

ORIGINAL ARTICLE

Clinical haemophilia

A new paradigm for personalized prophylaxis for patients with severe haemophilia A

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Abstract

Aim: For patients with severe haemophilia A, guidelines recommend prophylactic treatment with FVIII, with dose calculations targeting a predetermined FVIII trough level. However, this pharmacokinetic (PK) approach is suboptimal, with some patients experiencing breakthrough bleeds. We aimed to improve FVIII dosing by incorporating the thrombin generation assay, a global haemostasis assay whose main pharmacodynamic (PD) parameter, endogenous thrombin potential (ETP), predicts spontaneous bleeding risk.

Methods: We performed post hoc combined PK-PD modelling using data from 66 adults who received human-cl rhFVIII (Nuwiq[®], Octapharma AG) in a phase IIIb study. Time-to-event analyses simulated the probability of spontaneous bleeding for different FVIII exposures and baseline ETPs.

Results: Ninety-one spontaneous bleeds occurred in 20/66 patients. The relationship between FVIII:C and ETP was non-linear, and the sigmoid Emax model adequately described the data. Individual PK-PD Bayesian estimation significantly improved predictive performance. Simulations showed that the mean spontaneous annual bleeding rate decreased with increasing baseline ETP or dosing: with ETP values of 200, 400 and 600 (nmol/L)·min annual bleeding rates were 2.36, 1.25 and 0.66, respectively, on 40 IU/kg human-cl rhFVIII every 3 days; and annual bleeding rates were 2.09, 1.10, and 0.60, respectively, on 60 IU/kg every 3 days.

Conclusion: Prophylactic FVIII dosing is more clinically meaningful when incorporating ETP alongside FVIII level. For the first time, FVIII dosing can be personalized with the aim of eliminating spontaneous breakthrough bleeds.

KEYWORDS

bleeding, factor VIII, haemophilia A, pharmacokinetics, prophylaxis, thrombin generation assay

1 | INTRODUCTION

Haemophilia A is caused by a deficiency of functional plasma clotting factor VIII (FVIII), which is necessary for effective blood

coagulation.^{1,2} As well as excessive bleeding following surgery or trauma,³ patients with haemophilia A may experience spontaneous bleeding (with no apparent or known cause), which, if untreated, can be life-threatening.^{1,3} For patients with severe haemophilia A, the

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World Federation of Hemophilia recommends prophylaxis with factor VIII (FVIII) infusions, with dose calculations aiming to maintain a predetermined target FVIII trough level.³⁻⁵ This approach is based on the pharmacokinetics (PK) of FVIII, that is the fate of FVIII once it enters the body. However, it is suboptimal, with some patients experiencing breakthrough bleeds.⁶

We hypothesized that a pharmacodynamic (PD) endpoint, which could assess the overall coagulation capacity of each patient, would be an appropriate marker for breakthrough bleeds. The thrombin generation assay (TGA) incorporating not only FVIII activity but also the combined effect of all procoagulant and anticoagulant proteins⁷ provides a measurement of endogenous thrombin potential (ETP). In an analysis of a sub-set of patients from GENA-21, a prospective phase IIIb study investigating the safety and efficacy of human-cl rhFVIII (Nuwiq®, Octapharma AG) in patients with severe haemophilia A, we recently showed this PD endpoint to be a better marker of spontaneous bleeding than FVIII activity, with low ETP predicting patients at high risk for spontaneous bleeds during prophylaxis.⁸

Here, we used a joint PK-PD model to describe a new tool to help physicians personalize prophylaxis for patients with severe haemophilia A. By incorporating both FVIII activity (FVIII:C) and ETP into the model, prediction of the correct dosage and frequency of FVIII infusions is improved. The aim was not specifically to maintain FVIII trough activity, but to calculate a regimen that results in zero spontaneous bleeds.

2 | METHODS

2.1 | Study design

This post hoc modelling analysis was based on data from a phase IIIb study (NuPreviq/GENA-21, ClinicalTrials.gov identifier: NCT01863758), whose design, ethics and patient flow have been described.⁹ The study was conducted in compliance with Good Clinical Practice, the Declaration of Helsinki and national laws. Each

patient provided freely given written informed consent before commencing the study.

