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PERSEPT 3: A phase 3 clinical trial to evaluate the haemostatic efficacy of eptacog beta (recombinant human FVIIa) in perioperative care in subjects with haemophilia A or B with inhibitors

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Abstract

Introduction: Surgical procedures in persons with haemophilia A or B with inhibitors (PwHABI) require the use of bypassing agents (BPA) and carry a high risk of complications. Historically, only two BPAs have been available; these are reported to have variable responses.

Aim: To prospectively evaluate the efficacy and safety of a new bypassing agent, human recombinant factor VIIa (eptacog beta) in elective surgical procedures in PwHABI in a phase 3 clinical trial, PERSEPT 3.

Methods: Subjects were administered 200 μg/kg (major procedures) or 75 μg/kg eptacog beta (minor procedures) immediately prior to the initial surgical incision; subsequent 75 μg/kg doses were administered to achieve postoperative haemostasis and wound healing. Efficacy was assessed on a 4-point haemostatic scale during the intra- and postoperative periods. Anti-drug antibodies, thrombotic events and changes in clinical/laboratory parameters were monitored throughout the perioperative period.

Results: Twelve subjects underwent six major and six minor procedures. The primary efficacy endpoint success proportion was 100% (95% CI: 47.8%–100%) for minor procedures and 66.7% (95% CI: 22.3%–95.7%) for major procedures; 81.8% (95% CI: 48.2%–97.7%) of the procedures were considered successful using eptacog beta. There was one death due to bleeding from a nonsurgical site; this was assessed as unlikely related to eptacog beta. No thrombotic events or anti-eptacog beta antibodies were reported.

Conclusion: Two eptacog beta dosing regimens in PwHABI undergoing major and minor surgical procedures were well-tolerated, and the majority of procedures were successful based on surgeon/investigator assessments. Eptacog beta offers clinicians a new potential therapeutic option for procedures in PwHABI.

KEYWORDS
eptacog beta, haemophilia, inhibitors, PERSEPT, recombinant FVIIa, SEVENFACT, surgery

1 | INTRODUCTION

The bleeding defect in haemophilia A or B can be corrected by the intravenous administration of the missing coagulation factor; however, this may be complicated by the formation of neutralizing antibodies (inhibitors) to the administered factor. The lifetime risk for inhibitor development in an individual with haemophilia A is up to 35%; in haemophilia B, it is up to 10%.[1,2] The presence of high responding or high titre inhibitors (titre ≥5 Bethesda Units) renders the administration of replacement factor physiologically ineffective and instead bypassing agents (BPAs) (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) are required to control haemorrhage.[3]

Inhibitors result in bleeding episodes (BEs) that are more difficult to control, increased morbidity and mortality, and decreased quality of life.[4,5] Major surgical procedures in inhibitor patients are fraught with difficulties and many surgeons and clinicians have a low comfort level performing such procedures.[6] In a review of 317 major orthopaedic surgical procedures in inhibitor patients, Erturan et al. noted that bleeding complications occurred in 40.7% of procedures.[7] This high incidence of bleeding complications in a disease where traditional BPAs have historically been seen as having unpredictable efficacy[8] makes these procedures highly challenging. Consensus guidelines for perioperative care in inhibitor patients have been published.[9–11]

Eptacog beta (SEVENFACT®, HEMA Biologics, Louisville, KY, and LFB, Les Ulis, France) is a room-temperature stable, human rFVIIa analogue that is indicated in the USA for the treatment and control of BEs in adults and adolescents (≥12 years of age) with haemophilia A or B and inhibitors.[12] This product was approved for use by the FDA based on phase 3 clinical trial data (PERSEPT 1) in which 91% of BEs achieved haemostatic efficacy at 12 h with the 225 μg/kg initial dose regimen, as did 82% of BEs with the 75 μg/kg initial dose regimen.[12]

Based on these data, it was hypothesized that eptacog beta might be a safe and effective haemostatic agent for perioperative care in individuals with inhibitors. Therefore, PERSEPT 3, a phase 3 clinical trial, was conducted to assess the efficacy and safety of eptacog beta in elective major and minor procedures in persons with haemophilia A or B with inhibitors. The results of this study are presented here.

2 | METHODS

PERSEPT 3 (NCT02548143) was approved by the institutional boards of participating sites and was conducted in compliance with the Declaration of Helsinki. All participants/caregivers provided written informed consent/assent.

