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ORIGINAL ARTICLE

Clinical haemophilia

Bleed treatment with eptacog beta (rFVIIa) results in a low incidence of rebleeding in adult and adolescent patients with haemophilia A or B with inhibitors

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Abstract

Introduction: Eptacog beta is a novel human recombinant FVIIa approved for use in the United States, European Union, United Kingdom and Mexico for the treatment and control of bleeding in patients with haemophilia A or B with inhibitors (≥12 years). It is also indicated for perioperative care in the same patient population in Europe and the United Kingdom.

Aim: To assess the incidence of rebleeding and review treatment outcomes in subjects with haemophilia with inhibitors enrolled in the phase 3 PERSEPT 1 clinical trial.

Methods: To treat mild/moderate bleeding episodes (BEs), subjects administered an initial 75 or 225μg/kg dose of eptacog beta, followed (if necessary) by additional 75μg/kg doses at predefined intervals until bleed control. This analysis used subject-reported rebleeding to determine a rebleeding incidence for the first 24 h. Rebleeding through later timepoints was an exploratory, intention-to-treat analysis of bleed treatment data.

Results: Four hundred and sixty-five BEs were analysed. Through 24 h, the proportion of rebleeds was 0% (initial 75μg/kg dose) and 0.5% (initial 225μg/kg dose). Through 48 h, the proportion of rebleeds was 3.2% (75μg/kg initial dose) and 5.6% (225μg/kg initial dose); the difference between initial dose strategies was not statistically significant. The majority of rebleeds were controlled with a single dose of eptacog beta and no subject who treated a rebleed required hospitalization.

Conclusion: Subjects with haemophilia with inhibitors who used eptacog beta to treat mild/moderate BEs experienced a low incidence of rebleeding. Rebleeds that did occur were effectively controlled with eptacog beta (median, one dose) without the need for hospitalization.

KEYWORDS

efficacy, eptacog beta, haemophilia, inhibitors, rebleeding incidence, recombinant FVIIa

1 | INTRODUCTION

Congenital haemophilia is a rare X-linked bleeding disorder that results in reduced factor VIII (FVIII) or factor IX (FIX) activity and a corresponding functional impairment of the intrinsic coagulation pathway. The clinical consequences of haemophilia can be severe: spontaneous, traumatic and surgical bleeding episodes (BEs) can be life-threatening and can require the administration of a FVIII or FIX concentrate; in such cases, most mild/moderate BEs can be reliably and effectively controlled with a single infusion of an extended half-life agent.[1–3]

The most severe complication of haemophilia treatment is the development of antibodies (inhibitors) to FVIII or FIX; the lifetime risk of inhibitor development is up to 35% of persons with haemophilia A and up to 10% of persons with haemophilia B.[4,5] Historically, their presence has resulted in a more severe bleeding phenotype, and increased morbidity and mortality.[6] In addition, persons with inhibitors can experience variable responses to haemostatic agents [recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC)]; may require multiple infusions to control a bleed; and can have an increased risk of hospitalization.[7,8] Further complicating treatment, the incidence of rebleeding in patients using rFVIIa is reported to be variable, and in some studies high (up to 18.9% through 24 h).[9] In addition, certain types of severe bleeding (e.g. intracranial haemorrhage) require aggressive and lengthy treatment to achieve haemostasis and prevent rebleeding.[10]

Eptacog beta (SEVENFACT®, HEMA Biologics/LFB and CEVENFACTA®, LFB) is a human rFVIIa that is indicated for the treatment and control of bleeding in persons with haemophilia A or B with inhibitors (≥12 years of age) in the US, European Union (EU), United Kingdom (UK) and Mexico.[11–13] In the EU and the UK, it is additionally indicated to prevent bleeding in persons (≥12 years of age) undergoing surgery.[14]

In the pivotal phase 3 trial (PERSEPT 1),[15] bleed control (for US regulatory approval) was defined as a subject-reported haemostasis evaluation of excellent or good (on a predefined 4-point scale; Table S1), after which no additional eptacog beta, alternative haemostatic agents or blood products were administered, and no increase in pain occurred through 24 h following the last eptacog beta dose.[16,17] This trial demonstrated the efficacy and safety of two initial dose regimens (IDRs; Figure 1) of eptacog beta for bleed control in adults and adolescents,[15] with rapid 3-h bleed control observed in many mild/moderate BEs, and virtually all BEs (75μg/kg IDR: 96.7%; and 225μg/kg IDR: 99.5%) controlled at 24 h (Figure S1).[16]

The PERSEPT 1 data also showed a low patient-reported incidence of rebleeding of 0.2% through 24 h.[18] Here, we expand on the clinical trial definition of rebleeding with post-hoc exploratory analyses using timepoints consistent with those reported in the literature for other rFVIIa concentrates. In addition, we report on the treatment of those rebleeds, the potential benefits for the patient and healthcare system, and suggest possible mechanistic reasons for the observations.

