Clinical haemophilia

The safety of activated eptacog beta in the management of bleeding episodes and perioperative haemostasis in adult and paediatric haemophilia patients with inhibitors

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1 | INTRODUCTION

A major complication in the treatment of persons with haemophilia is the development of neutralizing alloantibodies (inhibitors) against factor VIII (FVIII) or factor IX (FIX) from factor replacement exposures. Inhibitor development occurs in about 20–30% and up to 10% of patients with severe haemophilia A and haemophilia B, respectively.1,2 Treatment options for patients with inhibitors are limited: immune tolerance induction (ITI) for inhibitor eradication is the preferred therapy, but is not always effective and is often not attempted in patients with haemophilia B.3 In lieu of inhibitor eradication, bypassing agents (BPAs) such as activated prothrombin complex concentrate (aPCC, FEIBA®; Takeda)4 and the recombinant activated human factor VII (rFVIIa) products eptacog alfa (EA, NovoSeven® RT; Novo Nordisk)5 and eptacog beta (EB, SEVENFACT®; HEMA Biologics, LLC and LFB SA)6 may be administered to control bleeding. These BPAs produce a
thrombin burst by supplying multiple clotting factors (aPCC), or by activating the extrinsic coagulation pathway (rFVIIa) at the site of injury.\textsuperscript{7} Emicizumab (Hemlibra\textsuperscript{®}; Chugai), a bispecific antibody, represents a prophylactic option for reducing bleeding incidence in haemophilia A patients with or without inhibitors.\textsuperscript{8}

EA has a well-established, favorable safety profile in haemophilia patients with inhibitors.\textsuperscript{9–12} Thrombotic events associated with EA treatment are rare in this population but nonetheless remain a safety consideration given the procoagulant properties of EA and the increased incidence of thrombotic complications when used off-label.\textsuperscript{13} EA has not been associated with an anamnestic response in haemophilia patients with inhibitors, shows low immunogenicity, and is generally well tolerated.\textsuperscript{10,11}

EB is a new human rFVIIa BPA that is produced in transgenic rabbits, and was approved by the FDA in 2020 for use in adults and adolescents (≥12 years of age) with haemophilia A or B and inhibitors for the treatment and control of bleeding episodes using either 75 or 225 µg/kg initial dose regimens (IDRs).\textsuperscript{6,14–16} Development of a new rFVIIa was motivated by the lack of predictable efficacy and a variable intra- and inter-patient response associated with existing BPAs.\textsuperscript{17} Clinicians needed a rFVIIa that exhibits a reliable dose-response and is safe and efficacious not only at a low dose, but also with a high-dose regimen and a prolonged interval between dosing. While EB and EA share a common amino acid sequence, EB has a distinct posttranslational modification profile.\textsuperscript{18} EB demonstrates enhanced binding (relative to EA) to the endothelial protein C receptor (EPCR) in preclinical studies.\textsuperscript{19} This enhanced EPCR binding may contribute to EB haemostatic activity, as studies suggest that rFVIIa-EPCR interactions promote haemostasis by downregulating the activated protein C (APC) anticoagulation pathway, promoting barrier protection,\textsuperscript{20} and transporting rFVIIa into extravascular tissue to extend bioavailability.\textsuperscript{21,22}

Results from earlier Phase 1b and Phase 3 (PERSEPT 1) trials with adult and adolescent haemophilia patients with inhibitors suggest that EB shares a similar safety profile to that of EA.\textsuperscript{15,16} We now extend our findings on EB safety in a second Phase 3 trial (PERSEPT 2) with 25 paediatric subjects less than twelve years of age, and in a third Phase 3 trial (PERSEPT 3) with 12 subjects who underwent elective surgery while receiving EB. The collective safety-related results from the three Phase 3 trials are described here.

