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PERSEPT 1: a phase 3 trial of activated eptacog beta for on-demand treatment of haemophilia inhibitor-related bleeding

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Introduction: Haemophilia A or B patients with inhibitors have been treated with FVIIa-containing bypassing agents for over 20 years. However, due to uncertainty regarding dose response and thrombotic risk, the use of a gradual, titrated, minimal dosing strategy remains prevalent, potentially hampering early haemostasis.

Aim: Evaluate the dose-dependent efficacy, safety and immunogenicity of activated eptacog beta (rhFVIIa), a new recombinant inhibitor bypassing agent for the treatment of bleeding episodes (BEs).

Methods: A Phase 3, randomized, cross-over study of initial dose regimens (IDRs) in 27 bleeding congenital haemophilia A or B subjects with inhibitors was conducted to evaluate on-demand treatment of mild/moderate BEs. Intravenous 75 μg/kg or 225 μg/kg initial doses with 75 μg/kg subsequent doses by schedule were administered until clinical response.

Results: The primary endpoint was sustained clinical response within 12 hours, determined by a composite of objective and pain measures. In the 75 μg/kg IDR, 84.9% (95% CI; 74.0%, 95.7%) of mild/moderate BEs at 12 hours were successfully treated compared to 93.2% (95% CI; 88.1%, 98.3%) treated in the 225 μg/kg IDR. Efficacy between the IDRs was statistically different (P<.020) in mild/moderate bleeding episodes. Both IDRs were well tolerated with no detectable immunogenic or thrombotic responses to rhFVIIa or host cell proteins.

Conclusion: The dose-dependent efficacy seen in this study supports individualizing the initial dose of eptacog beta to optimize clinical response. By reducing uncertainty, the PERSEPT 1 results should increase the adoption of early haemostasis as a treatment goal for clinicians who treat haemorrhage in the inhibitor population.

KEYWORDS
bypassing agent, clinical trial, haemophilia A or B, haemorrhage, inhibitors, PERSEPT 1, rFVIIa

1 | INTRODUCTION

The most serious complication of factor replacement therapy for haemophilia A and B is the development of inhibitors to FVIII or FIX.[1,2] Current therapeutic approaches exploit the extrinsic pathway using bypassing agents (eg activated recombinant Factor VII (FVII) or activated prothrombin complex concentrates) to induce a thrombin burst, which in the presence of adequate functional platelets, leads to

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haemostasis.[3,4] However, there is no standard dose that reliably treats all bleeding episodes, nor has the most efficacious dose for any given clinical scenario been prospectively identified.[5–12]

Thrombotic risk, unpredictable rFVIIa (eptacog alfa, NovoSeven®RT, Novo Nordisk A/S) dose requirements, the limited utility of surrogate laboratory markers of clinical response and challenges with patient access to therapy have hampered the adoption of early haemostasis (ie the shortest possible time spent bleeding) as a primary treatment goal.[13,14] Many years of clinical experience in patients with congenital haemophilia A or B with inhibitors have shown the thrombotic risk of rFVIIa administration to be acceptable, being primarily associated with patients who already possess prothrombotic risk factors.[15,16] In addition, retrospective analyses have confirmed the acceptable risk profile of initial doses of >240 μg/kg rFVIIa in this population.[17]

Variation in real-life treatment protocols is characteristic of on-demand rFVIIa (eptacog alfa) therapy.[5,18,19] Early clinical use began as empiric dose-finding; later, prospective clinical studies attempted to show improved efficacy with higher initial doses of rFVIIa. These studies demonstrated inconsistent efficacy and little conclusive evidence of reduction in time to symptom relief.[7,18–22] In addition, multiple large retrospective analyses failed to identify a dosing protocol that predictably led to early haemostasis across the spectrum of outpatient bleeding episodes.[15,19,20,23] Current best practices for rFVIIa dosing seek early bleed resolution by considering bleeding site and severity history, thrombotic risk factors, patient adherence and prior treatment response. Despite this, the use of intermittent, titrated dosing of rFVIIa remains prevalent, a practice which may delay haemostasis and result in some patients continuing to actively or (as some have speculated) sub-acutely haemorrhage over many hours.[19,24,25]

A new bypassing agent, activated eptacog beta (rhFVIIa, LFB SA), has been developed to address this advancing strategy.[26] rhFVIIa is a recombinant human FVIIa manufactured using rPro® Technology,[27] developed for the treatment of inhibitor-associated BEs. Following a prospective pharmacokinetic and pharmacodynamic dose-ranging study,[28,29] in which the relationship between Cmax (peak plasma concentration of rhFVIIa) and ex-vivo thrombin generation was quantified in subjects with haemophilia A or B, two initial doses for treatment of acute bleeding episodes (BEs) were chosen for activated eptacog beta (Figures S1 and S2).[28,29] Subsequently, we conducted the first PERSEPT Trial for the on-demand early treatment of bleeding episodes in adults and adolescents with haemophilia A or B with inhibitors and report the results here.

2 | METHODS

This study received approval by institutional review boards and was conducted in compliance with established good clinical practices as stated in the current Declaration of Helsinki.[30] Written informed consent was obtained from all subjects (or guardians) at the time of their enrolment. This study is registered at www.clinicaltrials.gov (#NCT02020369).

2.1 | Eligibility criteria

Male subjects with congenital haemophilia A or B and inhibitors to either FVIII or FIX were eligible for enrolment (inclusion/exclusion criteria are listed in Table 1). Demographic and baseline characteristics were collected during study enrolment.