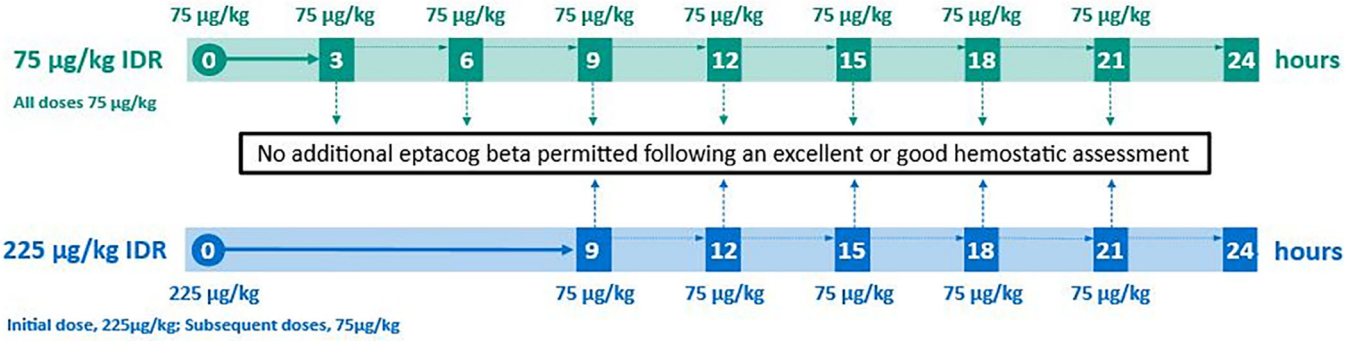

FIGURE 1 The 75 and 225µg/kg initial dose regimens (IDRs) as used in PERSEPT 1. Following the initial dose (75 or 225µg/kg, depending on the IDR the subject was using), subsequent doses (75µg/kg) were only administered if subject decided the bleed had not achieved haemostatic control (excellent or good haemostatic response), on a 4-point scale of excellent, good, moderate or none.

2 | METHODS

2.1 | Trial design

PERSEPT 1 (NCT02020369) was a phase 3 trial that evaluated the efficacy and safety of eptacog beta for the treatment and control of bleeding in subjects (≥12 years) with haemophilia A or B with inhibitors.[15] Subjects were randomized to use one IDR for the treatment of BEs (Figure 1) and then crossed over to use the alternate IDR every 3 months; subjects did not self-select an IDR based on the BE they were experiencing.[15] BE severity was determined by the subject using predefined criteria (Table S2).[15] No subject used any prophylactic agent [either bypassing agent or emicizumab (the trial was initiated prior to the regulatory approval of emicizumab)].

2.2 | Rebleeding, 0–24 h

The protocol definition of a bleed recurrence was one that occurred within 24 h following the first excellent or good efficacy evaluation and in the same anatomical location. As subjects only recorded efficacy data during the first 24 h following the initial infusion, in this analysis, a conservative approach was taken in that any rebleeding that was self-reported was assumed to have occurred within 24 h of the initial infusion. This approach aligns with definitions of rebleeding in the literature that are based on time from initial infusion.[8,9,19–22]

2.3 | Rebleeding, 24–48 h

Subjects did not report efficacy observations beyond 24 h, therefore rebleeding during the 24–48 h period was an exploratory, intention-to-treat analysis of all BE data on a subject-by-subject basis. If two subsequent BEs occurred in the same anatomical location, and the initial eptacog beta doses for each BE were administered within 24–48 h of each other, then the latter BE was considered a rebleed.

2.4 | Rebleeding, 0–48 h

Rebleeding during the 0–48 h was the combination of those experienced during the 0–24 and 24–48 h periods. If a subject experienced a rebleed during both the 0–24 and 24–48 h periods, two separate rebleeds were counted.