The study consisted of three phases: (a) a 72-h pharmacokinetic (PK) evaluation phase, (b) a 1- to 3-month standard prophylaxis treatment phase and (c) a 6-month PK-guided personalized prophylaxis phase. For the PK evaluation phase, patients received a single dose of 60 ± 5 IU/kg human-cl rhFVIII (Nuwiq, Octapharma AG) after a washout period. Ten blood samples were taken before infusion and at 72 hours after the end of infusion. For PK analysis, FVIII activity (FVIII:C) was measured before infusion and at 0.5, 1, 3, 6, 9, 24, 30, 48 and 72 hours after infusion. For pharmacodynamic (PD) analysis, TGA was performed on samples taken before infusion and at 0.5, 6, 24, 48 and 72 hours after infusion.

For the standard prophylaxis phase, 30-40 IU/kg was administered every other day or three times per week. Dose escalations were allowed in case of an unacceptable frequency or severity of breakthrough bleeds, in accordance with the institution's standard clinical care. No PK or PD data were recorded during this phase.

For the personalized prophylaxis phase, individual PK data were analysed to determine the dose and injection interval which would theoretically result in a FVIII trough level of ≥ 1 IU/dL and not exceed a maximum plasma FVIII:C of 200 IU/dL. During this phase, PK and PD trough levels were measured at 2, 4 and 6 months. Only patient-reported spontaneous bleeding events were included.

2.2 | Study outcomes

For PK data, plasma FVIII:C was measured at a central laboratory (LabCorp) using a one-stage assay (automated activated partial thromboplastin time [APTT] from Trinity Biotech, Siemens BCS-XP). For PD data, TGA was performed using platelet-poor plasma samples prepared according to a standardized protocol.⁸ Blood samples were drawn in tubes containing 1.45 µmol/L corn trypsin inhibitor (Haematologic Technologies). Thrombin generation was measured using the calibrated automated thrombin generation test (CAT).^{10,11} Endogenous thrombin potential (ETP) was calculated as the area under the TG curve of thrombin activity

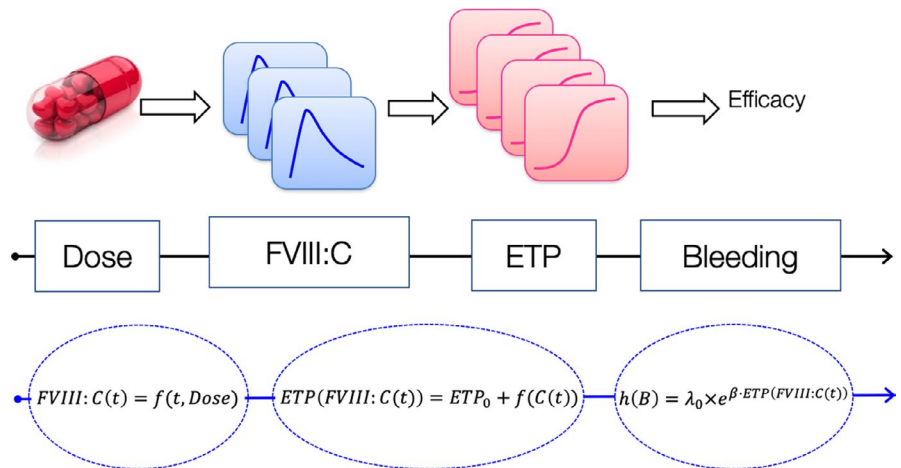


FIGURE 1 Full pharmacokinetic-pharmacodynamic time-to-event model of spontaneous bleeding. The full pharmacokinetic-pharmacodynamic model-building process was developed sequentially and resulted in the final model linking the predictors to overall survival. ETP, endogenous thrombin potential; FVIII:C, factor VIII activity [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Patients' baseline characteristics

Baseline characteristic	All patients (N = 66)
Age (years)	33 (18-67)
Body weight (kg)	78.9 (50-140)
Height (cm)	177 (155-196)
Spontaneous bleeding	91 (0-33)
Number of FVIII:C measurements	832 (10-14)
Number of TGA measurements	361 (1-10)

Note: Data are presented as median (range).

Abbreviations: FVIII:C, factor VIII activity; TGA, thrombin generation assay.

against time. Bleeding events were reported by patients in diaries, whereby each bleeding event was categorized as 'traumatic', 'spontaneous', 'postoperative' or 'other'. All diary entries were reviewed by the investigator. Only spontaneous bleeding events were included in the present analysis.

2.3 | Data analysis

The full PK-PD model-building process resulting in the final model linking the predictors to overall survival was developed sequentially (Figure 1).

