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REVIEW ARTICLE

Eptacog beta for the management of patients with haemophilia A and B with inhibitors: A European perspective

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Abstract

Eptacog beta (activated), a recombinant human factor VIIa (rFVIIa), was approved by the US Food and Drug Administration (FDA) in 2020 (SEVENFACT®, LFB & HEMA Biologics) and the European Medicines Agency (EMA) in 2022 (CEVENFACTA®, LFB). In Europe, eptacog beta is indicated for the treatment of bleeds and the prevention of bleeds during surgery or invasive procedures in adults and adolescents (≥12 years old) with congenital haemophilia A or B with high-titre inhibitors (≥5 BU) or with low-titre inhibitors who are expected to have a high anamnestic response to factor VIII or factor IX, or to be refractory to increased dosing of these factors. The efficacy and safety of eptacog beta were evaluated in three Phase III clinical studies, PERSEPT 1, 2 and 3. For the EMA filing dossier, the analysis of data from PERSEPT 1 and 2 differed from the analysis used to support the filing in the US. In this review, we summarise current data regarding the mode of action, clinical efficacy and safety of eptacog beta for the management of haemophilia A and B in patients with inhibitors from a European perspective. In addition to providing a valuable summary of the analyses of the clinical data for eptacog beta conducted for the EMA, our review summarises the potential differentiators for eptacog beta compared with other current bypassing agents.

KEYWORDS
eptacog alfa, eptacog beta, haemophilia A, haemophilia B, recombinant FVIIa

1 | INTRODUCTION

Congenital haemophilia A and B are X-linked coagulation disorders caused by a deficiency in factor VIII (FVIII) or factor IX (FIX), respectively.[1] The missing coagulation factor is usually administered to individuals with haemophilia A or B to prevent and treat bleeds.[2] However, individuals can develop neutralising alloantibodies (inhibitors) to replacement factors. The lifetime risk of developing inhibitors is as high as 40% in individuals with severe haemophilia A and up to 10% in those with severe haemophilia B.[3,4] The presence of inhibitors is associated with bleeds that are more difficult to manage, decreased quality of life and increased morbidity and mortality.[5–8]

In patients with low-titre inhibitors (LTI; < 5 Bethesda units [BU]), higher doses of replacement factors have traditionally been used,[2] but replacement factors are physiologically ineffective in individuals with high-titre inhibitors (HTI; ≥5 BU).[1] The only way to eradicate persistent inhibitors and induce tolerance to replacement factors is using immune tolerance induction (ITI).[9] However, the outcome of ITI is

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variable and patients with haemophilia B often have to discontinue due to severe allergic reactions to FIX or the development of nephrotic syndrome.[9] Furthermore, inhibitors can return even after successful ITI.[9] Bypassing agents, such as recombinant Factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC, FEIBA®, Takeda), have been the standard of care for the treatment and prevention of bleeds in individuals with haemophilia and inhibitors.[10] aPCC, a plasma-derived bypassing agent, comprises multiple zymogens/proenzymes and small quantities of activated coagulation factors, including prothrombin and activated factor X (FXa); while rFVIIa activates the extrinsic clotting pathway, bypassing the need for FVIII or FIX.[10] Eptacog alfa (Novoseven® RT, Novo Nordisk), the first rFVIIa, is quicker to administer than aPCC.[10] Eptacog alfa is expressed in baby hamster kidney cells and secreted into a cultured media containing foetal bovine serum.[11] However, mammalian cell cultures are associated with a poor yield, issues regarding production scale up and expense.[11] In addition, eptacog alfa demonstrates high intra- and inter-patient variability in response.[12]

Treatment options for individuals with haemophilia and inhibitors had been relatively static for 20 years,[10] until emicizumab was approved in the United States (US) in 2017[13] (Hemlibra®, Genentech, Inc) and in Europe in 2018 (Hemlibra®, F. Hoffmann-La Roche). In Europe, emicizumab is indicated for routine prophylaxis in individuals with congenital haemophilia A with FVIII inhibitors, mild and moderate haemophilia A with severe phenotype and in individuals with severe congenital haemophilia A (FVIII < 1%) without inhibitors.[14] Emicizumab, a bispecific antibody that functions as an activated FVIII mimetic,[15] improves haemostasis but does not normalise it.[16] Thus, patients with inhibitors using emicizumab will still require bypassing agents to treat breakthrough bleeds and to provide haemostatic coverage during surgical procedures.[17] Indeed, 72% of participants in the Phase III HAVEN 1 study who received emicizumab had breakthrough bleeding.[17] As thrombotic microangiopathy and thrombosis have been reported in individuals with haemophilia A and inhibitors receiving emicizumab who received aPCC for the treatment of breakthrough bleeding, but not in those who received eptacog alfa,[17] rFVIIa is preferred in these patients.[18] However, it should be noted that thrombotic complications have recently been reported in patients receiving concomitant treatment with emicizumab and eptacog alfa.[19]

