



## ORIGINAL ARTICLE

## Clinical haemophilia

# Concizumab restores thrombin generation potential in patients with haemophilia: Pharmacokinetic/pharmacodynamic modelling results of concizumab phase 1/1b data

Hermann Eichler<sup>1</sup>  | Pantep Angchaisuksiri<sup>2</sup> | Kaan Kavakli<sup>3</sup>  | Paul Knoebl<sup>4</sup> | Jerzy Windyga<sup>5</sup>  | Victor Jiménez-Yuste<sup>6</sup> | Philip Harder Delff<sup>7</sup> | Pratima Chowdary<sup>8</sup> 

<sup>1</sup>Institute of Clinical Hemostaseology and Transfusion Medicine, Saarland University and University Hospital, Homburg/Saar, Germany

<sup>2</sup>Division of Hematology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

<sup>3</sup>Department of Hematology, Ege University Children's Hospital, Izmir, Turkey

<sup>4</sup>Clinical Division of Hematology and Hemostasis, Medical University of Vienna, Vienna, Austria

<sup>5</sup>Department of Disorders of Hemostasis and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

<sup>6</sup>Haematology Department, La Paz University Hospital, Madrid, Spain

<sup>7</sup>Novo Nordisk A/S, Copenhagen, Denmark

<sup>8</sup>Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, UK

## Correspondence

Hermann Eichler, Institute of Clinical Hemostaseology and Transfusion Medicine, Saarland University and University Hospital, Homburg/Saar, Germany.  
Email: hermann.eichler@uks.eu

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**Introduction:** Concizumab enhances thrombin generation (TG) potential in haemophilia patients by inhibiting tissue factor pathway inhibitor (TFPI). In EXPLORER3 (phase 1b), a dose-dependent pharmacokinetic/pharmacodynamic (PK/PD) relationship was confirmed between concizumab dose, free TFPI and TG potential.

**Aim:** Determine the association between concizumab exposure, PD markers (free TFPI; peak TG) and bleeding episodes to establish the minimum concizumab concentration for achieving sufficient efficacy.

**Methods:** Free TFPI predictions were generated using an estimated concizumab-free TFPI exposure-response ( $E_{max}$ ) model based on concizumab phase 1/1b data for which simultaneously collected concizumab and free TFPI samples were available. Concizumab concentration at the time of a bleed was predicted using a PK model, based on available data for concizumab doses  $>50 \mu\text{g/kg}$  to  $\leq 9 \text{ mg/kg}$ . Peak TG vs concizumab concentration analyses and an  $E_{max}$  model were constructed based on EXPLORER3 observations.

**Results:** The  $E_{max}$  model showed a tight PK/PD relationship between concizumab exposure and free TFPI; free TFPI decreased with increasing concizumab concentration. A strong correlation between concizumab concentration and peak TG was observed; concizumab  $>100 \text{ ng/mL}$  re-established TG potential to within the normal reference range. Estimated  $EC_{50}$  values for the identified concizumab-free TFPI and concizumab-TG potential models were very similar, supporting free TFPI as an important biomarker. A correlation between bleeding episode frequency and concizumab concentration was indicated; patients with a concizumab concentration  $>100 \text{ ng/mL}$  experienced less frequent bleeding. The PK model predicted that once-daily dosing would minimize within-patient concizumab PK variability.

**Conclusion:** Concizumab phase 2 trials will target an exposure  $\geq 100 \text{ ng/mL}$ , with a once-daily regimen.

## KEYWORDS

concizumab, haemophilia, modelling, pharmacodynamics, pharmacokinetics, phase 1

## 1 | INTRODUCTION

Several novel therapeutic avenues are being explored with the aim of improving management strategies for people with haemophilia, including gene therapy approaches, RNA interference, factor VIII (FVIII) mimetics and blockade of tissue factor pathway inhibitor (TFPI). Although primary prophylaxis is considered optimal for people with severe haemophilia,<sup>1</sup> significant barriers to the efficient implementation of prophylaxis persist. These barriers include the development of inhibitors, which are neutralizing antibodies formed against allogeneic factor VIII (FVIII) or factor IX (FIX), resulting in the reduction or elimination of FVIII/FIX activity and ultimately leading to a suboptimal response to treatment, increased disease burden and morbidity, and reduced quality of life.<sup>2-4</sup> A further barrier is the need for intravenous (iv) injections, which are painful, time-consuming and require venous access that can be difficult to achieve, particularly in young children.<sup>5,6</sup>