Individual empirical Bayesian PK parameters were obtained using a previous PK model developed using data from 115 patients from phase II/III studies, the characteristics of which have been described previously.¹² These individual PK parameters were used to describe FVIII:C over time using patient-specific data: dose amounts, administration times, weight and age, recorded in case report forms.

The relationship between ETP and FVIII:C was modelled using a joint PK-PD model. Different non-linear (direct and indirect) response models were evaluated.

A parametric repeated time-to-event (TTE) model was developed to simulate the probability of spontaneous bleeding for different values of FVIII exposure (dosing) and baseline ETP. The mean spontaneous annual bleeding rate (ABR) was calculated for each scenario.

Refer to Appendix 1 for the spontaneous bleeding model equation, definitions of functions relating to it and details of TTE simulations.

3 | RESULTS

3.1 | Enrolled patients

A total of 66 adult patients were included in the study. At baseline, the mean (range) age was 33.6 (18-67) years and bodyweight was 80.5 (50-140) kg (Table 1). During the study, 832 FVIII:C and 361 TGA measurements were recorded. A total of 91 spontaneous bleeds occurred in 20 of the patients. The observed annualized rate of spontaneous bleeding was 5.2 (95% confidence interval 3.9-6.6).

3.2 | Relationship between FVIII:C and ETP

There was a non-linear relationship between FVIII:C and ETP (Figure 2) that was adequately described by the sigmoid Emax model. The Hill equation is widely used to describe the relationship between drug effect and drug concentration and is described by the following equation:

$$ETP = ETP_0 + \frac{ETP_{max} \times C^n}{EC_{50} + C^n}$$

where ETP_0 is the baseline ETP; ETP_{max} is the maximum ETP; C is the FVIII:C; and EC_{50} is the FVIII:C that produces half of ETP_{max} . The extra parameter n is a sigmoidicity coefficient included to provide a more flexible model. For $n = 1$, the model is simply known as an Emax model.

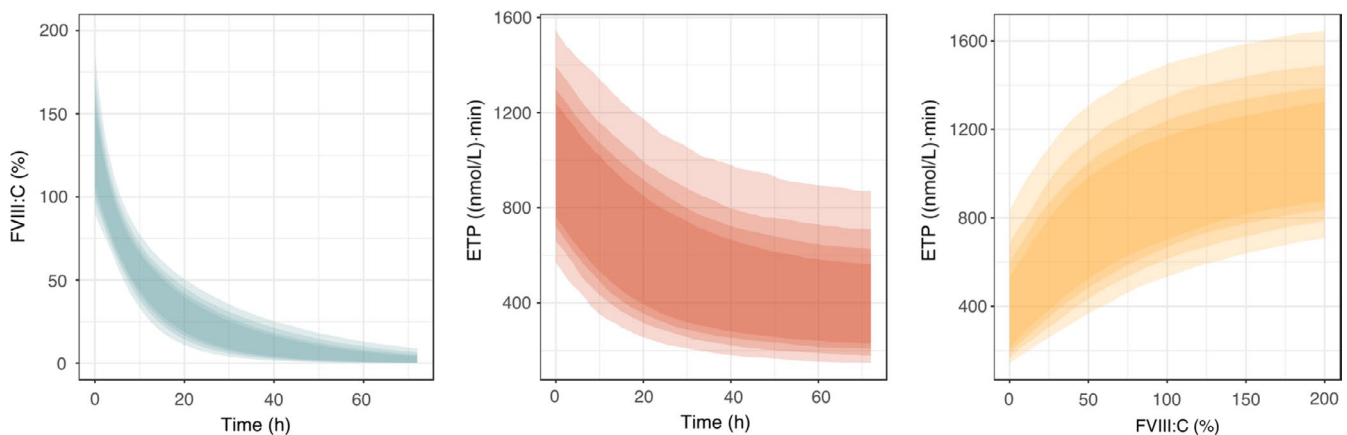


FIGURE 2 Visual predictive check for the model fitting of the observed PK-PD Data. Shaded areas represent the 90%, 80%, 70% and 60% prediction intervals of the curves estimated by the PK model (left panel), the PD model (middle panel) and the PK-PD model (right panel). ETP, endogenous thrombin potential; FVIII, coagulation factor VIII; FVIII:C, factor VIII activity; PD, pharmacodynamic; PK, pharmacokinetic [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Final model parameters