Eptacog beta (activated), a human rFVIIa, was approved by the US Food and Drug Administration (FDA) in April 2020 (SEVENFACT®, LFB & HEMA Biologics[20]), by the Mexican Sanitary Agency (COFEPRIS) in June 2022 (SEVENFACT®, LFB[21]), by the European Medicines Agency (EMA) in July 2022 (CEVENFACTA®, LFB[22]) as well as by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in August 2022 (CEVENFACTA®, LFB[22]). In the European Union and in Great Britain, eptacog beta is indicated for the treatment of bleeds and for the prevention of bleeding in individuals undergoing surgery or invasive procedures, in adults and adolescents (≥12 years of age) with congenital haemophilia A or B with HTI (≥5 BU) or LTI (<5 BU) who are expected to have a high anamnestic response to FVIII or FIX, or to be refractory to increased dosing of FVIII or FIX.[22] The efficacy and safety of eptacog beta were evaluated in three Phase III studies: PERSEPT 1, PERSEPT 2 and PERSEPT 3. The EMA filing required analyses of the data generated in the Phase III PERSEPT 1 and 2 studies in a different manner to those required by the US FDA. In particular, the EMA analysis was based on successful treatment of bleeds of *any severity* using the 4-point haemostatic scale, whereas the FDA analysis was based on successful treatment of *mild or moderate bleeds* using the 4-point haemostatic scale plus four additional objective criteria: no further treatment with eptacog beta beyond the timepoint for the bleeding episode where a 'good' or 'excellent' response was noted, no other haemostatic treatment needed for the bleeding episode, no administration of blood products that would indicate continuation of bleeding beyond the timepoint where a 'good' or 'excellent' response was noted and no increase of pain beyond the timepoint that could not otherwise be explained. In this review, we summarise the current data regarding the mode of action, efficacy and safety of eptacog beta for the management of haemophilia A and B in patients with inhibitors (PwHABI) from a European perspective, presenting the results of the analyses conducted for the EMA.

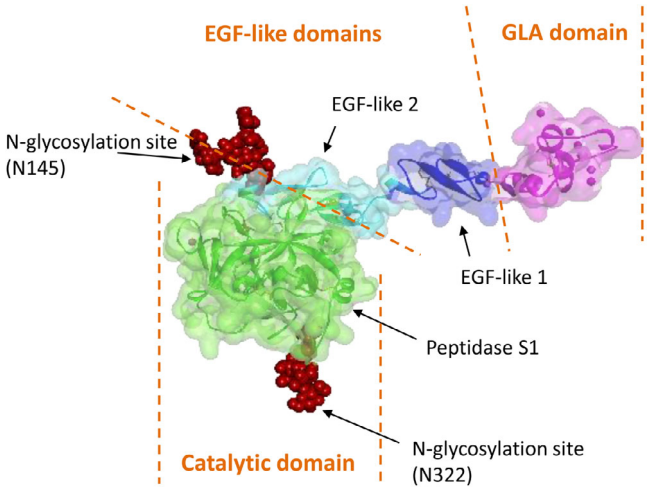

FIGURE 1 Structure of eptacog beta (published with permission from LFB BIOMEDICAMENTS), The FVIIa structure model was generated based on the FVIIa crystal structure (PDB code 1DAN) using Discovery Studio Visualizer v18.1.0.17334. EGF, epidermal growth factor; GLA domain, gamma-carboxyglutamic acid domain.

1.1 | Eptacog beta: Production

FVIIa, a highly post-translationally modified protein, requires post-translational modifications (PTMs) for full biological activity.[23] While eptacog beta and eptacog alfa have the same primary sequence and the same degree of γ-carboxylation, there are differences in N-glycosylation profiles between these rFVIIa molecules.[11] This difference is due to their different production techniques: eptacog alfa is expressed in baby hamster kidney cells and secreted into a cultured media containing foetal bovine serum;[11] whereas eptacog beta (Figure 1) is expressed in the rabbit mammary gland and secreted in the milk of transgenic rabbits.[11] N-glycosylation profile can influence the molecular stability, pharmacokinetic and pharmacodynamic

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properties of therapeutic proteins and can lead to improved performance.[24] Differences in N-glycosylation profiles have also been shown to have an impact on the therapeutic properties and stability of human antibodies.[24] For eptacog beta, the major N-glycosylation structures are complex biantennary structures sialylated at the α 2−6 position, among which 57% are monosialylated and 12% are bisialylated. In contrast, eptacog alfa presents approximately 50% bisialylated and 18% monosialylated biantennary N-glycans that are sialylated at the α 2−3 position. These differences in post-translational modifications may explain the functional differences between eptacog beta and eptacog alfa observed in preclinical studies.[25,26]

The production of recombinant proteins in the milk of transgenic animals is an innovative technology that (despite certain advantages, including relative ease of scale-up) is less commonly used than traditional cell culture production. The rationale behind the use of transgenic animals is that the mammary gland is a high yielding source of proteins (befitting its primary role of nurturing the young), and as such offers a unique opportunity for recombinant biopharmaceutical production. For example, with eptacog beta, the relevant transgene includes the coding for human FVII and a beta-casein specific promoter that results in expression of human rFVII in the rabbit mammary gland; this human rFVII is then isolated by standard milking techniques, and subsequently purified/activated to produce eptacog beta.[23] Importantly, the human rFVII protein does not circulate systemically and has not been shown to have any negative effect on the rabbit. The rabbits used in the production of eptacog beta are known to be specific pathogen free and the proprietary recombinant manufacturing process for eptacog beta produces a safe recombinant protein product. The manufacturing process of eptacog beta includes four virus reduction steps, namely a solvent/detergent treatment, a filtration step and two chromatography steps that were demonstrated to be very effective in the removal of enveloped and non-enveloped viruses. In addition to eptacog beta, the EMA has approved other recombinant products produced from transgenic animals, including human antithrombin [milk of transgenic goats (2006)] and a human recombinant C1 esterase inhibitor [milk of transgenic rabbits (2011)], establishing the process as a valid and safe technique.[27]

