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ORIGINAL ARTICLE

Efficacy, safety and pharmacokinetics of recombinant human coagulation factor VIII (omfiloctocog alfa) in previously treated Chinese children with severe hemophilia A

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Abstract

Introduction: Omfiloctocog alfa, the first China-developed recombinant factor VIII (FVIII), demonstrated efficacy and safety of prophylaxis in previously treated patients (PTPs) aged ≥12 years with severe hemophilia A in China.

Aims: To investigate efficacy, safety and pharmacokinetics (PK) of omfiloctocog alfa in pediatric PTPs with severe hemophilia A in China.

Methods: PTPs (>50 exposure days [ED] for Chinese patients aged <6 years; >150 EDs for patients aged 6–12 years) were treated with omfiloctocog alfa at 25–50 IU/kg every other day or three times per week for 24 weeks. PK was evaluated after single injection of 50 IU/kg. The primary efficacy endpoint was annualized bleeding rate (ABR).

Results: A total of 69 patients were enrolled (<6 years, $n = 35$; 6–12 years, $n = 34$) and mean exposure to omfiloctocog alfa was 78.9 days. Mean half-life was 6.7 and 10.2 h

in children < 6 years and 6–12 years, respectively. Estimated mean ABRs of all patients were 4.05 for overall bleeding episodes and 1.38 for spontaneous bleeding episodes. Of 127 bleeding episodes, the success rate was 92.1%. 39.7% patients did not experience any bleeding episodes and the mean weekly dose of FVIII was 109.1 IU/kg for these patients. 83% bleeding episodes were controlled with ≤2 injections. Adverse reactions occurred in 2.9% of the patients. One 2-year-old patient developed inhibitors after 12 EDs and it resolved with omfiloctocog alfa immune tolerance induction.

Conclusion: Omfiloctocog alfa was efficacious and well tolerated for the prevention and treatment of bleeding in Chinese pediatric PTPs with severe hemophilia A.

KEYWORDS
children, hemophilia A, omfiloctocog alfa, pharmacokinetics, prophylaxis

1 | INTRODUCTION

Prevention of joint bleeds is particularly important in the pediatric hemophilia patients because of the relationship between joint bleeds and development of chronic arthropathy over time.[1] Primary prophylaxis with recombinant factor VIII (rFVIII) or plasma-derived FVIII (pd FVIII) initiated at an early age prevents joint bleeds, hemophilic arthropathy and thereby decreasing the rate of disability and maintaining quality of life.[2] Even though the safety of FVIII concentrates has greatly improved over the past decades, the development of inhibitors to FVIII remains to be the most serious complication in the treatment of hemophilia A. From the latest PedNet study in >1000 previously untreated patients, the median inhibitor development was 14 EDs and 79% of all inhibitors developed within 20 EDs.[3,4]

Despite the achievements in hemophilia management within last decades,[5] hemophilia care in China lags far behind the developed countries and continues to remain unbalanced across regions. A real-world study[6] showed that among children receiving prophylactic treatment, the annual factor consumption for prophylaxis was 1328.0 IU/kg from 2014 to 2018, which is much lower than the average consumption for regular prophylaxis, mainly because of the supply deficiency and high price of FVIII in China.

Omfiloctocog alfa is the first rFVIII developed in China and approved for prophylactic and on-demand treatment of bleeding episodes in patients with hemophilia A. The advanced manufacturing process allows a production capacity up to 5–10 billion IU annually, which could contribute to reducing drug costs and improving accessibility of rFVIII in China and elsewhere.

Previous pivotal phase III trial with omfiloctocog alfa demonstrated favorable efficacy and safety profile in PTPs aged ≥12 year with severe hemophilia A (FVIII activity, FVIII:C < 1%), and none of these patients developed inhibitors.[7] In this study, we aimed to demonstrate the efficacy, safety, and PK properties of omfiloctocog alfa in PTPs aged <12 years with severe hemophilia A (NCT03947320).

2 | METHODS

2.1 | Patients

The study was conducted across 18 clinical sites from 28 May 2020 to 25 August 2021 (Table S1). Eligible patients were boys of <12 years with severe congenital hemophilia A previously treated with any FVIII products (>150 EDs for patients aged 6–12 years and >50 EDs for those aged <6 years), and with no evidence of FVIII inhibitors (<.6 Bethesda units [BU]/mL) as measured by the Nijmegen-modified Bethesda assay. Prior to study participation, HIV negative test, a viral load <200 particles/μl or <400,000 copies/ml and CD4 lymphocytes >200/μl were required. Key exclusion criteria included: any history of FVIII inhibitors, any bleeding disorder other than hemophilia A, platelet count <100 × 109/L, International Normalized Ratio ≤1.5, creatinine ≥2 times the upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase >5 times ULN, and known hypersensitivity to FVIII, mouse or hamster proteins.