Physical exams, vital signs, electrocardiograms and clinical laboratory tests were performed at screening[13]; subjects were monitored for adverse events (AEs), evidence of thrombotic events and anti-eptacog beta antibody formation.

2.1 | Eligibility criteria

Male paediatric and adult subjects (6 months to 75 years), with congenital haemophilia A or B and inhibitors who were scheduled for elective surgical or other invasive procedures were eligible for enrolment (Table S1).

2.2 | Study design

PERSEPT 3 was a phase 3, multicentre, single-arm, open-label trial that evaluated the efficacy and safety of intravenous eptacog beta in preventing excessive bleeding and achieving haemostasis in major and minor procedures. Subjects were assigned to one of two dosing regimens: for major procedures, a preoperative dose of eptacog beta (200 μg/kg) was administered immediately prior to the surgical incision or start of the procedure; for minor procedures a 75 μg/kg preoperative dose was administered. Subsequent doses of eptacog beta (75 μg/kg) were administered for at least 5 days (major procedures) or 2 days (minor procedures) (Table 1). Antifibrinolytics were permitted.

2.3 | Efficacy assessment

Response to treatment, recorded by the surgeon/investigator, was reported using a four-point haemostasis evaluation scale (Table 2). Haemostatic assessments were made intraoperatively; postoperatively at 24±2 h intervals following completion of the procedure, while eptacog beta continued to be administered; and at 24±2 and 48±2 h following the final eptacog beta administration. The primary efficacy endpoint was the percentage of procedures with a 'good' or 'excellent' assessment at 48±4 h following the last eptacog beta administration; this assessment was based on the totality of assessments performed including the intraoperative and postoperative haemostatic assessments; interventions for BEs, oozing, blood transfusions; and the total quantity of eptacog beta administered.

2.4 | Statistical analyses

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. Efficacy analyses were performed on all subjects who received eptacog beta, underwent a surgical/invasive procedure and had at least one efficacy assessment. Confidence

TABLE 1 Dosing regimens for minor and major procedures in the trial

Minor procedures	Dose	Frequency
Preoperative dose	75 μg/kg	Initial dose immediately prior to surgical incision
Subsequent doses		*Dosing intervals could be adjusted by the investigator*
Hours 2 - 48	75 μg/kg	Every 2 h
Hours 50+	75 μg/kg	Every 2 - 24 h (dosing beyond hour 48 is optional)

Major procedures	Dose	Frequency
Preoperative dose	200 μg/kg	Initial dose immediately prior to surgical incision
Operative doses	75 μg/kg	Every 2 h for the duration of the procedure (if needed)
Postoperative doses[a]		*Dose and dosing intervals could be adjusted by the investigator*
First 48 h	75 μg/kg	Every 2 h
Days 3 - 4	75 μg/kg	Every 2 - 4 h
Days 5 - 6	75 μg/kg	Every 2 - 6 h (dosing beyond day 5 is optional)
Days 7 - 10	75 μg/kg	Every 2 - 8 h
Day 11+	75 μg/kg	Every 2 - 12 h

[a]All timing of doses is measured from the time of the preoperative dose.

TABLE 2 The 4-point haemostasis evaluation scale used for evaluation of intraoperative and postoperative response to treatment with eptacog beta

Haemostatic evaluation	Intraoperative response assessment/description by the surgeon/investigator immediately following completion of the procedure	Postoperative haemostasis assessment/description by the investigator or designee at multiple time points
Excellent (success)	Intraoperative blood loss that was similar to or less than expected for this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure; no blood component transfusion was required.	Postoperative blood loss that was similar to or less than expected following this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure; no blood component transfusion was required.
Good (success)	Intraoperative blood loss that was greater than expected (but not more than 50% greater) for this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure; no unexpected increased blood component transfusion requirement.	Postoperative blood loss that was greater than expected following this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure, not explained by a surgical/medical issue other than haemophilia; no unexpected need for blood component transfusion.
Moderate (failure)	Intraoperative blood loss that was substantially greater than expected (more than 50% greater) for this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure, not explained by a surgical/medical issue other than haemophilia; additional blood component (within two-fold greater than expected) transfusion was necessary.	Postoperative blood loss that was substantially greater than expected following this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure, not explained by a surgical/medical issue other than haemophilia; additional blood component (within two-fold greater than expected) transfusion was necessary.
Poor (failure)	Uncontrolled intraoperative blood loss, not explained by a surgical/medical issue other than haemophilia, that required intervention (rescue therapy requirement [BPA or porcine FVIII], and/or increased blood component [>2-fold greater than expected] transfusion, and/or led to hypotension or unexpected transfer to the ICU)	Uncontrolled postoperative blood loss, not explained by a surgical/medical issue other than haemophilia that required intervention (rescue therapy requirement [BPA or porcine FVIII], and/or increased blood component [>2-fold greater than expected] transfusion, and/or led to hypotension or unexpected transfer to the ICU)

intervals were calculated using the Clopper-Pearson exact method. SAS v9.4 was used.