Eptacog beta produced in the milk of transgenic rabbits has the appropriate primary sequence, PTMs and secondary structure to be fully active FVII.[11] In addition, eptacog beta is highly pure and contains at most a low level of product-derived impurities, of the same order of magnitude as those in eptacog alfa.[11]

1.2 | Mechanism of action/preclinical data

Therapeutic rFVIIa drives coagulation via three distinct and complementary mechanisms.[28,29] The first mechanism is a tissue-factor (TF)-dependent mechanism, where rFVIIa competes with endogenous FVII to bind TF expressed on cell surfaces at the site of injury, which activates FX, leading to initial thrombin generation.[28] The second is a platelet-dependent mechanism, where haemostasis is achieved by the direct activation of FX by rFVIIa bound to phospholipids exposed on the surface of activated platelets.[28] The third mechanism is endothelial protein C receptor (EPCR)-dependent, where rFVIIa displaces protein C from EPCR, downregulating local generation of the anticoagulant activated protein C.[29]

Eptacog beta and eptacog alfa have similar affinities for soluble TF and TF in the absence of phospholipids.[30] This, together with similar generation of thrombin in vitro, highlights similar TF-mediated mechanisms for both eptacog beta and eptacog alfa.[31] In contrast, eptacog beta and eptacog alfa have shown differences in platelet binding affinity. While both agents bind to activated platelets relatively weakly and in a dose-dependent manner, at saturation, 40% more eptacog beta binds to platelets than eptacog alfa.[30] Similarly, at therapeutic concentrations, eptacog beta and eptacog alfa both bind to human umbilical vein endothelial cells (HUVEC) dose dependently, but binding is 25%−50% higher for eptacog beta.[30] Furthermore, Protein C, soluble EPCR and anti-EPCR antibodies, which compete for the same binding site, all reduced the binding of eptacog beta and eptacog alfa to HUVEC, indicating specificity for EPCR,[30] which is found on the cell endothelium. However, while anti-EPCR antibodies completely blocked eptacog alfa binding to HUVEC, they only blocked 91% of eptacog beta binding, suggesting that eptacog beta has a second, minor binding site.[30,31] These differences in the platelet- and EPCR-dependent mechanisms of eptacog beta and eptacog alpha observed in in vitro studies may reflect the different N-glycosylation profiles of the two agents. However, it should be noted that clinically, eptacog beta and eptacog alfa have similar kinetic constants and active site titration.

In mouse models of haemophilia, EPCR enhances rFVIIa-driven haemostasis[29,32] and it redistributes rFVIIa to the extravascular tissues where it remains functionally active and where it can be retained for extended periods of time far exceeding its plasma half-life.[33] In addition, by binding to EPCR, eptacog beta may protect against endothelial barrier dysfunction induced by thrombin.[34] However, the comparative mechanisms of action of eptacog beta and eptacog alfa hypothesised here are based on experimental data generated by the manufacturer of eptacog beta (LFB), which have not been confirmed by independent investigators, and the extrapolation of data from mice. Further investigation is required to demonstrate any potential clinical advantage of eptacog beta over eptacog alfa.

1.3 | Eptacog beta and emicizumab

aPCC and rFVIIa are different products with different procoagulant components exerting effects on thrombin generation.[17,22,35–37] In vitro, the addition of aPCC to SIA-emicizumab has a synergistic effect on thrombin generation, with peak levels more than 4-fold higher than those seen in normal plasma.[36] This may explain why thrombotic microangiopathy and thrombosis have been reported in patients receiving emicizumab whose breakthrough bleeds were treated with aPCC.[17,36,37] In contrast, the combination of eptacog alfa and emicizumab resulted in in vitro thrombin generation below that observed in normal plasma.[36]

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An in vitro study was undertaken to determine the level of thrombin generation induced by eptacog beta in plasma from individuals with haemophilia A with and without inhibitors and that contained clinically relevant levels of emicizumab.[37] The combination of eptacog beta and emicizumab increased thrombin generation, but the level of thrombin generation did not exceed that in normal plasma, as previously observed with eptacog alfa.[37]

These findings from the in vitro combination study are currently being confirmed in a US-centric, Phase IV clinical safety study (ATHN-16; NCT04647227) in patients with haemophilia A and inhibitors who are receiving emicizumab prophylaxis and on-demand eptacog beta for the treatment of breakthrough bleeds. This study, coordinated by the American Thrombosis and Haemostasis Network, is also enrolling individuals with haemophilia A who are not receiving emicizumab prophylaxis and haemophilia B patients with inhibitors.

1.4 | Eptacog beta Phase I study

In addition to overcoming the issues associated with the use of mammalian cell cultures, the development of eptacog beta was motivated by the lack of predictable efficacy of current bypassing agents, due to high intra- and inter-patient variability in response.[38] Clinicians require a rFVIIa that exhibits a reliable dose response that is not only effective and well tolerated at low doses, but also at high doses and when there are prolonged intervals between dosing.[38]

The safety, pharmacokinetics and ex vivo pharmacodynamics of eptacog beta (25, 75 and 225 μg/kg) were investigated in a prospective, multicentre, Phase Ib dose-escalation study undertaken in 15 adults (20–61 years of age) with moderate or severe congenital haemophilia A or B with or without inhibitors, in a non-bleeding state.[39] The doses were selected based on the results of preclinical in vitro and in vivo studies. At each dose level, eptacog beta was administered intravenously over 2−3 min to 10 participants, with each participant receiving two different dose levels. The dose was only escalated after the evaluation of safety data (30 ± 6 h after dosing) and pharmacodynamic data (coagulation markers) were assessed by an independent data monitoring committee.