2.2 | Study design

This phase III, prospective, uncontrolled, multicenter and open label study included patients who were stratified by age (< 6 years and 6–12 years). PK assessment of omfiloctocog alfa in both cohorts were performed for the first 16 children enrolled. Prior to PK assessment, each patient received a single dose of omfiloctocog alfa at a labelled potency. Upon completion, prophylactic treatment with omfiloctocog alfa was initiated. The next 19 children in each age cohort were started directly on prophylactic omfiloctocog alfa treatment. The patients were allowed to enter an optional extension study of long term prophylaxis and on-demand treatment (NCT03947567) when the trial ended.

All patients received omfiloctocog alfa prophylactic treatment with 25–50 IU/kg every other day or three times per week over a period of 24 weeks (≥50 EDs). Dose regimen was assigned by investigator and could be adjusted based on patients' conditions. Study visits were scheduled at 4-week interval.

Omfiloctocog alfa for bleeding treatment was assessed based on European Medicine Assessment (EMA) guidelines.[8] The dosage and duration for treating breakthrough bleeding episodes during prophylaxis depends on the location and severity of bleeding episodes, and the clinical condition of the child. Details of prophylactic treatment, and all treated bleeding episodes (including location, cause, and severity) were recorded in the patient's Diary.

The study protocol was reviewed and approved by the Independent Ethics Committee at each site. The study was conducted in compliance with the ethical requirements in the Declaration of Helsinki and Good Clinical Practice. All patients provided informed consent/assent prior to enrollment.

2.3 | PK assessment

A mandatory washout period of ≥72 h of any previous FVIII treatment was required prior to omfiloctocog alfa injection. Blood samples for PK assessment were collected before injection and 15 min, 1, 10, 24 and 48 h after injection. FVIII: C was measured with a one-stage (OS) assay at the central laboratory (Q2 Solutions, Beijing, China). An activated partial thromboplastin time assay kits was used and the test was calibrated with Siemens standard human plasma that had been calibrated against WHO approved standard. Data were obtained by an ACL TOP 700 automatic analyzer. Both of the one stage clotting and the chromogenic substrate assay were used in our previous study for evaluating pharmacokinetics of omfiloctocog alfa in adolescents and adults (>12 years). In that study, measured C_{max} using the one stage assay and the chromogenic substrate assay were 1.08 and 1.25 IU/mL, calculated AUC_{last} were 8.89 and 12.36 IU*h/mL, and $t_{1/2}$ were 10.26 and 11.52 h, respectively. Overall, both methods demonstrated reliable and consistent results, and were considered suitable for PK assessment.[7] Given the better sensitivity and limited blood volume collected from children as well as the widely accepted practice in China, the one stage assay was selected for this study.

FVIII: C for Incremental in-vivo recovery (IVR) assessment (50 IU/kg of omfiloctocog alfa) was performed pre-dose and 15 min post dose at baseline, at week 12 and week 24 during prophylaxis period.

2.4 | Efficacy assessment

The primary efficacy endpoint was ABR evaluating bleeding episodes (overall, spontaneous, and trauma) that required omfiloctocog alfa treatment during prophylaxis. The key secondary endpoint was annualized joint bleeding rate (AJBR). Other secondary efficacy endpoints were hemostatic efficacy, the number of injections for treatment of bleeding episode and the consumption (IU/kg) of omfiloctocog alfa per month, per year and per event (prophylaxis and bleeding episode). Hemostatic effect of omfiloctocog alfa was assessed based on a 4-point scale (excellent, good, moderate, and none).[9]

The classification of the bleeding types was defined as: Mild Bleeding Episode (superficial muscle or soft tissue bleeding, early hemarthrosis, and oral bleeding); Moderate Bleeding Episode (muscle bleeding/hematomas, joint bleeding, and mild surgery); Severe to Life-threatening Bleeding (life-threatening bleedings [including intracranial, intra-abdominal or intrathoracic bleeding, gastrointestinal tract bleeding, retropharyngeal, retroperitoneal or iliopsoas bleeding], fracture, head trauma, and major surgery).[10]

In addition, Hemophilia Joint Health Score (HJHS) and Canadian Hemophilia Outcomes – Kids' Life Assessment Tool (CHO-KLAT) were assessed at baseline and at week 24 or end of the treatment (EOT).