3 | RESULTS

3.1 | Subject population

Eighteen patients were screened at eight sites (five countries). Twelve subjects enrolled; four had previously participated in other SEVENFACT clinical trials.[13] Subject demographics are shown in Table 3.

3.2 | Efficacy

Six major procedures and six minor procedures were investigated (Table 4).

A 'good' or 'excellent' intraoperative haemostatic assessment (i.e. success) was reported for all procedures. The intraoperative assessment, efficacy at 24 h following the completion of the procedure, and efficacy 48 h following the last dose of eptacog beta are shown in Table 5. No subject required a surgical intervention/re-exploration for bleeding following the surgical procedure through 48 h after the last eptacog beta administration. The mean [SD] estimated actual intraoperative blood loss was lower than the mean maximum predicted blood loss (for a patient without a bleeding disorder undergoing the same procedure) for both minor surgeries (2.3 [1.4] mL actual, and 4.2 [5.4] mL maximum predicted) and major surgeries (270 [228] mL and 350 [173] mL, respectively). Antifibrinolytics were administered in two minor and two major procedures (Table 4).

The primary efficacy endpoint success proportion was 100% (95% CI: 47.8%–100%) for minor procedures with five successes and one procedure not evaluable (withdrawal of consent) (Table 5). The primary efficacy endpoint success proportion for major procedures was 66.7% (95% CI: 22.3%–95.7%): four procedures were successfully completed; two were considered failures. The number of infusions, duration of therapy and final eptacog beta dosing interval per procedure is shown in Table 4.

The primary efficacy endpoint was additionally stratified by age group: in subjects <12 years (four minor and one major procedure), the success proportion was 100% (95% CI: 39.8%–100%). In subjects ≥12 years undergoing two minor procedures, the success proportion was 100% [95% CI: 15.8%–100%); in subjects ≥12 undergoing five major procedures, the success proportion was 60% (95% CI: 14.7%–94.7%).

Two major orthopaedic procedures had bleeding complications that were not resolved with eptacog beta use and resulted in study discontinuation. A hip replacement procedure was an imputed failure due to discontinuation from the trial for an AE (post-procedural haematoma)

TABLE 3 Demographics and baseline characteristics of enrolled subjects

Parameter	Overall (N = 12 subjects)
Age, years	
Mean (SD)	25.0 (19.6)
Median	20.0
Minimum/maximum	2/56
Age categorized, n (%)	
<18 years	6 (50)
≥18 years	6 (50)
Race, n (%)	
Asian	0 (0)
Black or African American	4 (33.3)
White	8 (66.7)
Ethnicity, n (%)	
Hispanic or Latino	1 (8.3)
Not Hispanic or Latino	11 (91.7)
Weight, kg	
Mean (SD)	45.5 (24.6)
Median	42.5
Minimum/maximum	12.5/90
Haemophilia type and severity, n (%)	
Severe haemophilia A	12 (100)
Severe haemophilia B	0 (0)
Inhibitor titre, n (%)	
BU ≥5	5 (41.7)
BU <5 but refractory to increased factor dosing	1 (8.3)
BU <5 with high anamnestic response to factor dosing	6 (50.0)

BU, Bethesda Unit.

and administration of aPCC within 52 h of the last eptacog beta dose. A total knee replacement was also classified a failure: on postoperative day 7, efficacy was rated poor due to a moderate BE at the surgical site. This subject discontinued eptacog beta use and subsequently received packed red blood cells, eptacog alfa and aPCC; efficacy remained poor on postoperative day 9. Haemostasis was subsequently achieved with ongoing aPCC administration, and the subject was successfully discharged.

The dosing intervals used in individual major procedures are shown in Figure 1.