2.2 | Study design

PERSEPT 1 was a global, multicentre, open-label, prospective, randomized, cross-over Phase 3 study evaluating the efficacy, safety and immunogenicity of two initial dose regimens (IDR) of rhFVIIa (eptacog beta, activated) for in-clinic or at-home, on-demand treatment of bleeding episodes. Subjects were advised to treat with rhFVIIa as soon as symptoms of bleeding were recognized (within 4 hours). The primary endpoint was therapeutic response to the treatment of mild/moderate BEs; severe BEs were also evaluated (Table 2). Subjects were randomized 1:1 via web-based computation to a cross-over

TABLE 1 Key inclusion and exclusion criteria for the PERSEPT 1 Phase 3 study

Inclusion criteria	Exclusion criteria
Male with a diagnosis of congenital haemophilia A or B of any severity	Any coagulation disorder other than haemophilia A or B
Have one of the following: 1. A positive inhibitor test BU ≥5 (as confirmed at screening by the institutional lab), OR 2. A BU titre <5, but expected to have a high anamnestic response to FVIII or FIX, as demonstrated from the subject's medical history, precluding the use of FVIII or FIX products to treat bleedings, OR 3. A BU titre <5, but expected to be refractory to increased dosing of FVIII or FIX, as demonstrated from the subject's medical history, precluding the use of FVIII or FIX products to treat bleedings	A history of arterial and/or venous thromboembolic events (such as myocardial infarction, ischaemic strokes, transient ischaemic attacks, deep venous thrombosis or pulmonary embolism) within 2 y prior to first dose of study drug, or current New York Heart Association functional classification score of stage II-IV
Aged 12-75 (different local age regulations may have applied)	Known allergy or sensitivity to rabbits
At least three bleeding episodes of any severity in the past 6 mo	Immunosuppressed (CD4 count at screening ≤200/μL), or low platelet count (<100 000/mL)

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TABLE 2 Definitions of mild, moderate and severe bleeding episodes (BEs) used in the clinical study

BE	Description	Examples
Mild	A haemorrhage that just started and has few symptoms, ie little or no pain, little or no change in the range of motion of affected joint (if joint haemorrhage); mild restriction of mobility and activity	Early onset muscle and joint haemorrhage with no visible symptoms, such as little or no change in the range of motion of affected joint (if intraarticular); mild restriction of mobility and activity
		Scrapes, superficial cuts, bruises, superficial mouth haemorrhages and most nose bleeds
Moderate	Haemorrhage involving swelling or pain, including some decrease in range of motion of affected joint (if joint haemorrhage) or moderate decrease in mobility and activity	Advanced soft tissue and muscle haemorrhages into the limbs
		Haemorrhage into the joint space, such as the elbow, knee, ankle, wrist, shoulder, hip, foot or finger
Severe	Severe bleeding episodes that were potentially life/limb threatening, produce significant blood loss, pain or can cause permanent nerve damage	Mouth and neck region—Haemorrhage from the floor of the mouth, pharynx or epiglottic area can result in partial or complete airway obstruction
		Complicated joint bleeding episodes—Hip joint or acetabular haemorrhages
		Iliopsoas haemorrhages
		Haemorrhage leading to compartment syndrome, such as in hand, wrists, forearm and psoas or tibial compartments
		Central nervous system haemorrhages
		Gastrointestinal—bleeding that occurred in stomach or intestines
		Acute haemorrhage—such as bleeding into the abdomen
		Major trauma haemorrhage

treatment group by IDR that prescribed dosing intervals through 24-hours using 75 μg/kg or 225 μg/kg of rhFVIIa (Figure 1). IDR cross-over occurred every 3 months until study end. The dosing schedule for mild/moderate BEs is depicted in Figure 2.

The treatment protocol for severe BEs was similar to that for mild/moderate BEs. The requirements were as follows: same initial dose as current IDR, early first dose treatment at home, the requirement for rhFVIIa administration in a hospital setting and the use of 2-hour dosing/evaluation intervals (Figure 3).

2.3 | Efficacy assessment

The primary efficacy endpoint was the successful treatment of a BE 12 hours after initial administration of rhFVIIa and without rebleeding

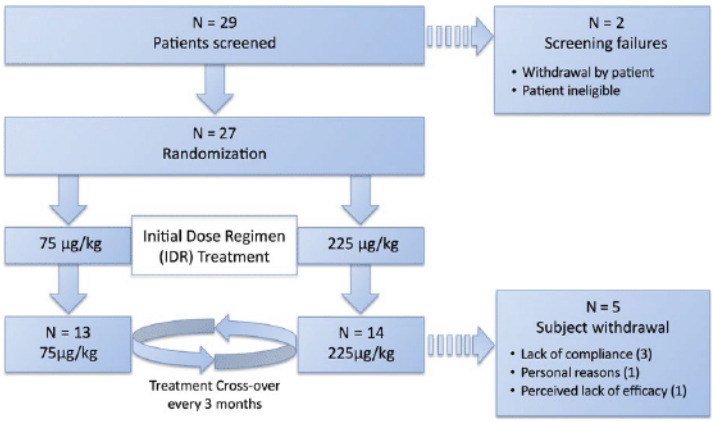

FIGURE 1 Subject disposition in the study. Subjects received the first infusion of their assigned initial dose regimen (IDR) study medication (either 75 μg/kg or 225 μg/kg) at their local study centre to evaluate for potential adverse events. Following a review of 20 mild/moderate bleeding episodes (BEs) by the data monitoring committee, severe BEs became eligible for study treatment. As some subjects withdrew from the study prior to initiating their second IDR (or did not experience a BE on an IDR), not all 27 subjects were evaluable for efficacy across both IDRs (safety evaluations were available for all 27 subjects, whereas efficacy assessments were available for only 25 subjects on each IDR). Treatment cross-over occurred every 3 months on treatment

