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ORIGINAL ARTICLE

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Pharmacokinetics, safety and efficacy of a recombinant factor IX product, trenonacog alfa in previously treated haemophilia B patients

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Introduction: Trenonacog alfa (IB1001) is a recombinant factor IX (rFIX) manufactured in Chinese hamster ovary (CHO) cells. IB1001 was evaluated in a multicentre clinical trial with haemophilia B patients.

Aim: The aim was to establish IB1001 pharmacokinetic non-inferiority to comparator rFIX, safety and efficacy in previously treated patients (PTPs) with haemophilia B.

Methods: Subjects were severe or moderately severe haemophilia B adult and adolescent PTPs with no history of FIX inhibitors.

Results: IB1001 PK non-inferiority to comparator rFIX was demonstrated through ratio of $AUC_{0-\infty}$ in 32 subjects. IB1001 was well tolerated in all 76 treated subjects; the most common adverse drug reaction was headache (2.6% of subjects) and there were no reports of FIX inhibitors. Transient non-inhibitory binding FIX antibodies and anti-CHO cell protein antibodies developed in 21% and 29% of subjects respectively; no safety concerns were associated with development of these antibodies. Prophylaxis (mean duration ± SD: 17.9 ± 9.6 months, mean dose: 55.5 ± 12.9 IU/kg, median 1.0 infusion per week) was effective in preventing bleeds (median annual bleed rate: 1.52, interquartile range: 0.0-3.46). One or two IB1001 infusions resolved 84% of the bleeds, while for 84% of treatments haemostatic efficacy of IB1001 was rated excellent or good. IB1001 haemostatic efficacy for all 19 major surgeries was rated adequate or better than adequate.

Conclusions: IB1001 is safe and efficacious for treatment of bleeds, routine prophylaxis and perioperative management in haemophilia B patients.

KEYWORDS
efficacy, haemophilia B, IB1001, pharmacokinetics, recombinant factor IX, safety

1 | INTRODUCTION

Haemophilia B is an X-linked recessive bleeding disorder caused by a deficiency of coagulation factor IX.[1] Severe forms of haemophilia B present in early life, at circumcision, or with joint and soft tissue bleeds when the child becomes mobile. Mild cases may present following haemostatic challenges such as surgery or trauma. Internal bleeding may occur anywhere and bleeding into joints is common.[2]

Haemophilia B is treated by infusion of FIX concentrate. Despite substantial improvements in the safety of plasma-derived coagulation factor concentrates recombinant products are currently considered to be optimum treatment.[3] Several recombinant versions of FIX have been marketed for treatment of haemophilia B[2] including standard half-life products and extended half-life products.

Trenonacog alfa (IB1001) is a standard half-life rFIX produced in a genetically engineered Chinese hamster ovary (CHO) cell line with no exogenous materials of human or animal origin used in the manufacture, purification, or formulation of the final product. The primary amino acid sequence of IB1001 contains a threonine at residue 148, in contrast to other available conventional half-life recombinant FIX products that have an alanine at that position.[4] The manufacturing process includes three independent viral removal/inactivation steps: solvent/detergent treatment, a chromatographic step and nanofiltration.

A Phase 3 controlled, multicentre study was designed to evaluate PK non-inferiority of IB1001 to a comparator standard half-life rFIX, as well as to establish safety and haemostatic efficacy of IB1001 in adolescent and adult (≥12 years of age) severe (FIX activity <1 IU/dL) and moderately severe (FIX activity ≤2 IU/dL) haemophilia B previously treated patients with severe bleeding phenotype. Based on the results of this study, IB1001 was licensed in the United States as IXINITY® (coagulation factor IX [recombinant]) for prevention and control of bleeding episodes, and for perioperative management in adults and children ≥12 years of age with haemophilia B.

2 | MATERIAL AND METHODS

2.1 | Study design

The study included a PK Phase that was a randomized, double-blinded cross-over comparison of IB1001 to a marketed rFIX comparator (nonacog alfa). Following a 5-day wash out period, subjects received 75 ± 5 IU/kg of the first treatment after which there was another 5-day wash out period before receiving the second treatment. There was also a repeat open-label, uncontrolled PK phase in a subset of patients that participated in the initial PK Phase. After at least 3 months of receiving IB1001, these subjects received an infusion of 75 ± 5 IU/kg of IB1001 prior to PK assessment.