3.3 | Safety

No thrombotic, hypersensitivity or anaphylactic events were reported. No subject tested positive for anti-eptacog beta antibodies. There were no changes in vital signs, physical examination or clinical laboratory parameters that were considered clinically important by the investigators. Treatment-emergent AEs are shown in Table 6. No AEs were related to concomitant eptacog beta/antifibrinolytic use.

There were three AEs that were considered possibly/probably related to eptacog beta by the investigator: all occurred in one subject (two were serious adverse events [SAEs]). This subject experienced a post-procedural haematoma following a hip replacement (AE considered possibly related to eptacog beta) and was discontinued from the trial. Following discontinuation and subsequent administration of aPCC, the subject experienced acute blood loss anaemia (SAE) resulting from a gastrointestinal haemorrhage (SAE) and died 3 days following the procedure. The investigator initially considered these two SAEs unlikely related to eptacog beta; however, the investigator subsequently reversed this finding to that of probably related. An analysis by the independent data monitoring committee (DMC) found no clinical evidence or autopsy findings to support relatedness: the short half-life of eptacog beta and the fact the subject had been switched to aPCC approximately 2 days before the gastrointestinal haemorrhage led the DMC to conclude that these two SAEs were unlikely related to eptacog beta.

4 | DISCUSSION

Major surgical procedures in patients with haemostatic disorders are uniquely challenging; this is further magnified in PwHABI due to the limited clinical expertise outside of specialized haemophilia treatment centres (HTCs). Major procedures remain relatively rare: typically, only those that are considered essential are performed due to the heightened risk of major post-operative bleeding, and then only by experienced clinicians at centres of excellence.[6,14] HTC clinicians are more comfortable performing minor procedures; therefore, these are more common and their risk/benefit ratio well understood.[6] The most commonly used bypassing agent for surgical procedures is rFVIIa, and although continuous infusion protocols are reported, repeated bolus infusion protocols are more common.[15,16] The issues associated with historical BPAs (e.g. limited choice, variation in individual response and lack of predictable efficacy) and the preference for rFVIIa in patients using emicizumab, support the clinical need for a new rFVIIa concentrate.

During the clinical development of the new rFVIIa concentrate eptacog beta, a surgical trial was initiated to investigate its ability to prevent and control haemorrhage in major and minor procedures. Although established endpoints exist to evaluate the efficacy of BPAs for the treatment of BEs in inhibitor patients, there are no comparable, widely-used definitions of haemostatic success in surgical clinical trials.[10,14,17,18] The PERSEPT 3 study protocol established and adopted a stringent definition of efficacy: the primary endpoint was a composite of a successful response at multiple timepoints through 48 h following

TABLE 4 Details of all major and minor procedures. The major/minor procedure classification was predefined in the clinical trial protocol based on the minimum amount of time that factor replacement would typically be required in haemophilia patients (major procedures were expected to require ≥5 days of factor replacement; they typically involved entry into a body cavity and/or organ removal or a similarly complex procedure)

Age	Classification	Procedure	Length of eptacog beta use (days)	Number of eptacog beta infusions[a]	Dosing regimen prior to final dose	Antifibrinolytic use	Primary efficacy endpoint outcome
2	Minor	Circumcision	3	25	q2h	None	Success
7	Minor	Circumcision	3	25	q2h	None	Success
9	Minor	Circumcision	3	25	q2h	None	Success
9	Minor	Tooth extraction	3	28	q4h	Aminocaproic acid (5%) administered postoperatively (100 mL iv bid)	Missing - withdrew consent
26	Minor	Tooth extraction	12	73	q8h	Tranexamic acid (12 mL, tid) administered on day 9 due to oozing	Success
43	Minor	Tooth extraction	8	53	q4h	None	Success
7	Major	Achilloplasty of the left ankle	33	132	q12h	None	Success
14	Major	Left transtibial amputation	16	94	q12h	Prophylactic aminocaproic acid (2700 mg qid, days 2–5)	Success
34	Major	Removal of the endoprosthesis of the left knee joint	31	97	q12h	None	Success
39	Major	Total knee replacement	8	64	q4h	None	Failure
54	Major	Amputation of the left leg at the upper third of the thigh	22	104	q12h	Aminocaproic acid (100 mL bid; days 3–8; wound infection)	Success
56	Major	Joint (hip) replacement	2	14	q2h		Discontinued due to AE

[a]Includes the preoperative dose of either 75 or 200 μg/kg.

