7.5	5.5
	6 to <12	14.5	9.5	7
	≥12	19	12.5	9.5
40	<6	12.5	8	6
	6 to <12	15.5	10	7.5
	≥12	20.5	13.5	10.5
50	<6	14	9	7
	6 to <12	17	11.5	9
	≥12	23	15.5	12.5
75	<6	17	12	9.5
	6 to <12	21	15	12
	≥12	27.5	19.5	16

Table 4 Median trough exogenous factor IX (FIX) activity levels following multiple doses of 25–100 IU kg⁻¹ of rIX-FP

Simulated multiple intravenous dose	Trough exogenous FIX activity, IU dL ⁻¹ (IQR)		
	<6 years	6 to <12 years	≥12 years
25 IU kg ⁻¹ weekly	2.6 (1.7–3.8)	4.3 (2.9–6.1)	7.5 (5.4–10.2)
35 IU kg ⁻¹ weekly	4.1 (2.8–5.9)	6.6 (4.6–9.3)	11.5 (8.4–15.4)
40 IU kg ⁻¹ weekly	4.9 (3.3–7.0)	7.9 (5.5–10.9)	13.6 (10.0–18.1)
50 IU kg ⁻¹ every 14 days	1.0 (0.5–1.8)	2.1 (1.2–3.4)	4.5 (2.9–6.7)
75 IU kg ⁻¹ every 14 days	2.1 (1.1–3.4)	3.9 (2.3–6.2)	8.0 (5.3–11.6)
100 IU kg ⁻¹ every 21 days	0.8 (0.3–1.6)	1.8 (0.9–3.3)	4.3 (2.5–7.0)

IQR, interquartile range.