2.5 | Safety assessment

The safety evaluation(s) included: (serious) adverse events ([S]AEs), adverse events of special interests (AESI, defined as inhibitor formation and hypersensitivity) related to omfiloctocog alfa, clinically significant changes in vital signs, physical examination, clinical laboratory tests (hematology, biochemistry, coagulation test, urine analysis) and electrocardiography (ECG). Inhibitor was measured in the central laboratory using the Nijmegen-modified Bethesda assay with heat inactivation of residual FVIII activity.[11] An inhibitor development was defined as the concentration of positive inhibitor ≥.6 BU/mL and confirmed using a second sample drawn separately. Blood samples for genetic mutation testing were collected for inhibitor positive patients.

2.6 | Statistical analysis

Following the EMA guideline, a total 70 patients and 25 patients (At least 12 evaluable patients for PK assessment) in each age cohort were required for assessing rFVIII treatment in hemophilia A. Statistical analyses were mainly descriptive, and data were summarized in overall patients and by age cohorts. The PK parameters were calculated with the standard non-compartmental[12] methods using WinNonlin® software (Phoenix Build 7.0, Pharsight Corporation). Efficacy analyses were conducted in patients who had at least one dose of omfiloctocog alfa and at least one post-baseline measurement. Safety was assessed in all patients exposed to omfiloctocog alfa. ABRs during prophylaxis were calculated according to the following formula: (number of treated bleed/efficacy evaluation period)/365.25 and presented as median (IQR), and an estimated mean (95% CI]) was calculated according to a negative binomial regression model corrected for overdispersion.[13] The safety endpoint of inhibitor development was evaluated using the Bayesian analysis model[14,15] and the β distribution was used to simulate the incidence of inhibitor development.

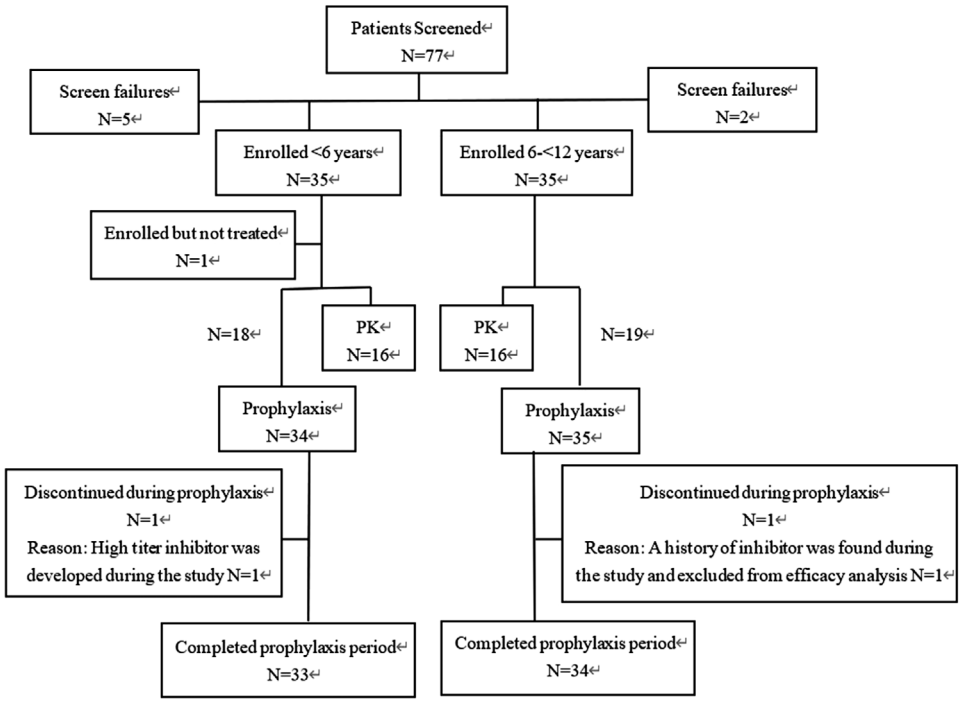

FIGURE 1 Patient disposition in the study

3 | RESULTS

3.1 | Patient distribution and baseline characteristics

In total, 77 patients were screened and 70 were enrolled. Of the 70 enrolled patients, three withdrew prematurely: one withdrew at screening during the informed consent process, one had a history of inhibitor during the study (excluded from full analysis set) and one developed high titer inhibitors in course of the study (Figure 1). Thirty-one patients participated in the PK assessment. Of the 69 patients, the mean exposure to omfiloctocog alfa was 78.9 ± 9.6 EDs and the overall study duration was 24.0 ± 2.3 weeks.