The study also consisted of an open-label Treatment Phase in which patients received IB1001 either as prophylaxis or on-demand, with a goal of acquiring 50 exposure days (ED) for prophylaxis patients or 6 months on study for on-demand patients. Patients from the PK Phase could transition into the Treatment Phase or patients could enter the Treatment Phase directly after performing a recovery assessment with IB1001. Patients on prophylaxis were recommended a dose of 50-75 IU/kg, twice weekly based on investigator discretion. Patients receiving on demand treatment received a recommended dose of 50-100 IU/kg depending on the severity of the bleeding episode. Following completion of the Treatment Phase, patients could continue in an open-label Continuation Phase. During the Continuation Phase, some subjects were found to have a high anti-CHOP antibody titre. As a result, an additional hydrophobic interaction chromatography step was validated for use in the IB1001 manufacturing process to reduce content of host cell proteins in the final drug product (ie, modified IB1001). Results of a non-clinical study comparing the previous IB1001 product and modified IB1001 showed that the modified process significantly reduced the immunogenic potential of IB1001.[5] The PK, safety, efficacy, and immunogenicity data in this manuscript are derived from IB1001 manufactured before this process change.

In addition, there was an open-label surgical sub-study that assessed IB1001 efficacy for perioperative management. Subjects received IB1001 by either bolus infusions or continuous infusion. The bolus infusion regimen consisted of an infusion of IB1001 up to 120 IU/kg 1 hour prior to the start of surgery, followed by 60 IU/kg every 12 hours for at least 3 days postsurgery. The continuous infusion regimen consisted of a bolus infusion of up to 120 IU/kg 1 hour prior to the start of surgery followed by continuous infusion of IB1001 with a target plasma FIX level between 70 and 110 IU/dL.

The study (clinicaltrials.gov number: NCT00768287) was run from February 10, 2009 until March 1, 2013 in accordance with the Declaration of Helsinki and was approved by local independent ethics committees for 23 sites in 7 countries throughout North America (US), Europe (UK, Italy, France, Poland), Middle East (Israel) and Asia (India). All patients provided informed consent prior to enrolment.

2.2 | Patient population

Eligible subjects included immunocompetent adolescents and adults (≥12 years of age) with documented severe (FIX activity <1 IU/dL) or moderately severe (FIX activity ≤2 IU/dL) haemophilia B, who had previously been treated with a FIX concentrate for at least 150 ED with no history of FIX inhibitors. On a country-specific basis, subjects <12 years of age were able to enter the study at the treatment phase. On-demand patients had a minimum of 3 bleeds requiring treatment within 6 months prior to enrolment or 6 bleeds over the preceding 12 months; subjects on prophylaxis had to have this bleeding pattern prior to starting prophylaxis.

2.3 | Pharmacokinetic assessments

The primary objective of the PK Phase was to evaluate PK non-inferiority of IB1001 to marketed standard half-life rFIX comparator (nonacog alfa). Factor IX activity levels using a one-stage clotting assay at a central laboratory were the basis for all PK parameter computations. Samples were taken pre-infusion and at the following time points post-infusion: 30 minutes ± 5 minutes, 1 hour ± 5 minutes, 3 hours ± 30 minutes, 6 hours ± 1 hour, 9 hours ± 1 hour, 12 hours ± 2 hours, 24 hours ± 3 hours, 36 hours ± 3 hours, 48 hours ± 3 hours, 60 hours ± 3 hours, and 72 hours ± 3 hours. The following PK parameters were computed per actual dose administered for IB1001 and the comparator rFIX: area under curve (AUC), referring to area under the plasma concentration vs time curve, at 0-72 hours ($AUC_{0\text{-}72\ h}$)

TABLE 1 Rating scale of haemostatic efficacy

Subject rating	
Excellent	A dramatic response with abrupt pain relief and clear reduction in joint or haemorrhage site size
Good	Pain relief or reduction in haemorrhage site size that may have required an additional infusion for resolution
Fair	Probable or slight beneficial response usually requiring one or more additional infusions for resolution
Poor	No improvement or condition worsens
Investigator rating	
Effective	Each bleeding episode treated in the interval was evaluated by the subject as either "excellent" or "good" at the majority of time points
Partially effective	Bleeding episodes treated in the interval were evaluated as either "excellent", "good", or "fair" at the majority of time points; or 1 bleeding episode received an evaluation of "poor" at the majority of time points
Not effective	More than one-third of bleeding episodes during the interval were evaluated as "poor" at the majority of time points
Not applicable	No bleeding episodes during the interval
Surgeon rating	
Less than expected	Blood loss estimate at time of surgery
Expected	
More than expected	
Haemostasis superior	Blood loss assessment at 12 and 24 h postsurgery
Haemostasis adequate	
Haemostasis poorly controlled	

and 0 to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), clearance, mean residence time (MRT), terminal half-life ($t_{1/2}$), incremental recovery and volume of distribution at steady state (Vd_{ss}).

