Safety and dose-dependency of eptacog beta (activated) in a dose escalation study of non-bleeding congenital haemophilia A or B patients, with or without inhibitors

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Introduction: Varying initial doses of activated eptacog beta (recombinant human FVIIa, rhFVIIa) may provide therapeutic options when treating bleeding in patients with congenital haemophilia who have developed inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX). This study evaluated escalated doses of a new rhFVIIa product as a prelude to selecting the doses for clinical efficacy evaluation in haemophilia patients.

Aim: To assess the safety, pharmacokinetics, and laboratory pharmacodynamics of 3 doses of rhFVIIa in non-bleeding patients with congenital haemophilia A or B with or without inhibitors.

Methods: Adult male patients (18-75 years old) with congenital haemophilia A or B (with or without inhibitors) received infusions of rhFVIIa at doses of 25, 75 or 225 μg/kg body weight. Ten patients were treated at each dose level, and each patient received 2 different dose levels. Descriptive methods were used to analyse the data.

Results: Administration of rhFVIIa at all doses was well tolerated. Pharmacokinetic analyses showed that peak FVIIa plasma levels (Cmax) were approximately proportional to dose and correlated well with peak thrombin generation. Total AUC0-inf also was approximately dose proportional. Clot formation and duration correlated with FVIIa activity. Repeat doses did not produce an immunological response.

Conclusion: In the first dose-escalation study of rhFVIIa to support product registration, eptacog beta at doses of 25, 75, and 225 μg/kg was pharmacodynamically active and well tolerated in non-bleeding patients with congenital haemophilia A or B.

Keywords
bypassing agents, eptacog beta, inhibitors, Phase Ib, recombinant activated factor VII, rhFVIIa

1 | INTRODUCTION

Haemophilia A and B are blood clotting disorders caused by congenital deficiency of factors VIII (FVIII) or IX (FIX) respectively. Bleeding episodes (BEs) in these patients are treated with factor replacement therapy; however, during their lifetime, 20%-30% of patients with haemophilia A and 5% with haemophilia B, will develop inhibitory antibodies (inhibitors) to FVIII or FIX. In such patients, haemostasis may not be achievable with replacement of the deficient factor (depending upon the inhibitor titre) and thus may require administration of bypassing agents, eptacog beta, inhibitors, Phase Ib, recombinant activated factor VII, rhFVIIa
agents, such as plasma-derived activated prothrombin complex concentrates (aPCC) or activated recombinant factor VII (rFVIIa),²⁻⁵

Primarily out of concern for thrombosis, most clinicians use a titrated, “lowest effective” dose of bypassing agent in acute bleeding episodes.⁶,⁷ In an early review of rFVIIa dosing, Abshire and Kenet⁸ proposed that optimization of the initial thrombin burst in patients at low thrombotic risk may lead to earlier and possibly more durable haemostasis. Optimal dose finding is further complicated by the absence of validated pharmacodynamic markers to predict clinical efficacy. Retrospective rFVIIa utilization data in the congenital haemophilia inhibitor population indicate the risk of thrombin generation at sites where pathologic thrombosis is triggered, rather than physiologic haemostasis, is related to the presence of pre-existing risk factors for thrombosis.⁹,¹⁰ To date, clinical evidence suggestive of dosedependent efficacy has been generated, but this has been difficult to confirm or reproduce for reasons that are not well understood.¹¹⁻¹⁵

Historically, various dosing regimens have been employed attempting improvements in overall rFVIIa haemostatic efficacy and dosing efficiency. In on-demand settings, there is weak evidence that the AUC of a bypassing agent is the primary correlate for the achievement of haemostasis, though the effect of sustained thrombin generation is thought to improve healing and may delay clot dissolution.¹⁶,¹⁷ Not surprisingly, continuous infusion in the setting of surgical interventions (with ongoing wound manipulation) has been shown to be efficacious, thus confirming that a steady concentration of agent may have benefit in certain clinical circumstances. In contrast, animal experiments and some prospective human studies make clear that the peak plasma concentration (Cmax) of administered FVIIa is correlated with thrombin generation, clot strength and faster onset of haemostasis.¹⁸⁻²² Whether incremental dosing could delay otherwise achievable early haemostasis is unclear.