Concizumab is among the novel therapeutics in clinical development for the treatment of haemophilia and is a potentially first-in-class TFPI inhibitor. It is a humanized, recombinant monoclonal antibody (mAb) that binds with high affinity to the Kunitz-2 domain of TFPI. TFPI plays a crucial role in controlling coagulation by acting as the primary regulator of the initiation phase of normal coagulation. Following vessel wall injury, the tissue factor (TF)-activated factor VII (FVIIa) complex is formed and activates FIX to FIXa and factor X (FX) to FXa. TFPI binds to and inhibits FXa (via its Kunitz-2 domain), followed by binding to FVIIa in the TF-FVIIa complex (via its Kunitz-1 domain), “turning off” the initiation phase of coagulation and ultimately resulting in the inhibition of thrombin generation. In normal coagulation, following inhibition of the initiation phase, FX activation and thrombin generation is ensured via the action of the intrinsic tenase complex (activated factor VIII [FVIIIa]-FIXa complex) during the propagation phase. People with haemophilia have impaired propagation due to reduced FVIII/FIX levels, leading to reduced FXa generation and increased bleeding. By inhibiting TFPI, concizumab prevents inhibition of not only FXa but also of the TF-FVIIa complex, thereby leading to ongoing FXa generation in the presence of tissue injury and subsequent activation of the remaining steps of the common coagulation pathway cascade, ultimately resulting in a thrombin “burst” even in the absence of functional FVIII (haemophilia A patients) or FIX (haemophilia B patients) or the presence of inhibitors.<sup>7-10</sup> Concizumab is therefore being developed for the prevention of bleeding episodes, including long-term prophylaxis, in patients with haemophilia A and B with or without inhibitors. As it is a mAb, concizumab allows subcutaneous (sc) administration, and as it exhibits good solubility and stability, it can be formulated as a liquid for use in a ready- and easy-to-use portable pen device.<sup>11</sup>

In EXPLORER1 (ClinicalTrials.gov identifier: NCT01228669), a first-in-human trial, concizumab exhibited a favourable safety profile following a single sc or iv dose administered to healthy volunteers or patients with haemophilia A or B. There were no serious adverse events and no anti-concizumab antibodies were reported.

In addition, a dose-dependent, pro-coagulant effect was observed, as well as a non-linear pharmacokinetic (PK) profile as a result of target-mediated clearance.<sup>12</sup> EXPLORER3 (NCT02490787) was a phase 1b, double-blind, multiple-dose escalation trial of sc concizumab in patients with severe haemophilia A without inhibitors. In the primary analysis of EXPLORER3, no serious adverse events were seen in the completed cohorts, and a PK/pharmacodynamic (PD) relationship for concizumab dose, free TFPI and thrombin generation was confirmed.<sup>13</sup> Currently, concizumab is being assessed in phase 2 clinical trials in patients with severe haemophilia A without inhibitors (EXPLORER5; NCT03196297), as well as in patients with haemophilia A or B with inhibitors (EXPLORER4; NCT03196284).