2.4 | Haemostatic efficacy

The haemostatic efficacy of IB1001 was evaluated by calculation of annualized bleed rate (ABR) for prophylaxis subjects and the number of infusions used to treat a bleed and overall rating of efficacy by subjects and investigators or surgeons (Table 1). Compliance to prophylactic regimen was calculated as the total number of IB1001 infusions administered, divided by the total expected number of IB1001 infusions, multiplied by 100. Investigator efficacy assessments were performed every 3 months.

2.5 | Perioperative haemostatic efficacy

The ability of IB1001 to provide adequate haemostasis during major surgeries was evaluated in the surgery sub-study. Blood loss at time of surgery and at 12 and 24 hours postsurgery were used to evaluate haemostatic efficacy of IB1001.

2.6 | Immunogenicity

Testing for FIX inhibitors was performed using a modified Nijmegen Bethesda assay in a central laboratory. The presence of non-neutralizing FIX binding antibodies and non-neutralizing anti-CHO cell protein (CHOP) antibodies was also tested in the central laboratory with enzyme-linked immunosorbent assays (ELISA) employing polyclonal anti-human Ig antibodies (IgG, IgM and IgA) adapted for detection of anti-FIX or anti-CHOP antibodies. If samples tested positive for anti-CHOP antibodies, they were further assessed to determine the titre.

2.7 | Safety assessments

Safety was evaluated through reports of adverse events (AEs), haematology, blood chemistry, physical examinations and vital signs at each study visit. The same safety assessments were conducted in study subjects that transitioned to modified IB1001 (ie, study drug manufactured with a modified process to reduce host cell proteins).

2.8 | Statistical analysis

A comparison of IB1001 and nonacog alfa was based on two-sided 90% confidence interval (CI) for the $AUC_{0-\infty}$ ratio of IB1001 over nonacog alfa (calculated on a log scale and then untransformed). The within-group standard deviation was determined using the pooled result for the 2 groups. Non-inferiority of IB1001 compared to nonacog alfa was declared if the lower bound of the 90% CI for the ratio of $AUC_{0-\infty}$ for IB1001/nonacog alfa was >0.80. All other PK parameters between IB1001 and nonacog alfa were reported as descriptive statistics. PK data from this study has been published previously;[6] however, a different software (WinNonlin) was used to derive the PK parameters for this manuscript and an additional subject was included in repeat PK analysis. The ABR was calculated as: (number of bleeding episodes × 12)/(observed treatment period in months). Since subjects were allowed to switch treatment regimens while on study, the efficacy analysis is based on the actual regimen.