TABLE 5 Surgeon/investigator assessments reported for the intraoperative period, 24±2 h following procedure completion and for the primary efficacy endpoint (48±4 h following the last dose of eptacog beta). Response to treatment was rated as 'Excellent' or 'Good' (i.e. success) and 'Moderate' or 'Poor' (i.e. failure) at all recorded time points

	Minor procedures	Major procedures	Overall
Intraoperative efficacy evaluation			
Number of successes	6 (100%)	6 (100%)	12 (100%)
Number of failures	0	0	0
Number of missing observations[a]	0	0	0
Success proportion [95% CI]	100% [54.1%, 100%]	100% [54.1%, 100%]	100% [73.5%, 100%]
Efficacy, 24h±2 after procedure completion			
Number of successes	6 (100%)	4 (66.7%)	10 (83.3%)
Number of failures	0	0	0
Number of missing observations	0	2	2
Success proportion [95% CI]	100% [54.1%, 100%]	100% [39.8%, 100%]	100% [69.2%, 100%]
Primary efficacy endpoint (48h±4 after last dose)			
Number of successes	5 (100%)	4 (66.7%)	9 (81.8%)
Number of failures	0	2 (33.3%)	2 (18.2%)
Number of missing observations	1	0	1
Success proportion [95% CI]	100% [47.8%, 100%]	66.7% [22.3%, 95.7%]	81.8% [48.2%, 97.7%]

[a]Missing observations were those that were required to be reported according to the protocol but were not entered in the eCRF by the investigator.

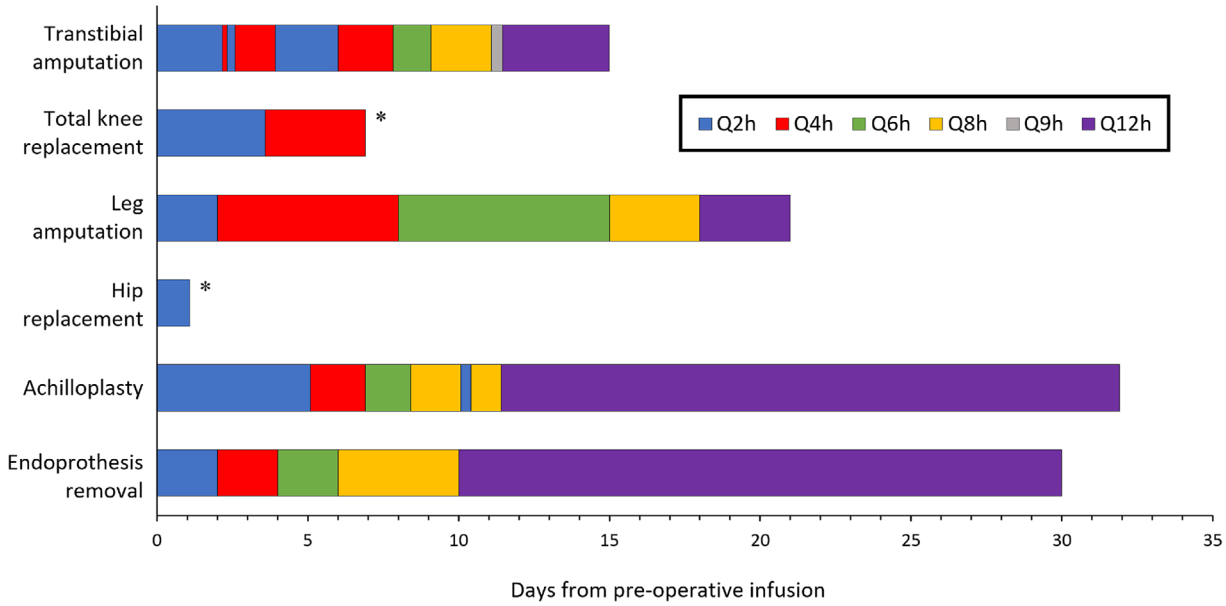

FIGURE 1 The actual dosing regimens used for the six major procedures (preoperative dose, 200 μg/kg; subsequent doses, 75 μg/kg). The dosing intervals for the 75 μg/kg doses are shown and were at the discretion of the investigator based on their expert opinion and the haemostatic needs of the subject. The administration of eptacog beta for multiple days following the procedure and the subsequent tapering off in dosing interval is consistent with literature use of eptacog alfa to support postoperative haemostasis and wound healing. The differences in dosing intervals and length of dosing between procedures are reflective of the different haemostatic needs of each subject and procedure. *Study drug was withdrawn in these procedures and alternative haemostatic agents were administered

