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ORIGINAL ARTICLE

Trenonacog alfa safety, efficacy, and pharmacokinetics in previously treated pediatric hemophilia B

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Abstract

Background: Trenonacog alfa is a recombinant factor IX approved for adolescents and adults with hemophilia B.

Objectives: The aim of this study was to assess the pharmacokinetics (PK), efficacy as prophylaxis, control of bleeding episodes, and safety of trenonacog alfa in previously treated participants aged <12 years with severe or moderately severe hemophilia B and no current or history of inhibitors.

Methods: The study had 3 phases: (1) PK evaluation after a single infusion of 75 ± 5 IU/kg, (2) treatment phase in which participants received trenonacog alfa prophylaxis 35 to 75 IU/kg for 50 exposure days, and (3) a continuation phase in which prophylaxis could be administered for ≥50 additional exposure days.

Results: The PK of trenonacog alfa was comparable between adolescents and adults except for higher clearance, shorter mean residence time and elimination half-life, and lower incremental recovery. Prophylaxis resulted in a median annualized bleeding rate of 0.86 (mean = 2.34) for the combined treatment and continuation phases; 33.3% of participants had zero bleeds; and 83.7% of bleeds treated resolved with 1 or 2 infusions. One adverse event was possibly related to trenonacog alfa, a nonserious hypersensitivity reaction leading to early study termination. The efficacy and safety of trenonacog alfa for prophylaxis and bleeding treatment in previously treated pediatric participants were consistent with those reported for adults and adolescents. There appeared to be no clinically important differences between the results for participants aged <6 years and those aged 6 to <12 years.

Conclusion: Trenonacog alfa is a suitable option for the management of pediatric persons with hemophilia B.

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blood coagulation disorders, blood coagulation factors, factor IX, hemophilia B, hemorrhage, pharmacokinetics, recombinant proteins

Essentials

- Trenonacog alfa's pharmacokinetics, efficacy, and safety are keys to its use as prophylaxis.
- We studied trenonacog alfa in children aged <12 years with severe or moderately severe hemophilia B.
- In this study, the effects of trenonacog alfa in children aged <12 were comparable with those in older people.
- Trenonacog alfa is suitable for the treatment of children aged <12 years with hemophilia B.

1 | INTRODUCTION

Trenonacog alfa is a standard half-life, third-generation human recombinant factor IX (rFIX), functionally and structurally similar to plasma-derived factor IX (FIX) [1] with high incremental recovery (98%) [2]. Trenonacog alfa has been evaluated in a phase 3 trial that included previously treated adult and adolescent (≥12 years of age) participants with severe or moderately severe hemophilia B. Efficacy results from this study indicated that prophylaxis with trenonacog alfa (mean dose of 55.5 IU/kg delivered at a mean frequency of 1.9 times per week) was effective in preventing bleeds (median annual bleed rate [ABR] = 1.52). In addition, 1 or 2 infusions resolved 84% of bleeds, and the hemostatic efficacy of trenonacog alfa was excellent or good for 84% of treatments. In this trial, the most common adverse event (AE) was headaches (2.6% of participants), and there were no reports of FIX inhibitors [2]. The results from this study supported the approval of trenonacog alfa for on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis to reduce the frequency of bleeding episodes in adults and children aged ≥12 years with hemophilia B [3]. International consensus recommendations for the management of people with hemophilia B indicate that prophylaxis should be initiated as early as possible [4], and it is, therefore, important to understand the pharmacokinetics (PK), efficacy, and safety of trenonacog alfa in younger patients. This study assessed these characteristics of trenonacog alfa in previously treated patients aged <12 years with severe or moderately severe hemophilia B.

2 | METHODS

2.1 | Study design

This phase 3/4, prospective, single-arm, open-label clinical trial evaluated the PK, safety, and efficacy of trenonacog alfa prophylaxis in previously treated participants aged <12 years with severe or moderately severe hemophilia B. Two groups of participants with ≥50 exposure days (EDs) to FIX replacement therapy were evaluated: those aged <6 years and those aged 6 to <12 years. The study was executed in 3 phases: (1) PK evaluation after administration of a single intravenous (IV) 75 ± 5 IU/kg infusion of trenonacog alfa with FIX activity and safety assessments up to 50 hours postinfusion, (2) treatment phase in which participants received trenonacog alfa prophylaxis (dose determined based on FIX recovery; ideally within the recommended dose range of 35-75 IU/kg, twice weekly) for 50 EDs (~6 months), and (3) a continuation phase in which participants could continue to receive trenonacog alfa prophylaxis (dosed as above) for an additional ≥50 EDs.

The study (ClinicalTrials.gov number: NCT03855280) was performed from January 28, 2020, to July 4, 2022, in accordance with the Declaration of Helsinki and was approved by local independent ethics committees for sites in Brazil, Georgia, Moldova, South Africa, Turkey, and Ukraine. Participants aged ≥6 years and their caregivers provided written informed assent and informed consent before enrollment and those for participants aged <6 years were provided by caregivers or guardians.