Here, we present results from exploratory PK/PD analyses of data from concizumab phase 1/1b trials, which aimed to determine the association between concizumab exposure and the PD markers free TFPI and peak thrombin generation. Although the EXPLORER3 trial was not sufficiently powered to establish a prophylactic effect in terms of bleeding, the reported bleeding episodes from the trial were also included in the analyses. Through these analyses, we aimed to confirm the mechanism of action of concizumab by showing a decrease in free TFPI, expected to be accompanied by an increase in coagulation (seen as an increase in thrombin generation potential), and ultimately reflected clinically as a reduction in the number of bleeding episodes. The PK/PD analyses presented herein guided the design of the concizumab phase 2 studies, specifically in terms of dose setting.

## 2 | MATERIALS AND METHODS

### 2.1 | Concizumab dosing in phase 1/1b clinical trials

Data from 4 trials involving 48 patients with haemophilia A/B and 40 healthy volunteers were included in the PK/PD analyses presented herein: 21 and 3 patients with haemophilia A and B, respectively, and 28 healthy volunteers from EXPLORER1; four and eight healthy volunteers from EXPLORER2 and the Japanese trial, respectively; and 24 patients with haemophilia A from EXPLORER3. In EXPLORER1, a phase 1, multicentre, randomized, double-blind, placebo-controlled trial, single, escalating, iv (0.0005-9 mg/kg) or sc (0.05-3 mg/kg) doses of concizumab were administered to healthy volunteers and patients with haemophilia A or B.<sup>12</sup> In EXPLORER2 (NCT01631942), a multicentre, open-labelled, multiple-dose trial, healthy volunteers received eight consecutive sc concizumab doses (0.25 mg/kg) every other day. In a study that assessed concizumab PK in healthy Japanese volunteers (NCT01555749), a randomized, double-blind, placebo-controlled, single-centre trial, single sc concizumab doses of 0.25 and 1.0 mg/kg were administered. In EXPLORER3, five escalating dose levels of sc concizumab (0.25, 0.5, 0.8, 1.1 and 1.5 mg/kg) were planned, but the trial was finalized after completion of the 0.8 mg/kg cohort based on coagulation and PK parameter changes that were observed in the 0.8 mg/kg cohort, as well as the high inter-patient variation in the PK parameters and pro-coagulant response



to concizumab in this cohort. No serious adverse events were observed in the completed dose groups.<sup>13</sup> Each patient in EXPLORER3 received the first two doses on two consecutive days to allow steady state to be reached rapidly, followed by subsequent administration once every 4 days.

All concizumab trials were conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice guidelines. The trials were approved by the relevant ethics committees or institutional review boards. Written signed informed consent was obtained from all participants.

## 2.2 | Concizumab population PK model

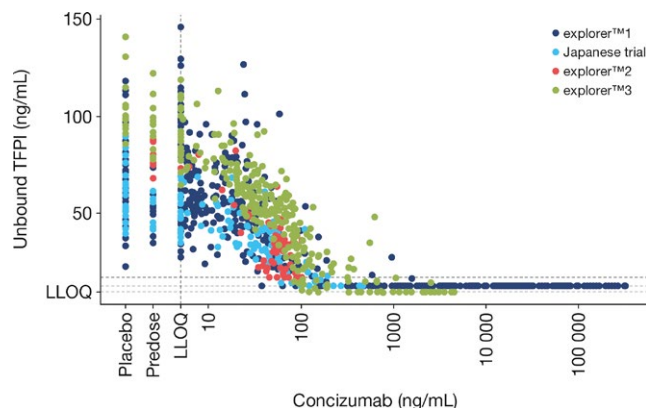
A PK model was constructed based on all available iv and sc clinical data for concizumab doses >0.05 mg/kg and up to 9 mg/kg (data from 42 patients and 13 healthy volunteers). Data were best described by a two-compartmental model with both a linear and non-linear clearance component. Classical disposition parameters (clearance [CL], central volume of distribution [V<sub>1</sub>], peripheral volume of distribution [V<sub>2</sub>] and inter-compartmental clearance [Q]) were comparable to those reported for other mAbs.<sup>14</sup> As the maximum elimination rate of the Michaelis Menten component ( $V_{\max}$ ) related to target-mediated clearance is high, the total clearance for low concentrations was estimated to be ~100-fold higher than at full saturation of the target. Variability simulations were performed by using individually estimated parameters, and by repeating inter-occasion variability components as estimated within patients. A detailed description of the PK model is provided in a separate manuscript (in preparation).