Parameters	Mean	Inter-individual variability
Cl, L/h	200 F	33.8 F
V1, L	2700 F	22 F
V2, L	451 F	27.8 F
Q, L/h	80.2 F	–
$\beta^{BW,Cl}$	0.75 F	–
$\beta^{Age,Cl}$	–0.00805 F	–
$\beta^{BW,V1}$	1 F	–
$\beta^{BW,V2}$	0.564 F	–
ETP ₀ , (nmol/L)·min	343	55.1
E _{max} , (nmol/L)·min	863	20.9
EC ₅₀ FVIII:C, %	60.8	48.1
N	1	–
Te, h	6390	182
Cov_PK/PD_TTE	–0.00313	–
Error model PK additive, IU/dL	0.0181 F	
Error model PK proportional, %	0.0867 F	
Error model PD proportional, %	0.3	

Note: $\beta^{BW,Cl}$, regression coefficient of bodyweight on Cl; $\beta^{BW,V1}$, regression coefficient of bodyweight on V1; $\beta^{BW,V2}$, regression coefficient of bodyweight on V2; Cl, clearance; Cov, covariate; EC₅₀, factor VIII activity that produces half of maximum ETP; E_{max}, maximum endogenous thrombin potential; ETP₀, endogenous thrombin potential without activated protein C; F, indicates fixed parameters not estimated in the model-building process but estimated in a previous study;¹² FVIII:C, factor VIII activity; N, number; PD, pharmacodynamic; PK, pharmacokinetic; Q, inter-compartment clearance; Te, time at which survival is approximately 0.4; TTE, time-to-event; V1, volume of central compartment; V2, volume of peripheral compartment.

Final parameter estimates of the model are shown in Table 2. Baseline ETP was the parameter most associated with inter-individual variability (55.1%); EC₅₀ was also associated with significant variability (48.1%). Although the error model for ETP was relatively large (0.3), it did not significantly affect the estimation of the individual risk of spontaneous bleeding. Individual Bayesian estimation (Figure 3) significantly improved predictive performance. Visual predictive check (VPC) indicated good predictive properties of the model regarding probability of spontaneous bleeding (Figure 4A).

3.3 | Time-to-event analyses for major bleeding

First, the model for survival data was selected. The probability of spontaneous bleeding was best described by an exponential distribution (constant hazard). Next, a joint model using ETP was developed. In the model, Te was estimated to be 6390 hours (approximately 8.75 months). Te represents the time at which survival is approximately 0.4. The beta

regression coefficient was estimated as –0.00313 (Table 2), indicating that higher ETP was associated with decreased hazard of spontaneous bleeding. The annual rate of spontaneous bleeding was estimated as 1.66 events per year (90% prediction interval 0.86–4.35). To evaluate the model's ability to predict bleed-free survival in the population, a VPC was performed on bleed-free survival and mean number of events; the mean and 90% prediction interval of the survival prediction were close to observed values (Figure 4A,B).

3.4 | Time-to-event simulations

To examine the potential benefit of adjusting human-cl rhFVIII dose in patients with different baseline ETP levels, the probabilities of spontaneous bleeding for different dosing regimens were simulated (Figure 5; Table 3; Appendix 2). We simulated typical patients with varying baseline ETP and computed the mean ABR which decreased with increasing baseline ETP or dosing. On a regimen of 40 IU/kg once every 3 days, mean ABR was: 2.36 for a patient with baseline ETP 200 (nmol/L)·min; 1.25 with baseline ETP 400 (nmol/L)·min; and 0.66 with baseline ETP 600 (nmol/L)·min. With 60 IU/kg once every 3 days, mean ABR was reduced to 2.09, 1.10 and 0.60 if baseline ETP was 200, 400 and 600 (nmol/L)·min, respectively.

4 | DISCUSSION

Dose tailoring for patients with haemophilia A is currently based on PK analysis and estimation of time spent below a threshold FVIII level, usually 1% of normal. We present the first PK-PD model describing the relationship between FVIII:C and ETP, the main PD parameter of the TGA. Recommendations on standardization of the TGA in haemophilia were recently published by the International Society on Thrombosis and Haemostasis.¹³ An earlier study reported good clinical correlation between the TGA and surgery-related bleeding risk in patients with haemophilia and inhibitors.