2.2 | Participant population

Participants were <12 years old throughout the treatment phase of the study, had severe or moderately severe hemophilia B (FIX activity ≤ 2 IU/dL or occurrence of one or more joint bleeding episodes requiring infusion to replace FIX at any point in the child's medical history), and were on prophylaxis or willing to switch to a prophylaxis regimen for the duration of the study. Patients were also required to have ≥50 EDs to prior FIX replacement therapy. Patients were immunocompetent (CD4 count > 400/mm^3); did not receive immunemodulating or chemotherapeutic agents; and had platelet counts of ≥150,000/mm^3, alanine transaminase and aspartate transaminase levels ≤2 times the upper limit of the normal range (ULN), total bilirubin levels ≤1.5 times the ULN, serum creatinine levels ≤1.25 times the ULN, and a hemoglobin level of ≥7 g/dL. Patients were excluded if they had a history of a FIX inhibitor level of ≥0.6 Bethesda Units or another bleeding disorder.

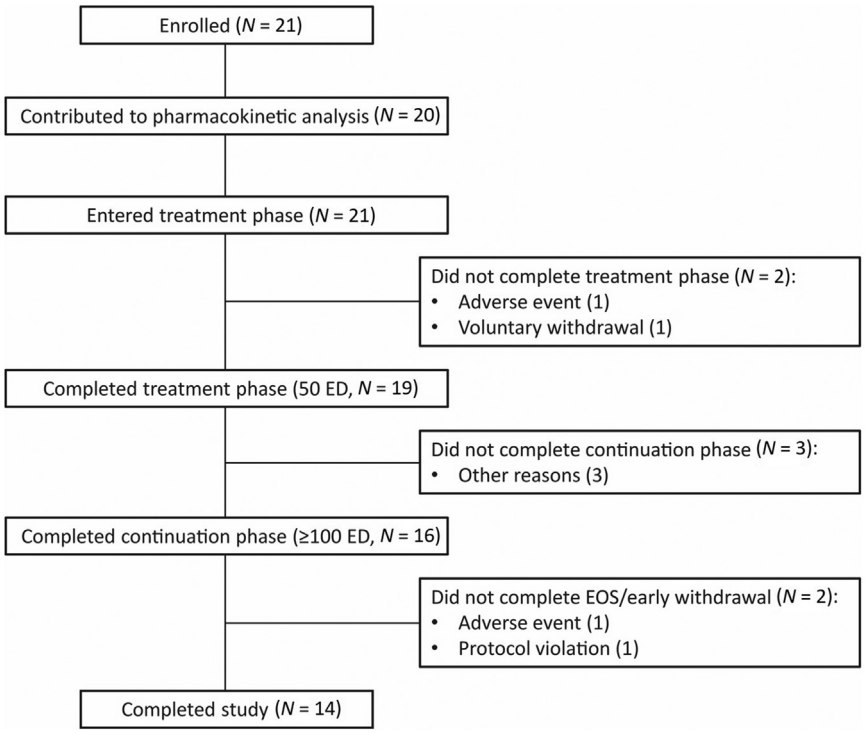

FIGURE 1 Patient disposition. ED, exposure day; EOS, end of study.

2.3 | PK assessment

The PK evaluation was preceded by a washout period of 4 days or three half-lives for a FIX product with an extended half-life, followed by PK and safety assessments completed within 50 hours after trenonacog alfa infusion. Blood samples were collected at the following time points: preinfusion, 15 to 30 minutes, 4 to 6 hours, 24 to 26 hours, and 46 to 50 hours postinfusion. Plasma concentrations of FIX were determined using a lower limit of quantification of 1 IU/dL. Pharmacokinetic parameters (calculated with WinNonlin) included area under the time–concentration curve from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$) and from time 0 to the last measurable concentration ($AUC_{0\text{-}t}$), clearance (CL), maximum plasma concentration (C_{max}), *in vivo* recovery (IVR), incremental recovery, mean residence time (MRT), the volume of distribution at steady state (Vd_{ss}), elimination rate constant (λ_z), and terminal half-life ($t_{1/2}$).

2.4 | Hemostatic efficacy

The hemostatic efficacy of trenonacog alfa was evaluated by the calculation of ABR for prophylaxis, the number of infusions used to treat bleeding episodes, and overall ratings of efficacy by participants (excellent: a dramatic response with abrupt pain relief and clear reduction in joint or hemorrhage site size; good: pain relief or reduction in hemorrhage 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; or poor: no improvement or condition worsens) and investigators (effective, partially effective, or not effective) [2]. Bleeding episodes were classified as minor (eg, uncomplicated hemarthrosis and superficial muscle [except iliopsoas] with no neurovascular compromise and other soft tissue bleeds), moderate (eg, hemarthrosis of longer duration, recurrent hemarthrosis, mucous membranes, deep lacerations, and hematuria), and major/life-threatening (eg, iliopsoas, deep muscle with neurovascular injury, substantial blood loss, central nervous system, pharyngeal, retropharyngeal, and retroperitoneal). Per protocol, minor and moderate bleeding episodes were treated with 40 to 60 IU/kg trenonacog alfa and major/life-threatening bleeding episodes were treated with 60 to 100 IU/kg.

2.5 | Safety

Safety was evaluated by the assessment of AEs, physical examinations, vital signs, and laboratory assessments.

2.6 | Immunogenicity/thrombogenicity

Immunogenicity was assessed by determining FIX inhibitor titers, noninhibitory FIX binding antibodies, and anti-Chinese hamster ovary protein (CHOP) antibodies. Thrombogenicity was evaluated by the measurement of markers that included a D-dimer, a thrombin–antithrombin III complex (TAT), and a prothrombin fragment 1+2 (F1 + 2).

TABLE 1 Participant baseline demographic and clinical characteristics and exposure to trenonacog alfa.