Peak plasma concentration (C_{max}) and area under the plasma-concentration-time curve (AUC) for eptacog beta seem to be dose dependent; according to the Cevenfacta® Summary of Product Characteristics, the non-compartmental analysis showed approximate dose proportionality between 75 and 225 μg/kg of eptacog beta.[22,39] In contrast, the following pharmacokinetic parameters were not considered to be dose dependent: clearance (25 μg/kg: 9.0 L/h; 75 μg/kg: 10.0 L/h; 225 μg/kg: 7.9 L/h), volume of distribution (29.8, 30.4 and 20.0 L, respectively) and terminal half-life (2.3, 2.1 and 1.8 h, respectively). FVIIa activity returned to baseline levels within 24 h of dosing.[39]

There were dose-dependent changes in several unvalidated surrogate markers for haemostasis after the administration of eptacog beta.[39] Peak thrombin generation was dose dependent for up to 24 h after dosing (measured using a plasma-spiked thrombin generation assay). Activated partial thromboplastin time (aPTT; a coagulation test) was also dose dependent. Prothrombin time was reduced, but it was unclear if the reductions were dose dependent, as the lower limit of the assay (~8 s) was reached with eptacog beta 75 and 225 μg/kg.

No significant coagulation activation was observed in assays that could potentially indicate pathological clot formation or a prothrombotic state.[39] D-dimer levels were unchanged, except in one participant whose levels at 24 h were 2-fold higher than baseline after receiving eptacog beta 225 μg/kg. Thrombin-antithrombin complexes were unaffected by eptacog beta 25 μg/kg, and the effects of the 75 and 225 μg/kg doses were variable and inconsistent among participants. Prothrombin fragment F1+2 increased dose dependently, peaking 1−2 h after eptacog beta dosing, indicating the formation of thrombin, and returned to baseline 6−12 h after dosing. Maximum clot firmness, indicating the absolute strength of the fibrin and platelet clot, was demonstrated 5 min after eptacog beta dosing, using modified rotational thromboelastometry.

All doses of eptacog beta were well tolerated.[39] There were three adverse events (AEs) within 36 h of dosing that were possibly related to eptacog beta: brief mild dizziness after 25 and 75 μg/kg eptacog beta in one participant and mild headache lasting 2 h after eptacog beta 25 μg/kg in another. No participant exhibited hypersensitivity or humoral immunogenicity to eptacog beta.

The authors of the study concluded that at its C_{max}, eptacog beta had relevant effects on platelet-augmented thrombin generation, suggesting possible dose-dependent increases in local thrombin generation at the site of bleeding.[39] They also concluded that the C_{max} of eptacog beta should guide the initial dose selection for the on-demand treatment of bleeds, while the AUC confirmed the feasibility of a 3-h dosing interval for 75 μg/kg and suggested a 9-h interval between the initial 225 μg/kg dose and subsequent doses of eptacog beta.[39] Data from this study were included in a computational pharmacokinetic and pharmacodynamic model that supported the selection of the eptacog beta initial dose regimens (IDRs) of 75 and 225 μg/kg for investigation in Phase III clinical trials for the on-demand treatment of bleeds in patients with haemophilia A or B and inhibitors.[39]

2 | CLINICAL EFFICACY IN PHASE III STUDIES: PERSEPT 1, 2 AND 3

2.1 | PERSEPT 1

2.1.1 | Study design and the EMA efficacy analysis

PERSEPT 1 was a global, multicentre, randomised, open-label, crossover Phase III study undertaken to evaluate the efficacy, safety and immunogenicity of eptacog beta for the early, on-demand treatment of bleeds in individuals with haemophilia A or B with HTI (≥5 BU) and those with LTI (<5 BU) who were expected to have a high anamnestic response to FVIII or FIX, or be refractory to increased dosing of FVIII or FIX.[40] In this study, 27 males (12−54 years of age; 5 adolescents, 22 adults) with congenital haemophilia A or B who had ≥3 bleeds in the previous 6 months were randomized to receive eptacog

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TABLE 1 Summary of outcomes from PERSEPT 1.[42–44]

	75 μg/kg (*n* = 25)	225 μg/kg (*n* = 25)	Overall (*N* = 27)
Bleeding events, *n*	**252**	**216**	**468**
Events treated successfully[a] at 12 h, any severity, *n*	204	195	399
Success proportion[a] at 12 h, any severity, % (95% CI)	81.0 (70.9–91.0)	90.3 (82.9–97.7)	85.3 (77.0–93.5)
Response at 24 h, % (95% CI)	96.7 (93.3–100)	99.5 (98.6–100)	–
Time to patient-reported response,[b] h	5.98	3.00	–
No recurrence of bleeding, % (95% CI)	100	99.5 (98.6–100)	–
Eptacog beta infusions per bleeding episode, median, *n*	2	1	–