## 2.3 | Concizumab PK/PD modelling

### 2.3.1 | Concizumab exposure-free TFPI $E_{\max}$ model

An estimated exposure-response ( $E_{\max}$ ) model, based on all concizumab phase 1/1b data for which simultaneously collected concizumab and free TFPI samples were available, was constructed to determine the relationship between concizumab concentration and the affinity to its target (ie, TFPI) (Figure 1). A basic assumption in this approach is that the effect of concizumab on free TFPI concentration is in steady state and is based on the half-life of concizumab being much larger than the half-life of TFPI.<sup>12,15</sup> All pre-dose samples from EXPLORER1 patients treated with concizumab iv were excluded from the analysis as some of them had been spiked with concizumab prior to the analysis. Sigmoidal  $E_{\max}$  models with between-subject variability on baseline and half-maximal effective concentration ( $EC_{50}$ ) and covariates on baseline and  $EC_{50}$  were investigated. Both statistical tests and visual inspection of goodness-of-fit were used for decisions on model structure. Terms were only considered if they were judged to be pharmacologically meaningful. Likelihood ratio tests at 5% significance level were used throughout.

The sigmoidal  $E_{\max}$  model of the free TFPI concentration predicted by the concizumab concentration was designed as an  $E_{\max}$



**FIGURE 1** Concizumab concentration and free tissue factor pathway inhibitor (TFPI) observations. Concizumab phase 1/1b data used to build an estimated exposure-response ( $E_{\max}$ ) model for concizumab-free TFPI are shown. The lower limit of quantification values varied between trials. Free TFPI values were generally higher in EXPLORER2 and EXPLORER3 than in EXPLORER1 and the Japanese trial. This was observed in both placebo and pre-dose samples, as well as in post-dose samples. This observation was included as a baseline fixed effect in the concizumab exposure-free TFPI model

model of free TFPI reduction from baseline (at zero concizumab concentration). Full reduction resulted in a free TFPI concentration at the lower limit of quantification (LLOQ). TFPI LLOQ varied between trials (12.5 ng/mL for EXPLORER1 and the Japanese trial, and 17.0 and 9.6 ng/mL for EXPLORER2 and EXPLORER3, respectively). The model was developed in a stepwise fashion. First, the model structure (non-sigmoidal vs sigmoidal) and residual error model (additive, proportional, or combined) were tested. Then, subject-level random effects were included and, finally, covariates were sequentially included based on likelihood ratio testing. Trial effects were tested on the model-predicted baseline free TFPI concentration. The effect of each individual trial, as well as of different trial groupings was assessed. The effect of Asian vs non-Asian ethnicity was tested on both model-predicted baseline and  $EC_{50}$ . The effect of healthy volunteers vs haemophilia (A and B) patients was tested on model-predicted baseline, but not on  $EC_{50}$ , as the doses in the two groups were too unbalanced, with healthy volunteers receiving doses up to 0.25 mg/kg (except for six subjects receiving 1 mg/kg sc). When no more covariates were significant, all included terms were tested separately and alternative residual error models (proportional and additive) were retested.

### 2.3.2 | Concizumab exposure-thrombin generation potential association

Analyses of peak thrombin generation vs concizumab concentrations were constructed based on observations in the EXPLORER3 trial (data from 24 patients). A sigmoidal  $E_{\max}$  model of the logarithm of peak thrombin generation was fitted with concizumab concentration as explanatory variable.