Clinical characteristic	Parameter	Age group: <6 y (*n* = 10)	Age group: 6 to <12 y (*n* = 11)	All participants (*N* = 21)
Age (y)	Mean (SD)	3.3 (1.36)	8.7 (1.00)	6.2 (2.99)
	Median (min-max)	3.4 (1-5)	8.6 (7-10)	7.2 (1-10)
Race, *n* (%)	Black or African American	2 (20.0)	1 (9.1)	3 (14.3)
	White	8 (80.0)	10 (90.9)	18 (85.7)
Ethnicity, *n* (%)	Hispanic or Latino	1 (10.0)	1 (9.1)	2 (9.5)
	Non-Hispanic or Latino	9 (90.0)	10 (90.9)	19 (90.5)
Age at diagnosis (y)	Mean (SD)	0.3 (0.67)	1.1 (1.22)	0.7 (1.06)
	Median (min-max)	0 (0-2)	1.0 (0-4)	0 (0-4)
Time since diagnosis (mo)	Mean (SD)	29.98 (15.174)	86.82 (19.953)	59.76 (33.894)
	Median (min-max)	28.39 (9.2-60.5)	88.02 (52.2-120.5)	60.48 (9.2-120.5)
Severity, *n* (%)	Severe (FIX activity <1%)	5 (50.0)	8 (72.7)	13 (61.9)
	Moderately severe (FIX activity: 1% to <2%)	5 (50.0)	3 (27.3)	8 (38.1)
Time from the first treated bleeding episode (mo)	Mean (SD)	30.46 (15.341)	83.41 (16.816)	58.19 (31.33)
	Median (min-max)	29.78 (9.2-63.2)	81.12 (51.6-102.4)	63.24 (9.2-102.4)
Receiving prophylaxis	*n* (%)	8 (80.0)	3 (27.2)	11 (52.4)
Total number of EDs of factor IX replacement therapy	Mean (SD)	122.60 (73.809)	311.73 (243.563)	221.67 (203.669)
	Median (min-max)	97.00 (50-275)	249.00 (50-900)	182.0 (50-900)
Any target joints, *n* (%)	Yes	0 (0.0)	2 (18.2)	2 (9.5)
	No	10 (100)	9 (81.8)	19 (90.5)
No. of bleeding episodes in 6 mo before screening	Mean (SD)	3.0 (4.97)	3.9 (3.59)	3.5 (4.21)
	Median (min-max)	1 (0-16)	4.0 (0-12)	2.0 (0-16)
Percent of bleeding episodes that were spontaneous	Mean (SD)	18.3 (33.73)	39.8 (39.97)	29.6 (37.84)
	Median (min-max)	0 (0-100)	0 (0-100)	0 (0-100)
EDs to trenonacog alfa	Mean (SD)	107.9 (60.78)	204.9 (51.26)	158.7 (73.76)
	Median (min-max)	108.0 (13-194)	233.0 (108-256)	108.0 (13-256)
	≥50, *n* (%)	8 (90.0)	11 (100.0)	19 (90.5)
	≥100, *n* (%)	5 (50.0)	11 (100.0)	16 (76.2)
	≥150, *n* (%)	3 (30.0)	9 (81.1)	12 (57.1)
	≥200, *n* (%)	0 (0.0)	7 (63.6)	7 (33.3)

ED, exposure day; FIX, factor IX; max, maximum; min, minimum.

2.7 | Statistical analysis

All quantitative PK assessments were summarized with descriptive statistics that included the mean, median, geometric mean, SD, range, and 95% CI for the mean. An ED was defined as a day on which replacement treatment was given to a patient (if a participant received more than 1 infusion in a single day, all infusions on that day counted as 1 ED). Descriptive summaries for all efficacy endpoints were performed. The ABR was calculated and summarized, including the mean, SD, median, and range. All AEs and serious AEs (SAEs) were coded using the Medical Dictionary for Regulatory Activities. The analyses of AEs included descriptive statistics. Summary statistics for laboratory tests (including noninhibitory and inhibitory FIX antibody levels, anti-CHOP antibodies, and levels of thrombogenic markers) are also provided.

3 | RESULTS

3.1 | Participants

A total of 21 participants were enrolled (10 participants aged <6 years and 11 participants aged 6 to <12 years; Figure 1). Twenty participants contributed to the PK analysis, 19 participants (8 participants aged <6 years and 11 participants aged 6 to <12 years) completed the treatment phase (50 EDs), and 16 participants (5 participants aged <6 years and 11 participants aged 6 to <12 years) completed the continuation phase (≥100 EDs; Table 1). One participant discontinued due to an AE (nonserious hypersensitivity reaction) and a second participant voluntarily withdrew before completing 50 EDs. In the continuation phase, 3 participants discontinued for various reasons, 1 participant withdrew due to a protocol deviation, and 1 patient withdrew due to a nontreatment-related SAE. Fourteen participants completed the study. The participants' baseline, demographic, and clinical characteristics and exposure to trenonacog alfa are summarized in Table 1. Overall, 13 participants had severe hemophilia (FIX activity < 1%) and 8 had moderately severe disease (FIX activity, 1% to <2%). During the 6 months before screening, 52.4% of participants (80.0% of those aged <6 years and 27.3% of those aged 6 to <12 years) were receiving prophylaxis. During this period, the mean ± SD number of bleeding episodes for the participants aged <6 years was 3.0 ± 4.97 and that for participants aged 6 to <12 years was 3.9 ± 3.59.

