

Eptacog beta efficacy and safety in the treatment and control of bleeding in pediatric subjects (<12 years) with hemophilia A or B with inhibitors

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Abstract

Introduction: Eptacog beta is a new recombinant activated human factor VII bypassing agent approved in the United States for the treatment and control of bleeding in patients with hemophilia A or B with inhibitors 12 years of age or older.

Aim: To prospectively assess in a phase 3 clinical trial (PERSEPT 2) eptacog beta efficacy and safety for treatment of bleeding in children <12 years of age with hemophilia A or B with inhibitors.

Methods: Using a randomized crossover design, subjects received initial doses of 75 or 225 $\mu\text{g}/\text{kg}$ eptacog beta followed by 75 $\mu\text{g}/\text{kg}$ dosing at predefined intervals (as determined by clinical response) to treat bleeding episodes (BEs). Treatment success criteria included a hemostasis evaluation of “excellent” or “good” without use of additional eptacog beta, alternative hemostatic agent or blood product, and no increase in pain following the first “excellent” or “good” assessment.

Results: Treatment success proportions in 25 subjects (1-11 years) who experienced 546 mild or moderate BEs were 65% in the 75 $\mu\text{g}/\text{kg}$ initial dose regimen (IDR) and 60% in the 225 $\mu\text{g}/\text{kg}$ IDR 12 h following initial eptacog beta infusion. By 24 h, the treatment success proportions were 97% for the 75 $\mu\text{g}/\text{kg}$ IDR and 98% for the 225 $\mu\text{g}/\text{kg}$ IDR. No thrombotic events, allergic reactions, neutralizing antibodies, or treatment-related adverse events were reported.

Conclusion: Both 75 and 225 $\mu\text{g}/\text{kg}$ eptacog beta IDRs provided safe and effective treatment and control of bleeding in children <12 years of age.

Keywords: recombinant FVIIa, hemophilia, eptacog beta, inhibitors, PERSEPT, pediatric.

Introduction

Inhibitor development against factor VIII (FVIII) or factor IX (FIX) represents a serious complication in the management of hemophilia, resulting in compromised therapy effectiveness, increased morbidity and mortality, progressive joint disease, and reduced quality of life.¹⁻³ Inhibitors develop in about 20-30% of patients with severe hemophilia A and up to 10% of patients with severe hemophilia B.^{4,5} Inhibitor eradication can be achieved through immune tolerance induction (ITI), but this approach is not effective in all patients (notably less success for hemophilia B patients with inhibitors).^{6,7} During ITI or in the absence of inhibitor eradication, bypassing agents (BPAs) such as the recombinant activated human factor VII (rFVIIa) products eptacog beta (SEVENFACT[®]; HEMA Biologics, LLC and LFB SA)⁸ and eptacog alfa (NovoSeven[®] RT; Novo Nordisk)⁹, and the plasma-derived activated prothrombin complex concentrate (aPCC, FEIBA[®]; Takeda)¹⁰ are needed to manage bleeding episodes (BEs) in inhibitor patients. Emicizumab (Hemlibra[®]; Roche) is a humanized bispecific antibody with affinity for FIX/activated FIX and factor X (substituting for the cofactor activity of FVIII), and promotes effective hemostasis in patients with hemophilia A, even in the presence of inhibitors.¹¹ However, emicizumab is administered as a prophylactic therapy and cannot treat breakthrough bleeding events. Thus, BPAs are still required for management of acute bleeds. rFVIIa (either eptacog beta or eptacog alfa) is the recommended treatment for breakthrough bleeds in hemophilia A patients with inhibitors who use emicizumab prophylaxis.¹²