2.5 | Statistical methods

Incidence of rebleeding and proportion of rebleeds successfully treated with a single dose of eptacog beta, and their corresponding standard errors were estimated based on rebleed counts that take into account the correlation among BEs for a given patient. The resulting point estimator has a normal distribution based on large sample approximation. Comparison between the 75 and 225µg/kg IDRs was based on a two-sided large sample normal test that adjusts existing correlation among BEs for a given patient.

3 | RESULTS

Twenty-seven subjects with haemophilia with inhibitors (aged 12–54 years) treated 465 mild/moderate BEs and three severe BEs.[15] This rebleeding analysis is limited to mild/moderate BEs, as no rebleeds were associated with the severe BEs. When reported, all rebleeds were classified as mild/moderate by the subject, and the rebleed was treated using the same IDR as the precursor bleed. No rebleed was reported to require hospital care or rescue therapy.

3.1 | Rebleeding, 0–24 h

A single subject (Subject 11) recorded one rebleed (spontaneous, forearm soft tissue) in PERSEPT 1 during the 0–24 h period. This was the only subject-reported rebleed (1/465 BEs; 0.2% incidence; Figure 2).

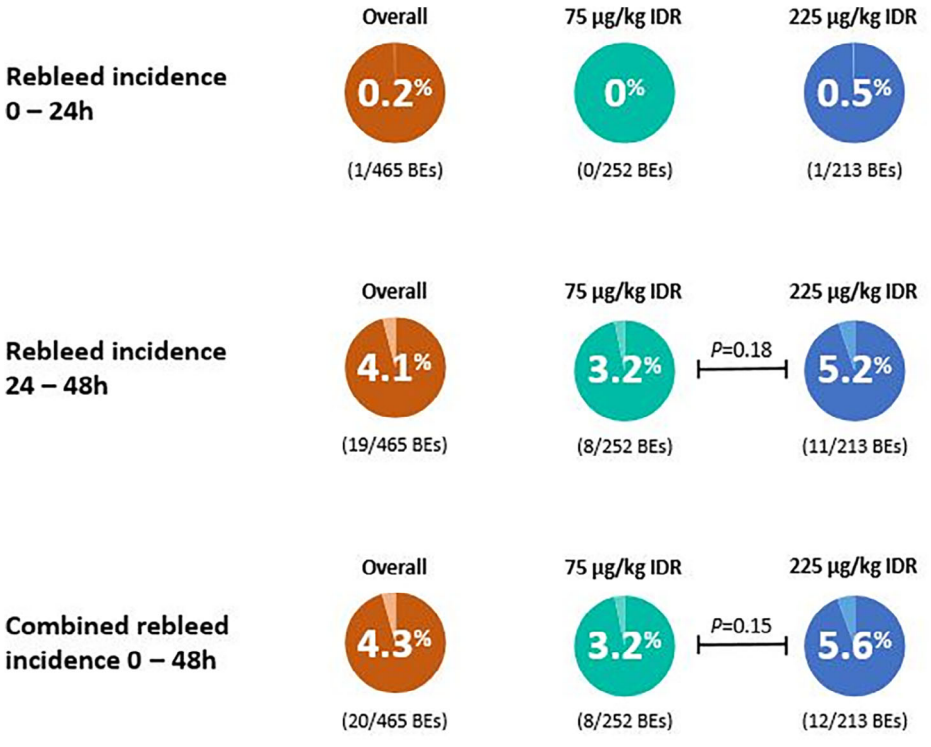

FIGURE 2 Rebleed proportions for the 0–24 , 24–48 and 0–48 h periods following the start of eptacog beta treatment for the precursor BE. Data show the proportion of rebleeds for each IDR and both IDRs combined. BE, bleeding episode; h, hour; IDR, initial dose regimen.

Subject 11 treated the precursor BE with the 225µg/kg IDR, using a single 225µg/kg eptacog beta dose.

3.2 | Rebleeding, 24–48 h

Eleven subjects (42%) experienced 19 rebleeds during the 24–48 h period (median, 1; range 1–4) (Table 1). The proportion of rebleeds was 3.2% (8/252 BEs; 75µg/kg IDR) and 5.2% (11/213 BEs; 225µg/kg IDR) (Figure 2). Subject 11 (who recorded a rebleed during the 0–24 h period) also experienced a second rebleed at 28 h that was associated with the same original BE (rebleed 19).