**TABLE 1** Concizumab-free TFPI exposure-response model parameter estimates

	Estimate	95% CI (lower)	95% CI (upper)	Relative standard error (%)	Between-subject variability (% CV)	Shrinkage (%)
Baseline (ng/mL)	81.5	75.4	87.5	3.77	19.5	10.2
EC <sub>50</sub> (ng/mL)	62.2	52.4	72	8.02	62.6	21.3
Hill coefficient	1.75	1.47	2.03	8.05	NA	NA
EXPLORER1/Japanese trial (effect on baseline)	0.742	0.676	0.808	4.51	NA	NA
Concizumab 9 mg/kg iv (effect on EC <sub>50</sub> )	11.1	8.61	13.5	11.3	NA	NA
Proportional error (% CV)	22.1	NA	NA	NA	NA	4.0311

NA, not applicable; TFPI, tissue factor pathway inhibitor.

The model was based on all concizumab phase 1/1b data for which simultaneously collected concizumab and free TFPI samples were available.

### 2.3.3 | Concizumab exposure-free TFPI association at bleeding episodes

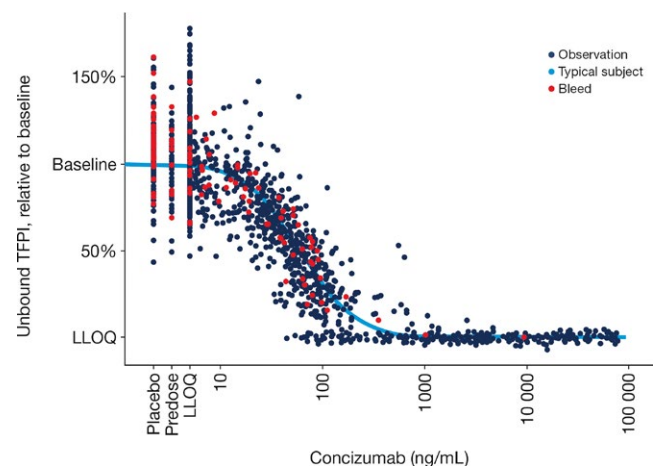
Concizumab concentration at the time of a bleeding episode in EXPLORER3 was predicted using the population PK model. Predictions of free TFPI at the time of bleeds were then generated using the concizumab-free TFPI  $E_{\max}$  model. A total of 106 bleeding episodes were included in the analysis; 91 bleeding episodes recorded in 21 patients (of whom 5 were on placebo) during EXPLORER3,<sup>13</sup> and 15 treated bleeds that occurred prior to initiation of dosing.

## 3 | RESULTS

### 3.1 | Concizumab exposure-free TFPI association

A sigmoidal model with proportional error was chosen for the concizumab-free TFPI  $E_{\max}$  model. A sigmoidal  $E_{\max}$  relationship was identified between concizumab concentration and reduction of free TFPI in plasma, with a significant sigmoidal Hill coefficient (1.75 [95% confidence interval: 1.47-2.03]) (Table 1). Subject-level random effects were significant on both baseline free TFPI concentration and EC<sub>50</sub>. The trial effect leading to the smallest *P*-value was obtained by grouping EXPLORER1 with the Japanese trial data and the EXPLORER2 with EXPLORER3 data. It was observed that the random effect on EC<sub>50</sub> led to very large EC<sub>50</sub> values for two of the three patients receiving 9 mg/kg iv. As 9 mg/kg is considerably higher than the concizumab doses administered to patients in clinical trials, it was decided to test the effect of this dose level on EC<sub>50</sub> in order for these observations not to have too large an influence on the EC<sub>50</sub> estimate for a typical subject. The estimated typical value for EC<sub>50</sub> was 62 ng/mL. The combined trial effect of EXPLORER1 and the Japanese study was significant on model-predicted baseline TFPI concentration, while data for concizumab 9 mg/kg iv had a significant effect on EC<sub>50</sub>.