Abbreviation: CI, confidence interval.
[a]Assessed as 'good' or 'excellent' on a 4-point haemostatic scale.
[b]Kaplan–Meier estimate.

beta at an IDR of 75 μg/kg (*n* = 13) or 225 μg/kg (*n* = 14). In the event of an unsatisfactory therapeutic response, participants using the eptacog beta 75 μg/kg IDR could receive further 75 μg/kg doses administered every 3 h for mild/moderate bleeds, and every 2 h for severe bleeds (See Table S1 for definitions of severity), for up to 21 or 22 h after the initial dose, respectively. An unsatisfactory therapeutic response was defined as no noticeable effect on bleeding or the participant's condition worsened, or some effect (e.g., decreased pain or improved bleeding) but the episode continued and required further treatment (Table S2). In subjects using the eptacog beta 225 μg/kg IDR, participants with mild/moderate bleeds who had an unsatisfactory therapeutic response could receive eptacog beta 75 μg/kg every 3 h beginning 9 h after dosing, for up to 21 h after the initial dose. For patients with severe bleeds, eptacog beta 75 μg/kg could be administered every 2 h between 6 and 22 h after the initial dose in the event of an unsatisfactory therapeutic response. Alternative therapy, if required, could be initiated 24 h after the initial dose of eptacog beta for bleeds of any severity. Participants crossed over to the other eptacog beta IDR every 3 months.

Eptacog beta could be administered at home or in the clinic.[40] Participants were advised to treat bleeds at home as soon as symptoms were recognised. Participants with severe bleeds who administered the initial dose of eptacog beta at home, were required to have any further doses administered in a hospital setting. Bleeding was assessed every 3 h for 24 h after dosing, beginning 3 h after the initial dose in the eptacog beta 75 μg/kg IDR dose group and beginning 9 h after the initial dose in the eptacog beta 225 μg/kg IDR dose group (with an optional assessment at 3 h).

In total, the participants experienced 465 mild or moderate bleeds and 3 severe bleeds (traumatic intramuscular haemorrhage, spontaneous right hip joint haemorrhage and a spontaneous renal haemorrhage) over a median of 7.5 months, with a median number of bleeding events per participant of 12.[40,41]

The EMA analysis focussed on a response of 'good' or 'excellent' on the 4-point haemostatic scale (Table S2) for bleeds of any severity 12 h after the initial dose of eptacog beta.[42–44] The haemostatic evaluation was undertaken by the patient or their caregiver for mild/moderate bleeds and by a physician for severe bleeds.[40] The proportion of bleeds successfully treated at 12 h was compared with an objective performance criterion (OPC) of 55%—this OPC was prospectively chosen as a benchmark for minimal efficacy to be demonstrated in the pivotal clinical trials, and was agreed to by the US FDA (and subsequently other agencies including the EMA). PERSEPT 1 was designed to detect a meaningful (15% or better) improvement over the OPC with at least 80% power. Other key outcomes evaluated included time to patient/carer-reported assessment of a 'good' or 'excellent' response for bleeds regardless of severity and number of doses administered, and total amount of drug administered per bleed regardless of severity.

2.1.2 | Key results

The results from PERSEPT 1 are summarised in Table 1. The overall success proportion for the treatment of all bleeds with eptacog beta (both regimens) at 12 h was 85.3% (95% CI 77.0–93.5), with missing responses treated as failures.[42] In the eptacog beta 75 μg/kg IDR group, the success proportion was 81% (95% CI 70.9–91.0) for all bleeds and was 90.3% (95% CI 82.9–97.7) in the eptacog beta 225 μg/kg IDR group.[42] A single 225 μg/kg dose of eptacog beta successfully treated 81.3% of bleeds, and 66.3% of bleeds were successfully treated with 1–2 doses in the 75 μg/kg IDR.[43] Indeed, a median of 1 injection of eptacog beta 225 μg/kg or 2 injections of eptacog beta 75 μg/kg were required to successfully treat bleeds.[42] The median time to response was 5.98 h in the eptacog beta 75 μg/kg IDR group and 3 h in the eptacog beta 225 μg/kg IDR group.[42]

At 24 h, the success proportion was 96.7% (95% CI 93.3–100) with the eptacog beta 75 μg/kg IDR and 99.5% (95% CI 98.6–100) with the eptacog beta 225 μg/kg IDR.[42,43] Furthermore, bleeding did not recur within 24 h in 100% of events treated with the eptacog beta 75 μg/kg IDR and in 99.5% (95% CI 98.6–100) of events treated with the eptacog beta 225 μg/kg IDR.[44]

Pain was successfully relieved 12 h after dosing in 91.6% (95% CI 84.8–98.4) and 89.9% (95% CI 82.2–97.6) of bleeds treated with the eptacog beta 75 μg/kg and 225 μg/kg IDRs, respectively (data on file).[44]

In summary, in PERSEPT 1, eptacog beta rapidly controlled bleeds in adults and adolescents with haemophilia A or B and inhibitors, with a

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TABLE 2 Summary of outcomes from PERSEPT 2.[42,46]

	75 μg/kg (*n* = 23)	225 μg/kg (*n* = 24)	Overall (*N* = 25)
Bleeding events, *n*	**239**	**310**	**549**
Events treated successfully[a] at 12 h, any severity, *n*	158	190	348
Success proportion[a] at 12 h, any severity, % (95% CI)	66.1 (53.0–79.2)	61.3 (48.7–73.9)	63.4 (51.7–75.1)
Response at 24 h, % (95% CI)	97.4 (91.3–100)	97.7 (94.1–100)	–
Time to patient-reported response,[b] h	9	12	–
No recurrence of bleeding, % (95% CI)	99.2 (97.6–100)	98.1 (96.1–100)	–
Eptacog beta infusions per bleeding episode, median, *n*	3	2	–

Abbreviation: CI, Confidence Interval.
[a]Assessed as 'good' or 'excellent' on a 4-point haemostatic scale.
[b]Kaplan–Meier estimate.

high success proportion at 24 h and very few bleeding events requiring alternative therapy, despite a median of only 1 and 2 doses of the 225 μg/kg and 75 μg/kg IDRs, respectively, being administered per event.