3.3 | Rebleeding, 0–48 h

Eleven subjects (42%) experienced a total of 20 rebleeds during the 0–48 h period following initial eptacog beta infusion (median: 1; range: 1–4 rebleeds). The proportion of rebleeds was 3.2% (75µg/kg IDR) and 5.6% (225µg/kg IDR) (Figure 2). Through 48 h, 3.0% (4/135) of target joint BEs and 4.2% (11/261) of non-target joint BEs were associated with a rebleed when treated with eptacog beta.

3.4 | Treatment of rebleeds

Eleven rebleeds (24–48 h period) were treated with the 225µg/kg IDR, and eight with the 75µg/kg IDR (Table 1). Ten of the 11 rebleeds (91%) treated with the 225µg/kg IDR achieved bleed control with a single 225µg/kg eptacog beta infusion with no further haemostatic treatment required (Figure 3). The remaining rebleed (traumatic injury; rebleed 18; Table 1) required one additional 75µg/kg dose 9 h later to control the bleed. Fifty percent of rebleeds treated with the 75µg/kg IDR were successfully controlled with a single eptacog beta dose; 25% required two 75µg/kg doses, and 25% required three 75µg/kg doses.

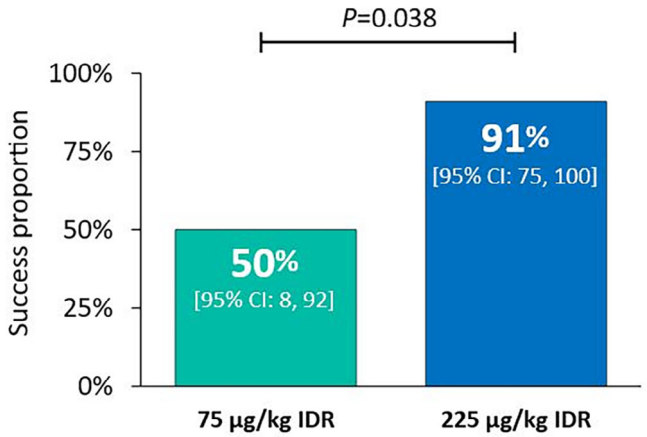

FIGURE 3 Proportion of rebleeds successfully controlled with a single 75µg/kg or a single 225µg/kg dose of eptacog beta. This analysis excludes the single rebleed that was reported during the first 24 h for which treatment was not reported. CI, confidence interval; IDR, initial dose regimen.

TABLE 1 Detail of the subjects who experienced a rebleed during the 24–48 h period (based on this exploratory analysis) following the initial dose of eptacog beta administered for treatment of the precursor BE, and the types of precursor BEs/rebleeds experienced.

Subject ID	Number of rebleeds/BEs on study	Rebleed ID	Location of BE and rebleed	Type of precursor BE	Type of rebleed	Treatment IDR
1	1/25	1	Hip	Spontaneous	Spontaneous	225μg/kg
2	4/39	2	Hip	Spontaneous	Spontaneous	225μg/kg
		3	Hip	Spontaneous	Spontaneous	225μg/kg
		4	Shoulder	Spontaneous	Spontaneous	75μg/kg
		5	Shoulder	Spontaneous	Spontaneous	75μg/kg
3	2/80	6	Knee[a]	Spontaneous	Spontaneous	75μg/kg
		7	Knee[a]	Spontaneous	Spontaneous	75μg/kg
4[b]	1/8	8	Elbow	Spontaneous	Spontaneous	225μg/kg
5	1/18	9	Knee[a]	Spontaneous	Spontaneous	225μg/kg
6	2/27	10	Nostril	Spontaneous	Spontaneous	75μg/kg
		11	Nose	Spontaneous	Spontaneous	225μg/kg
7[c]	2/4	12	Elbow	Spontaneous	Spontaneous	225μg/kg
		13	Knee	Spontaneous	Spontaneous	225μg/kg
8	1/32	14	Elbow[a]	Traumatic	Spontaneous	75μg/kg
9	1/12	15	Haematuria	Spontaneous	Spontaneous	75μg/kg
10	1/12	16	Knee	Spontaneous	Spontaneous	225μg/kg
11	3/39	17	Hip	Spontaneous	Spontaneous	75μg/kg
		18	Elbow	Spontaneous	Traumatic	225μg/kg
		19	Forearm (soft tissue)	Spontaneous	Spontaneous	225μg/kg

Abbreviations: BE, bleeding episode; IDR, initial dose regimen.