In data described by the  $E_{\max}$  model, a tight PK/PD relationship was observed between concizumab exposure and free TFPI, with



**FIGURE 2** Relationship between concizumab exposure, free tissue factor pathway inhibitor (TFPI) and bleeding episodes. Estimated exposure-response ( $E_{\max}$ ) model of free TFPI predictions based on all concizumab phase 1/1b data for which simultaneously collected concizumab and free TFPI samples were available are shown. Free TFPI predictions relative to the predicted baseline free TFPI concentration vs observed concizumab concentration are shown. At bleeding events in EXPLORER3 (red dots), concizumab concentration was predicted using a population pharmacokinetic model (based on all available intravenous and subcutaneous clinical data for concizumab doses >0.05 mg/kg and up to 9 mg/kg) and, subsequently, free TFPI concentration was predicted using a concizumab-free TFPI  $E_{\max}$  model. The solid line represents predictions of free TFPI concentration vs concizumab concentration for a typical subject. A typical subject was defined as a subject from EXPLORER2 or EXPLORER3 with typical baseline TFPI concentration and EC<sub>50</sub> value. Jitter has been added to free TFPI levels for bleeds at predicted PK levels below 10 ng/mL in order to distinguish points graphically. The same has been done to observations at full reduction of free TFPI. Predictions are not shown for concizumab 9 mg/kg

free TFPI decreasing with increasing concizumab concentration (Figure 2). A similar TFPI baseline distribution (at zero concizumab concentration) was predicted for patients receiving placebo and for pre-dose samples.



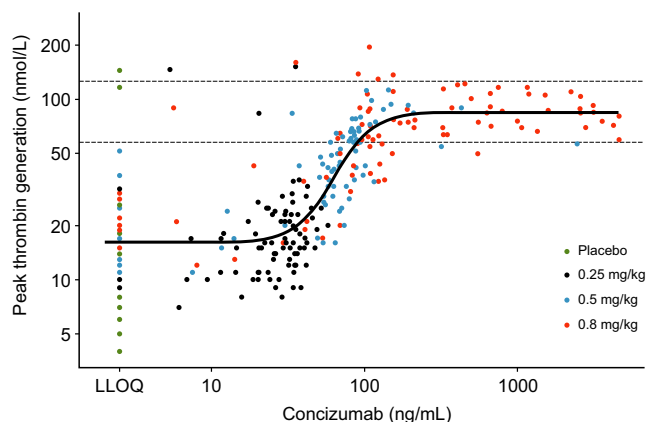
### 3.2 | Concizumab exposure-thrombin generation potential association

A sigmoidal  $E_{\max}$  relationship was identified between concizumab plasma concentration and peak thrombin generation potential in EXPLORER3 (Figure 3). A number of observations of peak thrombin generation within the normal range were noted at low concizumab levels, potentially representing the effect of residual FVIII, which, in theory, could be either through secondary missense mutations or due to the long terminal half-life of administered FVIII. Since these observations constitute a considerable part of the residual variability, more detailed effects, such as random effects, were not investigated. The estimated typical  $EC_{50}$  value (ie, the concizumab concentration predicted to give 50% of the maximum possible effect on peak thrombin generation) was 63 ng/mL.

There was a strong correlation between concizumab concentration and peak thrombin generation potential in data collected in EXPLORER3, with concizumab >100 ng/mL re-establishing thrombin generation potential within a normal range (60–130 nmol/L) (Figure 4). Median (interquartile range [IQR]) peak thrombin was 15 (10–24), 31.5 (17.25–61) and 81 (65.5–100) nmol/L for concizumab  $\leq 20$ , >20 to  $\leq 100$  and >100 ng/mL, respectively.