2.2 | PERSEPT 2

2.2.1 | Study design and the EMA efficacy analysis

PERSEPT 2, a prospective, multicentre, randomised, open-label, cross-over Phase III study, was undertaken to evaluate the efficacy, safety and immunogenicity of eptacog beta for the treatment of bleeds in a paediatric population (<12 years of age)—the first prospective study of a rFVIIa to enrol an exclusively paediatric population.[45] In this global study, 25 children (<6 years of age: *n* = 13; ≥6 to <12 years of age: *n* = 12) with congenital haemophilia A or B and inhibitors (≥5 BU or those with <5 BU who were expected to have a high anamnestic response to FVIII or FIX, or be refractory to increased dosing of FVIII or FIX) who had ≥3 bleeds in the previous 6 months or since birth if <6 months of age were randomised to receive the eptacog beta 75 μg/kg (*n* = 12) or 225 μg/kg (*n* = 13) IDR using the same infusion frequency schedule and cross-over design as in PERSEPT 1.[45]

In total, the participants had 546 mild or moderate bleeds and 3 severe bleeds (spontaneous renal haemorrhage, traumatic intracranial bleed and traumatic left elbow bleed).[45] The median number of events per participant was 17.[42]

As for the PERSEPT 1 study, the focus of the EMA analysis of data from PERSEPT 2 was the successful treatment of bleeds of any severity at 12 h (primary endpoint), defined as a 'good' or 'excellent' response on the 4-point haemostasis evaluation scale (Table S2), assessed by the parent/caregiver of the participant or the physician for severe bleeds.[46] Other key endpoints included the proportion of bleeds of any severity successfully treated at all other timepoints, time to patient-reported assessment of a 'good' or 'excellent' response for bleeds regardless of severity and number of administrations, total amount of drug administered per bleed, and duration of bleeds, regardless of severity.

2.2.2 | Key results

A summary of the results from PERSEPT 2 is provided in Table 2. The overall success proportion for the treatment of all bleeds with eptacog beta (both regimens) at 12 h was 63.4% (95% CI 51.7–75.1), with missing responses treated as failures.[42] The success proportion was 66.1% (95% CI 53.0-79.2) with the eptacog beta 75 μg/kg IDR at 12 h and was 61.3% (95% CI 48.7–73.9) for the 225 μg/kg IDR.[42] It should be noted that the lower bounds of the 95% CIs for these success proportions at 12 h failed to meet the predefined OPC of 55%. Median time to response was 9 and 12 h in the eptacog beta 75 μg/kg and 225 μg/kg IDRs, respectively, and efficacy was achieved with a median of 3 or 2 doses, respectively.[46]

At 24 h, the success proportion for treating bleeds with eptacog beta 75 μg/kg IDR was 97.4% (95% CI 91.3–100) and was 97.7% (95% CI 94.1–100) for the 225 μg/kg IDR.[46] Bleeding did not recur within 24 h in 99.2% (95% CI 97.6–100) of events treated with the eptacog beta 75 μg/kg IDR and in 98.1% (95% CI 96.1–100) of those treated with the 225 μg/kg IDR.[46]

Pain was relieved at 12 h in 92.8% (95% CI 85.6–100) and 90.2% (95% CI 82.7–97.7) of bleeds treated with eptacog beta 75 and 225 μg/kg IDRs, respectively.[46]

In summary, eptacog beta (both IDRs) controlled bleeds effectively by 24 h in a paediatric population (<12y) with haemophilia A or B and inhibitors.

2.3 | Pain relief in PERSEPT 1 and PERSEPT 2

The reduction in pain associated with the use of eptacog beta in adults and children was evaluated in a *post-hoc* analysis of data from PERSEPT 1 and PERSEPT 2.[47] Successful pain relief was defined as a reduction in the pain score on a visual analogue scale. In total, 1017 bleeds experienced by 52 individuals were analysed, comprising 468 events in adolescents and adults participating in PERSEPT 1 and 549 events in children participating in PERSEPT 2.