3.2 | PK

After a single IV infusion of 75 ± 5 IU/kg trenonacog alfa, C_{max} was reached after 0.5 hours. The mean $t_{1/2}$ value for FIX was 16.3 hours and the mean MRT was 20.0 hours. Mean exposure values for FIX (C_{max}, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$) were 60.1 IU/dL, 1170 IU•h/dL, and 1003 IU•h/dL, respectively. Clearance and Vd_{ss} were 6.8 mL/(kg h) and 134 mL/kg, respectively (Table 2). The mean incremental recovery was 0.790 IU/dL:IU/kg. Mean $t_{1/2}$ and MRT appeared comparable for the <6 year and 6 to <12 year age groups. The mean exposure values for FIX (C_{max}, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$) for the 6 to <12 year age group were slightly higher than those for the participants aged <6 years. Clearance and Vd_{ss} appeared slightly higher for the <6 year age group, although ranges overlapped (Table 2).

3.3 | Hemostatic efficacy

The mean exposure to trenonacog alfa ± SD was 158.7 ± 73.76 EDs, and the mean compliance was 100.2% ± 3.40%. The mean exposure to trenonacog alfa was 54.81 ± 10.468 IU/kg. The ABR for the entire study was 2.34 ± 4.226 (median = 0.86, range = 0-18.7). Overall, 33.3% of all participants had zero bleeds throughout the study. The respective values for spontaneous ABR were 0.63 ± 1.257 (median = 0, range = 0-4.7), and 61.9% had

TABLE 2 Pharmacokinetic parameters of trenonacog alfa.

Pharmacokinetics of baseline-corrected factor IX (mean [SD])	Single IV infusion of 75 ± 5 IU/kg trenonacog alfa age < 6 y (*n* = 10)[a]	Single IV infusion of 75 ± 5 IU/kg trenonacog alfa age 6 to <12 y (*n* = 10)[b]	Single IV infusion of 75 ± 5 IU/kg trenonacog alfa all participants (*N* = 20)[c]
C_{max} (IU/dL)	56.4 (13.7)	63.7 (9.86)	60.1 (12.2)
$AUC_{0\text{-}\infty}$ (IU h/dL)	1118 (307)	1232 (81.7)	1170 (231)
$AUC_{0\text{-}t}$ (IU h/dL)	909 (227)	1098 (137)	1003 (207)
MRT (h)	19.9 (2.48)	20.0 (2.87)	20 (2.53)
λ_z (1/h)	0.0439 (0.00405)	0.0423 (0.00701)	0.0431 (0.00553)
$t_{1/2}$ (h)	15.9 (1.4)	16.8 (2.8)	16.3 (2.2)
CL (mL/[kg h])	7.3 (1.9)	6.1 (0.5)	6.8 (1.5)
Vd_{ss} (mL/kg)	144 (36.7)	123 (18.9)	134 (30.6)
Incremental recovery (IU/dL:IU/kg)	0.731 (0.149)	0.849 (0.147)	0.790 (0.156)
IVR	0.329 (0.0671)	0.382 (0.0666)	0.335 (0.0707)

All values are presented as mean (SD).

$AUC_{0\text{-}\infty}$, area under the curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the curve from time 0 to the last measurable concentration; CL, clearance; C_{max}, maximum plasma concentration; IV, intravenous; IVR, *in vivo* recovery; MRT, mean residence time; $t_{1/2}$, terminal half-life; Vd_{ss}, volume of distribution at steady state; λ_z, elimination rate constant.

[a] n = 6 for $AUC_{0\text{-}\infty}$, MRT, λ_z, $t_{1/2}$, CL, and Vd_{ss}.

[b] n = 6 for λ_z and $t_{1/2}$ and n = 5 for $AUC_{0\text{-}\infty}$, MRT, CL, and Vd_{ss}.

[c] n = 12 for λ_z and $t_{1/2}$ and n = 11 for $AUC_{0\text{-}\infty}$, MRT, CL, and Vd_{ss}.