2 | METHODS

2.1 | Adverse event definitions

Adverse events were characterized as treatment-emergent adverse events (TEAEs), defined as adverse events that occurred following initial EB administration (regardless of whether the adverse event is drug-related); treatment-related TEAEs, those deemed definitely, probably or possibly related to EB administration; and serious adverse events (SAEs), defined as adverse events that were potentially life-threatening, led to hospital admission, prolonged an existing hospitalization, or resulted in significant disability or death.

2.2 | Eligibility criteria

Male subjects with congenital haemophilia A or B with inhibitors to either FVIII or FIX were eligible for trial enrollment. Additional eligibility criteria are given in Supporting Information (Table S1). PERSEPT 1 or PERSEPT 2 subjects were allowed to participate in PERSEPT 3, provided all PERSEPT 3 eligibility criteria were met.

2.3 | PERSEPT 1 and PERSEPT 2 trial design

PERSEPT 1 and PERSEPT 2 were global, multicentre, open-label, randomized Phase 3 trials for evaluating the safety, immunogenicity, pharmacokinetics (PK), and efficacy of two EB IDRs. PERSEPT 1 and PERSEPT 2 were designed as crossover trials, with subject randomization to either a 75 or a 225 µg/kg IDR, and IDR crossover every 3 months without a washout period for the duration of the trial (Figure 1A). Subjects received an initial infusion of 75 or 225 µg/kg EB (per IDR randomization) for PK measurement purposes. TEAE and vital sign assessments were performed periodically for at least 2 h (PERSEPT 1) or 8 h (PERSEPT 2) post-initial infusion. Safety evaluations were performed at screening and at 3, 6, 12, 18 and 24 weeks after the initial EB infusion; every 6 weeks after the Week 24 visit; and at end of study or early termination visits. Safety evaluations included physical exams, vital signs, electrocardiograms (for PERSEPT 1), immunogenicity tests and clinical laboratory tests (haematology, serum chemistry, urinalysis [for PERSEPT 1], coagulation and viral serology [hepatitis B, hepatitis C and human immunodeficiency virus; PERSEPT 1 only, at screening]), as well as TEAE assessments.

Following a bleeding episode, EB was administered as a 2-min bolus intravenous infusion. Subjects were advised to treat as soon as possible within 4 h of recognizing bleeding symptoms. Efficacy evaluation and further treatment occurred at timepoints described in Figure 1B. Severe bleeding episodes were treated according to the severe bleeding episode treatment protocol described by Wang et al.\textsuperscript{15}

2.4 | PERSEPT 3 trial design

PERSEPT 3 was a global, multicentre, single-arm Phase 3 trial for assessing the safety, immunogenicity and efficacy of EB in haemophilia A or B patients with inhibitors undergoing elective surgical or other invasive procedures. Physical exams, vital signs, electrocardiograms, and clinical laboratory tests (haematology, serum chemistry, urinalysis, coagulation and viral serology [hepatitis B, hepatitis C and human immunodeficiency virus for subjects ≥12 kg]) were performed at screening. Subjects undergoing minor procedures (i.e. procedures that typically require <5 days of factor replacement in haemophilia patients) received an initial dose of 75 µg/kg EB by intravenous bolus infusion within 2 min of surgical incision or start of invasive procedure. Subjects undergoing a major procedure (i.e. procedures that typically require ≥5 days of factor replacement, and involve entry into a body cavity and/or organ removal or similarly complex procedure)
received 200 μg/kg (Figure 2A). The choice of initial dose for minor procedures was guided by previous PK studies16 and the safety and efficacy results from PERSEPT 1,15 which suggested 75 μg/kg as the preincision dose prior to minor procedures. For major procedures, 200 μg/kg was selected as the preincision dose in anticipation of more extensive tissue damage and an increased haemostatic challenge. Efficacy evaluation and further treatment took place as described in Figure 2B. The minimum treatment duration was 5 days for major surgeries and 2 days for minor procedures. Subjects were followed postoperatively according to the standard of care at the study site. Clinical laboratory tests were performed 24 h after procedure completion, as well as 2 and 28 days after the last EB infusion or at early trial termination. Adverse events were recorded from trial enrollment until adverse event resolution, 28 (± 3) days after the last dose, or early trial termination (whichever occurred first). Immunogenicity testing samples were collected prior to the planned procedure, 7–14 days following the initial EB dose, and 2 and 28 days following the final EB infusion, or at early trial termination.