Using a full joint model, we demonstrate that PK and PD of human-cl rhFVIII partly explain spontaneous bleeding risk. We suggest that sampling blood at baseline, 3 and 8 hours after human-cl rhFVIII administration for measurement of FVIII:C and ETP should enable robust estimation of individual PK and PD parameters using a Bayesian approach. Our modelling analysis establishes proof of concept for a novel approach to dose tailoring based on both PK and PD data. The simulations demonstrated that baseline ETP is a key factor for dose tailoring, which is supported by clinical data which shows that ETP correlates well with spontaneous bleeding tendency.^{8,14,15}

An advantage of using this mechanistic joint PK-PD model is that the parameters have a biological interpretation, whereby putative scenarios can be performed to anticipate the impact of various experimental settings, including simulating the effect of drug on spontaneous bleeding risk. As discussed in the introduction, some patients experience breakthrough bleeds⁶ and results from this study (Table 3) show that for patients with a low baseline ETP

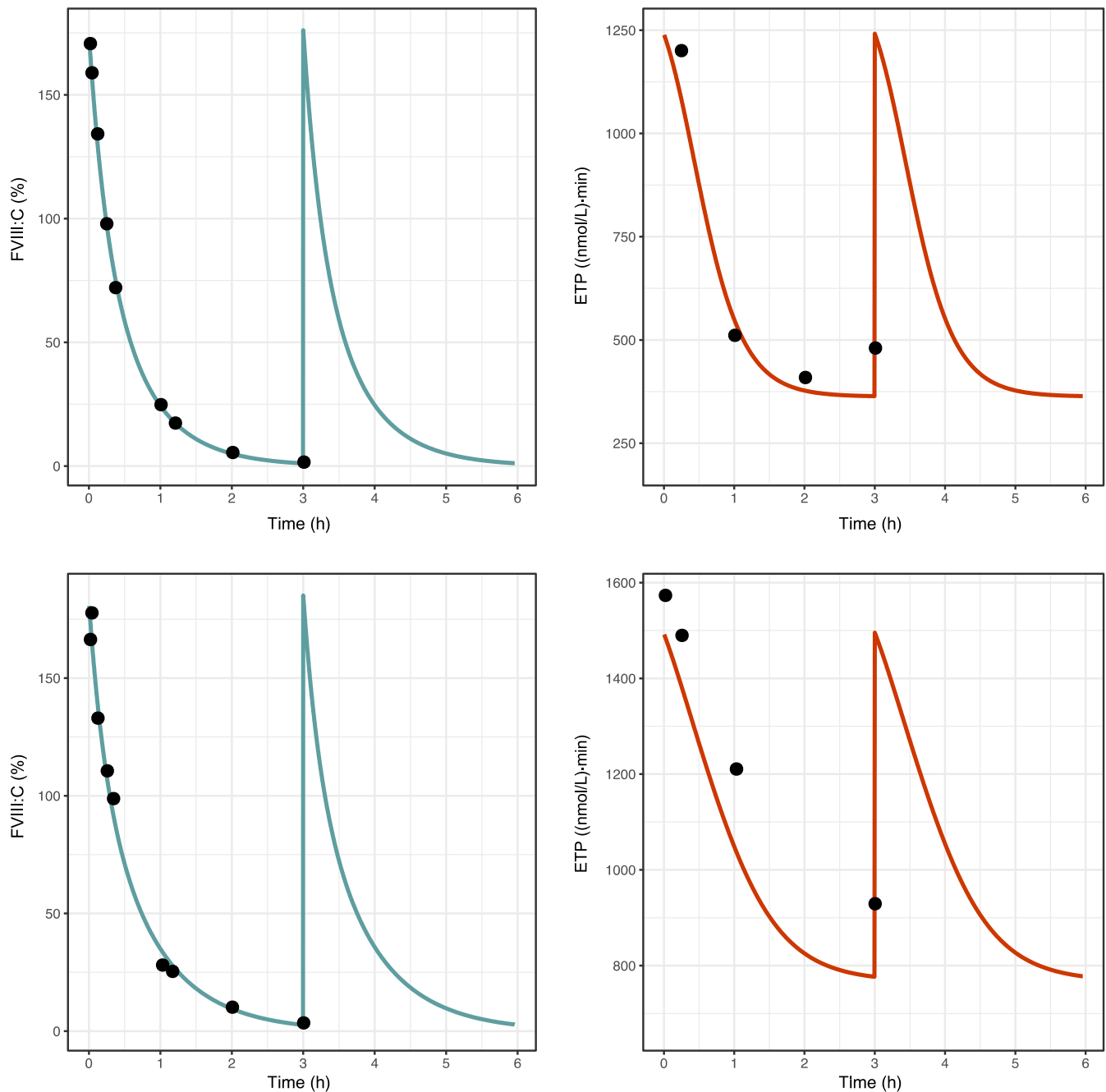


FIGURE 3 Individual estimation of FVIII:C and ETP. ETP, endogenous thrombin potential; FVIII:C, factor VIII activity [Colour figure can be viewed at wileyonlinelibrary.com]