Eptacog beta was associated with clinically relevant pain reduction.[47] Successful pain reduction was achieved in ~90% of

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individuals 12 h after the initial administration of eptacog beta in each study, irrespective of the severity of the bleed. The median time to pain relief (when the pain score decreased ≥11 points from baseline) was 3.03 h (95% CI 3.00–5.83) in PERSEPT 1 and more than 5 h for PERSEPT 2, regardless of the severity of the bleed (Kaplan-Meier estimates). Pain relief correlated well with efficacy and was sustained at 12 and 24 h after initial eptacog beta administration.[47]

2.4 | PERSEPT 3

2.4.1 | Study design

PERSEPT 3 was a multicentre, single-arm, open-label Phase III study undertaken to evaluate the efficacy and safety of eptacog beta to prevent excessive bleeding in males with haemophilia A or B with inhibitors undergoing elective surgery/invasive procedures.[48] Participants scheduled to undergo a minor surgical procedure received eptacog beta 75 μg/kg immediately prior to surgery, every 2 h up to 48 h and then every 2–24 h thereafter. However, after the preoperative dose, the dosing interval could be adjusted by the investigator, and dosing beyond 48 h was optional. Participants scheduled to undergo a major surgical procedure received eptacog beta 200 μg/kg immediately prior to surgery, 75 μg/kg every 2 h during surgery and during the first 48 h, then every 2–4 h during days 3–4, every 2–6 h during days 5–6, every 2–8 h during days 7–10 and every 2–12 h thereafter. The postoperative dosing interval could be adjusted by the investigator; dosing beyond day 5 was optional.

In total, 12 participants (2–56 years of age; 6 < 18 years and 6 ≥18 years) underwent an invasive procedure (6 minor [3 circumcisions and 3 tooth extractions] and 6 major procedures [2 lower extremities amputations, 2 knee surgeries, a hip replacement and an achilloplasty]) and received eptacog beta.[48] The primary efficacy endpoint was the percentage of procedures assessed as successful at 48 ± 2 h following the last dose of eptacog beta, based on all assessments performed, including intraoperative and postoperative haemostatic assessments, interventions for bleeds, oozing, blood transfusions and the total quantity of eptacog beta administered.

Haemostatic assessments were made on a 4-point scale intraoperatively, post-operatively at intervals of 24 ± 2 h after the completion of the procedure, while eptacog beta was being administered, and 24 ± 2 h and 48 ± 2 h following the final dose of eptacog beta.[48] Haemostatic response was defined as excellent, good, moderate or none (Table S3).

2.4.2 | Key results

The success proportion for all procedures 48 ± 2 h following the last dose of eptacog beta was 81.8% (95% CI 48.2–97.7).[48] All evaluable minor procedures were assessed as successful 48 ± 2 h following the last dose of eptacog beta (100%, 95% CI 47.8–100; one procedure was not evaluable due to the participant withdrawing consent). The success proportion for major procedures was 66.7% (95% CI 22.3–95.7) 48 ± 2 h following the last dose of eptacog beta; 4/6 procedures were successful with 2 considered failures. The first failed procedure was in an individual undergoing hip replacement surgery who had received eptacog beta every 2 h for 2 days and was discontinued from the study due to a treatment-related AE of post-procedural haematoma that ultimately led to the patient's death, although the death was considered unrelated to treatment. This patient also required rescue therapy (aPCC) within 52 h of the last dose of eptacog beta. This case is described in more detail in the safety section below. The second failed procedure was in an individual undergoing knee replacement surgery who had received 64 doses of eptacog beta. Efficacy was rated as poor 7 days after surgery due to a moderate bleeding event at the surgical site. Eptacog beta was discontinued and, despite the administration of packed red blood cells, eptacog alfa and aPCC, efficacy remained poor on day 9. Haemostasis was subsequently achieved with ongoing aPCC use.

All minor and major procedures were associated with good or excellent intraoperative haemostatic assessment with no participant requiring surgical reintervention for bleeding.[48] For the minor procedures, estimated intra-operative blood loss was lower than would be expected in individuals without a bleeding disorder undergoing the same procedure (mean [SD] 2.3 [1.4] vs. 4.2 [5.4] mL) and major procedures (270 [228] vs. 350 [173] mL).

2.5 | Safety and tolerability

A pooled safety analysis of the PERSEPT studies included 60 participants: 27 who participated in PERSEPT 1, 25 from PERSEPT 2 and 12 from PERSEPT 3 (2 participants in PERSEPT 1 and 2 in PERSEPT 2 also participated in PERSEPT 3).[38] These 60 individuals experienced 1029 bleeds or invasive procedures and received 3388 doses of eptacog beta.

Eptacog beta was well tolerated.[38] No allergic, hypersensitivity or anaphylactic reactions were reported in any participant. No participant had a thrombotic event, including in the surgical setting. No neutralising anti-eptacog beta antibodies were detected in any participant. Testing for antibodies against rFVIIa 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.[38]

The most common AEs across the three PERSEPT studies were nasopharyngitis (11.7%), procedural pain (8.3%), anaemia (6.7%), bronchitis (6.7%), cough (6.7%), rhinitis (6.7%), diarrhoea (5.0%), headache (5.0%), vomiting (5.0%) and wound secretion (5.0%) (Table 3).[38] There were 10 AEs that were considered treatment related by the investigator in three participants (0.01 events per exposure episode). A single participant in PERSEPT 1, who received the eptacog beta 75 μg/kg IDR to treat a bleed, had 6 treatment-related AEs (4 episodes of infusion-site discomfort and 2 of infusion-site haematoma), all of which resolved and were considered by the investigator to be mild. The remaining treatment-related AE in PERSEPT 1 was increased body

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TABLE 3 Safety and tolerability of eptacog beta in the PERSEPT studies.[38]