Eptacog beta is a new rFVIIa BPA produced in a transgenic rabbit expression system.¹³ Approval of eptacog beta for treatment and control of BEs occurring in adult and adolescent hemophilia A or B patients with inhibitors (≥ 12 years of age) was obtained from the U.S. Food and Drug Administration (FDA) in 2020.⁸ The pivotal phase 3 trial (PERSEPT 1; NCT02020369) demonstrated both 75 and 225 $\mu\text{g}/\text{kg}$ initial dose regimens (IDRs) of eptacog beta were effective in

controlling mild or moderate BEs, with three severe BEs being successfully treated.¹⁴ At 12 h post-initial eptacog beta infusion, the reported treatment success proportions for mild or moderate BEs were 82% (75 µg/kg IDR) and 91% (225 µg/kg IDR)⁸ Following an initial 225 µg/kg dose, 84% of mild or moderate BEs were controlled within 3 h and required no further dosing. A low rebleeding rate (1/465 mild or moderate BEs, 0.2%) was reported.¹⁴ The unpredictable inter- and intra-patient efficacy of existing BPAs¹⁵ has highlighted the need to further optimize treatment outcomes through continued development of new safe and efficacious BPAs such as eptacog beta.^{14,16,17}

The safety and efficacy of eptacog beta for BE treatment and control were further examined in a prospective phase 3 clinical trial (PERSEPT 2) enrolling pediatric subjects younger than 12 years of age with hemophilia A or B and inhibitors. PERSEPT 2 is the first reported prospective study to focus exclusively on this population for bleed treatment with a rFVIIa BPA. Results from this trial are described here.

Methods:

Eligibility criteria. Male subjects younger than 12 years of age with hemophilia A or B with inhibitors to FVIII or FIX respectively were eligible to enroll. Additional inclusion and exclusion criteria are listed in Table S1.

Trial design. PERSEPT 2 was a multicenter, open-label, randomized phase 3 trial evaluating the safety, immunogenicity, pharmacokinetics (PK), and efficacy of two IDRs of eptacog beta for treatment of BEs (NCT02448680). PERSEPT 2 was designed as a crossover trial, with subject randomization to either a 75 or a 225 µg/kg IDR with crossover to the alternate IDR every 3 months without a washout period for the duration of the trial (replicating the trial design and dosing schedules

of PERSEPT 1;¹⁴ Figure 1). Subjects received an initial infusion of 75 or 225 $\mu\text{g}/\text{kg}$ eptacog beta (per IDR randomization) in a non-bleeding state for safety assessment and PK measurement purposes. Serum sample testing for anti-eptacog beta antibodies was performed as previously described.¹⁸

BEs were characterized as mild, moderate, or severe (Table S2). Subjects were advised to initiate treatment with a 2-minute intravenous infusion of either 75 or 225 $\mu\text{g}/\text{kg}$ eptacog beta (depending upon IDR randomization) as soon as possible after recognizing bleeding symptoms. BE treatment was anticipated to occur in the home or community setting in most cases. Evaluations of efficacy and need for additional dosing were made at 3 and 9 h after initial infusion for subjects in the 75 and 225 $\mu\text{g}/\text{kg}$ IDRs, respectively. Need for additional 75 $\mu\text{g}/\text{kg}$ dosing was assessed every 3 h thereafter for subjects in both IDRs until the 21 h timepoint, with a final efficacy assessment at 24 h (Figure 1b). No additional study drug was permitted after 21 h in either IDR; if further treatment was required at 24 h, then alternative therapies could be initiated. Subjects who received at least 3 doses of eptacog beta while in the 75 $\mu\text{g}/\text{kg}$ IDR received the same cumulative amount of eptacog beta by 9 h post-initial infusion as subjects in the 225 $\mu\text{g}/\text{kg}$ IDR (Figure 1b). The 9 h interval between initial and subsequent doses of eptacog beta in the 225 $\mu\text{g}/\text{kg}$ IDR is supported by previous PK analyses.¹⁹ The protocol for treating severe BEs is described by Wang et al.¹⁴

Control of mild or moderate BEs following eptacog beta treatment was rated by the parent or caregiver according to a four-point hemostasis evaluation scale (“excellent”, “good”, “moderate”, or “none”; Table S3). Assessments took place in conjunction with the pediatric subject when possible, depending upon age and verbal abilities. Hemostasis evaluations for severe BEs were reported by the treating physician.