### 3.3 | Concizumab exposure-bleeding episode association

As EXPLORER3 was not an efficacy trial, a prophylactic effect of concizumab administration in terms of bleeding events could not be assessed. However, a correlation between the frequency of bleeding episodes and concizumab concentration was indicated, with



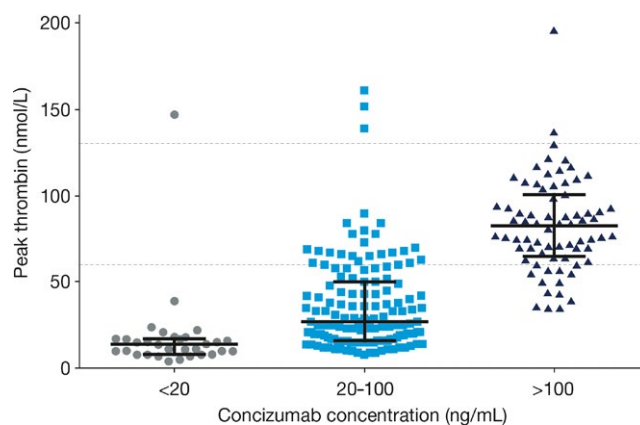
**FIGURE 3** Concizumab plasma concentration and peak thrombin generation potential in EXPLORER3. Peak thrombin generation vs concizumab concentration based on observations in the EXPLORER3 trial for the three concizumab doses tested (0.25, 0.5 and 0.8 mg/kg) are shown, excluding data obtained  $\leq 72$  h following factor VIII administration. The solid line represents predictions from an  $E_{\max}$  model in which the peak thrombin generation logarithm was fitted with concizumab concentration as explanatory variable. The dotted horizontal lines indicate the normal range of thrombin generation potential (60–130 nmol/L)

fewer bleeds observed at concizumab concentrations >100 ng/mL and at free TFPI levels <25% relative to baseline (Figure 2). It should be noted that there was substantially less exposure time with concizumab concentrations above 100 ng/mL vs those below 100 ng/mL.

## 4 | DISCUSSION

In PK/PD analyses of EXPLORER3 data, it was noted that at concizumab exposure levels >100 ng/mL, the thrombin generation potential was re-established to predominantly within the normal range. Additionally, results from PK/PD analyses of concizumab phase 1/1b data indicated a clinically relevant prophylactic effect for haemophilia patients at concizumab exposure levels >100 ng/mL, based on the decrease in reported bleeding episodes noted at estimated concizumab exposure above that level. The PK/PD results obtained were consistent across all concizumab phase 1/1b trials. Based on these results, the concizumab phase 2 clinical development programme has been designed to target a concizumab exposure of at least 100 ng/mL. In addition, a once-daily, efficacy-based, individual, dose-escalation regimen has been selected for the phase 2 trials with the aim of reducing PK variability (previously noted in the highest dose cohort in EXPLORER3, receiving 0.8 mg/kg, once every 4 days).<sup>16</sup> The results from the current PK/PD analyses should be considered in the light of the fact that patients had not been randomized to concizumab exposure/dose, which represents a limitation when conducting exposure-response analyses.

In EXPLORER4, patients with haemophilia A or B with inhibitors will receive a loading dose of concizumab 0.5 mg/kg as the first dose, followed by 0.15 mg/kg (sc, daily), with potential



**FIGURE 4** Correlation between concizumab concentration and peak thrombin generation in EXPLORER3. Based on all EXPLORER3 data for which simultaneously collected concizumab and peak thrombin generation samples were available. Observations excluding data  $\leq 72$  h following factor VIII administration due to bleeding events are shown. Peak thrombin is shown as individual values and medians (central horizontal line) with interquartile ranges (error bars). The dotted horizontal lines indicate the normal range of thrombin generation potential (60–130 nmol/L)



stepwise dose escalation to 0.25 mg/kg in case of recurrent bleeds. In the EXPLORER5 trial, patients with severe haemophilia A without inhibitors will receive concizumab 0.15 mg/kg (sc, daily), with potential stepwise dose administration to 0.25 mg/kg in case of recurrent bleeds. For a typical subject,  $C_{trough}$  values of 140, 250 and 440 ng/mL are expected with concizumab 0.15, 0.20 and 0.25 mg/kg daily, respectively. Additional data from these phase 2 trials will help fine-tune the therapeutic window for concizumab in different populations of haemophilia patients. They will also provide a larger data set and results based on a longer exposure to concizumab, thus expanding the scope of the current analyses.