(200 (nmol/L)-min), even the highest dose of FVIII (60 IU/kg every 2 days) results in an ABR of 1.66. These observations highlight that for this group of patients current treatment strategies may be inadequate. Stratifying patients by baseline ETP level may identify those at risk of spontaneous bleeds, regardless of FVIII dosing levels. Moreover, the model could be used to simulate more frequent dosing strategies to attempt to reduce or eliminate spontaneous bleeds in these patients. Conversely, Table 3 also shows that for patients with a high baseline ETP (600 (nmol/L)-min), an acceptable ABR may be achieved with low FVIII dosing; thus, identifying these patients may help to avoid unnecessary and expensive overdosing of FVIII.

We and others have shown previously that TGAs are prone to intra-individual variability due to a number of preanalytical variables, including assay temperature, tissue factor concentration, and inappropriate preparation and storage of plasma samples.^{13,16} In this study, ETP measurements were performed in a central laboratory where the intra-assay coefficient of variability of the ETP was found to be 5.8% and the inter-assay coefficient of variability was 9.4%, as published previously.¹⁷ We did not evaluate inter-occasion variability of ETP as it was measured only once during the GENA-21 study. Although the impact of IOV could not be estimated in this study, it would be worth exploring in future studies

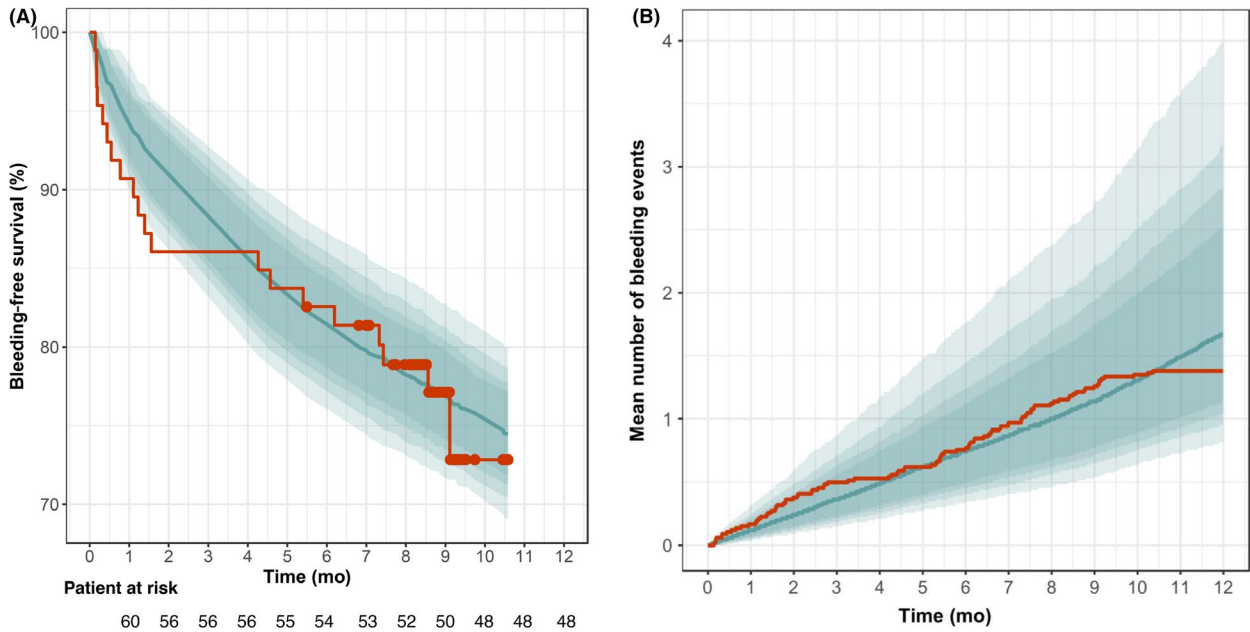


FIGURE 4 Visual predictive check for the model fitting of the observed Kaplan-Meier plot. (A) Kaplan-Meier plot of bleeding-free survival. (B) Number of bleeding events over time. Solid red lines represent curves based on (A) Kaplan-Meier analysis of the observed percentage of patients surviving without bleeds ($N = 66$), or (B) the mean number of bleeding events, vs time. Solid green lines represent the time-to-event (TTE) model estimated median curves; shaded areas represent the TTE model estimated 90%, 80%, 70% and 60% prediction intervals of the curves [Colour figure can be viewed at wileyonlinelibrary.com]