Within this clinical context, activated eptacog beta (rhFVIIa), a new recombinant human coagulation FVIIa molecule produced by LFB USA using rPro® Technology,² is being developed as a haemostatic bypassing agent for treating bleeding episodes in patients with haemophilia A or B who develop inhibitors. A dose-escalation study was performed to assess the safety, pharmacokinetic profile (PK), and laboratory pharmacodynamic markers (PD) of rhFVIIa activity in non-bleeding subjects with haemophilia A or B, with or without inhibitors. Computationally modelled pharmacokinetic behaviour supported the selection of doses for Phase 3 clinical trials of rhFVIIa for the treatment of bleeding episodes in patients with inhibitors.²³,²⁴

The primary sequence and the degree of gamma carboxylation of eptacog beta and eptacog alfa are identical. The ex vivo molar potency of eptacog beta is greater, and differences in glycosylation and binding to cellular sites such as Endothelial Protein C Receptor and platelets have been observed.

2 | MATERIALS AND METHODS

This study received approval by institutional review boards, and was conducted in compliance with established good clinical practice as stated in the current Declaration of Helsinki.²⁵ Written informed consent was obtained from all subjects at the time of their enrollment. The study is registered at clinicaltrials.gov (NCT01708564).

2.1 | Study design

Three doses of rhFVIIa (25, 75 and 225 µg/kg) were examined using a Phase Ib dose-escalation study design. Doses were preselected based on preclinical in vitro and in vivo studies of activity [LFB SA Data on File]. The first 10 subjects received the lowest dose of rhFVIIa. Following review of the 30 ± 6 hour safety and PD coagulation data by an independent, external Data Monitoring Committee (DMC), 5 of these subjects were randomly selected and 5 new subjects received the second treatment dose. Following a similar safety review by the DMC, the 5 remaining subjects treated at dose level 1, and the 5 newly treated subjects from dose level 2 were treated with the highest dose. Open label study drug was administered intravenously over 2-3 minutes; a single lot of drug product was used throughout the study. Two centres in the US and 1 in The Netherlands enrolled subjects Figure 1.

2.2 | Patients

Male subjects, aged 18-75 years, with moderate or severe congenital haemophilia A or B (FVIII or FIX levels <5% of normal) were eligible to enrol. Subjects with prothrombotic risk factors were excluded from the study. Key inclusion and exclusion criteria are listed in Table 1.

2.3 | Pharmacokinetic, pharmacodynamic and safety evaluations

PK, PD and safety assessments were obtained not more than 30 minutes prior to dosing (baseline); at 5, 15 and 30 minutes; and at 1, 2,
TABLE 1  Key inclusion and exclusion criteria for the Phase Ib study

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male with a diagnosis of congenital haemophilia A or B (with or without inhibitors), FVIII or FIX &lt;5%</td>
<td>Any coagulation disorder other than haemophilia A or B</td>
</tr>
<tr>
<td>Aged between 18 and 75 y</td>
<td>Received any FVII or FVIIa-containing product within 72 h of administration of study medication</td>
</tr>
<tr>
<td></td>
<td>Major surgical procedure within the previous 1 mo</td>
</tr>
<tr>
<td></td>
<td>Any history of arterial and/or venous thromboembolic events within 2 y, have an arterial stent in place or have clinically significant atherosclerotic disease</td>
</tr>
<tr>
<td></td>
<td>Known allergy or sensitivity to rabbitsa</td>
</tr>
<tr>
<td></td>
<td>Any active, ongoing bleeding, for which the subject is being treated (or was treated in the previous 24 h)</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed (CD4 count at screening ≤200/μL), or low platelet count (&lt;100 000/μL)</td>
</tr>
</tbody>
</table>

aEptacog beta is a recombinant protease manufactured from the milk of transgenic rabbits.

4, 6, 8, 12 and 24 hours after rhFVIIa administration. Safety evaluations were also conducted at 30 ± 6 hours along with the collection of a final blood sample. Follow-up safety evaluations were performed at the 14 ± 1 and 28 ± 2-day time points. Plasma samples were processed to remove platelets prior to analysis.