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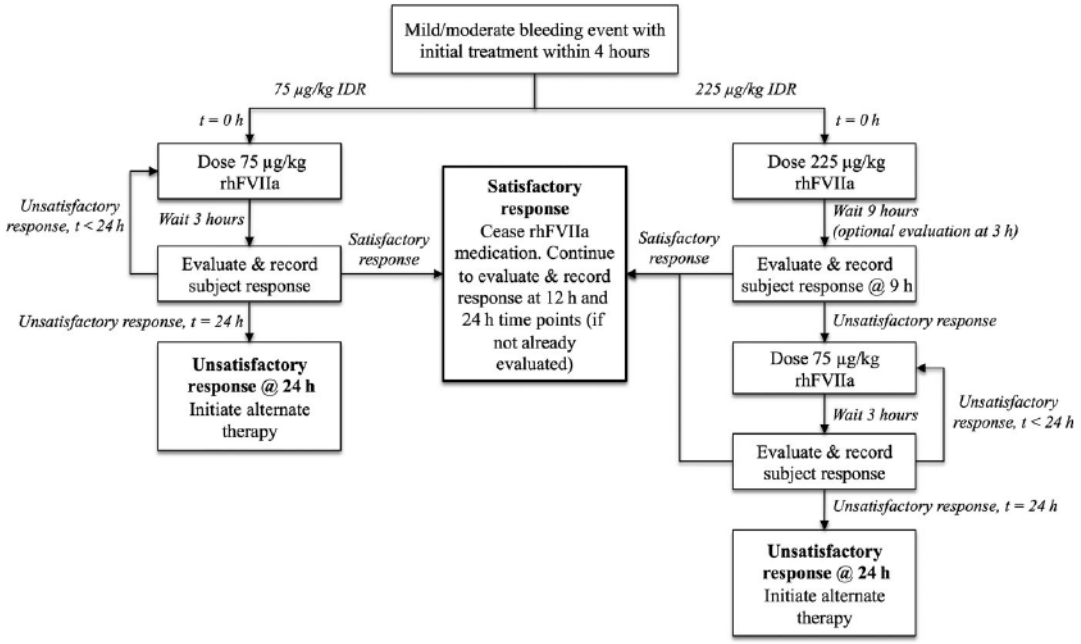

All possible doses and dosing intervals for treatment of mild/moderate BEs

	0 h	3 h	6 h	9 h	12 h	15 h	18 h	21 h	24 h
75 µg/kg IDR	75	75	75	75	75	75	75	75	-
225 µg/kg IDR	225	-	-	75	75	75	75	75	-

FIGURE 2 Mild and moderate bleeding episode (BE) protocol. Subjects were advised to treat a BE as soon as possible, at most within 4 hours of the first sign of any symptoms. Subjects kept detailed diaries of all BEs, treatments and outcomes during the study. Subjects treated in the 75 µg/kg initial dose regimen (IDR) evaluated and recorded efficacy every 3 hours until a satisfactory outcome was achieved. If a satisfactory outcome was achieved prior to the 12- or 24-hour time points, evaluations were also taken at those two time points. Subjects treated in the 225 µg/kg IDR opted to evaluate and record efficacy in their treatment diaries at the 3-hour time point. They then evaluated and recorded efficacy at the 9-hour time point, and every 3 hours thereafter until a satisfactory outcome was achieved. If a satisfactory outcome was achieved prior to the 12- or 24-hour time points, evaluations were also taken at those two time points. If an unsatisfactory response was reported at 24 hours on either IDR, then alternative therapies could be initiated at the discretion of the investigator

FIGURE 3 All possible doses and dosing intervals for treatment of severe bleeding episodes

	0 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h	22 h	24 h
75 µg/kg IDR	75	75	75	75	75	75	75	75	75	75	75	75	-
225 µg/kg IDR	225	-	-	75	75	75	75	75	75	75	75	75	-

prior to 24 hours. The subject (and physician, if present) used a haemostasis evaluation scale to assess efficacy as a means of determining need for further treatment at the next-scheduled dose (Table 3). Missing assessments at 12 hours were not included in the analysis.

Haemostatic efficacy for each IDR was the success proportion of BEs treated having a satisfactory and sustained therapeutic response. Thus, a BE could have a satisfactory clinical response at 12 hours, but be deemed a treatment failure if sustained haemostasis at 24 hours was not achieved (Figure 4). After 24 hours, subjects followed their primary physician's instructions for follow-up dosing with their regular bypassing agent (rFVIIa or aPCC, activated prothrombin complex concentrate).

2.4 | Pain assessment

Subjects used a Visual Analog Scale (VAS) to assess pain on a scale from 0 (no pain) to 100 mm (worst possible pain) at the time of efficacy assessment. A baseline assessment was made immediately prior to the first infusion of study medication for each BE, with subsequent assessments being made during each efficacy evaluation and at 12 and 24 hours.