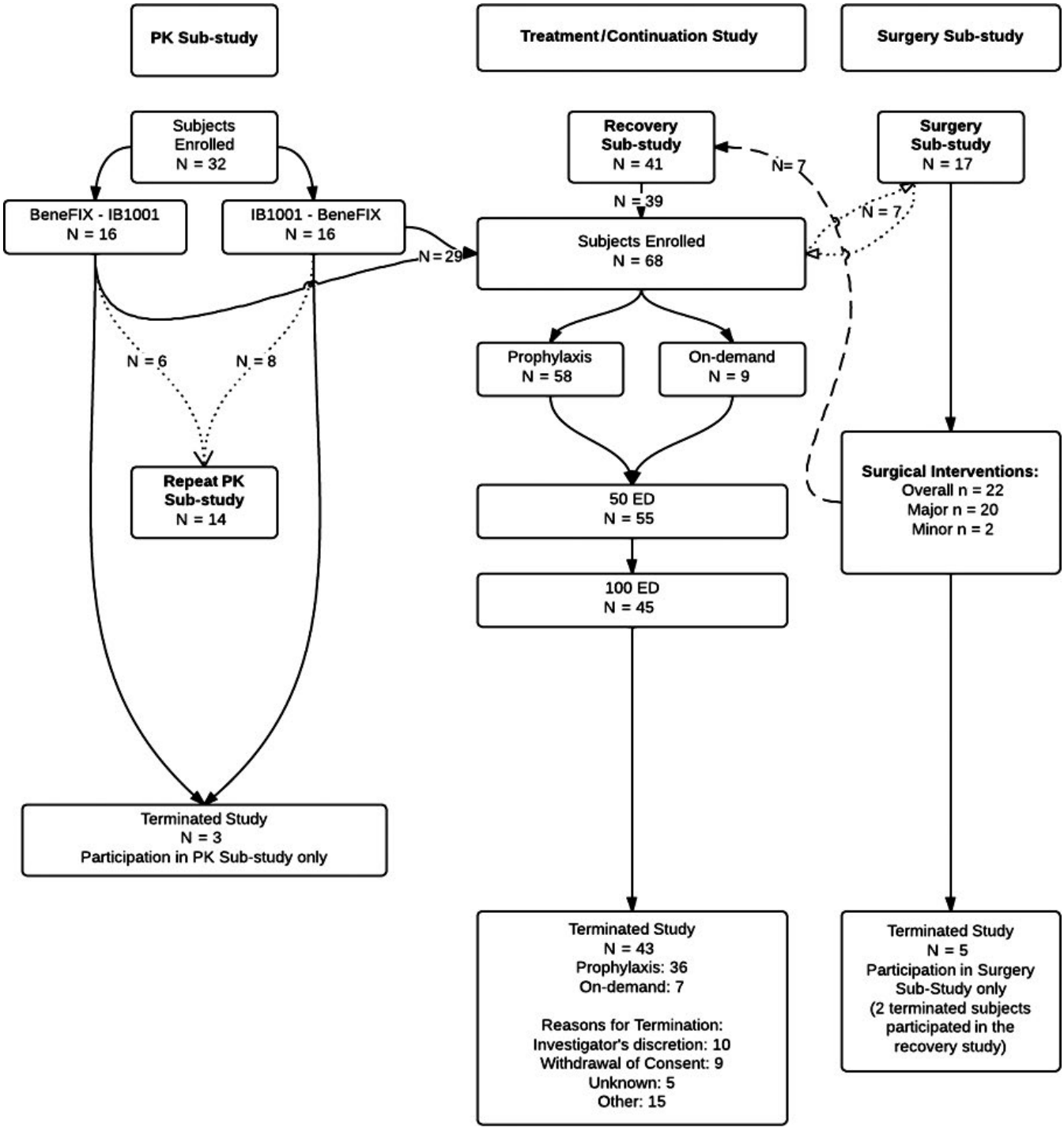

FIGURE 1 Overview of subject disposition

3 | RESULTS

3.1 | Study patient population

A total of 76 subjects were enrolled and received at least one infusion of IB1001 (Figure 1). Patient demography is presented in Table 2. The mean age was 30.5 years (median: 26; min, max: 7, 64). There were 3 subjects <12 years of age who received waivers to enrol in the treatment phase of the study. Most of the subjects were severe (14.5%) or moderately severe (81.6%) haemophilia B males. Median number of bleeding episodes within 6 months prior to enrolment was 1.0 (min, max: 0.0, 21.0) and the majority of subjects had arthropathy and target joints at screening. All subjects were treated with FIX replacement therapy prior to enrolment. There were 32 subjects that completed the PK Phase and following completion of the PK Phase, 29 of those subjects continued into the Treatment Phase (14 of these

TABLE 2 Demography characteristics of study subjects

Demography parameter	Initial PK crossover N = 32	Repeat PK N = 14	Treatment/continuation phase		Surgery sub-study N = 16	Overall N = 76
			Prophylaxis N = 58	On-demand N = 9		
Gender n (%)						
Male	32 (100.0)	14 (100.0)	58 (100.0)	9 (100.0)	16 (100)	76 (98.7)
Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age (y)						
Mean ± SD	32.7 ± 15.0	31.5 ± 16.5	28.8 ± 14.2	36.4 ± 10.9	31.5 ± 12.4	30.5 ± 14.4
Median (min-max)	29.9 (14.8-64.5)	25.4 (15.3-65.8)	23.3 (7.4-64.5)	39.4 (19.1-48.9)	32.6 (12.2-56.8)	26.0 (7.0-64.0)
Race n (%)						
American Indian/ Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	7 (12.1)	0 (0.0)	5 (31.3)	8 (10.5)
Black or African American	1 (3.1)	0 (0.0)	3 (5.2)	0 (0.0)	1 (6.3)	3 (3.9)
Caucasian	30 (93.8)	13 (92.9)	44 (75.9)	9 (100.0)	9 (56.3)	60 (78.9)
Native Hawaiian/ Pacific Islander	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)	2 (2.6)
Other	1 (3.1)	1 (7.1)	2 (3.4)	0 (0.0)	1 (6.3)	3 (3.9)
Baseline FIX activity (% FIX activity) n (%)						
<1%						11 (14.5)
1-2%						62 (81.6)
>2%						3[a] (3.9)