Treatment of a mild or moderate BE was considered successful if the following four criteria were met: (i) a hemostasis evaluation of “excellent” or “good” was obtained; (ii) no additional eptacog beta was given within 24 h after the first “excellent” or “good” response was noted; (iii) no alternative

hemostatic agent or blood product was needed; and (iv) pain associated with the BE did not increase following the initial “excellent” or “good” response. A Visual Analogue Scale (VAS) was used to rate pain on a scale of 0 (no pain) to 100 mm (worst possible pain), with subject or caregiver marking a position on a straight 100 mm line to represent relative pain severity.²⁰ The primary efficacy endpoint for PERSEPT 2 was defined as the successful treatment of mild or moderate BEs at 12 h following initial rFVIIa administration. The proportion of mild or moderate BEs successfully treated at 12 h was compared to an objective performance criterion (OPC) of 55%, which was derived from analysis of published studies examining rFVIIa efficacy in adult and pediatric subjects with hemophilia A or B and inhibitors, as previously described.¹⁴ As prospective clinical trials of bleed control with BPAs in children under 12 years of age are without precedent, such an OPC was considered the only benchmark available when the PERSEPT 2 trial was designed.

Statistical analysis. PERSEPT 2 was designed to detect a true treatment success proportion of 0.70 for mild or moderate BEs with at least 80% power when comparing with the OPC of 0.55, assuming a one-sided asymptotically normal test adjusted for multiplicity ($\alpha = 0.0125$) for each dosing regimen, correlated BEs, and 8 BEs per IDR per patient. Success proportion estimates at 12 and 24 h were based on observed cases reported and summarized using descriptive statistics. Estimates and test comparisons were based on an asymptotically normal estimator taking into account within-patient correlation. Statistical analyses were performed using SAS[®] 9.4.

Ethics. The study protocol was reviewed and approved by institutional review boards or independent ethics committees at each study site, and were conducted in compliance with good clinical practice as described in the principles stated in the Declaration of Helsinki.²¹ Assent from the subjects and written informed consent from parents or legal guardians of the subjects were obtained at enrollment.

Results:

Subject population. Subject demographics are shown in Table 1. Twenty-five subjects were enrolled from 31 screened (Figure 1a). None were receiving BPA or emicizumab prophylaxis (PERSEPT 2 was completed prior to emicizumab regulatory approval.). Four subjects discontinued PERSEPT 2 early, either by physician decision (2 subjects: one was nonadherent and another was placed on prophylaxis) or due to withdrawal of consent (2 subjects). No subject was discontinued due to an adverse event.²²

Efficacy. Subjects experienced 549 BEs: 546 BEs were mild or moderate and 3 were severe. Subjects experienced 239 mild or moderate BEs in the 75 µg/kg IDR and 307 mild or moderate BEs in the 225 µg/kg IDR, with 92% of all mild or moderate BEs treated at home. The treatment success proportions and 95% confidence intervals (CIs) at 12 h for mild or moderate BEs were 65.4% (95% CI: [52.3%, 78.5%]) for the 75 µg/kg IDR and 60.3% (95% CI: [48.2%, 72.3%]) for the 225 µg/kg IDR. At 24 h, the treatment success proportions were 97.4% (95% CI: [91.3%, 100.0%]) for the 75 µg/kg IDR and 98.0% (95% CI: [94.5%, 100.0%]) for the 225 µg/kg IDR (Figure 2). The difference in treatment success proportion between the two IDRs was not statistically significant at 12 or 24 h. Overall treatment success proportion for all mild or moderate BEs in both IDRs combined was 62.5% (95% CI: [51.1%, 74.0%]) at 12 h and 97.8% (95% CI: [93.1%, 100.0%]) at 24 h (Figure 2). Three subjects experienced a single severe BE and were treated using a severe BE dosing regimen (Table 2). Twelve (2.2%) of the mild or moderate BEs required an alternative hemostatic agent (either aPCC or eptacog alfa) for bleed control, with 8 of these BEs occurring in a single subject.