Our analyses showed a strong correlation between concizumab exposure and free TFPI. The estimated typical  $EC_{50}$  values for concizumab-free TFPI and concizumab-thrombin generation were very similar (62 and 63 ng/mL, respectively), a result that supports free TFPI (ie, TFPI in plasma, not bound to concizumab) as a useful biomarker for concizumab efficacy. Moreover, there was an indication of fewer bleeds at lower free TFPI concentrations.

There are several advantages associated with the use of concizumab for the treatment of patients with haemophilia. As previously noted, its unique mechanism of action renders it applicable for both haemophilia A and B patients, both with or without inhibitors. As a sc therapeutic, treatment with concizumab should result in a significant improvement in compliance in terms of prophylaxis and therefore lead to improved treatment outcomes, including in patients with severe haemophilia, in whom prophylactic treatment is recommended and can help maintain normal musculoskeletal function.<sup>1</sup> An additional advantage associated with concizumab is its availability as a liquid formulation with a long shelf-life that can be easily administered at small volumes via a portable pen device stored at room temperature. In a small pen injector handling test among haemophilia patients accustomed to using syringe-to-vial systems, a positive response to the pen device was noted, with no handling difficulties or errors documented.<sup>11</sup> Crucially, as concizumab is a mAb, there is no risk of developing inhibitors towards coagulation factors, the most significant complication associated with factor replacement treatment.<sup>2-4</sup> Finally, and of note, no neutralizing anti-drug antibodies were observed following treatment with concizumab in any of the phase 1/1b trials.

## 5 | CONCLUSION

Based on the results of the PK/PD analyses presented herein, the phase 2 concizumab clinical development programme has been designed to target an exposure of at least 100 ng/mL, and a once-daily, efficacy-based, individual dose-escalation regimen has been selected to reduce exposure variability. The minimum concizumab exposure level required to achieve sufficient haemostatic efficacy will be fine-tuned following the availability of phase 2 clinical data.

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## DISCLOSURES

HE has acted as a paid consultant for Novo Nordisk and has received funding (reimbursement for attending meetings). PA has nothing to disclose. KK has acted as an advisory board member and study investigator and has received reimbursement for attending congresses and fees for speaking from Novo Nordisk and Shire. PK has received reimbursement for attending a symposium, fees for speaking, research support and consulting fees from Novo Nordisk. JW has received grant/research/clinical trial support from Amgen, Aspen, Baxalta, Biogen Idec, Baxter Healthcare, Bayer, CSL Behring, Novo Nordisk, Octapharma, Roche, Sanofi and Shire. VJY has received reimbursement for attending symposia/congresses, and/or honoraria for speaking, and/or honoraria for consulting, and/or funds for research from Bayer, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Shire and Sobi. PHD is an employee of Novo Nordisk A/S. PC has received grants from CSL Behring, Bayer, Novo Nordisk, Pfizer and Swedish Orphan Biovitrum (AB) (publ) (Sobi), and personal fees from Bayer, Baxalta (Shire), Biogen Idec, Chugai, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche and Sobi, outside the submitted work.

## AUTHOR CONTRIBUTIONS

HE, PA, KK, PK, JW, VJY and PC recruited patients into the trial, and analyzed and interpreted the data. PHD performed the modelling analyses and analyzed and interpreted the data. All authors had access to the trial data, contributed to the writing and review of the manuscript and approved the final version.

## ORCID

Hermann Eichler  <http://orcid.org/0000-0002-1372-0619>

Kaan Kavakli  <http://orcid.org/0000-0002-4910-2142>

Jerzy Windyga  <http://orcid.org/0000-0001-7877-4784>

Pratima Chowdary  <http://orcid.org/0000-0002-6690-8586>

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