2.5 Immunogenicity tests

Serum samples were analysed for anti-EB antibodies (all isotypes) at a central laboratory using an electrochemiluminescent assay; any positive samples were retested in a confirmatory assay to verify signal specificity. Samples that tested positive in both initial and confirmatory assays were further analysed for functional FVIIa inhibition. Since EB is isolated from the milk of transgenic rabbits, serum samples were also tested for antibodies against rabbit milk proteins.

2.6 Ethics

All study protocols were 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.23 Written informed consent was obtained from all subjects (or their parents or legal guardians if under 18 years of age) at enrollment. PERSEPT 1, PERSEPT 2 and PERSEPT 3 trials are registered at www.clinicaltrials.gov (NCT02020369, NCT02448680 and NCT02548143, respectively).

3 RESULTS

3.1 Subject population

Trial participant demographics are shown in Supporting Information (Table S2). No subject was receiving emicizumab prophylaxis. Subjects from the PERSEPT 1 trial have been previously described.15 Briefly,
29 subjects were screened and 27 enrolled in PERSEPT 1; 31 subjects were screened for the PERSEPT 2 trial with 25 subjects being enrolled (Figure 1A). Five subjects discontinued PERSEPT 1 early due to noncompliance (two subjects); withdrawal of consent (two subjects; one for personal reasons and another for perceived lack of efficacy of the lower IDR given past experience with high dose EA); or by physician decision (one subject noncompliant and having difficulty administering EB independently). Four subjects discontinued PERSEPT 2 before the end of the trial, either due to withdrawal of consent (two subjects) or by physician decision (two subjects; one subject was noncompliant and another needed to be placed on prophylaxis; Figure 1A). No subject in PERSEPT 1 or PERSEPT 2 was discontinued from a trial due to an adverse event.

Eighteen subjects were screened for PERSEPT 3 and 12 subjects were enrolled (six each in the minor and major surgery groups; Figure 2A). Two subjects left PERSEPT 3 early: one subject (age 9) in the minor surgery group due to withdrawal of consent (for perceived lack of efficacy), and another subject in the major surgery group due to an adverse event.

3.2 Safety

Subjects in these three trials experienced 1029 bleeding episodes or invasive procedures and received 3388 EB infusions during 1087 EB exposure episodes (Table 1). An exposure episode (a period of study drug exposure) was characterized as any of the following: (i) the course of all EB infusions given to treat a bleeding episode; (ii) a single EB dose given for PK assessment purposes; (iii) all EB infusions administered just prior to and during an invasive procedure; or (iv) the course of all EB infusions given during post-operative recovery following an invasive procedure. Mean drug exposure levels and duration were also recorded (Table 1).

Adverse event summary statistics are shown in Table 2. Adverse events were further examined by IDR and surgery type (Figure 3). In PERSEPT 1, eight subjects in the 75 µg/kg IDR experienced 15 TEAEs and six subjects in the 225 µg/kg IDR experienced 12 TEAEs. Both EB IDRs were well tolerated.

One patient in the 75 µg/kg IDR of PERSEPT 1 experienced six treatment-related TEAEs (four instances of infusion-site discomfort...
TABLE 1  PERSEPT trial characteristics. The number of bleeding episodes, surgeries, exposure episodes, EB infusions, the extent of EB exposure and the time that subjects participated in PERSEPT 1, PERSEPT 2 and PERSEPT 3 trials are shown