2.4 | Pharmacokinetics

The StaClot® FVIIa rTF assay (Diagnostica Stago™), modified and validated to accommodate high FVIIa concentrations, was used to measure functional plasma rhFVIIa concentrations against a validated in vitro standard. Sampling was planned to evaluate peak thrombin generation at intervals, allowing dose proportional statistical modelling of plasma rhFVIIa activity over time. This assay does not distinguish exogenous rhFVIIa from endogenous FVIIa; however, as administered doses of rhFVIIa produce plasma levels that greatly exceed levels of endogenous FVIIa,26 the assay is a valid measure of clinically relevant rhFVIIa plasma levels.

2.5 | Pharmacodynamics

Activated partial thromboplastin time (aPTT); prothrombin time (PT) in normal and diluted plasma; prothrombin fragments F1+2; D-dimer levels; and thrombin-antithrombin complexes (TAT; Enzygnost® TAT micro) were measured per the assay kit directions that called for sample collection in citrated tubes. Platelet Factor 4 (PF4; Asserachrom PF4, Diagnostica Stago) was assessed in a limited number of samples to verify correct sample handling. A thrombin generation assay (TGA), was performed using a calibrated automated thrombogram [CAT] both with and without added platelets (platelets serving as the specific source of phospholipid). To accommodate frozen samples, modified and validated rotational thromboelastometry (ROTEM-FIBTEM) was performed.

2.6 | Immunogenicity

Blood samples were analyzed for antibodies against rhFVIIa (all antibody isotypes) and potential production-related impurities immediately prior to rhFVIIa administration; at the 30 ± 6 hour safety evaluation, and at the 14 ± 1 day and 28 ± 2 day follow-up visits. Per the immunogenicity testing protocol, neutralizing antibodies in the sensitive screening immunochemical assay required the confirmation of antibody specificity by inhibition by study drug. All samples were confirmed negative for antidrug antibody. Thus, no functional inhibitory assays were required.

2.7 | Safety

Safety assessments included full medical history, concomitant medication use, and a standard physical examination at screening and at the 28-day follow-up visit. Electrocardiograms were conducted at screening, baseline, and 30 ± 6 hours after drug administration. Clinical laboratory tests included haematology, urinalysis, coagulation-based antibody screening, antibody assays and serum chemistry at screening, baseline, 30 ± 6 hours, and 14 days after drug administration (FVIII or FIX inhibitors, HBsAg, HCV, HIV).

2.8 | Statistical methods

Descriptive statistics for plasma concentrations of rhFVIIa activity at each protocol designated time point were tabulated and individual PK parameters were determined using a non-compartmental PK analysis. For each PD variable, descriptive statistics were analyzed by time point and dose group for actual values and change from baseline. Baseline-corrected levels were reported as indicated. The 24-hour safety evaluation time point was not used in the PK analysis. Due to the study design, significance testing was not performed.

3 | RESULTS

3.1 | Subject population

Eighteen subjects were screened: 15 of these satisfied the inclusion and exclusion criteria and received both assigned doses of rhFVIIa. 14 of these subjects completed all follow-up evaluations, with 1 subject being lost to both the 14 and 28-day safety assessments following the second dose. Demographics are shown in Table 2.

3.2 | Pharmacokinetics

Table 3 summarizes the baseline-corrected PK parameters for all 3 doses. Both the Cmax and the AUC were dose dependent across all
**TABLE 2** Demographics of subjects receiving study medication

<table>
<thead>
<tr>
<th>Parameter, N = 15</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33.0 [10.8]</td>
</tr>
<tr>
<td>Mean [SD]</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>20/61</td>
</tr>
<tr>
<td>Race/ethnicity, n</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Moroccan</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Haemophilia type</td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Haemophilia severity</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Inhibitor titre</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>≤0.8 BU</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1 (6.7)</td>
</tr>
</tbody>
</table>