TABLE 6 Treatment-emergent adverse events (TEAEs) that occurred in two or more subjects in PERSEPT 3

	Minor procedures		Major procedures		Overall	
TEAE	Number of subjects (N = 6)	Number of events	Number of subjects (N = 6)	Number of events	Number of subjects (N = 12)	Number of events
Anaemia	–	–	2 (33%)	2	2 (17%)	2
Postoperative anaemia	–	–	2 (33%)	3	2 (17%)	3
Procedural pain	–	–	5 (83%)	7	5 (42%)	7
Wound secretion	2 (33%)	4	1 (17%)	2	3 (25%)	6
Haemorrhage	1 (17%)	2	1 (17%)	1	2 (17%)	3

the last administration of eptacog beta; the intraoperative haemostatic assessment; the number of interventions for BEs, oozing and blood transfusions; the estimated blood loss; and the quantity of eptacog beta administered.

The PERSEPT 3 dosing regimens were selected based on a Phase 1b study, PK/PD modelling and a phase 3 study (PERSEPT 1) that confirmed the clinical efficacy and safety of the 75 and 225 μg/kg initial dose regimens for treating mild/moderate BEs, and the modified 225 μg/kg regimen for treating severe BEs.[19,20] Based on these observations, 75 μg/kg was selected as the pre-operative dose administered immediately prior to a minor procedure. To account for the more extensive tissue damage and the increased haemostatic challenge likely to be encountered, 200 μg/kg was selected as the preoperative dose for major procedures. All subsequent intra- and postoperative doses were 75 μg/kg. The number of doses administered for different procedures (Table 4) were comparable in range to those reported in a prospective surgical trial with eptacog alfa[17]; however, the lower dose (75 μg/kg eptacog beta compared to 90 μg/kg eptacog alfa) might be expected to result in reduced product consumption.

Five minor procedures were evaluated as successful at the primary endpoint based on surgeon/investigator assessments (one procedure was not evaluable due to subject withdrawal). This positive outcome may be reflective of the previously established haemostatic efficacy of eptacog beta[19]; the strict every-2-h surgical and initial postsurgical dosing schedule (to maintain haemostasis and support wound healing); and the experience of clinicians when performing

minor procedures.[6,19] Antifibrinolytics are often used during dental extractions[21]; in this trial, tranexamic acid was used to successfully treat oozing following a tooth extraction, and aminocaproic acid was used during another extraction.

All major procedures were orthopaedic procedures of the lower extremities (Table 4). The use of a higher preoperative dose (200 μg/kg) may have contributed to the high intraoperative success, lack of surgical complications, and the low mean estimated blood loss reported by the surgeon/investigator. Although some clinicians have expressed concerns regarding eptacog alfa doses greater than the FDA-approved dose of 90 μg/kg, high-dose eptacog beta (225 μg/kg) is approved for use by the FDA and no thrombotic events have been associated with this dose in clinical trials.[19]

Most major procedures (4/6) were considered successful at the primary endpoint based on surgeon/investigator assessments, with no bleeding that could not be controlled with eptacog beta (Table 5). The dosing interval following the initial 48 h of eptacog beta administration could be adjusted at the discretion of the investigator to meet the haemostatic needs of each subject (Figure 1); the dosing interval for all successful procedures was progressively extended to q12h prior to the final eptacog beta administration. In one procedure with bleeding complications (total knee replacement), the inability of eptacog beta to control a moderate bleed at the surgical site on postoperative day 7 and the subsequent success of aPCC reflects surgical experiences reported elsewhere[7]; this observation is consistent with the variable inter- and intra-patient response to BPAs (this subject had previously used aPCC to treat BEs).[22] It's possible that the resumption of a 2-hour regimen with eptacog beta, or the use of anti-fibrinolytics, might have helped control the bleeding, but the protocol provided the investigator with the autonomy to make the decision about haemostatic control. One subject who underwent hip replacement surgery experienced a post-procedural haematoma; the subject was subsequently discontinued from the study and treated with aPCC. The subject died approximately 2 days later from acute blood loss anaemia resulting from a gastrointestinal haemorrhage (both SAEs). The independent DMC concluded that these SAEs were unlikely related to eptacog beta due to its short half-life and the subsequent use of aPCC (this subject had previously participated in PERSEPT 1 and successfully treated 25 BEs with eptacog beta without experiencing any AEs).