[a]3 subjects had FIX activity >2% at baseline after the wash-out period, however all 3 subjects in their medical history had records of FIX activity <2%, as well as symptoms consistent with severe form of haemophilia B, therefore these 3 subjects were deemed eligible for study enrollment.

subjects underwent a repeat PK evaluation), while 41 subjects directly entered the Treatment Phase after an initial recovery assessment. At the start of Treatment Phase, 58 subjects elected prophylaxis and 9 subjects chose an on-demand regimen. For surgical sub-study, there were 16 subjects that underwent 19 major surgeries.

3.2 | Pharmacokinetic parameters

The lower bound 90% CI for ratio of $AUC_{0-\infty}$ for IB1001/nonacog alfa was 0.89 demonstrating that the primary PK endpoint criterion of >0.80 was met. Other PK parameters between the two rFIX products were comparable (Table S1). The repeat PK analysis demonstrated the stability of initial PK parameters during long-term exposure (median: 5.8 months; min, max: 3.1, 18 months) to IB1001 (Table S1).

3.3 | Haemostatic efficacy

Most of the subjects (37/61) who treated prophylactically in the Treatment/Continuation phases of the study fulfilled the criteria for secondary or tertiary prophylaxis as defined in the WFH guidelines.[4] However, subjects were allowed to switch regimens at discretion of the investigator and the subject; therefore, the analysis of efficacy includes data based on the actual treatment regimen followed. In total, there were 61 subjects who received prophylaxis and 12 subjects who received on-demand regimen. Compliance to prophylactic treatment was 88% (median; Table 3). The summary of IB1001 treatment and ABR for prophylaxis and on-demand cohorts is presented in Table 4. The mean ± SD duration of treatment for prophylaxis subjects was 17.9 ± 9.6 months (median: 16.2; min, max: 2.4, 39.6), with a mean dose of 55.5 ± 12.8 IU/kg (median: 53; min, max: 26, 80) and a mean of 1.9 infusions per week (median: 1.0; min, max: 1.0, 2.0). For on-demand subjects, mean duration of treatment was 15.9 ± 11.5 months (median: 14.1; min, max: 2.3, 36.9), with a mean dose of 60.0 ± 18.2 IU/kg (median: 59; min, max: 24, 94). The overall mean exposure to IB1001 was 183 ± 91 ED (median: 127.5; min, max: 1, 430); there were 55 subjects with ≥50 ED and 45 subjects with ≥100 ED. For prophylaxis subjects, the mean exposure to IB1001 was 149 ± 93 ED (median: 136; min, max: 1, 430) and for on-demand subjects it was 84 ± 35 ED (median: 94; min, max: 40, 131). As expected, the ABR for prophylaxis group (median: 1.52; IQR: 0.0-3.46) was lower when compared to on-demand ABR (median: 16.1; IQR: 6.60-23.71) (Table 3).

A total of 508 bleeding episodes were treated with IB1001 (286 reported by 42/61 prophylaxis subjects and 222 bleeding episodes reported by 10/12 on-demand subjects). There were 426 bleeding episodes (84%) that resolved with one or two IB1001 infusions (71% of bleeding episodes were resolved with one infusion; the majority of these [59%] were joint haemorrhages). For 24 bleeding episodes

TABLE 3 Summary of IB1001 treatment and annualized bleed rate (ABR)