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Patient evaluation	Therapeutic response	Description
None	Unsatisfactory	No noticeable effect of the treatment on the BE or worsening of subject's condition. Continuation of treatment with the study drug was needed
Moderate	Unsatisfactory	Some effect of the treatment on the BE was noticed (eg pain decreased or bleeding signs improved), but the BE continued and required continued treatment with the study drug
Good	Satisfactory	Symptoms of the BE (eg swelling, tenderness and decreased range of motion in the case of musculo-skeletal haemorrhage) had largely been reduced by the treatment but had not completely disappeared. Symptoms had improved enough to not require more infusions of the study drug
Excellent	Satisfactory	Full relief of pain and cessation of objective signs of the BE (eg swelling, tenderness and decreased range of motion in the case of musculoskeletal haemorrhage). No additional infusion of study drug was required

TABLE 3 Haemostasis evaluation scale. Therapeutic response was binary for the endpoint analysis. Patient responses of good or excellent were considered satisfactory therapeutic responses, and were used as an indication that haemostasis had been achieved, and that no further infusion of study medication was required for that bleeding episode (BE)

2.5 | Safety assessment

All subjects underwent evaluations, including physical examination, ECG, vital signs, clinical laboratory tests (serum chemistry, haematology and urinalysis) and immunology tests (including sample storage for potential future use). Screening thrombophilia laboratory evaluations were not performed. Safety assessments occurred at enrolment and clinic visits (weeks 3, 6 and 12; and at 12-wk intervals thereafter).

Serum samples to test for antibodies against rhFVIIa and any production-related impurities were collected during the study. Testing for antibodies against rhFVIIa was performed with an electrochemiluminescent assay able to detect all antibody isotypes. If confirmed in a repeat assay, the antibody was then tested for anti-rhFVIIa neutralizing potential.

As rhFVIIa is isolated from the milk of transgenic rabbits, additional assays analysed the subject samples for the development of antibodies specific to host proteins and casein.

2.6 | Statistical analysis

Continuous variables were summarized using descriptive statistics (sample size (N), mean, median, standard deviation (SD), range, number of observations with non-missing values and number of observations with missing values). Categorical variables were summarized by frequencies and percentages.

Haemostatic efficacy analyses were performed on BE data from all enrolled and randomized subjects who received study drug and for whom assessments were available. The minimum sample size with 80% power required 22 subjects with 352 mild/moderate BEs. Assumptions included a true proportion of success of 0.70, a correlation among bleeding episodes for a given subject of 0.1, and 8 mild/moderate bleeding episodes per treatment regimen per subject. The true success proportion was defined as 15% greater than a 12-hour objective performance criterion (OPC) of 0.55, derived from the success rates used to support eptacog alfa registration or reported in the inhibitor literature between 1998 and 2013.[5,7,19,20,31,32]

3 | RESULTS

3.1 | Subject Population

Twenty-nine subjects were screened at 13 centres in the US and Europe, with 27 subjects participating (Figure 1). Detailed demographics are listed in Table 4.

Four hundred and sixty-five mild/moderate BEs and three severe BEs were treated during the study (Table 5). The median time on the study for all randomized subjects was 7.5 months (mean: 6.6 months), with the maximum time on study being 9.5 months. The median number of BEs during the study was 11 per subject. Where both subject- and physician-reported assessments of efficacy were available (47/465; 10%), there was a 97.9% (46/47) concordance. Two subjects received concomitant ITI therapy during the study. One of these experienced two mild/moderate BEs (neither of which were successfully treated within 12 hours on the 75 μg/kg IDR), and he withdrew from the study after 19 days. The second ITI subject remained on the study for 200 days and experienced a single BE that was successfully treated with 1 infusion of 75 μg/kg rhFVIIa.

3.2 | Efficacy

The overall success proportion at 12 hours across both IDRs was 0.887 (88.7% response rate). A higher success proportion (93.2%) was observed in the 225 μg/kg IDR compared to the 75 μg/kg IDR (84.9%). These success proportions were statistically significant ($P<.001$, one-sided 0.0125 significance level) (Table 6). An inter-regimen comparison demonstrated superiority of the 225 μg/kg IDR in treating

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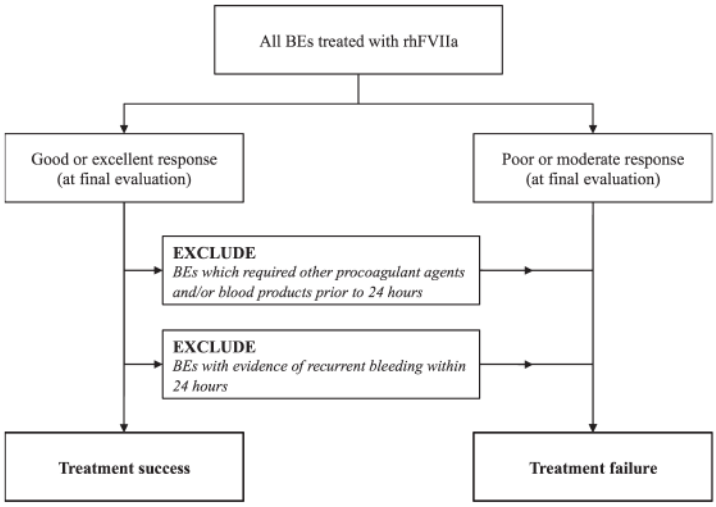