Unexpected bleeding during the postoperative period of major procedures is common due to the normal lysis of the fibrin mesh following a period of apparent successful haemostasis. The multi-day maintenance of an effective postoperative dose is therefore essential to permit the completion of the tissue repair processes[23]; to support this goal, dosing was continued for a minimum of 2 days (minor procedures) and 5 days (major procedures). As noted by Erturan et al., both hip and knee arthroplasty have a historically high incidence of bleeding complications in inhibitor patients (>50%),[7] and it can be common to see delayed postoperative haemorrhage that requires treatment with alternative or alternating haemostatic agents, readmission and/or an extended treatment period.[14,24,25] Bossard et al. noted that complications are common in orthopaedic surgery, particularly knee replacement surgery, which can include delayed hemarthrosis 7–10 days following the procedure.[25] Thus the observation of a hematoma or moderate bleeding at the surgical site in two out of six major orthopaedic procedures might be considered an expected, albeit unwanted, outcome. Minor bleeding was observed in some procedures (Figure 1); this was successfully controlled with the resumption of a q2h dosing interval based on existing surgical guidelines.[10] Two major procedures successfully used antifibrinolytics for a short time during the postoperative period; one in response to a wound infection and the other prophylactically. The lack of thrombotic adverse events associated with the combined use of eptacog beta and antifibrinolytics is not surprising, as there are no compelling data in the literature to suggest that antifibrinolytic/rFVIIa use increases the risk of thrombosis. Although the resumption of a more frequent rFVIIa dosing interval or the use of antifibrinolytics is a standard therapeutic option, the use of alternative haemostatic medications is necessary if adequate haemostasis cannot be obtained.

No thromboembolic events or anti-rFVIIa antibodies were reported in PERSEPT 3, and no treatment-related or serious AEs were observed in subjects <12 years of age or in subjects undergoing minor procedures. The only treatment-related AEs and SAEs that occurred were in a single subject who underwent hip replacement surgery.

Guidelines note that major surgical procedures should only be undertaken in centres of excellence by those with experience performing procedures in inhibitor patients.[9] A multidisciplinary team must be involved; a plan should be created that includes risk mitigation strategies; and the aggressive and lengthy postoperative use of BPAs must be utilized. Furthermore, it is recommended that intensive care facilities be utilized for early postoperative care because delayed bleeding following major procedures is common, and experienced staff and suitable haemostatic agents need to be readily available to deal with this eventuality.[26]

Several limitations are inherent to this trial: first, only a small number of procedures were evaluated; however, some of the strengths of the trial (i.e. the diversity of procedures, the use of antifibrinolytics and the inclusion of both adult and paediatric subjects) may alleviate this limitation. Secondly, given the small number of subjects enrolled, selection bias may have existed. Thirdly, non-orthopaedic major procedures were not examined; further studies or real-world data will be required to provide data in this area. Finally, this trial did not investigate procedures in individuals receiving non-factor prophylactic agents that were not commercially available at the time (e.g. emicizumab), and as such the trial results cannot currently provide guidance in this patient population; however, in vitro data suggest that emicizumab and eptacog beta combined do not result in excessive thrombin generation.[27] The World Federation of Hemophilia prefers the use of rFVIIa due to the risk of thrombotic microangiopathy when aPCC is used in these patients.[28] Additionally, the Medical and Advisory Scientific Committee of the National Hemophilia Foundation recommends the use of eptacog beta for the treatment of breakthrough bleeding in individuals using emicizumab.[29]

Non-factor prophylactic agents[30] may one day change the requirements for BPAs in surgical procedures; however, for the foreseeable future, BPAs (specifically, rFVIIa) will remain a mainstay of therapy.

5 | CONCLUSION

The PERSEPT 3 clinical trial evaluated the efficacy and safety of eptacog beta in major and minor elective procedures. The surgeon/investigator reported successful intraoperative efficacy in all procedures and successful postoperative efficacy in most procedures. Overall, 81.8% of procedures were considered successful at the primary efficacy endpoint based on surgeon/investigator assessments. The concomitant use of eptacog beta and antifibrinolytics is supported by their use in several procedures in this trial.