[a]Target joint.

[b]Subject 4 was one of two subjects with haemophilia B (the other subject with haemophilia B did not experience any rebleeds).

[c]Subject 7 was non-treatment adherent and failed to follow the prescribed IDRs and efficacy reporting requirements; he was subsequently withdrawn from the trial by the Sponsor.

Subject 11 recorded a rebleed during the 0–24 h reporting period; the treatment administered (if any) for that rebleed was not recorded by the subject. This subject also experienced a second rebleed that was attributed to the same precursor BE during the 24–48 h period; this required a single 225μg/kg dose for control.

4 | DISCUSSION

The long-held goal for persons with haemophilia is to achieve health equity with those lacking a bleeding disorder. By definition, this would include the absence of BEs that require treatment with haemostatic agents and a lack of restrictions on physical activities; however, even novel prophylactic agents are currently unable to offer this ideal.[23] As such, individuals may still need to carry factor products with them, as any bleeding would still need to be treated in an expeditious manner. When bleeding occurs, the optimal choice of haemostatic agent is one with the potential to reduce the individual's infusion burden by achieving rapid and reliable haemostasis with a single dose and have a low risk of rebleeding (i.e. sustained haemostasis).

Guidelines for evaluating bleed recurrence in individuals with haemophilia without inhibitors have been published[24,25]; however, no similar guidelines are available for those with inhibitors. As such, published prospective and retrospective data on the incidence of rebleeding with eptacog alfa (NOVOSEVEN® RT, Novo Nordisk) variously refer to individuals being monitored for 24 h and/or 48 h. For example, through 24 h, Kenet et al. reported that eptacog alfa (300μg/kg) resulted in a rebleed rate of 9.6% (11/114 BEs)[20]; Key et al. noted that haemostasis was not maintained within 24 h of the final eptacog alfa dose in 4.9% (28/566) of BEs (eptacog alfa, 90μg/kg)[22]; and Astermark et al. reported a 24 h rebleed rate of 4.2% (2/48 BEs) in the FENOC study (90–120μg/kg eptacog alfa), although only a small number of BEs were treated.[19] In a similarly small study, a 24 h rebleed rate of 1.5% (1/32 hemarthroses treated with 90μg/kg, and 0/36 treated with 270μg/kg eptacog alfa) was reported by Santagostino et al.[26] Lentz et al. did not specifically report on rebleeding in the adept™ 2 trial (90μg/kg eptacog alfa); however, the authors did note that 31/225 BEs required additional hemostatic agent within 24 h, suggesting a rebleed rate of up to 13.8% (the absence of subject/bleed-level data limits the ability to calculate a specific rebleed rate).[21] The observational WIRK study also recorded a higher rebleed rate of

≥18.9% through 24 h, although the dose of eptacog alfa (53–344μg/kg) was not prespecified.[9]

Rebleeding data for eptacog alfa through 48 h are limited: Salaj et al. reported an 8.6% (11/128 BEs) rebleed rate through 48 h in the HemoRec registry,[8] while Santagostino et al. showed a 48 h rebleed rate of 2.9% (1/32 BEs treated with 90μg/kg and 1/36 BEs treated with 270μg/kg eptacog alfa).[26] Astermark et al. recorded 3/48 rebleeds (6.3%) through 48 h in the FENOC study.[19] Although not specifically reported by Lentz et al., the authors noted that 51/214 BEs (90μg/kg eptacog alfa) failed to maintain sustained bleed control through 48 h, suggesting a rebleed rate of up to 23.8%.[21] These data suggest that rebleeding with eptacog alfa can be a common occurrence during the first 24 and 48 h following treatment initiation, an observation that may be part of the reasoning behind long-established guidance to continue dosing of eptacog alfa even once it is believed that haemostasis has been achieved.[22,27]

In PERSEPT 1, the proportion of BEs treated with eptacog beta that were associated with a rebleed was 0.2% (0–24 h) and 4.3% (0–48 h). There was no statistically significant difference in rebleed proportion between IDRs through 48 h, suggesting physicians can select the most appropriate IDR for their patient without concern for an increased risk of rebleeding. Salaj et al. previously reported that there was no statistically significant relationship between the incidence of rebleeding and eptacog alfa dose, an observation mirrored with these data for eptacog beta.[8] Additionally, Salaj et al. and Key et al. reported no clear association between the type of original BE and the incidence of rebleeding with eptacog alfa[8,22]; the large PERSEPT 1 dataset suggests a similar finding for eptacog beta.