| Trial          | Number of subjects | Number of bleeding episodes or surgeries | Number of exposure episodes | Number of infusions | Drug exposure (µg/kg), mean (SD) | Time in trial, mean (SD) |
|---------------|--------------------|-----------------------------------------|-----------------------------|---------------------|----------------------------------|-------------------------|
| PERSEPT 1     | 27                 | 468                                     | 508                         | 968                 | 4016 (3258)                      | 6.6 (2.6) months        |
| PERSEPT 2     | 25                 | 549                                     | 555                         | 1686                | 7053 (6653)                      | 11.2 (5.3) months       |
| ages 6 to <12 | 12                 | 296                                     | 297                         | 881                 | 7647 (4526)                      | 12.6 (5.4) months       |
| PERSEPT 3     | 12                 | 12                                      | 24                          | 734                 | 4650 (2961)                      | 11.0 (5.3) tx days      |
| minor surgery | 6                  | 6                                       | 12                          | 229                 | 2863 (1521)                      | 4.3 (3.7) tx days       |
| ages 6 to <12 | 12                 | 297                                     | 297                         | 881                 | 7647 (4526)                      | 12.6 (5.4) months       |
| PERSEPT 3     | 12                 | 12                                      | 24                          | 734                 | 4650 (2961)                      | 11.0 (5.3) tx days      |
| minor surgery | 6                  | 6                                       | 12                          | 229                 | 2863 (1521)                      | 4.3 (3.7) tx days       |
| major surgery | 6                  | 6                                       | 12                          | 505                 | 6438 (3051)                      | 17.6 (12.4) tx days     |
| All studies   | 60                 | 1029                                    | 1087                        | 3388                | 5676 (5261)                      | 7.7 (5.2) months        |

SD, standard deviation; tx, treatment.  
<sup>a</sup>PERSEPT 1, PERSEPT 2 and PERSEPT 3 collectively enrolled 64 subjects; however, as two subjects from PERSEPT 1 and two subjects from PERSEPT 2 also participated in PERSEPT 3, in total only 60 individuals participated in the three trials.

and two infusion-site hematoma events), which were considered to be mild by the site investigator and all resolved. Another patient in the 225 µg/kg IDR experienced one treatment-related TEAE (increased body temperature), which was considered moderate in severity and resolved upon treatment with ibuprofen and other non-steroidal anti-inflammatory medications. Overall, 0.01 treatment-related TEAEs per exposure episode were observed in PERSEPT 1. One PERSEPT 1 subject in the 75 µg/kg IDR experienced acute tonsillitis and subarachnoid haemorrhage, two SAEs that required hospitalization and ultimately resolved upon treatment; neither of these two SAEs were considered to be related to EB administration by the site investigator.

In PERSEPT 2, 12 subjects experienced 29 TEAEs in the 75 µg/kg IDR and 15 subjects experienced 41 TEAEs in the 225 µg/kg IDR. None of these TEAEs were treatment-related (Figure 3), and both IDRs were well tolerated in this cohort. One subject in the 225 µg/kg IDR experienced an intracranial bleed and paresis that required prolonged hospitalization; these two episodes were characterized as SAEs. A second PERSEPT 2 subject from the 225 µg/kg IDR experienced dysentery, which was characterized as a SAE (an acute infection). Each of these three SAEs ultimately resolved with treatment, and were not considered to be related to EB administration by the site investigator.

The six minor procedures in PERSEPT 3 included three circumcisions and three tooth extractions, while the six major surgeries were all orthopaedic procedures of the lower extremities and included two amputations, two knee surgeries, a hip replacement and an achilloplasty. Four subjects in the minor surgery group experienced eight TEAEs, while six subjects in the major surgery group experienced 28
TEAEs and treatment-related TEAEs per exposure episode following EB infusion, stratified by IDR (PERSEPT 1 and PERSEPT 2) or pre-incision dose used in each surgery type (PERSEPT 3). Overall TEAEs and treatment-related TEAEs per exposure episode from the three clinical trials (grouped by IDR or pre-incision dose) are also shown.