**TABLE 3** Geometric mean (CV) of non-compartmental PK parameter analyses

<table>
<thead>
<tr>
<th>Parameter, N = 15</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter, 25 μg/kg</td>
<td>75 μg/kg</td>
</tr>
<tr>
<td>CL, L/h</td>
<td>9.0 (42.9)</td>
</tr>
<tr>
<td>V_{ss}, L</td>
<td>29.8 (50.3)</td>
</tr>
<tr>
<td>C_{max}, ng/mL</td>
<td>230 (42.8)</td>
</tr>
<tr>
<td>AUC_{0-ss}, ng·h/mL</td>
<td>212 (41.1)</td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>2.3 (29.6)</td>
</tr>
</tbody>
</table>

CL, apparent clearance; V_{ss}, apparent volume of distribution at steady state; C_{max}, maximum observed concentration; AUC_{0-ss}, area under the plasma-concentration time curve, time of dosing to infinity; t_{1/2}, terminal half-life. For all PK parameters, baseline FVIIa levels were subtracted from the measured FVIIa values.

3.3 | Pharmacodynamics

The effects of binding of rhFVIIa to platelets is more prominent than those of tissue factor binding. Thus, a platelet-spiked TGA assay (TGAp) is more representative of its clinical mode of action than the platelet-free assay. Plasma samples were obtained at prespecified times after rhFVIIa administration. Thrombin generation was measured and mean thrombin generation peaks were calculated. Dose-dependent effects were seen in the peak thrombin generation when measured from 5 minutes to 24 hours (Figure 3 and Table 4). The platelet-free TGA showed significant variability, and the results are not reported here.

Baseline aPTT uniformly exceeded the upper limit of the normal range (23 to 34 seconds) (Table 4). The aPTT following treatment with rhFVIIa was dose-dependent, with the 225 μg/kg dose producing the greatest effect: 5 minutes postinfusion, the mean aPTT was reduced by 6.9, 11.5 and 22.2 seconds for the 25, 75, and 225 μg/kg dose groups respectively. The aPTT returned to baseline values after 1 hour following the 25 μg/kg dose and by 4-12 hours following the higher doses.

Reduction in prothrombin time was observed at all doses, but greatest in the 75 and 225 μg/kg dose groups (Table 4). At baseline, the mean PTs were comparable for all groups and were within the normal range (13.1-15.7 seconds). Full evidence of dose dependency was obscured, as the lower limit of the assay (approximately 8 seconds) was reached with both the 75 and 225 μg/kg doses. The PT returned to baseline by 12 hours following the 25 μg/kg dose, and by 24 hours following the higher doses.

3.4 | ROTEM (modified)

Clot firmness is a measure of the absolute strength of the fibrin and platelet clot and in this study, the change from baseline also exhibited a dose-dependent relationship (Figure 4). Maximum clot firmness (MCF) was observed 5 minutes postinfusion, with the change from baseline being 5.9 ± 3.7, 7.0 ± 2.8, and 9.7 ± 3.3 mm for the 25, 75, and 225 μg/kg dose groups respectively. The aPTT returned to baseline values after 1 hour following the 25 μg/kg dose and by 4-12 hours following the higher doses.

3.5 | Measures of coagulation activation

Baseline D-dimer levels were variable among subjects; however, individual subject levels remained largely unchanged throughout the evaluation period, as did the mean levels. One subject had elevated levels at the 24 hours time point on the 225 μg/kg dose, being 2-fold higher than baseline, and occurring 24 hours postinfusion.

Prothrombin fragment F1+2 showed a dose-dependent increase with a peak 1 to 2 hours postinfusion, indicating the formation of thrombin following rhFVIIa administration. Levels returned to baseline between 6 and 12 hours postinfusion. When the change from baseline value was calculated, a low level dose-response was observed: the median change from baseline at 2 hours was 33, 94 and 164 pmol/L for the 25, 75, and 225 μg/kg dose groups, respectively. (Table 4)

TAT, a complex between thrombin and antithrombin, is a marker of coagulation activation, and is highly variable among normal individuals. Overall, the 25 μg/kg dose appeared to have no effect on thrombin-antithrombin complex behaviour. TAT levels for the 75 and 225 μg/kg dose groups were variable and inconsistent between patients, with
some patients showing evidence of minimal thrombin generation immediately following rhFVIIa administration.

3.6 | Immunogenicity

No hypersensitivity or humoral immunogenicity was detected in any subject during primary or re-exposure assessments.