Bleeding into joints accounted for 68% of the 546 mild or moderate BEs (Figure 3), and recurrent BEs in the same joint (a target joint) represented 19.9% of all joint BEs. The

difference in treatment success proportions between target joint and non-target joint BEs was not statistically significant, for either IDR considered separately or for both IDRs combined. A median of 2 doses was required for bleed control in the 225 µg/kg IDR, and a median of 3 doses was required in the 75 µg/kg IDR. Eight (1.5%) of all mild or moderate BEs experienced a recurrence of bleeding (defined as bleeding in the same joint or anatomical location within 24 h after an initial “good” or “excellent” hemostasis evaluation). No assessments of BE recurrence were made beyond 24 h.

The overall proportion of BE treatments assessed as “excellent” or “good” at 12 h (64.3%; 95% CI: [52.6%, 76.1%]) and at 24 h (97.6%; 95% CI: [93.0%, 100%]) were similar to the success proportions calculated at 12 and 24 h when applying all four treatment success criteria. Successful pain relief was observed at 12 h after initial eptacog beta administration in 92.8% (75 µg/kg IDR) and 90.8% (225 µg/kg IDR) of mild or moderate BEs. Mean percent decreases in VAS pain score from baseline at 12 h after initial infusion were 70.9% (75 µg/kg IDR) and 64.5% (225 µg/kg IDR).

A 4-year-old subject with hemophilia A and a low body mass index (11.5 kg/m²) experienced 46 (8.4%) of the 546 mild or moderate BEs in PERSEPT 2, and had an outsized effect on efficacy results. This subject exhibited a delayed response to eptacog beta treatment, with a treatment success proportion at 12 h of 5.6% for the 75 µg/kg IDR and 14.3% for the 225 µg/kg IDR. Treatment success proportions at 24 h for both IDRs were 100%. Serum samples from this subject tested negative for anti-eptacog beta antibodies. When excluding this outlier subject from the PERSEPT 2 analyses, the treatment success proportions and 95% CIs at 12 h for mild or moderate BEs increase to 70.3% (95% CI: [59.8%, 80.8%]) for the 75 µg/kg IDR and 65.0% (95% CI: [54.5%, 75.4%]) for the 225

µg/kg IDR.

Safety. As previously described, eptacog beta was well tolerated: no thrombotic events, allergic, hypersensitivity, or anaphylactic reactions, neutralizing anti-eptacog beta antibodies, or treatment-related adverse events were observed.²² Three serious adverse events (paresis, intracranial bleed, and dysentery, all resolving with treatment) were assessed as unrelated to eptacog beta administration.²²

Discussion:

In the current study, the safety and efficacy of a new rFVIIa BPA (eptacog beta) for BE treatment was examined: 549 BEs in 25 pediatric subjects with hemophilia A or B and inhibitors under 12 years of age were evaluated. As with the study in adults and adolescents (PERSEPT 1),¹⁴ a four-part composite of hemostasis and pain criteria (see Methods) was used to determine treatment success in PERSEPT 2. This extensive set of treatment success criteria provides confidence that satisfactory clinical benefits were received by study subjects, acknowledging the subjective nature of hemostasis evaluations and pain assessment in young children.

The subjective aspects of determining bleeding control are well-recognized challenges in assessing treatment efficacy in hemophilia patients, particularly in pediatric subjects.²³ Decisions to cease or continue treating BEs in children with hemophilia have a significant subjective component^{24,25} and are frequently made indirectly by the caregiver, as younger patients may not be fully capable of identifying and communicating when bleeds have resolved. Caregivers report uncertainty in ascertaining exactly when BEs have resolved, and may base continued treatment on rebleeding concerns or on prior experience with similar bleeds.²⁴ Such factors may contribute to the longer rFVIIa treatment duration seen in children over that observed in adults.²⁶ The subjective

aspects of evaluating pain in children²⁰ further complicate hemostasis assessments made by caregivers.

The treatment success proportion for eptacog beta at 12 h was compared to an OPC (55%) derived from published rFVIIa clinical studies including adult and pediatric subjects with hemophilia A or B and inhibitors. This OPC had been previously used in the PERSEPT 1 trial as a benchmark for eptacog beta treatment success in treatment-experienced adults and adolescents¹⁴, and was the only primary endpoint comparator available at the time the PERSEPT 2 trial was designed. An appropriate primary efficacy threshold specifically for prospective pediatric hemophilia trials such as PERSEPT 2 has never been determined.