One subject from the major surgery group experienced three TEAEs that were considered treatment-related by the site investigator. This subject had undergone a right hip replacement that proceeded without complications using a 200 µg/kg pre-incision EB dose followed by 75 µg/kg intraoperative/postoperative EB infusions (Figure 2B), and experienced a post-procedural hematoma one day after the surgery. The site investigator considered this TEAE as possibly related to EB treatment, withdrew study drug and discontinued the subject from the trial. The subject received concomitant medication (including FEIBA®) for two more days but the post-procedural hematoma did not resolve. The subject died approximately two days after study discontinuation from acute blood loss anaemia stemming from gastrointestinal haemorrhage. The site investigator considered the blood loss anaemia and gastrointestinal haemorrhage (both SAEs) as probably related to EB administration, but the study’s independent data monitoring committee (DMC) did not agree: given the 2-day interval between study discontinuation and SAE onset along with the approximately 1.6-h half-life of EB, the lack of clinical evidence or autopsy findings that supported study drug relatedness, and other subject risk factors, the DMC concluded that both the blood loss anaemia and the gastrointestinal haemorrhage (and hence the subject’s death) were unlikely related to EB treatment. This subject had previously participated in and completed the PERSEPT 1 trial, where he was treated for 25 bleeding episodes without experiencing any TEAEs. No other death, SAE or discontinuation from the study due to a TEAE occurred in PERSEPT 3.

The most common TEAEs experienced by two or more subjects in at least one clinical study are shown in Table 3. PERSEPT 1 and PERSEPT 2 adverse events are consolidated in Figure 4 to compare adverse event occurrences in a bleed treatment setting (stratified by IDR) with those in the minor and major surgery environments from PERSEPT 3. In total, 133 TEAEs and 10 treatment-related TEAEs were observed during the three clinical trials and 1087 exposure episodes were recorded, yielding 0.12 and 0.01 TEAEs and treatment-related TEAEs per exposure episode, respectively (Table 2).

### 3.3 Thromboembolic events

No thromboembolic events were recorded in any of the subjects, either during episodic use (PERSEPT 1 and PERSEPT 2) or in the surgical setting (PERSEPT 3). A history of thrombosis, thromboembolism or known risk factors for thrombosis were exclusion criteria.

### 3.4 Immunogenicity

No allergic, hypersensitivity or anaphylactic events were reported in any of the trials. A positive anti-EB antibody test was confirmed for one PERSEPT 1 subject 12 weeks after initial EB infusion, and was negative at weeks 18, 24 and the end of study visit. Anti-EB antibody was also confirmed in a PERSEPT 2 subject at every safety assessment time-point (including prior to EB exposure) except for the end of study visit. In all cases, the antibodies detected were non-neutralizing. Another PERSEPT 2 patient tested positive for antibodies against rabbit milk protein at week 66, with two subsequent assays at week 72 and the end of study visit being negative. The lack of any other clinical manifestations indicating an immune response in this subject suggests that the transient reactivity to milk protein was likely a false-positive result.
TABLE 3  TEAEs that occurred in two or more subjects in at least one clinical trial. The number (n) and percentage (%) of subjects that experienced a given TEAE in each trial is shown in the table.

| TEAE                              | PERSEPT 1 | PERSEPT 2 | PERSEPT 3 | All trials |
|-----------------------------------|-----------|-----------|-----------|------------|
| Nasopharyngitis (common cold)     | 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)    |
| Diarrhea                          | 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)    |

FIGURE 4  TEAEs and treatment-related TEAEs per exposure episode following EB administration for both bleeding episode treatment and perioperative settings. The panel showing results from the perioperative setting is further subdivided into minor and major surgery groups.