3.7 | Safety

In all 3 cohorts, both doses of rhFVIIa (25/75, 25/225 or 75/225 μg/kg) were well tolerated. Three adverse events that occurred within 36 hours of infusion were possibly related to the drug based upon the temporal relationship between the events and drug infusion. One patient experienced mild dizziness of short duration after receiving doses of 25 and 75 μg/kg rhFVIIa (11 and 3 minutes’ duration respectively). A second patient experienced a mild headache that lasted for 2 hours following administration of 25 μg/kg rhFVIIa. All events resolved without intervention. There were no clinically meaningful excursions in hematologic or serum chemistry measures following administration. There was no evidence of administration-related allergic reaction.

**TABLE 4** Summary in vitro assay values, mean (SD), stratified by dosing group

<table>
<thead>
<tr>
<th>Assay</th>
<th>25 μg/kg, (N = 10)</th>
<th>75 μg/kg, (N = 10)</th>
<th>225 μg/kg, (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA, nmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion (~30 min)</td>
<td>0.86 (0.39)</td>
<td>0.82 (0.49)</td>
<td>0.68 (0.55)</td>
</tr>
<tr>
<td>Peak thrombin generation postinfusion</td>
<td>11.8 (3.7)</td>
<td>16.7 (4.1)</td>
<td>20.5 (3.5)</td>
</tr>
<tr>
<td>aPTT, s^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion (~30 min)</td>
<td>55.4 (9.0)</td>
<td>53.2 (13.3)</td>
<td>57.7 (13.7)</td>
</tr>
<tr>
<td>5 min postinfusion</td>
<td>48.5 (6.3)</td>
<td>41.7 (7.8)</td>
<td>35.5 (3.6)</td>
</tr>
<tr>
<td>Prothrombin time, s^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion (~30 min)</td>
<td>14.0 (1.0)</td>
<td>13.6 (0.5)</td>
<td>13.9 (0.8)</td>
</tr>
<tr>
<td>5 min postinfusion</td>
<td>9.0 (0.5)</td>
<td>8.3 (0.5)</td>
<td>8.0 (0.6)</td>
</tr>
<tr>
<td>Maximum clot firmness, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion (~30 min)</td>
<td>5.5 (3.5)</td>
<td>5.2 (2.9)</td>
<td>4.4 (2.1)</td>
</tr>
<tr>
<td>5 min postinfusion</td>
<td>11.5 (1.9)</td>
<td>12.2 (2.8)</td>
<td>14.1 (2.3)</td>
</tr>
</tbody>
</table>

Normal range 13.1-15.7 s.

^aNormal range 23-34 s.

^bThe shortest measurable time in the PT assay was 8 s.
DISCUSSION

Bypassing agent therapy is a core treatment modality for haemophilia patients who develop inhibitors to FVIII or FIX. This Phase Ib study evaluated a second-generation bypassing agent, recombinant human FVIIa (rhFVIIa; activated eptacog beta), to guide dosing levels and provide initial safety data for Phase 3 clinical studies. Multiple surrogate pharmacodynamic markers for haemostasis demonstrated dose dependent changes upon treatment with rhFVIIa, a result that was consistent with the dose-dependent PK observed in the same patients. The findings indicate that the highest 2 doses (75 and 225 μg/kg) produced the greatest effect in these assays and were therefore considered suitable for further clinical investigation.

The baseline-corrected FVIIa peak plasma activities and AUCs were non-linearly dose proportional, a result comparable to that previously reported for in vitro studies of FVIIa thrombin generation. As rhFVIIa exerts its pharmacological effect in plasma, the PK results were analyzed using a non-compartmental methodology; however, as in vivo endothelial and platelet receptor binding does affect the plasma concentration, the non-compartmental analysis may not accurately reflect levels of bioavailable rhFVIIa.