	PERSEPT 1 ($n = 27$)	PERSEPT 2 ($n = 25$)	PERSEPT 3 ($n = 12$)	Combined[a] ($N = 60$)
Number of infusions, *n*	968	1686	734	3388
≥1 Serious AE	1[b] (3.7)	2 (8.0)[c]	1 (8.3) [d]	4 (6.7)
≥1 AE	12 (44.4)	17 (68.0)	10 (83.3)	39 (65.0)
AEs reported in ≥2 participants in at least one study				
Nasopharyngitis	3 (11.1)	4 (16.0)	0 (0)	7 (11.7)
Headache	3 (11.1)	0 (0)	0 (0)	3 (5.0)
Anaemia	0 (0)	2 (8.0)	2 (16.7)	4 (6.7)
Diarrhoea	0 (0)	3 (12.0)	0 (0)	3 (5.0)
Vomiting	0 (0)	3 (12.0)	0 (0)	3 (5.0)
Bronchitis	0 (0)	4 (16.0)	0 (0)	4 (6.7)
Viral respiratory tract infection	0 (0)	2 (8.0)	0 (0)	2 (3.3)
Rhinitis	0 (0)	4 (16.0)	0 (0)	4 (6.7)
Cough	0 (0)	4 (16.0)	0 (0)	4 (6.7)
Postoperative anaemia	0 (0)	0 (0)	2 (16.7)	2 (3.3)
Procedural pain	0 (0)	0 (0)	5 (41.7)	5 (8.3)
Wound secretion	0 (0)	0 (0)	3 (25.0)	3 (5.0)
Haemorrhage	0 (0)	0 (0)	2 (16.7)	2 (3.3)
≥1 treatment-related AEs	2 (7.4)	0 (0)	1 (8.3)	3 (5.0)

Data are presented as the number (%) of participants, unless stated otherwise.
Abbreviation: AE, adverse events (treatment-emergent).
[a]Collectively, there were 64 participants in PERSEPT 1, PERSEPT 2 and PERSEPT 3, as two participants in PERSEPT 1 also participated in PERSEPT 3 as did two participants in PERSEPT 2; a total of 60 individuals participated across the three studies.
[b]Severe tonsillitis and intracranial haemorrhage in one patient not considered related to eptacog beta treatment.
[c]Paresis, intracranial bleed and dysentery in one patient each, all resolving with treatment and assessed as unrelated to eptacog beta treatment.
[d]Acute blood loss anaemia and gastrointestinal haemorrhage in one patient, considered related to eptacog beta treatment.

temperature in a participant who received eptacog beta 225 μg/kg, which resolved after treatment with ibuprofen and non-steroidal anti-inflammatory drugs. A participant in PERSEPT 3 who received eptacog beta 200 μg/kg prior to major surgery and 75 μg/kg infusions post-operatively had one treatment-related AE. This individual had a post-procedural haematoma the day following surgery, which led to them being discontinued from the study by the investigator. The haematoma did not resolve despite concomitant medications (including aPCC) and the patient died approximately 2 days after study discontinuation from acute blood loss due to a gastrointestinal haemorrhage—both serious AEs that were initially reported as unrelated to treatment and then updated to possibly drug related by the investigator. However, based on re-assessment by the independent data monitoring committee, the events (and hence the participant's death) were ultimately considered unrelated to eptacog beta, based on the lack of clinical evidence or autopsy findings supporting a relationship, other subject risk factors, the short half-life of eptacog beta, which was discontinued 2 days prior to the gastrointestinal haemorrhage, and that the patient had been receiving aPCC for 2 days prior to the event. Serious AEs occurred in ≤2 patients in each of the PERSEPT studies and are summarised in Table 3.

A further analysis of safety for the eptacog beta 75 and 225 μg/kg IDRs using pooled data from the three Phase III studies in addition to data from 7 additional participants who received these doses in a Phase 1b dose escalation study ($N = 67$) also concluded that eptacog beta was well tolerated, with both IDRs having favourable safety profiles.[49]

3 | CONCLUSION

Following a period of stagnation in the successful development of therapies to manage bleeds in patients with haemophilia A or B with inhibitors, the recent approval of eptacog beta in adolescents and adults for bleed management is an important addition to the treatment landscape.[1,10,50] Eptacog beta has several possible advantages over current bypassing agents. Firstly, it is produced in a transgenic animal, potentially overcoming issues associated with cell culture production techniques.[11] Secondly, differences in glycosylation and in binding of eptacog beta to EPCR and platelets compared with eptacog alfa may confer clinical benefit.[29–34] Finally, eptacog beta has predictable, dose-dependent efficacy as shown by the results of the PERSEPT 1 trial as well as PK and PD findings.[39,40] In particular, the results of PERSEPT 1 showed that a single dose of eptacog beta 225 μg/kg successfully treated 81.3% of bleeds, compared with 66.3% after 1–2 doses of 75 μg/kg. In addition, the 225 μg/kg IDR led to a faster resolution of bleeding compared with the 75 μg/kg IDR (3 h vs. 5.98 h). This

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study included a diverse patient population and a high number of bleeding events ($n = 468$). Finally, like eptacog alfa, eptacog beta can be administered to patients using other haemostatic agents including emicizumab.[37]

Eptacog beta has an important role in the management of individuals with haemophilia and inhibitors, particularly given that no currently available therapy is 100% effective in preventing bleeds in these individuals, therefore, an effective and well tolerated therapy for the treatment of breakthrough bleeds and the prevention of excessive bleeding during surgeries and invasive procedures is required.

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DATA AVAILIABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

This is a review article, therefore no ethics approval was required.

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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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