FIGURE 4 Definitions of haemostatic success and haemostatic failure at the 24-hour time point. Haemostatic efficacy for each initial dose regimen (IDR) was the success proportion of bleeding episodes (BEs) treated having a satisfactory therapeutic response, minus those requiring other procoagulant agents and/or blood products prior to 24 hours and those with recurrent bleeding within 24 hours (visual confirmation, recurrent pain, swelling or other symptoms suggestive of active bleeding)

mild/moderate BEs (P=.020, multiplicity-adjusted). The number of BEs requiring additional dosing at 12 hours (ie., treatment failures) was more than twice as high for BEs treated by the 75 μg/kg IDR (14.3%) compared to the 225 μg/kg IDR (6.6%). A sensitivity analysis utilizing an intention to treat correction for missing data (missing data treated as failures) was performed and both the IDR (P<.001) and the inter-IDR (P=.02) comparisons were also found significant. There were no home-care to clinic-care escalations in the mild/moderate BEs studied.

Bleeding episodes treated with the 225 μg/kg IDR demonstrated a higher incidence of successful treatment, occurring with fewer doses in a shorter period of time, compared to BEs treated with the 75 μg/kg IDR (Figure 5). In the 225 μg/kg IDR, 85% of BEs were successfully treated with just a single infusion. Overall, 90.1% of traumatic BEs were successfully treated by 12 hours as were 88.5% of spontaneous BEs. Protocol dosing was continued through 24 hours for unresolved bleeding; by that time, BEs (96.3%) across both IDRs were successfully resolved with rhFVIIa. At the 24-hour time point, 8/255 BEs on the 75 μg/kg IDR, and 1/213 BEs on the 225 μg/kg IDR required alternative therapy. One BE (225 μg/kg IDR) was counted as treatment failure after recurrent symptoms of bleeding prior to 24 hours. No subject received alternative therapy prior to 24 hours.

Three severe BEs occurred, one was traumatic (intramuscular haemorrhage), and the others were spontaneous (right hip joint and renal haemorrhage). All occurred while being treated with the 225 μg/kg IDR, thus they were treated with the 225 μg/kg severe bleeding protocol (Figure 3). All had a good or excellent response as evaluated by a physician at 12 hours.

3.3 | Pain relief

Overall, pain relief paralleled reported efficacy. Twelve hours after initial administration of rhFVIIa, pain decreased in 86.5% and 86.4% of subjects in the 75 μg/kg and 225 μg/kg IDRs respectively (Figure 6). Eight subjects (29.6%) used pain medications, two of whom used opioids.

3.4 | Safety

Twelve subjects (44.4%) reported a total of 14 treatment-emergent adverse events (TEAE) (Table 7). These were predominantly non-haemophilia related, mild and self-resolving. The most common TEAEs are listed in Table 8. Two subjects experienced treatment-related TEAEs: 1 (low grade fever) was considered possibly related to rhFVIIa administration, and 1 (injection site discomfort/haematoma) was considered related to rhFVIIa. Two SAEs (considered unrelated to study medication) were observed in a single subject with a prior history of intracranial haemorrhage (ICH). Five days following that subject's final treatment with rhFVIIa, he was hospitalized for severe tonsillitis and 3 days later developed an ICH, which was successfully treated. No SAEs were observed in any other subject and no deaths were reported.

3.5 | Immunogenicity

No neutralizing anti-rhFVIIa or specific antihost protein antibodies were observed following 27 first treatment exposures and 469 re-exposure events, including pretreatment exposures in 14 of the subjects. Neither allergic responses nor specific antibody development were observed during follow-up lasting up to 9.5 months.

4 | DISCUSSION

Variations in acute bleeding aetiologies, sites of bleeding, intermittent telephonic guidance and an accumulating disease burden, combine to make at-home treatment difficult in patients with inhibitors. We examined the hypothesis that a new recombinant FVIIa molecule with differing posttranslational modifications and binding affinities, would demonstrate dose-proportional and acceptable efficacy in a prospective, randomized, cross-over study of BE response to

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TABLE 4 Demographics of all subjects on the study (stratified by treatment initial dose regimen [IDR] at randomization). 22 (81.5%) of subjects were from Eastern European countries