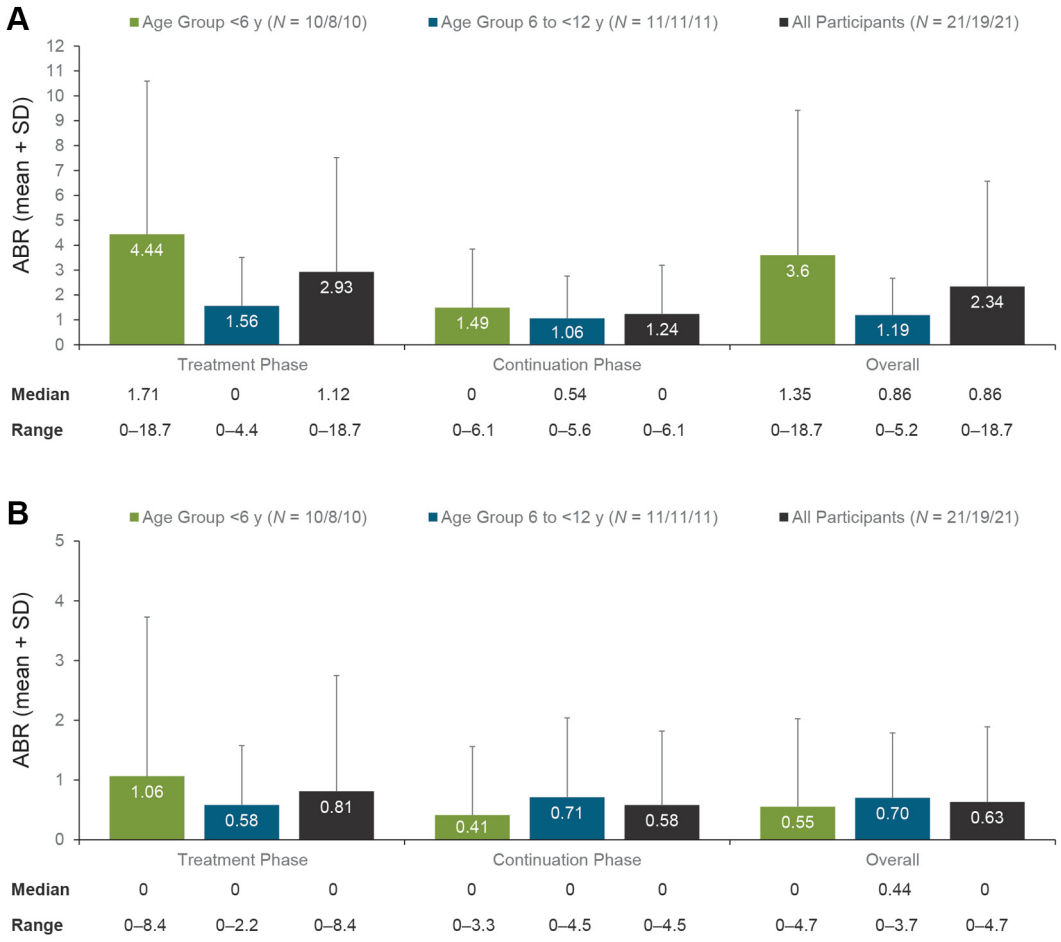

FIGURE 2 Annualized bleeding rate. (A) All bleeds. (B) Spontaneous bleeds. The *N*/*N*/*N* are for the treatment phase, continuation phase, and overall study, respectively. ABR, annualized bleeding rate.

zero spontaneous bleeds. Results were similar for participants aged <6 years and those aged 6 to <12 years (Figures 2A, B and 3A, B).

A total of 52 bleeding episodes were reported (Table 3). There was no significant correlation between the total dose of trenonacog alfa delivered over the course of the study and the number of bleeding

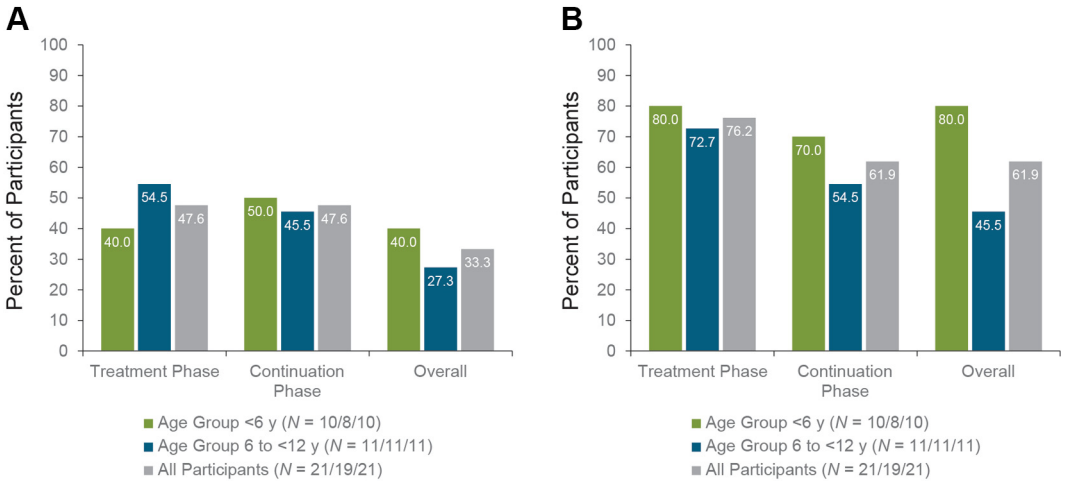

FIGURE 3 (A) Percentages of participants with zero incidences for all bleeds. (B) Percentages of participants with zero incidences of spontaneous bleeds. *Ns* are for the treatment phase, continuation phase, and overall study.

TABLE 3 Types of bleeds by location.

<6 y of age	Spontaneous	Due to trauma	Case unknown
Joint bleeds			
Knee	1	1	0
Ankle	0	1	0
Other bleeds			
Nose	8	1	1
Head (superficial)	0	7	1
Head (intracranial)	0	0	0
Mouth (lip, gums, and tooth)	0	4	0
Leg	0	2	0
Foot	0	1	0
6-12 y of age	**Spontaneous**	**Due to trauma**	**Cause unknown**
Joint bleeds			
Knee	3	3	1
Ankle	3	2	0
Elbow	1	0	0
Other bleeds			
Nose	2	0	0
Head (superficial)	0	1	0
Head (intracranial)	0	0	0
Mouth (lip, gums, and tooth)	0	1	1
Hematuria	3	0	0
Leg	0	0	1
Toe	0	1	0
Vertebral[a]	0	1	0
All participants	**Spontaneous**	**Due to trauma**	**Cause unknown**
Joint bleeds			
Knee	4	4	1
Ankle	3	3	0
Elbow	1	0	0
Other bleeds			
Nose	10	1	1
Head/forehead	0	7	1
Mouth (lip, gums, and tooth)	0	5	1
Hematuria	3	0	0
Leg	0	2	1
Foot	0	1	0
Toe	0	1	0
Vertebral	0	1	0