The overall treatment success proportion of 546 mild or moderate BEs in PERSEPT 2 was 63% at 12 h (Figure 2). As the lower bound of the 95% CI for this point estimate did not exceed 55%, the treatment success proportion at 12 h was not significantly different from the OPC. Similarly, the bleed treatment success proportions at 12 h of 65% for the 75 µg/kg IDR and 60% for the 225 µg/kg IDR (Figure 2) did not significantly differ from the OPC. While the 12-h primary endpoint and the OPC were not statistically different, by 24 h the bleed treatment success proportions were much higher: the overall treatment success was 98% at 24 h (Figure 2), with bleed treatment success proportions of 97% for the 75 µg/kg IDR and 98% for the 225 µg/kg IDR (Figure 2). Several other trial findings support the efficacy of eptacog beta in PERSEPT 2 subjects: (i) only 1.5% of all mild or moderate BEs recurred at the same anatomical site within 24 h of the first “excellent” or “good” hemostasis evaluation; (ii) bleed control was achieved with a median of 2 doses in the 225 µg/kg IDR and 3 doses in the 75 µg/kg IDR for mild or moderate BEs; (iii) only 2.2% of all BEs required alternative treatment; and (iv) by 12 h after initial eptacog beta infusion, mean VAS pain scores were reduced by 70.9% (75 µg/kg IDR) and 64.5% (225 µg/kg IDR) from baseline values at BE onset. No thrombotic events, allergic, hypersensitivity, or anaphylactic reactions, neutralizing anti-eptacog beta

antibodies or treatment-related adverse events were reported. The totality of these data indicate that eptacog beta was safe and effective by 24 h in treating and controlling mild or moderate bleeding in the study participants. As BE resolution was achieved using fewer median number of infusions in the 225 µg/kg IDR as compared to the 75 µg/kg IDR, the 225 µg/kg IDR may potentially be more attractive for patients and less burdensome to caregivers.

Previous pharmacokinetic and laboratory pharmacodynamics analyses have demonstrated peak eptacog beta plasma levels (C_{max}), peak thrombin generation, and clot firmness exhibit a dose-dependent relationship with eptacog beta.¹⁹ In accord with these findings, clinical trial data from adults and adolescents in PERSEPT 1 showed a higher treatment success proportion in the 225 µg/kg IDR as compared to the 75 µg/kg IDR at 12 h (91% and 82% in the 225 and 75 µg/kg IDRs, respectively),⁸ a result consistent with a dose-dependent thrombin burst driving hemostasis at the site of injury. A similar outcome in PERSEPT 2 might be reasonably anticipated; however, observed efficacies for the two IDRs at 12 h were instead comparable in magnitude (60% and 65% in the 225 and 75 µg/kg IDRs, respectively), and lower overall than those seen in PERSEPT 1. An elevated weight-adjusted clearance of eptacog beta in pediatric subjects (as previously reported for eptacog alfa²⁷⁻²⁹) provides a plausible explanation for the observed 12-h hemostatic response (Figure 2); however, the comparable efficacies observed for the two IDRs at 12 h might not be consistent with such a model being the sole factor for the observed results. Assuming similar weight-adjusted eptacog beta clearance for subjects in either IDR, any increased clearance in pediatric subjects should impact treatment success proportions for both IDRs to the same degree, preserving the same higher treatment success proportion in the 225 µg/kg IDR relative to the 75 µg/kg IDR seen in PERSEPT 1. The observed hemostatic response might be better explained by the subjective nature that surrounds the determination of BE resolution by caregivers, as well as a bias towards continued treatment out of rebleeding concerns^{24,25} (regardless of IDR). A lack of caregiver clarity regarding BE cessation along

with a bias towards retreatment would contribute towards conservative estimates of treatment success proportions at the 12-h timepoint, and could effectively mask any real differences between treatment success proportions for the two IDRs at 12 h.