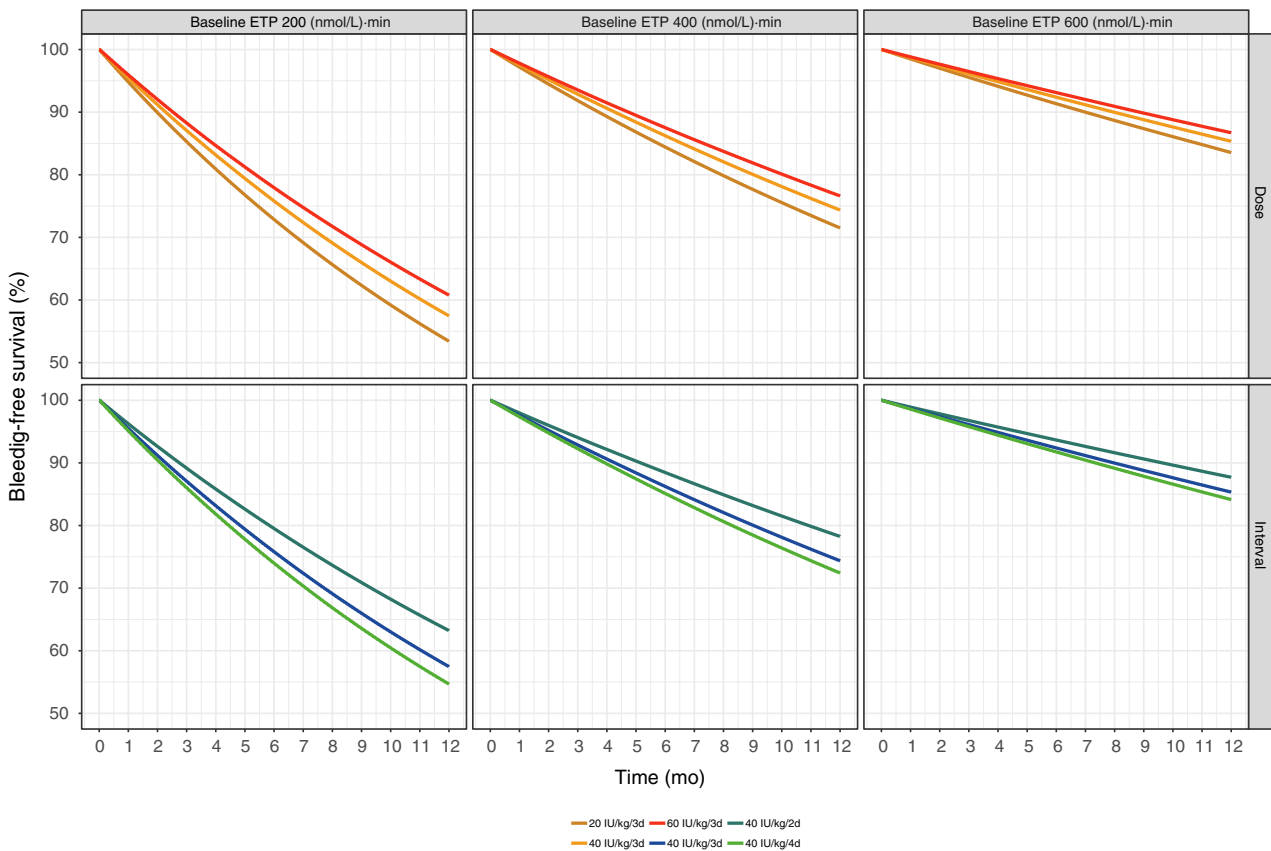


FIGURE 5 Spontaneous bleeding-free survival simulations. Each panel presents the percentage of patients without bleeding (vertical axis) over time (horizontal axis) for different dose amounts (top panels) or intervals (bottom panels). ETP, endogenous thrombin potential; IU, international units [Colour figure can be viewed at wileyonlinelibrary.com]