The success of the majority of procedures at the primary endpoint; the proven efficacy of eptacog beta in PERSEPT 1 to control and treat BEs[12,19]; the absence of anti-rFVIIa antibodies, and thrombotic, hypersensitivity and anaphylactic events[13]; and the reported safety profile of eptacog beta in 4 clinical trials[12,13] suggest that eptacog beta is a well-tolerated rFVIIa concentrate for bleed management in major and minor surgical procedures in paediatric and adult patients with haemophilia A or B with inhibitors. Thus, eptacog beta may be considered a new haemostatic agent for perioperative care in this patient population.

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CONFLICTS OF INTEREST

M.E. has received honoraria for consulting and participating in advisory boards from BioMarin, Novo Nordisk, Genentech, Sanofi, Takeda, Pfizer, Kedrion, CSL Behring and NHF. J.L. has acted as a paid consultant to Novo Nordisk. J.D. has acted as a consultant for Bayer and HEMA Biologics, and has been on the speaker's bureau for Bayer. A.G. was co-investigator in research funded by the sponsor. D.P.H. has received research grants from Bayer, Octapharma and Takeda, and has received speaker or consultancy honoraria from Bayer, BioMarin, Biotest, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark, SOBI, Takeda and UniQure. C.K. received research support from Bayer, Genentech, Novo Nordisk, Octapharma and Takeda; and has served on advisory boards for Bayer, CSL, Genentech, Novo Nordisk, Octapharma, Takeda, Pfizer and HEMA Biologics. C.L. has received honoraria for advisory board participation for Bayer, Catalyst, CSL Behring, Genentech, Sanofi and Takeda. J.M. has received research grants from Bayer, Biogen, BioMarin, CSL, Novo Nordisk, Sobi, Roche and uniQure; has served on scientific advisory committees of Amgen, Bayer, Biotest, Biogen, Baxalta, CSL Behring, Catalyst Biosciences, Novo Nordisk, Roche and Spark; and has been a member of the speaker bureau of Alnylam, Bayer, Biotest, Biogen, Novo Nordisk, Pfizer, Sobi, Shire, Roche, ISTH and WFH. W.M. declares interests with Alnylam, Bayer, Biogen, Chugai, CSL Behring, Novo Nordisk, Octapharma, Pfizer, LFB, Roche, Takeda, Freeline, BioMarin, Sobi and uniQure. D.Q. had received honoraria/consulting fees from Bayer, BioMarin, Bioverativ/Sanofi, Catalyst, Novo Nordisk and Roche/Genentech; and has been on the speaker's bureau for BioMarin, Bioverativ/Sanofi, Novo Nordisk, Takeda and Roche/Genentech. M.T.R. has served as a consultant, advisory board member and/or speaker for Bayer, CSL Behring, Novo Nordisk, Sanofi Genzyme and Takeda; and has received institutional research support from Bayer and BioMarin. J.F.S has received grants from Pfizer, Bayer, Novo Nordisk and LFB, and has fees for consulting to Sobi. M.W. has been a consultant and/or advisor to Bioverativ/Sanofi, Takeda, CSL Behring, Catalyst Biosciences, Novo Nordisk, Bayer, Octapharma, Genentech, HEMA Biologics, BioMarin and uniQure, and was a study investigator for HEMA Biologics for research carried out in this work. J.W. has received grant support from Alnylam, Baxalta, Novo Nordisk, Octapharma, Rigel Pharmaceuticals, Roche, Shire/Takeda and Sobi; and has received honoraria from Alexion, Baxalta, CSL Behring, Ferring Pharmaceuticals, LFB, Novo Nordisk, Octapharma, Roche, Sanofi/Genzyme, Shire/Takeda, Siemens, Sobi and Werfen. W.A.A. works as a consultant for HEMA Biologics, LLC, and has received fees for speaking and consulting. A.A-S. and D.B. are employees of LFB-USA. I.S.M. is an employee of HEMA Biologics and was formerly a consultant with HEMA Biologics. T.A.W. is a medical writer for GLOVAL LLC. Y.A., M.F.L.F., J.J., L.V.M., I.H.M., O.S., K.V.V. and C.H. have no competing interests to declare.

AUTHOR CONTRIBUTIONS

All of the authors analysed and interpreted the data. I.S.M. wrote the manuscript, and all authors edited the manuscript. Y.A., J.D., M.F.L.F., A.G., J.J., J.M., L.V.M., I.H.M., O.S. and K.V.V. were clinical trial investigators, and M.E. was the global principal investigator. C.K. served on the data monitoring committee. All authors reviewed and approved the manuscript.

DATA AVAILABILITY STATEMENT

Data available from the authors upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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