	Prophylaxis N = 61	On-demand N = 12
Treatment duration (mo)		
Mean ± SD	17.9 ± 9.6	15.9 ± 11.5
25th percentile	9.2	5.5
Median (min-max)	16.2 (2.4-39.6)	14.1 (2.3-36.9)
75th percentile	24.2	25.2
Number of exposure days		
Mean ± SD	148.8 ± 93.1	84.2 ± 34.7
Median (min-max)	135.5 (1-430)	94.0 (40-131)
Number of infusions per wk		
Mean ± SD	1.9 ± 2.2	Not applicable
25th percentile	1	
Median (min-max)	1.0 (1.0-20.0)	
75th percentile	2	
Dose per infusion (IU/kg)		
Mean ± SD	55.0 ± 12.8	60.0 ± 18.2
25th percentile	49.9	49.9
Median (min-max)	53.0 (26.1-80.2)	59.3 (23.9-94.1)
75th percentile	64.0	71.8
Total ABR		
Mean ± SD	3.55 ± 7.19	16.39 ± 11.83
25th percentile	0.00	6.60
Median (min-max)	1.52 (0.0-47.5)	16.10 (0.0-39.4)
75th percentile	3.46	23.71
Patients with zero bleeds n (%)	19 (31.1)	Not applicable
Compliance		
Mean ± SD	87.7 ± 11.9%	Not applicable
Median (min-max)	90.3% (53.4%-103.0%)	

(4.7%) that were predominantly related to trauma, target joints, or muscle bleeds, 5 or more infusions were required.

Haemostatic efficacy at bleed resolution was rated by the subjects as "excellent" or "good" in 84% of all treated bleeds. Overall, IB1001 haemostatic efficacy was rated as "effective" 92% of the times by the investigators, with 8% rated as "partially effective." None of the investigator ratings were reported as "not effective."

3.4 | Perioperative haemostatic efficacy

Surgery sub-study involved 16 subjects who underwent 19 evaluable major surgeries; IB1001 was administered as bolus infusions in 13 procedures or as continuous infusion in 6 procedures. Mean loading bolus dose prior to the surgical procedure was 120 ± 11.4 IU/kg (median: 120 IU/kg, min-max: 103.2, 142 IU/kg). Maintenance bolus infusions were given every twelve hours and the corresponding mean maintenance bolus dose was 59.7 ± 12.2 IU/kg (median 60 IU/kg; min-max: 23.8, 120.0 IU/kg), as dictated by the subject's needs. For procedures managed by continuous infusions, subjects first received a mean loading dose of 95.4 ± 14.5 IU/kg (median 99.1 IU/kg; min-max: 67.2-109.0 IU/kg), followed by a mean continuous infusion of 7.1 ± 4.0 IU/kg h^{-1} (median 6.9 IU/kg h^{-1}; range: 3.0, 21.5 IU/kg h^{-1}). Blood loss at the time of surgery was rated by the surgeon as "expected" (n = 6) or "less than expected" (n = 13), while at 12 and 24 hours postsurgery IB1001 was rated by the surgeon as "superior" (n = 7) or "adequate" (n = 12) in controlling haemostasis. There were no transfusion requirements during the surgical procedures (Table 4).

3.5 | Safety

IB1001 appeared well tolerated in all 76 study subjects exposed. There were no deaths, severe allergic reactions, anaphylaxis, thromboembolic events or related serious adverse events (SAEs). A total of 444 AEs were reported by 57/76 subjects (75%), including 15 AEs in 7 subjects (9%) that were considered related to IB1001 treatment or adverse drug reactions (ADRs, Table 5). The most common ADR was headache [5 events in 2 subjects (2.6%)]. None of the subjects developed FIX inhibitors during the study, while 16/77 (21%) subjects developed non-neutralizing FIX antibodies after screening. After receiving IB1001, 68 subjects have been tested for anti-CHOP reactivity; 20 subjects (29%) seroconverted (developed persistent anti-CHOP reactivity), 37 subjects (54%) remained negative, while 11 subjects (16%) were considered indeterminate (2 subjects were positive at screening, 5 subjects had persistent non-specific antibody binding, 3 subjects had an isolated positive test result and one subject had no sufficient follow-up samples). There were no safety concerns related to development of non-neutralizing FIX antibodies or anti-CHOP antibodies. After at least 12 months of treatment with modified IB1001, there were no new seroconversions in previously anti-CHOP negative subjects (n = 10) or in subjects (n = 3) with indeterminate assay results (ie, reactive for non-specific assay control). Two subjects with anti-CHOP titres demonstrated negative anti-CHOP results after ≥12 months of modified IB1001 treatment, while the other 2 subjects had stable titres (Table S2).

4 | DISCUSSION

This was the first clinical trial with IB1001 (trenonacog alfa), a standard half-life rFIX. The results of the PK Phase demonstrated IB1001 PK non-inferiority to the comparator rFIX, and IB1001 incremental recovery of 0.98 ± 0.21 IU/dL.