Parameter	Treatment IDR at randomization		Overall (N=27)
	75 µg/kg (N=13)	225 µg/kg (N=14)	
Age, y			
Mean (SD)	31.8 (12.1)	30.1 (13)	31.0 (12.4)
Median	31.0	30.5	31.0
Minimum/maximum	13/51	12/54	12/54
Age categorized, n (%)			
<18 y	2 (15.4)	3 (21.4)	5 (18.5)
≥18 y	11 (84.6)	11 (78.6)	22 (81.5)
Race, n (%)			
Asian	1 (7.7)	0 (0)	1 (3.7)
Black or African American	0 (0)	1 (7.1)	1 (3.7)
White	12 (92.3)	13 (92.9)	25 (92.6)
Ethnicity, n (%)			
Hispanic or Latino	1 (7.7)	0 (0)	1 (3.7)
Not Hispanic or Latino	12 (92.3)	14 (100)	26 (96.3)
Weight, kg			
Mean (SD)	61.4 (16.4)	71.2 (23.2)	66.5 (20.4)
Median	62.0	68.3	68.0
Minimum/maximum	25.0/81.2	36.0/107.0	25.0/107.0
BMI, kg/m^2			
Mean (SD)	20.4 (3.6)	23.2 (5.6)	21.9 (4.9)
Median	21.4	22.6	22.0
Minimum/maximum	13.7/25.2	15.4/32.7	13.7/32.7
Haemophilia type & severity, n (%)[a]			
Severe Haemophilia A	12 (92.3)	11 (78.6)	23 (85.2)
Moderate Haemophilia A	1 (7.7)	1 (7.1)	2 (7.4)
Severe Haemophilia B	0 (0)	2 (14.3)	2 (7.4)
Moderate Haemophilia B	0 (0)	0 (0)	0 (0)
Inhibitor titre, n (%)			
BU≥5	6 (46.2)	8 (57.1)	14 (51.9)
BU <5 but refractory to increased factor dosing	1 (7.7)	1 (7.1)	2 (7.4)
BU <5 with high anamnestic response to factor dosing	6 (46.2)	5 (35.7)	11 (40.7)
Bleeding episodes in 6 mo prior to enrolment			
Mean (SD)	14.5 (12.6)	11.0 (7.1)	12.7 (10.1)
Median	9.0	11.0	10.0
Minimum/maximum	3/50	3/24	3/50
Subjects with target joints, n (%)[b]	9 (69.2)	8 (57.1)	17 (63.0)
Subjects receiving bypassing agents in 6 mo prior to enrolment			
rFVIIa, n (%)	6 (46.2)	10 (71.4)	16 (59.3)
aPCC, n (%)	4 (30.8)	2 (14.3)	6 (22.2)
rFVIIa and aPCC, n (%)	1 (7.7)	1 7.1)	2 (7.4)
PCC, n (%)	1 (7.7)	1 (7.1)	2 (7.4)
None, n (%)	1 (7.7)	0 (0)	1 (3.7)
Subjects receiving concomitant ITI therapy	2 (15.4)	0 (0)	2 (7.4)

[a]Severe haemophilia is defined as FVIII or FIX levels <1%; moderate haemophilia is defined as FVIII or FIX levels between 1% and 5%.
[b]A target joint is defined as a joint in which 3 or more spontaneous bleeds have occurred within a consecutive 6-month period.

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TABLE 5 Bleeding episode characteristics treated during the study

Type of bleeding episode (BE)	75 μg/kg IDR	225 μg/kg IDR	Overall
Mild/moderate BEs treated during the study, n	252	213	465
Number self-treated at home, n (%)[a]	247 (98.8)	213 (100)	460 (99.3)
Number treated within 1 h of symptom onset, n (%)[b]	209 (83.6)	183 (85.9)	392 (84.7)
Number treated ≥4 h after symptom onset, n (%)[b]	7 (2.8)	4 (1.9)	11 (2.4)
Severe BEs treated during the study, n	0	3	3
Target joint BEs, n (%)			
Knee	32 (41.6)	35 (60.3)	67 (49.6)
Elbow	37 (48.1)	17 (29.3)	54 (40.0)
Ankle/foot	8 (10.4)	2 (3.4)	10 (7.4)
Shoulder	0 (0)	4 (6.9)	4 (3.0)
Most common joint BEs, n (%)			
Knee	66 (26.2)	56 (25.9)	122 (26.1)
Elbow	63 (25.0)	49 (22.7)	112 (23.9)
Ankle/foot	36 (14.3)	21 (9.7)	57 (12.2)
Hip	18 (7.1)	26 (12.0)	44 (9.4)
Spontaneous BEs, n (%)	197 (78.2)	184 (85.2)	381 (81.4)

[a]Locations of study drug administration are not available for 2 BEs occurring in one subject that were treated in the 75 μg/kg initial dose regimen (IDR).
[b]Time intervals from bleed recognition to treatment are not available for 2 BEs occurring in one subject that were treated in the 75 μg/kg IDR.

different IDRs.[26,27] Results show that both the 75 μg/kg and 225 μg/kg IDRs provided a high likelihood of efficacy at 12 hours without requiring redosing once symptom relief was obtained. Furthermore, the study demonstrated that time to satisfactory relief is based on the initial dose of eptacog beta, as is the sustained efficacy observed after 12 hours (75 μg/kg IDR, 84.9%; 225 μg/kg IDR, 93.2%), a result presumably due to a dose-proportional initial thrombin burst at the bleeding site. Consequently, these data suggest that adoption of a 225 μg/kg eptacog beta initial dose regimen may provide an increased likelihood of single dose, early and sustained symptom relief for home-treated BEs.

An axiom of haemophilic therapy is that the time spent bleeding impacts short- and long-term outcomes. Convincing studies have demonstrated that delay of treatment initiation during an active bleeding episode impacts the achievement of haemostasis.[31,33] In addition, multiple lines of evidence suggest that total haeme (iron) accumulation within a haemophilic joint affects the temporal progression of haemophilic arthropathy and may be difficult to detect.[33–36] Efforts to reduce haeme accumulation in target joints through prophylaxis and/or early haemostasis are most effective in preventing arthropathic progression.[37,38]

Eptacog beta is not functionally equivalent to eptacog alfa; the in vitro, ex vivo, preclinical and human pharmacokinetic studies consistently have held rhFVIIa thrombin generation potential to be clinically important at doses *less* than those reported in the eptacog alfa literature.[29] Molecular characterizations theoretically may provide structural rationale for that difference; research into the effects of molecular differences on relative FVIIa potency is ongoing.[27] Functional distinctions have previously been sought for rFVIIa variants.[39]