4  | DISCUSSION

Bypassing agents are a mainstay for treatment of bleeding in haemophilia A and haemophilia B patients with inhibitors, both in acute bleed treatment and periisurgical settings. The safety record of EA has been followed closely in this patient population since 198824 and has been associated with a low incidence of thrombotic events.11 In addition, no cases of neutralizing antibodies against EA have been reported in haemophilia patients with inhibitors.10,13 The clinical experience of EA in paediatric cohorts has been similar to that in adults: an analysis of safety data from paediatric trials involving 172 subjects, 1184 bleeding episodes and 28 surgeries revealed one confirmed treatment-related thrombotic event.25 Surgical procedures (both minor and major) have been performed with EA without treatment-related TEAEs in the majority of cases.26–29 Doses as high as 300 µg/kg EA have been used without apparent safety issues.30,31 Monotherapy with rFVIIa (either EA or EB) has emerged as the recommended treatment for breakthrough bleeds in haemophilia A patients...
with inhibitors on emicizumab, a consequence of thrombotic complications arising from breakthrough bleeds that were treated with aPCC or aPCC and EA combined but not EA alone. The favourable safety profile of FDA-approved rFVIIa products stems from localized rFVIIa activity while bound to exposed tissue factor (TF) or activated platelets at the site of vascular injury: absent exposed TF or activated platelets, coagulation at undamaged tissue is disfavoured. The rFVIIa safety profile is further boosted by rapid plasma elimination (T1/2 of 2–3 h in haemophilia A or B individuals), which may be aided by EPCR-mediated transport from plasma into extravascular tissue.

The clinical trial data reported here show that EB is safe and well tolerated in haemophilia patients with inhibitors, a clinical experience that mirrors that of EA. The three Phase 3 clinical trials enrolled 60 subjects, and recorded 1087 EB exposure episodes that were associated with 3388 infusions of study drug during 1029 bleeding episodes or surgeries. Ten treatment-related TEAEs (0.01 treatment-related TEAEs per exposure episode) arose during the PERSEPT studies (Table 2), with six of those being experienced by a single PERSEPT 1 subject. Treatment-related TEAE occurrences showed no apparent correlation with IDR (Figures 3 and 4), though a rigorous statistical comparison was not made owing to the small number of treatment-related TEAEs available for analysis. One death occurred during the PERSEPT 3 trial, and was considered to be unlikely related to EB administration by the independent DMC.

No allergic, hypersensitivity or anaphylactic events were reported in any of these trials. While emergence of neutralizing antibodies against other investigational rFVIIa molecules has been previously observed, no neutralizing antibodies against EB were detected during the three PERSEPT trials. Transient and non-neutralizing anti-EB antibodies were detected in one subject from PERSEPT 1 and another from PERSEPT 2, with anti-EB antibody being confirmed in the PERSEPT 2 subject prior to EB exposure. This subject had received EA therapy a few months prior to study entry, which may have given rise to an antibody that cross-reacted with EB. No thrombotic or thromboembolic events were observed, even in the surgical setting. Clinical experience demonstrates that thrombotic events related to the administration of rFVIIa (EA) in haemophilia patients with inhibitors are quite rare: one report by Abshire and Kenet describes just 30 thrombotic events from an estimated 800,000 infusions, and another study of haemophilia patients with inhibitors in both bleed treatment and prophylactic settings by Shapiro et al. found no thrombotic events after 61,734 EA infusions. While the lack of EB-related thrombotic events is a welcome observation and congruent with published data for EA, additional clinical experience is necessary to characterize the risk of thrombotic events associated with EB utilization in haemophilia patients with inhibitors.

5 | CONCLUSION

The collective results from three trials demonstrate an excellent EB clinical safety profile. EB provides clinicians with a new option for bleeding episode treatment and perioperative care in haemophilia A or B patients with inhibitors. Additional clinical use in real-world settings and in post-approval studies such as ATHN 16 (NCT04647227) will augment our understanding of EB safety.