[a]The vertebral bleed was due to compression fractures of the thoracic 3, 4, 5, and 6 vertebral bodies.

episodes reported for a given participant. There were 16 joint bleeds, 7 resulting from trauma, 8 spontaneous, and 1 with an unknown cause. The remaining bleeds most often involved the nose (epistaxis), mouth, and head (all superficial), and most were associated with trauma. Of these, 17.3% did not require FIX infusion. Of the bleeding episodes that required treatment, 83.7% resolved after 1 or 2 infusions (Figure 4A). Participants rated hemostatic efficacy as "excellent" or "good" in 100% of all episodes (Figure 4B). Results for these measures were similar for the participants aged <6 years and those aged 6 to <12 years. Overall, investigators rated trenonacog alfa prophylaxis effective; there were 3 ratings of "partially effective" during the study. All investigator ratings for control over bleeding episodes were "effective."

3.4 | Safety

AEs are summarized in Table 4. Overall, 76.2% of participants had at least 1 AE; only 1 AE was considered treatment-related (a nonserious hypersensitivity reaction described as rash, urticaria, and pruritus that resolved after discontinuation of the study treatment). This patient had no detectable anti-FIX or anti-CHOP antibodies. The most frequently reported AEs were nasopharyngitis (23.8%) and bronchitis (14.3%). There were no deaths.

3.5 | Immunogenicity/thrombogenicity

Three of the 21 participants tested positive for noninhibitory FIX antibodies. One participant tested positive at screening; at the fifth ED visit, a second participant tested positive during the PK phase; and a third participant repeatedly tested positive starting at screening and throughout the study (screening; 5, 12, 25, 50, and 75 EDs; and at the end of study). No inhibitory FIX antibodies were detected. Three participants developed anti-CHOP antibodies. One tested positive at 25, 50, 100, and 125 EDs and at the end of the study. A second participant tested positive at 50 EDs at the end of the study; a third participant tested positive at the end of the study. No participant developed both anti-CHOP and anti-FIX antibodies. There were no apparent effects of these antibodies on the efficacy or safety of trenonacog alfa. In addition, there was no significant effect of anti-FIX antibodies on the PK parameters for trenonacog alfa. The mean MRT and $t_{1/2}$ for 2 evaluable participants with anti-FIX antibodies detected before or during the PK portion of the study were 22.6 and

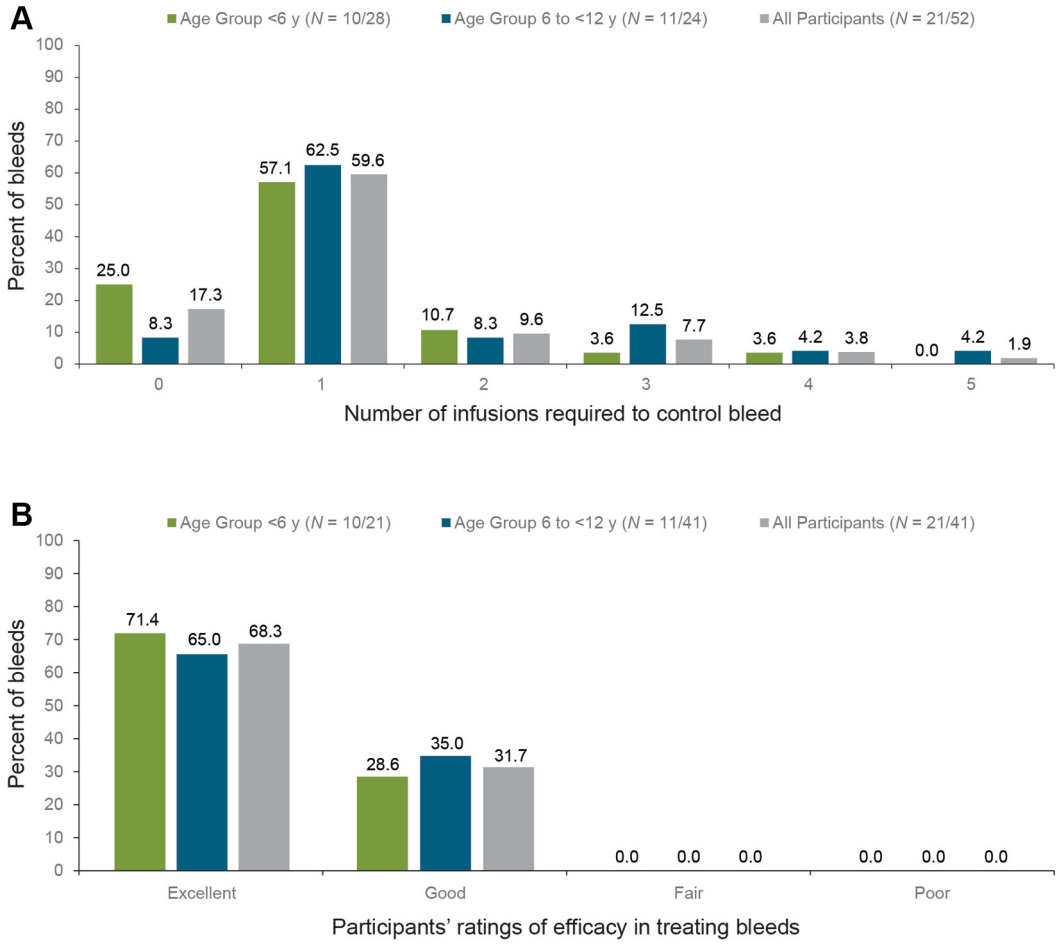

FIGURE 4 Number of FIX infusions required to treat bleeding episodes (A) and participants' efficacy ratings (B). Data are for combined treatment and continuation phases. *N* indicates the number of participants/number of bleeds for A and the number of participants/number of bleeds that were treated and evaluated for B. FIX, factor IX.