A definitive comparison between eptacog alfa and eptacog beta cannot be made using previously published studies due to differences in enrolment, study design, number of BEs, determinants of efficacy and a lack of head-to-head clinical trial data. Despite this, the low rebleed rate for eptacog beta of 0.2% across a wide range of subjects, spontaneous/traumatic BEs and anatomical locations through 24 h could be compared to that reported for eptacog alfa (4.2% to ≥18.9%). Similarly, a rebleed rate of 4.3% through 48 h might be compared to that for eptacog alfa of 3% to ≤23.8%.

It might be tempting to suggest this low incidence of rebleeding is a property of the patient population enrolled in PERSEPT 1, rather than eptacog beta itself; however, a separate eptacog beta paediatric trial (PERSEPT 2)[28] that enrolled 25 subjects and recorded data on 549 BEs also reported a low proportion of rebleeding (0–24h: 1.6%; and 0–48h: 2.4%).[29] This additional observation lends support to the hypothesis that the low incidence of rebleeding is an inherent property of eptacog beta and its indicated dosing regimens rather than the specific patient population. As such, this low incidence of rebleeding might also apply to the broader real-world population of persons with inhibitors, although additional data would need to be collected for confirmation.

No authoritative data are reported in the literature regarding the treatment of rebleeds. In PERSEPT 1, no rebleeds required rescue therapy or hospital care: all were successfully controlled with one to three doses (median, one dose) of eptacog beta. Ninety-one percent of rebleeds treated with the 225μg/kg IDR achieved bleed control with a single dose, as did 50% of rebleeds treated with the 75μg/kg IDR. This difference in efficacy between the two IDRs was statistically significant, suggesting a clinical benefit for the use of the 225μg/kg IDR for the treatment of rebleeds. This high proportion of rebleeds controlled with a single 225μg/kg eptacog beta dose (91%) aligns closely with that previously reported for mild/moderate BEs of 84% (225μg/kg IDR)[16] suggesting that rebleeds may be no more difficult to control than the precursor BE, if the 225μg/kg eptacog beta IDR is used.[11]

In PERSEPT 1, there was a single rebleed reported during the 0–24 h period; this subject (Subject 11) did not report treatment for that rebleed. Emphasizing the importance of always treating BEs and (in this case) rebleeds, this subject subsequently experienced a second rebleed in the same location at the 28 h timepoint, possibly indicating he had not treated the initial rebleed. This second rebleed was effectively controlled with a single 225μg/kg dose of eptacog beta with no further bleeding being reported at that anatomical location.

Although not studied head-to-head, if clinical differences do exist between the two rFVIIa concentrates, they may not be easy to explain as plasma half-lives are reported to be similar and both have the same human amino acid sequence.[11,12,30,31] Despite this, there are known differences in production technique, glycosylation profile, endothelial cell interactions and binding to the endothelial protein C receptor (EPCR).[30,32,33] EPCR is known to transport rFVIIa to the extravascular space in animal models; once there, it has been suggested that rFVIIa can complex with tissue factor, generate low levels of thrombin and potentially stop bleeds in the microvasculature.[34] Additionally, these models suggest that rFVIIa stored in the extravascular space is not subject to the same short half-life observed in plasma (these observations have been used to explain the prophylactic efficacy of rFVIIa.)[34] Furthermore, mouse models show a non-statistically significant increase in functional activity of eptacog beta in the joint compared to eptacog alfa (although, unfortunately, no similar data exist in human joints).[34] Based on these observations, we might speculate that differences in extravascular transfer and storage between eptacog alfa and eptacog beta might result in differences in their ability to stop emergent bleeding in the microvasculature (and hence rebleeding), although such an explanation remains unproven at this time.