When correcting haemophilic coagulopathy with replacement factor, classic laboratory assessment of intrinsic and extrinsic coagulation, along with factor level assays, represent the standard of care for guiding therapy. For bypassing agents, however, no laboratory assay has been validated for monitoring or anticipating clinical coagulation response. Several pharmacodynamic markers of coagulation activation, although not validated as surrogate markers of in vivo haemostasis, did indicate a dose-dependent response after infusion of rhFVIIa. Specifically, for the TGA with platelets, MCF, PT and aPTT, a dose-dependent relationship was observed. Measures of clot formation (TAT, F1+2) and dissolution (D-dimer) were highly variable and subject to confounding secondary to the use of citrate for coagulation activation. There were substantial inter-patient variations in F1+2, with some patients demonstrating a proportional relationship with study dose. The PT assay demonstrated persistent shortening; however, the initial dose-response relationship was obscured as the lower limits of the assay were reached.

Only 2 subjects in this study had inhibitors to FVIII or FIX. Deficient thrombin generation in patients with haemophilia A or B is common to patients with or without inhibitors though the severity of the defect may be greater in the inhibitor population. Variations in FVIIa pharmacologic half-life have only been demonstrated in patients with acquired FVIIa inhibitors; nevertheless, the trends observed in these data provide a meaningful basis for the selection of doses to be evaluated in Phase 3 clinical studies examining on-demand treatment of mild/moderate bleeding in patients with inhibitors.

All doses of rhFVIIa were well tolerated. No consistent elevations of D-dimer or TAT were noted. D-dimer measurement in samples collected in citrate have been shown to vary widely, a result of time to analysis due to Ca++-independent plasmin activity in vitro. Nevertheless, while D-dimer is non-specific and does not exclude pathologic clot formation, there were no consistent elevations following rhFVIIa.

No hypersensitivity or other clinical events occurred that would indicate an immunological response following primary or repeat

FIGURE 4 Rotational thromboelastometry (ROTEM) to assess clot firmness level. A dose-dependent effect on clot firmness was observed, with the maximum clot firmness being observed at 5 min.
exposure to the product. This clinical tolerability was corroborated by negative immunologic assays.

5 | CONCLUSION

Data from this dose escalation study provide guidance for clinical dose selection for future rhFVIIa studies. The peak plasma concentration of rhFVIIa has relevant effects on platelet augmented thrombin generation, suggesting dose-dependent increases in local thrombin concentration at the site of bleeding. Further, time to clot formation and clot structure, strength and retractive force development are directly related to the peak thrombin generation within the forming clot.\textsuperscript{18,33-35} Thus, \( C_{\text{max}} \) considerations should guide the choice of the initial dose for on-demand treatment of bleeding episodes. In addition, the total AUC determined at different doses confirms the viability of a 3-hour dosing interval for the 75 \( \mu \)g/kg and 225 \( \mu \)g/kg and suggests that a 9-hour dose-dependent interval between the initial 225 \( \mu \)g/kg and subsequent doses are pharmacokinetically supported. This key consideration permits design of an on-demand dosing regimen. Without clinically validated PD markers to predict bypassing agent efficacy in bleeding haemophilia subjects with inhibitors, a subsequent Phase 3 study was initiated (using 75 and 225 \( \mu \)g/kg as initial doses) to validate these results.\textsuperscript{23,24}

Activated eptacog beta (rhFVIIa), a new second-generation rhFVIIa, was well tolerated in haemophilia patients with or without inhibitors, and had dose-dependent PK and PD profiles that support further evaluation of its potential efficacy in studies of bleeding episodes in haemophilia patients with inhibitors.

ACKNOWLEDGEMENTS

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DISCLOSURES

JD, MLS, LB and MW were study investigators and have received compensation from Hema Biologics/LFB/rEVO Biologics. JD has provided consultation or been an investigator for Bayer, Shire, Octapharma, Biogen, CSL, Sparks, OPKO. MLS has been a consultant for Biogen, CSL Behring, Grifols, NovoNordisk, Octapharma, and Shire. LB has served as a consultant or investigator for Biogen, Bayer, Shire, OPKO, NovoNordisk, Grifols and Octapharma. MW has provided consultation for Shire, NovoNordisk, Biogen, CSL Behring. JL (USA), AB (Paris) and JF are/were employees of LFB. JB, MM, JS and JR are employees of CHDR, Leiden, The Netherlands, and were compensated for analytical work supporting this study. JF is no longer employed by LFB Paris. He currently has no competing interests which may be perceived as posing a conflict or bias.

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