17.4 hours, respectively. The respective values for the entire study population were 20.0 and 16.3 hours, respectively.

There was significant variability in the results of the thrombogenic marker assays (Table 5); however, there was no clinical evidence of thromboembolic complications in any participants. Out-of-range values for thrombogenicity markers (F1 + 2, TAT, and D-dimer) determined during the PK phase of the study did not reveal any pattern indicative of thrombogenicity with trenonacog alfa.

4 | DISCUSSION

The availability of additional treatment options has increased the opportunity to individualize therapy for children with hemophilia B. This includes the volume of the dose, the frequency of dosing, and the selection of the factor replacement product itself. In the past, a trough factor level of 1 IU/dL (1%) was deemed an adequate goal. Now recognizing that with a 1% trough level, patients remain at the risk of bleeding, most clinicians would prefer to target higher trough levels (>3% to 5% or higher). Recent studies show that such trough levels achieve less bleeding. However, the trade-off is that higher trough levels may require higher doses or more frequent infusions of clotting factor concentrates. Therefore, this should be personalized based on the individual's activities, lifestyle, and PK handling of the factor [5].

Initiating or transitioning treatment in a child with hemophilia B can be challenging and involves input from the family. Many factors need to be considered to optimize the quality of life for the patients and their families, including the activity level of the child, compliance with administration, and safety profile of the replacement factor concentrate. It is important to have multiple treatment options to support individualization of therapy for these patients.

This study showed that trenonacog alfa was safe and effective as prophylaxis and for controlling bleeds in previously treated persons with hemophilia aged <12 years. After a single IV infusion of 75 ± 5 IU/kg, the mean $t_{1/2}$ value for FIX was 16.3 hours and the MRT was 20.0 hours. These values support a twice-weekly dosing regimen. In 32 previously treated adolescents and children aged ≥12 years, the mean terminal half-life and MRT were somewhat longer ($t_{1/2}$ = 24.2

TABLE 4 Summary of the safety profile for trenonacog alfa.

TEAEs	Age group: <6 y (*n* = 10) *n* (%)	Age group: 6 to <12 y (*n* = 11) *n* (%)	All participants: <12 y (*N* = 21) *n* (%)
Participants with at least one:			
TEAE	9 (90.0)	7 (63.6)	16 (76.2)
Serious TEAE	0 (0.0)	2 (18.2)	2 (9.5)
Nonserious TEAE	9 (90.0)	7 (63.6)	16 (76.2)
Drug-related TEAE	1 (10.0)	0 (0.0)	1 (4.8)
TEAE leading to study termination	1 (10.0)	1 (9.1)	2 (9.5)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Individual TEAEs reported for ≥2 participants			
Nasopharyngitis	2 (20.0)	3 (27.3)	5 (23.8)
Bronchitis	1 (10.0)	2 (18.2)	3 (14.3)
Influenza	2 (20.0)	0 (0.0)	2 (9.5)
Respiratory tract infection	2 (20.0)	0 (0.0)	2 (9.5)
Respiratory tract infection viral	1 (10.0)	1 (9.1)	2 (9.5)
Oropharyngeal pain	1 (10.0)	1 (9.1)	2 (9.5)
Rhinorrhea	2 (20.0)	0 (0.0)	2 (9.5)

TEAE, treatment-emergent adverse event.

hours and MRT = 31.9 hours) [2]. The mean $t_{1/2}$ and MRT values were comparable for the <6 year and 6 to <12 year age groups. The mean incremental recovery for the participants treated in this study (0.790 IU/dL:IU/kg) was lower than that reported previously for adolescent and adult participants (0.98 IU/dL:IU/kg) [2]. A shorter $t_{1/2}$ and recovery in children aged <12 years vs adults and adolescents has also been reported for other rFIX preparations [6–11]), and it may be related to higher clearance in pediatric participants than adults (eg, 6.8 mL/(kg h) for pediatric participants vs 5.1 mL/(kg h) in adolescents and adults) [2,11].

Trenonacog alfa was effective as prophylaxis with a mean ABR for the entire study of 2.34 (median = 0.86) for all bleeds and 0.63 (median = 0) for spontaneous bleeds. In addition, 33.3% of all participants had no bleeds and 61.9% had zero spontaneous bleeds. Although there was no planned comparison between results for the 6 months before the administration of trenonacog alfa and results from the treatment and continuation phases of the study, it is worth noting that the median number of bleeding episodes for the 6 months before enrollment was 2.0, which would translate into a median ABR of 4.0 [12] vs 0.86 for the entire trenonacog alfa treatment period. Importantly, 61.9% of all participants were receiving prophylaxis in the 6 months prior to enrollment. The results from the present study appear comparable to those achieved with trenonacog alfa prophylaxis in adolescents and adults, where the mean ABR was 3.55 (median = 1.52), the mean spontaneous ABR was 1.07 (median = 0), and 31.1% of participants had zero bleeds [2]. The efficacy of trenonacog alfa as prophylaxis for participants aged <12 years in the present study was comparable with the results obtained with both standard half-life and extended half-life rFIX preparations in pediatric participants [10,13–17].