Additional factors further inform interpretation of trial results. While a limited number of subjects participated in PERSEPT 2 (25 subjects), hemostatic efficacy was reported as the proportion of successfully-treated BEs and a substantial number of mild or moderate BEs were available for analysis (546 BEs). A 4-year-old subject with hemophilia A who experienced 46 of the 546 mild or moderate BEs and a delayed response to eptacog beta exerted an outsized effect on efficacy results, resulting in a reduced treatment success proportion for each IDR at 12 h after initial BE treatment. The treatment success proportions for these 46 BEs at 24 h were 100% for both IDRs, demonstrating the effectiveness of eptacog beta for control of bleeding in this subject by the 24-h timepoint.

Conclusion:

PERSEPT 2 is the first prospective study of bleed treatment with a rFVIIa BPA focused solely on interval analysis of clinical response in hemophilia A or B subjects with inhibitors younger than 12 years of age. Both eptacog beta IDRs (75 and 225 $\mu\text{g}/\text{kg}$) provided safe and effective treatment and control of bleeding by 24 h to the trial subjects: no thrombotic events, allergic reactions, or treatment-related adverse events were reported; a significant proportion of BEs were successfully treated at 12 h; and nearly all BEs were resolved at 24 h. As such, eptacog beta potentially offers an important therapeutic option to patients, caregivers and health care providers for BE treatment.

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Author Contributions

All of the authors analyzed and interpreted the data. T.A.W. developed the initial draft, and all authors provided critical input and edited the manuscript. All authors reviewed and approved the final submission.

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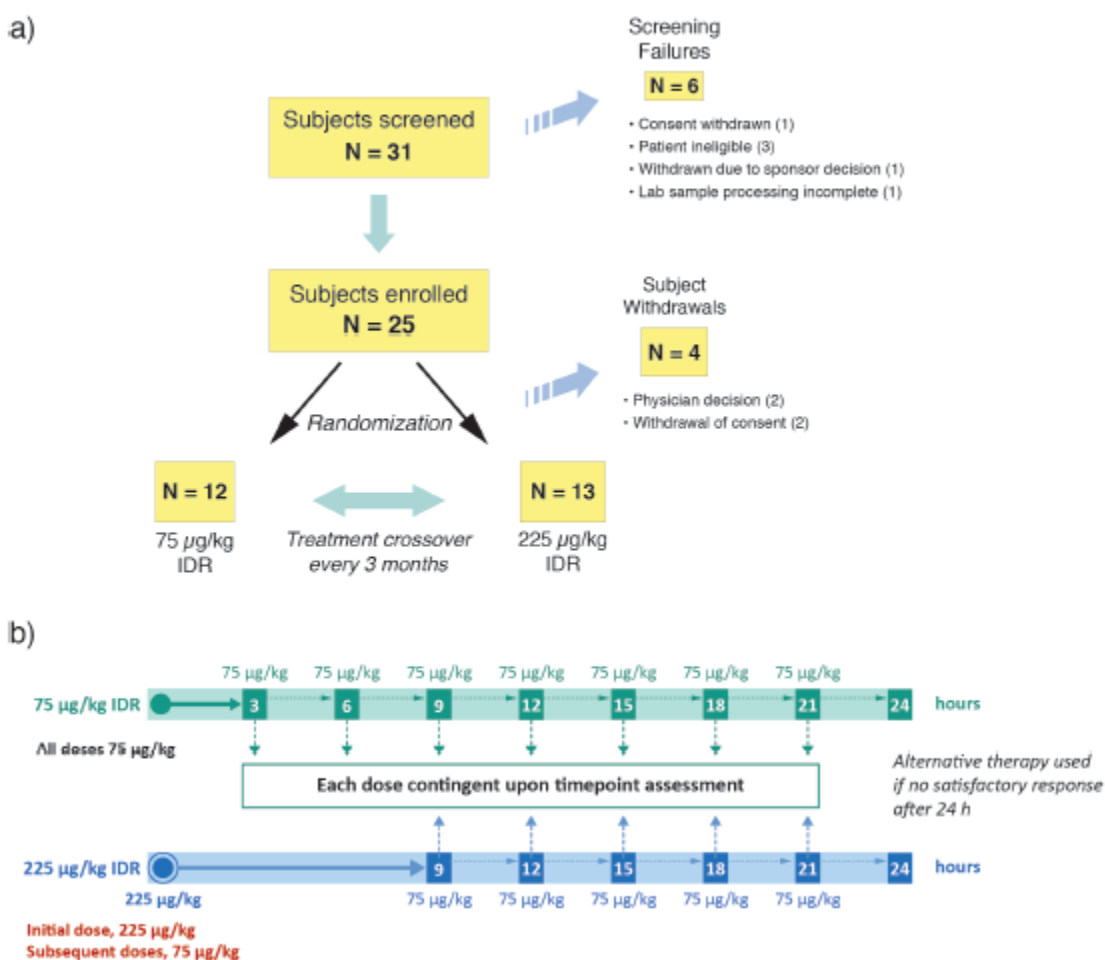
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Figure Legends