Prophylactic treatment and in particular early prophylaxis has been associated with reduction in bleeding episodes.[7,8] In this clinical trial, 61 subjects received routine prophylaxis (median duration: 16.2 months), of which 19 subjects (31%) reported no bleeding episodes. In addition, there were 12 on-demand subjects (median duration: 16.1 months) in the study. The dose ranges used to treat bleeding episodes in this study (50-100 IU/kg) are similar to the dosing recommendations for

TABLE 4 Summary of perioperative haemostatic IB1001 efficacy

Type of major surgical procedure	Number of procedures N = 19	Type of IB1001 dosing	Perioperative haemostasis assessment			Requirement for transfusion (yes/no)
			At time of surgery (number of procedures)	12 h postsurgery (number of procedures)	24 h postsurgery (number of procedures)	
Knee arthroplasty	5	Bolus	Expected (5)	Superior (1)	Superior (1)	No
				Adequate (4)	Adequate (4)	
	3	CI	Expected (3)	Superior (1)	Superior (1)	
				Adequate (2)	Adequate (2)	
Knee amputation	1	Bolus	Expected (1)	Superior (1)	Superior (1)	No
Elbow arthroplasty	2	CI	Less than expected (2)	Superior (1)	Superior (1)	No
				Adequate (1)	Adequate (1)	
Arthroscopic synovectomy	2	Bolus	Less than expected (1)	Adequate (2)	Adequate (2)	No
			Expected (1)			
Ankle debridement	2	Bolus	Less than expected (1)	Superior (1)	Superior (1)	No
			Expected (1)	Adequate (1)	Adequate (1)	
Knee debridement	1	Bolus	Expected (1)	Superior (1)	Superior (1)	No
Percutaneous Achilles tendon lengthening	1	CI	Expected (1)	Adequate (1)	Adequate (1)	No
Open inguinal hernia repair	1	Bolus	Less than expected (1)	Superior (1)	Superior (1)	No
Tibiotalar fusion	1	Bolus	Less than expected (1)	Adequate (1)	Adequate (1)	No

CI, continuous infusion.

major bleeds with both nonacog alfa and nonacog gamma, which target a circulating FIX level of 50-100 IU/dL and are also consistent with WFH guidelines[2] for moderate bleeds (circulating FIX level of 40-60 IU/dL) and major bleeds (circulating FIX level of 80-100 IU/dL). As expected, the ABR of prophylaxis cohort (median: 1.52) was lower when compared to the ABR of on-demand cohort (median: 16.10). This is consistent with the previously published data on rFIX therapy.[9,10] The percentage of subjects with baseline FIX levels 1-2 IU/dL is 81%, which is higher than in other studies, although all subjects in this study had a severe bleeding phenotype prior to study entry.

Haemostatic efficacy of IB1001 was evaluated in the Treatment and Continuation phases of the study. Of the 508 bleeding episodes, regardless of treatment regimen or type of bleeding episode (ie, spontaneous or due to trauma) where IB1001 efficacy was rated by subjects, the efficacy was considered "good" or "excellent" 84% of the time. The majority of bleeds (84%) were resolved with one to two IB1001 infusions, similar to results derived from studies with other standard half-life rFIX products.[9,11]

Perioperative haemostatic efficacy of IB1001 was evaluated in 16 subjects who underwent 19 major surgeries, including 13 surgeries supported by bolus IB1001 infusions and 6 surgeries supported by continuous infusion. The dosing FIX trough target of >60 IU/dL in this study is less than the recommended target for nonacog gamma (80-100 IU/dL), but is consistent with the WFH guidelines which target 60-80 IU/dL preoperatively and then range from 20 to 60 IU/dL postoperatively. For all 19 major surgeries, the surgeon's assessment of blood loss at the time of surgery was "less than expected" or "expected". Consistent with this, haemostasis postsurgery was considered "superior" (n = 6) or "adequate" (n = 13) at 12 and 24 hours postsurgery. Across the subjects' procedures, there was no consistent pattern between the ratings at the time of surgery and the postsurgery ratings. However, all ratings of haemostasis with IB1001 at the time of surgery were at least "expected" and all ratings postsurgery were at least "adequate" when compared to similar procedures in non-haemophilic patients. This is supported by the lack of transfusion requirements during the procedures.