Dosing regimen	Baseline ETP 200 (nmol/L)·min	Baseline ETP 400 (nmol/L)·min	Baseline ETP 600 (nmol/L)·min
20 IU/kg			
Every 2 d	2.39 (1.27-5.57)	1.31 (0.67-2.8)	0.69 (0.34-1.77)
Every 3 d	2.66 (1.51-5.78)	1.47 (0.78-3.21)	0.8 (0.42-1.69)
Every 4 d	2.92 (1.56-6.42)	1.53 (0.78-3.50)	0.88 (0.42-1.87)
40 IU/kg			
Every 2 d	1.95 (1.06-4.34)	1.03 (0.51-2.31)	0.57 (0.28-1.25)
Every 3 d	2.36 (1.28-5.52)	1.25 (0.66-2.72)	0.66 (0.33-1.56)
Every 4 d	2.60 (1.40-5.86)	1.42 (0.74-3.10)	0.75 (0.39-1.59)
60 IU/kg			
Every 2 d	1.66 (0.84-3.57)	0.88 (0.45-1.92)	0.48 (0.22-1.12)
Every 3 d	2.09 (1.12-4.65)	1.10 (0.57-2.39)	0.60 (0.28-1.45)
Every 4 d	2.36 (1.33-4.91)	1.25 (0.69-2.83)	0.68 (0.33-1.60)

ETP, endogenous thrombin potential; IU, international units.

as a large inter-occasion coefficient of variability would reduce the value of modelling ETP. Clinically, this issue should be addressed by repeating therapeutic drug monitoring and adjusting the dosage if the patient becomes unstable. Standardized conditions for presampling and thrombin generation measurement in patients with haemophilia were recently proposed by the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on FVIII, FIX and Rare Coagulation Disorders,¹³ which should promote applicability of this model for general practice.

It is important to note that as for PK parameters, PD parameters are also associated with a large between- and within-subject variability, that is variability typically exists between drug concentration and effect intensity.¹⁸ In our study, baseline ETP and EC_{50} were associated with large inter-individual variability (55% and 48%, respectively; Table 2). Similarly, a cross-sectional study of 123 patients demonstrated variability in thrombin generation in those with severe haemophilia A, both at baseline and at different correction levels.¹⁹ The authors found no significant correlations between the severity of haemophilia (assessed by the haemophilia severity score) and thrombin generation parameters at baseline. However, thrombin generation parameters were predictive of response to treatment. Thus, incorporating both FVIII trough levels and ETP into personalized prophylaxis regimens takes into account both the extent of FVIII deficiency and treatment response.

This is an innovative approach beyond the classical concept of prophylaxis based only on maintaining a predetermined target FVIII trough level. The aim is to avoid spontaneous bleeding whatever the FVIII level, according to the individual needs of each patient.

4.1 | Limitations

Limitations of this study include that it is a proof-of-concept analysis and prospective clinical studies are needed to validate the model and explore the potential for refining it further by integrating other

TABLE 3 Mean annual spontaneous bleeding rate simulations

bleeding risk factors, such as bone and joint markers and lifestyle. Validation of this combined PK/PD model, both in future clinical trials and in later clinical practice, may help to improve management of patients with severe haemophilia A on prophylaxis.

The model developed in this study is specific of human-cl rhFVIII. However, it would be easy to transpose this model to other rFVIII products using the PK parameters estimated in other published PK population studies.

4.2 | Conclusions

Prophylactic FVIII dosing for patients with severe haemophilia A can be improved and made more clinically meaningful by incorporating ETP, a PD parameter that provides a global measure of coagulation and predicts spontaneous bleeding risk, alongside the conventional PK parameter of FVIII trough level. Using this innovative approach, individual dosing regimens can be calculated that aim to eliminate spontaneous breakthrough bleeds. For the first time, it is possible to personalize FVIII dosing according to a clinical endpoint. If symptomatic and asymptomatic spontaneous breakthrough bleeds can be avoided using this approach, prophylaxis aimed at achieving no arthropathy might be possible for patients with severe haemophilia A.

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DISCLOSURES

XD has received honoraria for participation in symposia by CSL Behring, Shire, Octapharma and Sobi. YD has received grants/research support from Bayer, Baxter, Novo Nordisk, CSL Behring, LFB

Biomedicaments, Pfizer, LEO Pharma, Octapharma, Baxalta-Shire and Diagnostica Stago; speaker's honoraria from Bayer, Baxter, Novo Nordisk, CSL Behring, Sobi, Octapharma and Sanofi; consultancy honoraria from Bayer and Baxalta-Shire; and instructor honoraria from Novo Nordisk. EO and AL have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

XD and YD conceived and designed the study and drafted the manuscript. XD and EO performed the statistical analysis. YD supervised the study. All authors contributed to acquisition, analysis or interpretation of data and critically revised the manuscript for important intellectual content.

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SUPPORTING INFORMATION

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

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