From a cost perspective, pharmacoeconomic analyses of eptacog alfa typically model a rebleed rate of 15%, although as definitions of a rebleed vary between analyses that number is not directly comparable to those referenced here.[35] Reports also indicate that rFVIIa can be more cost-effective than aPCC primarily due to a lower incidence of rebleeding.[36] If the results observed in PERSEPT 1 are confirmed in real-world situations, the low incidence of rebleeding associated with eptacog beta might result in reduced rFVIIa usage and lower costs to the healthcare system. Additionally, as 91% of rebleeds were controlled with a single 225μg/kg dose and none required hospitalization, the use of eptacog beta might also reduce costs associated with inpatient care—and possibly permit hospital pharmacies to reduce the quantity of rFVIIa stocked for bleed treatment.

There are several limitations inherent to these analyses. Firstly, these conclusions reflect the post-hoc analysis of data from a single clinical trial that enrolled 27 subjects; as such, it might reflect

the bleeding phenotype of those participants rather than the haemostatic potential of eptacog beta across the broader population with inhibitors; however, the large number of BEs reported, and the low rebleed rate reported in a second clinical trial with a different population might imply a wider applicability of these observations. Secondly, although a 48-h period was used to review the incidence of rebleeding, if a bleed occurred in another anatomical location during that period, that treatment may have prevented a potential rebleed, masking the true rebleed rate of eptacog beta. Thirdly, although we examined rebleeding through 24 and 48 h for consistency with data published on eptacog alfa, there are several definitions of rebleeding in the literature and individual clinicians may define rebleeding differently. Finally, PERSEPT 1 did not enrol subjects on emicizumab prophylaxis, and so guidance on rebleeding in that population cannot be provided.[37]

5 | CONCLUSION

Eptacog beta is a rFVIIa concentrate that has been demonstrated to be safe and effective for the treatment of bleeding in persons (≥12 years) with haemophilia with inhibitors. Clinical trial data demonstrate that eptacog beta can rapidly control a high proportion of BEs,[15] and subjects experience a low rate of rebleeding through 24 h (0.2%) and 48 h (4.3%). When rebleeds did occur, treatment with eptacog beta was able to achieve predictable bleed control with a minimal number of doses (91% of rebleeds treated with the 225μg/kg IDR were controlled with a single dose.) These observations, if repeated in real-world situations, may help close the bleed treatment health equity gap between persons with and without inhibitors, improve convenience by reducing the infusion burden, reduce rFVIIa usage (and potentially cost) associated with rebleeds in the healthcare system, and offer persons with inhibitors an alternative treatment option.

As more subcutaneously administered prophylactic agents become available, it might be anticipated that patients will never learn (or alternatively, forget) intravenous infusion techniques and instead require treatment at a clinic or hospital. Therefore, the high efficacy of eptacog beta and the low rebleed rate might offer an advantageous treatment option for those patients and their healthcare providers by reducing the duration of any inpatient or outpatient medical care.

AUTHOR CONTRIBUTIONS

All of the authors analysed and interpreted the data, and all authors provided critical input and edited the manuscript. All authors reviewed and approved the final submission.

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CONFLICT OF INTEREST STATEMENT