Trenonacog alfa effectively controlled bleeding episodes in both age groups, with 83.7% of bleeds requiring treatment being resolved with 1 or 2 infusions. The participants rated hemostatic efficacy as "excellent" or "good" in 100% of all episodes in which trenonacog alfa administration was required.

Treatment with trenonacog alfa in pediatric participants did not result in any new safety concerns. Of the AEs reported, 1 AE was assessed as possibly related to treatment (nonserious hypersensitivity reaction described as rash, urticaria, and pruritus). Two participants had SAEs, both unrelated to treatment.

The frequency of development of anti-FIX antibodies in the pediatric participants enrolled in this study was similar to that observed (21%) in previously treated adolescent and adult participants who received trenonacog alfa [2]. As in the present study, no participants developed neutralizing antibodies. Anti-CHOP antibodies that developed in adolescent and adult participants who received trenonacog alfa, like those in pediatric participants, had no clinically significant consequences [2].

TABLE 5 Thrombogenicity markers.

Parameter/visit	Age group: <6 y (*n* = 10)		Age group: 6 to <12 y (*n* = 11)		Total (*N* = 21)	
	Value at time indicated	Change from baseline	Value at time indicated	Change from baseline	Value at time indicated	Change from baseline
Prothrombin fragments 1 + 2 (pmol/L)						
Baseline						
n	3	NA	10	NA	13	NA
Mean (SD)	91.7 (23.59)		102.4 (46.40)		99.9 (41.59)	
15-30 min postinfusion						
n	3	3	10	10	13	13
Mean (SD)	681.7 (566.46)	590.0 (550.80)	208.9 (349.45)	106.5 (360.78)	318.0 (433.64)	218.1 (439.48)
4-6 h postinfusion						
n	1	1	10	10	11	11
Mean	337.0 (NA)	270.0 (NA)	228.8 (346.82)	126.4 (316.82)	238.6 (330.63)	139.5 (303.66)
24-26 h postinfusion						
n	3	3	10	10	13	13
Mean (SD)	493.0 (421.32)	401.3 (425.88)	142.0 (99.77)	39.6 (102.31)	223.0 (246.46)	123.1 (251.48)
Thrombin/antithrombin (μg/L)						
Baseline						
n	3	NA	10	NA	13	NA
Mean (SD)	6.67 (0.473)		5.69 (2.928)		5.92 (2.579)	
15-30 min postinfusion						
n	3	3	11	10	14	13
Mean (SD)	42.80 (29.791)	36.13 (30.253)	11.14 (16.496)	5.68 (18.520)	17.92 (22.971)	12.71 (24.252)
4-6 h postinfusion						
N	1	1	11	10	12	11
Mean	3.10 (NA)	−4.10 (NA)	12.99 (16.496)	7.70 (17.952)	12.17 (15.986)	6.63 (17.399)
24-26 h postinfusion						
n	3	3	11	10	14	13
Mean (SD)	24.30 (31.067)	17.63 (31.419)	9.22 (10.273)	3.53 (10.893)	12.45 (16.459)	6.78 (17.081)
D-dimer (mg/L FEU)						
Baseline						
n	3	NA	10	NA	13	NA
Mean (SD)	0.463 (0.0503)		0.422 (0.2660)		0.432 (0.2320)	
15-30 min postinfusion						
N	3	3	11	10	14	13
Mean (SD)	0.443 (0.0451)	−0.020 (0.0781)	0.416 (0.2266)	0.014 (0.1168)	0.422 (0.1999)	0.006 (0.1071)
4-6 h postinfusion						
n	1	1	11	10	12	11
Mean (SD)	0.340 (NA)	−0.170 (NA)	0.462 (0.3077)	0.067 (0.2027)	0.452 (0.2955)	0.045 (0.2051)

(Continues)

TABLE 5 (Continued)

Parameter/visit	Age group: <6 y (*n* = 10)		Age group: 6 to <12 y (*n* = 11)		Total (*N* = 21)	
	Value at time indicated	Change from baseline	Value at time indicated	Change from baseline	Value at time indicated	Change from baseline
24-26 h postinfusion						
n	3	3	11	10	14	13
Mean (SD)	0.507 (0.2631)	0.043 (0.2801)	0.597 (0.2892)	0.135 (0.2638)	0.578 (0.2766)	0.114 (0.2586)

Data from 1 patient whose predose prothrombin fragments' 1 + 2 values were significantly higher than postbaseline values were excluded.
NA, not applicable.

5 | CONCLUSIONS

The consideration of multiple elements has the potential to improve the impact of hemophilia B on caregivers, family members, and patients through evaluation and selection of an appropriate factor replacement product. Results from this study indicated that the efficacy and safety of trenonacog alfa for prophylaxis in previously treated pediatric participants aged <12 years were comparable with those reported previously for adults and adolescents [2]. In addition, there appeared to be no clinically important differences between results for participants aged <6 years and those aged 6 to <12 years old. Trenonacog alfa was also effective for managing bleeding episodes in these participants and had a safety profile comparable with that reported for older participants. These results support the suitability of trenonacog alfa as a suitable option for prophylaxis and managing bleeding episodes in pediatric persons with hemophilia B.

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AUTHOR CONTRIBUTIONS

All authors were involved in all stages of manuscript development and approved the final version.

RELATIONSHIP DISCLOSURE

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