Figure 1: (a) Subject dispositions for PERSEPT 2. (b) Treatment protocol for mild and moderate bleeding episodes in PERSEPT 2, with dosing schedules for 75 and 225 $\mu\text{g}/\text{kg}$ IDRs indicated.

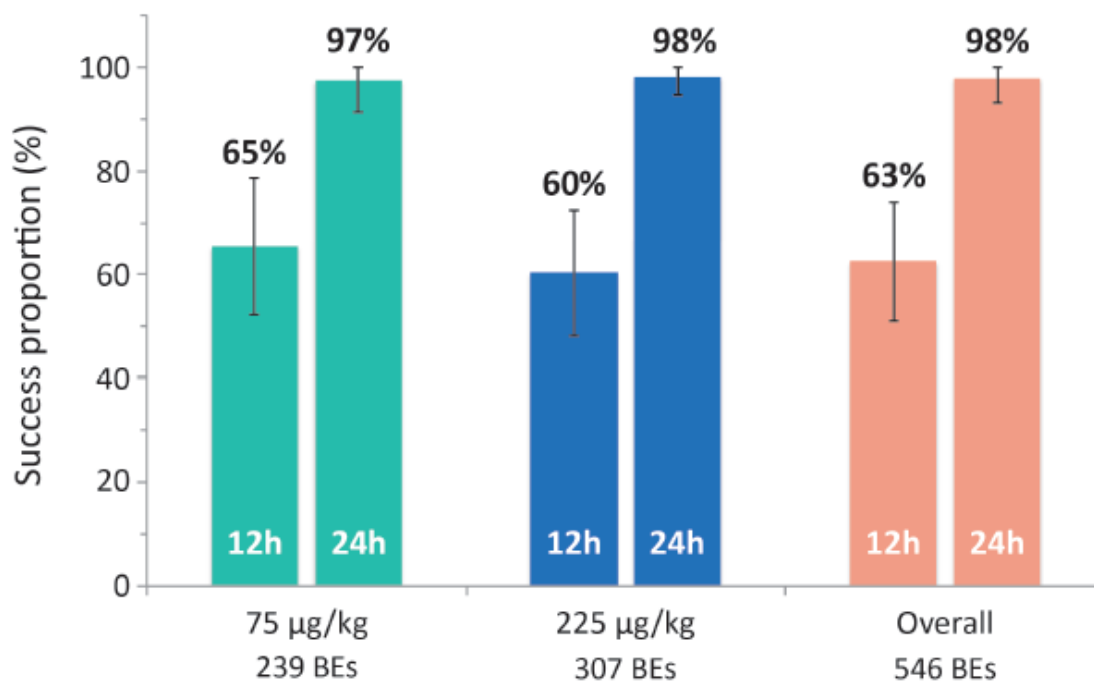
Figure 1



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Figure 2: Success proportions and 95% confidence intervals for mild or moderate bleeding episode treatment at 12 and 24 h.