Amy Dunn has received consulting fees from Genentech, Kedrion, CSL Behring, BioMarin, uniQure, Sanofi, Novo Nordisk and HEMA Biologics; has received research funding from Takeda, BioMarin, Freeline, Novo Nordisk, Sanofi, Pfizer, Genentech and ATHN; is on the board of the World Federation of Hemophilia USA; is Chair of MASAC of the National Bleeding Disorders Foundation; and is on the Board of Cascade. Yesim Dargaud has received research funding from CSL Behring, Novo Nordisk and LFB; has served as a member on the Board of Directors or advisory committees for CSL Behring, Sobi, LFB, BioMarin and Pfizer; and has served as a member of an expert board for CSL Behring, Sobi, LFB, BioMarin, and Pfizer. Yasmina Abajas has acted as a paid consultant to Sanofi. Manuel Carcao has received research funding from Bioverativ/Sanofi, Novartis, Novo Nordisk, Pfizer, Roche and Shire/Takeda; and has received honoraria from Bayer, Bioverativ/Sanofi, LFB, Novo Nordisk, Pfizer, Roche and Shire/Takeda. Giancarlo Castaman has received honoraria as a speaker/participant on advisory boards for Bayer, Takeda, CSL Behring, Novo Nordisk, Sobi, Roche, Pfizer, LFB, BIOVIIIx and BioMarin. Adam Giermasz has served as a consultant or advisory board member for Sanofi, HEMA Biologics, Vega Therapeutics, Alexion and Genzyme; has been a member of DSMC committee for Adrenas, and has acted as a speaker for Sanofi, Alexion and Genzyme. Cédric Hermans has received research funding from Bayer, BioMarin, CSL Behring, Novo Nordisk, Pfizer, Shire/Takeda and Sobi; and has received honoraria and speakers' bureau fees from LFB, Bayer, CAF-DCF, CSL Behring, Hoffmann-La Roche, LFB, Novo Nordisk, Octapharma, Pfizer, Shire/Takeda, Sobi and uniQure. Victor Jiménez-Yuste has received consulting fees from Grifols, Novo Nordisk, F. Hoffmann-La Roche Ltd, Takeda, Bayer, CSL Behring, Pfizer, BioMarin, Sanofi and Sobi; has received honoraria from Grifols, Novo Nordisk, F. Hoffmann-La Roche Ltd, Takeda, Bayer, CSL Behring, Pfizer, Sanofi and Sobi; and has received research funding from Grifols, Novo Nordisk, F. Hoffmann-La Roche Ltd, Takeda, Bayer, CSL Behring, Pfizer, Sanofi and Sobi. Magdalena Lewandowska has no competing interests to declare. Johnny Mahlangu has received research grants from BioMarin, Catalyst Biosciences, CSL, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Spark and uniQure; has served as a consultant or member of the scientific board for BioMarin, CSL Behring, Catalyst Biosciences, Novo Nordisk, Roche, Sanofi, Spark and Takeda; and has received speaker bureau fees from ISTH, Novo Nordisk, Pfizer, Roche, Sanofi, Takeda and WFH. Shannon Meeks has received payment as a member of medical and scientific advisory boards for BioMarin, CSL Behring, Genentech and Sanofi; has acted as a paid consultant for Spark, Pfizer and Teraimmune; and has received research funding from Genentech and Octapharma. Wolfgang Miesbach has acted a consultant for Bayer, BioMarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, Sigilon, Sobi, Takeda/Shire, uniQure. Michael Recht's employers have received research funding from Bayer, BioMarin, CSL Behring, Genentech, Grifols, HEMA Biologics, LFB, NovoNordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda and uniQure; has served as a paid advisor to CSL Behring, Genentech, HEMA Biologics, Kedrion, NovoNordisk, Pfizer, Sanofi, Takeda and uniQure; and is on the Board of Directors of Partners in

Bleeding Disorders. Vanessa Salinas has received consulting fees from Bayer, Genentech, and Sanofi; and has served on a speakers' bureau for Bayer, Sanofi and Genentech. Tammuella Chrisentery-Singleton has received consulting fees from Sanofi, GBT, Octapharma, Genentech, BioMarin, HEMA Biologics, Novo Nordisk, Takeda, BPL, CSL Behring, Pfizer, Bayer, Grifols and Kedrion; has received honoraria from Sanofi, GBT, Octapharma, Genentech, BioMarin, HEMA Biologics, Novo Nordisk, Takeda, BPL, CSL Behring, Pfizer, Bayer, Grifols and Kedrion; has participated in a speakers bureau for Sanofi, GBT, Octapharma, Genentech, BioMarin, HEMA Biologics, Novo Nordisk, Takeda, BPL, CSL Behring and Pfizer; and has received research funding from Pfizer. Daniel Bonzo is an employee of LFB-USA, Inc. Ian S. Mitchell is an employee of HEMA Biologics and US WorldMeds; he was formerly a consultant with HEMA Biologics. Thomas A. Wilkinson is an analyst/medical writer for GLOVAL LLC that has received consulting fees from HEMA Biologics and LFB. Guy Young has received consulting fees from BioMarin, Centessa, CSL Behring, Genentech/Roche, HEMA Biologics/LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Genzyme, Spark and Takeda; and has received funds for research support from Genentech/Roche, Sanofi and Takeda.

DATA AVAILABILITY STATEMENT

Data available from the authors upon request.

ETHICS STATEMENT

The trial was approved by institutional boards and was conducted in compliance with the Declaration of Helsinki.[38] Written informed consent/assent was obtained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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