The efficacy of eptacog beta was similar for spontaneous, traumatic and target joint bleeding episodes. However, the outcome of BEs treated with the two IDRs differ by a reduction in the required number of infusions while on the 225 μg/kg IDR as compared to BEs treated with the 75 μg/kg IDR. Approximately 85% of BEs were successfully treated by 9 hours with a single infusion when treated with the 225 μg/kg IDR with 93.2% ultimately achieving sustained haemostasis by 12 hours (Figure 5). These results differ from current practice and the prospective dosing studies of eptacog alfa; clinical use will determine whether these observations are borne out in actual practice. These data are novel: reliable treatment expectations with the goal of early haemostasis have been considered aspirational for eptacog alfa. These results appear to offer a standardized treatment protocol that covers a spectrum of mild and moderate BEs while providing predictable early and sustained effectiveness, reduced overt and covert bleeding times, simpler home management, and a low occurrence of rebleeding without frequently requiring non-protocol or alternate dosing in the first 24 hours. Empiric dosing adjustments are likely to be necessary for some patients whose bleeding episodes do not respond to the dosing studied here. Additional data from future clinical use could verify (via prospective observation) the typical number of infusions, total dose and the practical need, if any, for supplemental dosing.

The large number of BEs treated across both IDRs through the cross-over design enriched this pivotal study; however, studies such as this have been historically difficult to perform, and accordingly, there are several inherent limitations: (1) Although statistical power was achieved through BE analysis, the study examined a limited number of inhibitor subjects (N=27). (2) The power calculations were made using a threshold, literature based, true success criteria of 70%, which may be lower than what current practice would suggest. (3) Patient treatment bias was not eliminated in the design, since dosing intervals differed by IDR. It is possible that patients preferred one IDR over another, subset analyses did not exclude this effect. (4) The study has limitations inherent in time to haemostasis studies such as variations in the subject's perception of haemostatic effect. Patient definition of success drives care escalation, thus the validity of the success criteria must be presumed accurate enough for home therapy. (5) Inclusion of low titre inhibitor subjects and the two subjects on ITI added variability to both the time to haemostasis analysis and the number of BEs per subject. The large number of events studied and the cross-over design mitigate these effects to some degree.

There were no thrombotic or thromboembolic events in this study; however, patients with a significant history of thrombosis or other known thrombotic risk were not eligible for enrolment. Overall,

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TABLE 6 Analysis of bleeding episodes at 12 hours (stratified by initial dose regimen [IDR] at time of bleed)

	Treatment IDR at the time of mild/moderate bleeding episode		
	75 μg/kg (N=25)	225 μg/kg (N=25)	Overall (N=27)
Number of bleeding episodes, n	252	213	465
Number of successes, n (%)	202 (80.2)	191 (89.7)	393 (84.5)
Number of failures, n (%)	36 (14.3)	14 (6.6)	50 (10.8)
Number of missing assessments, n (%)	14 (5.6)	8 (3.8)	22 (4.7)
Success proportion[a]	0.849	0.932	0.887
95% CI[a]	0.740, 0.957	0.881, 0.983	0.807, 0.967
P-value[b]	<.001	<.001	<.001
P-value[c]	Inter-regimen comparison		.020

[a]Analysis was based on data as observed. No missing value imputation was made. CI, confidence interval.
[b]*P*-value from one-sided normal approximation test of *P*, where *P* is the true proportion of successfully treated mild/moderate bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given subject.
[c]*P*-value from two-sided normal approximation test considering adjustment for interim analysis, multiplicity, correlation between bleeding episodes receiving the same treatment for a given subject and the correlation between bleeding episodes receiving different treatments for a given subject, with an overall study-wise alpha of 0.05. No interim efficacy analyses were performed.

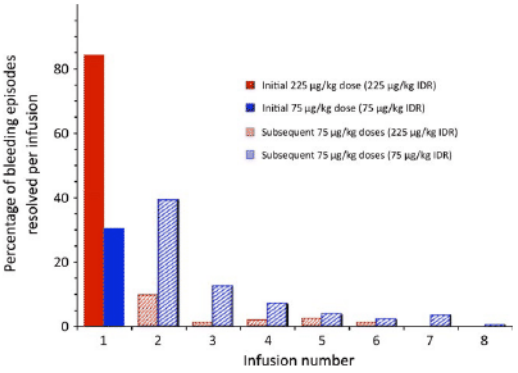

FIGURE 5 Percentage of bleeding episodes (BEs) resolved with each initial dose, and each subsequent indicated dose of rhFVIIa for both initial dose regimens (IDRs). Once a good or excellent response was recorded, no further infusions were permitted without treatment failure. Within the 24-hour treatment window, there were up to five possible follow-up doses in the 225 μg/kg IDR and up to seven possible follow-up doses in the 75 μg/kg IDR. Durability of response derives from the results at the 24-hour assessment. In an exploratory analysis of spontaneous 3-hour efficacy assessments, 64% of the BEs in the 225 μg/kg IDR were considered to have good or excellent response