Figure 2

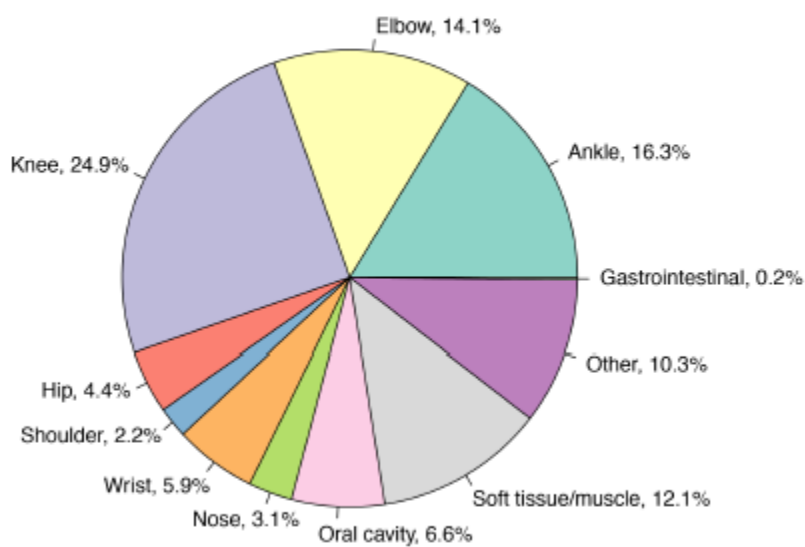


Author 1

Figure 3: Anatomical distribution of the 546 mild or moderate bleeding episodes in PERSEPT 2. The percentage for each anatomical site of the total number of mild or moderate bleeding episodes is indicated.

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Figure 3



Author M

Tables

Table 1

Table 1: PERSEPT 2 trial demographics.

Subjects (N = 25)	Summary
Age, y	
Mean (SD)	4.9 (3.3)
Median	5.0
1st/3rd quartile	2/8
Minimum/maximum	1/11
Race, n (%)	
Black or African American	7 (28.0)
White	18 (72.0)
Ethnicity, n (%)	
Hispanic or Latino	3 (12.0)
Not Hispanic or Latino	22 (88.0)
Weight, kg	
Mean (SD)	20.9 (10.8)
Median	19.0
1st/3rd quartile	12.5/26.9
Minimum/maximum	8.2/52.0
Hemophilia type, n (%)	
Hemophilia A	23 (92.0)
Hemophilia B	2 (8.0)

Inhibitor titer, n (%)^a

BU ≥ 5	18 (72.0)
BU < 5 and high anamnestic response expected	6 (24.0)
BU < 5 and refractory to increased factor replacement dosing anticipated	1 (4.0)

SD, standard deviation; BU, Bethesda units.

^aInhibitor titer assessment performed at screening. Anamnestic and refractory response as indicated in disease history.

Table 2: Severe BEs in PERSEPT 2.

Subject	Age (y)	Hemophilia type	Severe BE type	Severe BE dosing regimen (µg/kg)	Hospital visit	Hemostasis evaluation (12 h)	Hemostasis evaluation (24 h)
Subject 1	9	Hemophilia A	Spontaneous renal hemorrhage ^a	225	Yes	Moderate	Moderate
Subject 2	8	Hemophilia A	Traumatic intracranial bleed ^b	225 ^c	Yes	None	None
Subject 3	6	Hemophilia B	Traumatic left elbow bleed	225 ^c	No	Not recorded	Not recorded

BE, bleeding episode

^aSubject- and physician-reported hemostasis evaluations were both “good” after approximately 4 days of treatment with eptacog beta, a treatment duration consistent with consensus management guidelines.³⁰

^bThe intracranial bleed (confirmed by computed tomography [CT] scan) was caused by head trauma and resolved with treatment. Subject 2 received eptacog beta for 3 days followed by aPCC (FEIBA[®]) for 17 days, a treatment duration that is consistent with previously-described intracranial hemorrhage management for hemophilia A or B patients with inhibitors³¹ as well as with consensus treatment guidelines.³⁰ CT scans on days 2, 4, and 5 following BE onset showed no further intracranial bleeding.

^cThe 225 µg/kg severe BE dosing regimen (as detailed by Wang et al.¹⁴) was not followed: either scheduled eptacog beta infusions were delayed by as long as 3 h (for the left elbow BE) or eptacog beta amounts and dosing intervals other than those specified by the protocol were used (for the intracranial bleed).

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