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CONFLICT 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. G.C. has received honoraria as a speaker/participant on advisory boards for Alexion, Bayer, Shire/Takeda, CSL Behring, Novo Nordisk, Sobi, Roche, uniQure, Sanofi, Werfen, Kedrion, LFB and Grifols; M.C. has received research support from Roche/Genentech; has participated in speaker’s bureaus with Takeda, Genentech, Bayer and Novo Nordisk; has received honoraria from Takeda, Roche/Genentech, Pfizer, HEMA Biologics, Spark, BioMarin, Sanofi, Kedrion, Grifols and Bayer; is a major stock shareholder in Alnylum; and has served on advisory boards for Takeda, Roche/Genentech, Pfizer, HEMA Biologics, Spark, uniQure, BioMarin, Sanofi, Kedrion, Grifols and Bayer. P.d.M. has received consulting fees from Novo Nordisk, LFB and Bayer. J.D. has acted as a consultant for Bayer and HEMA Biologics, and has been on the speaker’s bureau for Bayer. C.L. has received honoraria for advisory board participation for Bayer, Catalyst, CSL Behring, Genentech, Sanofi and Takeda. J.L. has acted as a paid consultant to Novo Nordisk. J.M. has received research grants from Bayer, BioMarin, CSL, Novo Nordisk, Sobi, Roche and uniQure; has served on scientific advisory committees of Amgen, Bayer, Biotec, Biogen, Baxalta, CSL Behring, Catalyst Biosciences, Novo Nordisk, Roche and Spark; and has been a member of the speaker bureau of Alnylam, Bayer, Biotec, Biogen, Novo Nordisk, Pfizer, Sobi, Shire, Roche, ISTH and WFH. W.M. declares interests with Alnylum, Bayer, Biogen, Chugai, CSL Behring, Novo Nordisk, Octapharma, Pfizer, LFB, Roche, Takeda, Freeleine, BioMarin, Sobi and uniQure. C.N. has received honoraria/consultation fees or grants/research support from Bayer, CSL Behring, Freeleine, LFB, Novo Nordisk, Octapharma, Pfizer, Roche-Chugai, Sanofi, Shire-Takeda, Sobi and Spark Therapeutics. D.Q. has 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.R.’s employers have received research funding from Bayer, BioMarin, CSL Behring, Genentech, Kedrion, Novo Nordisk, Pfizer, Sanofi, Takeda and uniQure. M.R. is on the board of directors of Foundation for Women and Girls with Blood...
Disorders and Partners in Bleeding Disorders. M.R. is an employee of the American Thrombosis and Hemostasis Network and Oregon Health & Science University. J.F.S has received grants from Pfizer, Bayer, Novo Nordisk and LFB, and has fees for consulting to Sobi. A.D.S. has served on advisory boards or as consultant for Genentech, Roche, Novo Nordisk, BioMarin, Bioverativ, Sanofi, ProMetric Bio Sciences, Sangamo, Sigilon and Takeda; and has received research funding from these organizations plus Agios, OPKO Global Bio Therapeutics, Kedrion, Octapharma and Novartis. R.F.S. has acted as a paid consultant for Takeda, Sanofi, Sobi, Catalyst, BioMarin, Novo Nordisk, Genentech, Octapharma, Bayer, Pfizer, Grifols, Kedrion and HEMA Biologics; and has investigator-initiated grants from Grifols (Mexico Inhibitor Study), Takeda (ATHN 9), Genentech and Octapharma (Emi PUPs and Nuviq ITI) and Octapharma (MOTIVATE study). A.S. has served as the chair of the DMC for this study. 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. G.Y. has received honoraria for consulting for Genentech/Roche and a grant from Genentech. G.Y. also has received honoraria from BioMarin, Grifols, Pfizer, Sanofi, Spark, and Takeda; and has grants from Grifols and Takeda. 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. C.M. is an employee of HEMA Biologics, LLC. T.A.W. is a medical writer for GLOVAL LLC. 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. S.B.B., C.H., J.J., I.H.M., O.S. and K.V.V. have no competing interests to declare.

AUTHOR CONTRIBUTIONS
All of the authors analysed and interpreted the data. W.A.A. and T.A.W. co-wrote the manuscript, and all authors edited the manuscript. G.C., S.B.B., J.D., J.J., I.H.M., D.Q., J.F.S., O.S., K.V. and M.W. were clinical trial investigators; A.S., P.d.M. and C.K. served on the data monitoring committee (A.S. as chair). All authors reviewed and approved the manuscript.

DATA AVAILABILITY STATEMENT
Data available from the authors upon reasonable request.

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