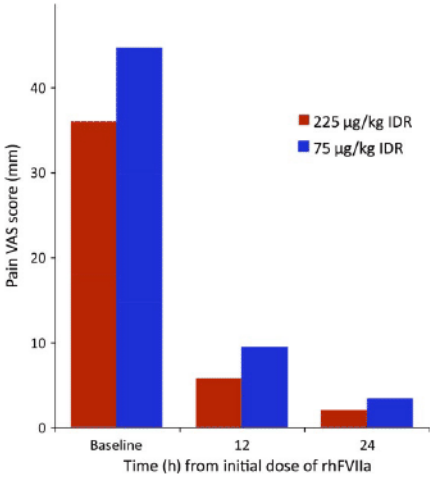

FIGURE 6 Reported pain VAS scores immediately prior to initial administration of rhFVIIa, and at 12 and 24 hours following initial administration of rhFVIIa. Similar to the overall efficacy results, sustained pain relief was observed at 12 and 24 hours following initial dose. In the 75 μg/kg initial dose regimen (IDR) there was a mean VAS pain score decrease of 35.2 mm at 12 h and 41.2 mm at 24 h. In the 225 μg/kg IDR, pain decreased by 30.2 mm at 12 hour and 34.0 mm at 24 hour. There was no a priori statistical hypothesis testing specified for the VAS pain assessments

the adverse events reported resemble those seen in the greater outpatient medical population. By itself this is reassuring, but not definitive evidence of eptacog beta tolerability. As noted by Neufeld, et al.,[15] the incidence of thrombotic adverse events in the eptacog alfa clinical study data (in the congenital haemophilia A or B with inhibitor population) is low (0.2% or less). Thus, among the 468 bleeding episodes treated in our adult and adolescent population, the lack of thrombotic complications was expected. Nevertheless, the existence of pro-thrombotic risk factors is considered predictive

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TABLE 7 Summary of serious adverse events and treatment-emergent adverse events (TEAE—adverse events occurring at any time after study drug exposure) occurring in more than one subject

	75 μg/kg IDR (N=25)[a]		225 μg/kg IDR (N=25)[a]		Overall (N=27)[a]	
Category of observation	#Subjects	#TEAEs	#Subjects	#TEAEs	#Subjects[b]	#TEAEs
All TEAEs	8	15	6	10	12	25
Treatment-related TEAE	1	6	1	1	2	7
SAE (Severe tonsillitis, ICH)[c]	1	2	0	0	1	2
TEAE leading to withdrawal	1	1	0	0	1	1
TEAE and death	0	0	0	0	0	0

[a]Four of the subjects who received study drug were only treated with one IDR.
[b]Some subjects experienced the same TEAE during treatment with both IDRs.
[c]ICH, intracranial haemorrhage.

TABLE 8 Treatment-Emergent Adverse Events (TEAE) occurring in more than one subject

Body system	TEAE	# TEAEs (N=468 treatments)	# Subjects (N=27 subjects)
Body as a whole	Fatigue	2	2
Infections	Nasopharyngitis	3	3
Musculoskeletal	Haemarthrosis	10	4
Nervous system disorders	Dizziness	3	2
	Headache	4	3

of thrombotic and thromboembolic events in patients with inhibitors receiving bypassing agents; it follows that in similar patients with thrombotic risk factors treated with eptacog beta, we would expect a similar incidence of such events.[16,40,41] In this study, on-demand, home treatment with activated eptacog beta of an apparently low thrombotic risk population was safe and well tolerated when treated with either IDR.

New and novel molecules are currently under investigation that may, one day, change how we approach preventing BEs in patients with haemophilia and inhibitors. However, despite such potential advancements, haemostatic bypassing agent therapies, which provide an early, rapid thrombin burst at the site of vascular disruption followed by rapid clearance, will remain a mainstay of therapy for acute bleeding in the inhibitor population.

5 | CONCLUSIONS

The PERSEPT 1 trial of rhFVIIa (activated eptacog beta) demonstrated sustained efficacy and establishes dose-dependent clinically important target times for achievement of haemostasis in mild and moderate bleeding episodes in haemophilia patients with inhibitors. Although not observed here, it is likely that the thromboembolic risk associated with rhFVIIa will be like that of other FVIIa-containing products. The observed dose response in this study supports clinical decisions that tailor rhFVIIa bypassing therapy to an early haemostasis goal that includes a potentially predictable response across of a range of mild and moderate bleeding episodes.

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DISCLOSURES

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1. **New and novel molecules are currently under investigation that may, one day, change how we approach...**
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as a consultant for HEMA Biologics; and serves on advisory boards for Biogen, CSL Behring, Griffols, Novo Nordisk, Octapharma and Shire. L.N.B. acts as a consultant, serves on advisory boards and receives research funding from Novo Nordisk, Shire, Bayer, Biogen and Pfizer; receives research funding from Opko; and acts as a consultant and serves on advisory boards for Griffols. G.Y. is an employee of LFB USA, Inc. I.S.M. is a contractual employee of HEMA Biologics, LLC. W.A.A. is an employee of HEMA Biologics, LLC. J.-F.S. receives research support from LFB, CSL Behring, NovoNordisk and Bayer-Schering.

AUTHOR CONTRIBUTION

Contribution: M.W. performed research, collected data and co-wrote the manuscript; J.B.L. oversaw the trial, performed research, collected, analysed and interpreted data and performed statistical analyses; D.V.Q. performed research, and collected, analysed and interpreted data; J.D. analysed and interpreted data; M.L.S analysed and interpreted data; L.N.B. analysed and interpreted data; I.S.M. analysed and interpreted data, and co-wrote the manuscript; G.Y. analysed and interpreted data and performed statistical analyses; W.A.A. analysed and interpreted data, and co-wrote the manuscript; and J.-F.S. performed research, and analysed and interpreted data. All authors reviewed and edited the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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