IB1001 was well tolerated as there were no reports of deaths, allergic reactions, anaphylaxis, thromboembolic events or related SAEs. The most common ADR was headache (2.6% of subjects). There were no reports of FIX inhibitors at any point during the study. Some subjects (21%) developed transient non-inhibitory binding FIX antibodies with no apparent effect on subject safety or efficacy of IB1001. Presence of non-inhibitory binding FIX binding antibodies has been reported in haemophilia B patients treated with FIX replacement therapy,[12] albeit the clinical significance is unknown. Antibodies to CHO cell proteins have been previously reported with CHO cell-derived recombinant factor concentrates.[13,14] In this study, 20/68 subjects (29%) tested positive for anti-CHOP antibodies with no apparent effect on subject safety or efficacy of IB1001. The ongoing study subjects (n = 17) in the Continuation Phase were then transitioned to modified IB1001; after ≥12 months of treatment with modified IB1001 no new seroconversions were observed in previously anti-CHOP negative subjects

TABLE 5 Summary of adverse drug reactions (ADRs)

MedDRA standard system organ class	Adverse drug reaction[a]	No. of events	No. of subjects N = 76 n (%)	Reporting frequency (%)[b]
Congenital, familial and genetic disorders	Haemophilia[c]	1	1 (1.3)	Rare (0.010)
General disorders and administration site conditions	Asthenia	1	1 (1.3)	Rare (0.010)
	Injection site discomfort	1	1 (1.3)	Rare (0.010)
Infections and infestations	Influenza	1	1 (1.3)	Rare (0.010)
Investigations	Anti factor IX antibody positive[d]	1	1 (1.3)	Rare (0.010)
Nervous system disorders	Headache	5	2 (2.6)	Rare (0.052)
	Dysgeusia	1	1 (1.3)	Rare (0.010)
	Lethargy	1	1 (1.3)	Rare (0.010)
Psychiatric disorders	Apathy	1	1 (1.3)	Rare (0.010)
	Depression	1	1 (1.3)	Rare (0.010)
Skin and subcutaneous tissue disorders	Rash pruritic	1	1 (1.3)	Rare (0.010)

[a]Adverse events assessed by the study investigators as related to IB1001.
[b]Frequency percentage equals total number of ADRs/total number of IB1001 infusions (ie, 9629 infusions).
[c]Reported as exacerbation of haemophilia.
[d]Non-inhibitory FIX antibody.

(n = 10). Two out of 4 subjects with anti-CHOP titres reverted to anti-CHOP negative status, while the other 2 subjects had stable titres. Overall, these results may indicate that the anti-CHOP immunogenicity potential of modified IB1001 has been reduced with the addition of the validated step to IB1001 manufacturing process.

5 | CONCLUSION

The non-inferior PK profile of IB1001 to nonacog alfa, the generally positive assessment of control and treatment of breakthrough and other bleeding episodes during the Treatment/Continuation phase by both patients and investigators, and the uniformly positive assessments of haemostatic adequacy or superiority of IB1001 for perioperative management of major surgeries, provide strong evidence of the efficacy of IB1001 for the control, prevention, and reduction in bleeding in subjects with haemophilia B. The lack of significant safety findings, specifically lack of any detected FIX inhibitors and all other serious class specific adverse events provide support that the safety profile of IB1001 is acceptable for treatment of subjects with haemophilia B.

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DISCLOSURES

BD and TB are employed by Emergent BioSolutions Inc. YH was an employee of Emergent BioSolutions Inc. EG was a consultant for Emergent BioSolutions Inc. P Collins, DVQ, MM, P Chowdary, CLK, SJA and MVR acted as principal investigators for the study and conducted the research. P Collins, CK and CH declared no conflict of interest. SJA and MVR received honoraria for conducting the research. DVQ consulted for and received honoraria from Baxalta, Biogen, CSL, NovoNordisk, Bayer and Grifols. MM consulted for NovoNordisk, CSL Behring and Grifols. P Chowdary received honoraria from Bayer, Baxalta, Biogen Idec, CSL Behring, NovoNordisk, Pfizer and Sobi.

AUTHORS' CONTRIBUTIONS

PC and DVQ conducted the research and provided data and edited the manuscript, MM, CLK, SJA, MVR, CH and JB conducted the study and contributed data, YH analysed the data, BD wrote the manuscript,

EG was involved in study conception and design as well as medical oversight of the study and TB provided medical consultancy for the sponsor during the study conduct. All authors reviewed and approved the final manuscript.

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SUPPORTING INFORMATION

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