All patients were males and the mean (range) age was 6.5 (2.0–11.5) years (3.7 for <6 years and 9.4 for 6–12 years). Prior to enrolment, 36 (52.9%) patients were on prophylaxis, while 32 (47.1%) were on on-demand treatment or irregular prophylaxis with low dose and frequency. Baseline demographic and clinical characteristics are shown in Table 1.

3.2 | PK

Post-injection FVIII levels exhibited a typical biphasic decay pattern and declined exponentially. The FVIII: C profiles were similar between the two age cohorts (Figure 2). PK parameters are summarized in Table 2. Values for half-life ($t_{1/2}$) and area under curve (AUCinf) were lower and clearance (CL) was higher in <6 years children than those in 6–12 years children ($t_{1/2}$, 6.73 and 10.20 h; AUCinf, 7.52 IU*h/mL and 10.61 IU*h/mL; CL, 7.78 mL/h/kg and 5.68 mL/h/kg for the <6 years and 6–12 years, respectively). The mean FVIII level of patients <6 years, 6–12 years, and 0–12 years measured at 24 h were .0646, .1230, and .0918 IU/mL, respectively.

During prophylaxis, IVR (mean ± SD) was 1.99 ± .54 (IU/mL)/(IU/kg) for all three visits (1.88 ± .58, 2.09 ± .51, and 1.99 ± .51 at baseline, 12 weeks and 24 weeks, respectively) and was similar in both age cohorts (1.88 ± .63 for <6 years and 2.09 ± .41 for 6–12 years).

3.3 | Efficacy

3.3.1 | Prevention of bleeding episodes

The mean consumption per patient for prophylactic treatment was 467.8 IU/kg per month and 5613.3 IU/kg per year, with a mean dose level of 34.1 IU/kg. The estimated mean ABRs (95% CI) for overall bleeding episodes were 4.05 (2.96, 5.55) with ABRs (95% CI) of 4.08 (2.75, 6.05) in the <6 years cohort and 4.03 (2.46, 6.62) in 6–12 years cohort (Table 3). Traumatic bleeding episodes were the main contributors to the total ABRs with an estimated mean ABRs (95% CI) of 2.68(1.87, 3.86), which was nearly twice as high as the mean ABRs for spontaneous ABRs (1.38, 95% CI: .93, 2.05). The estimated mean AJBRs (95% CI) was 2.36 (1.59, 3.52) with AJBRs (95% CI) of 3.15 (1.91, 5.21) in 6–12 years cohort and 1.56 (.84, 2.90) in < 6 years cohort. For those patients on prior prevention (52.9%), ABR (95 CI %) was 5.75 (3.75, 8.81) before the study and 4.90 (3.27, 7.34) after the study. Of the 68 treated patients, majority of the patients (75.0%) started the

TABLE 1 Demographic and clinical characteristics

	<6 years (*N* = 34)	6-12 years (*N* = 34)	Total (*N* = 68)
Age (years)			
Mean (SD)	3.7 (1.2)	9.4 (1.8)	6.5 (3.2)
Median (Min, Max)	3.5 (2.0, 5.5)	9.8 (6.0, 11.5)	5.8 (2.0, 11.5)
Race, (% Asian)	100	100	100
Weight (kg)			
Mean (SD)	17.3 (4.7)	32.8 (7.7)	25.0 (10.1)
Median (Min, Max)	15.8 (11.0, 34.0)	31.5 (20.0, 48.0)	23.5 (11.0, 48.0)
Previous treatment, *n* (%)			
Prophylaxis	16 (47.1)	20 (58.8)	36 (52.9)
On demand	18 (53.9)	14 (41.2)	32 (47.1)
Annualized bleeding rates in previous 3 months			
Previously treated with Prophylaxis			
Median (Q1, Q3)	.00 (.00, 3.53)	3.73 (3.11, 10.85)	3.88 (.00,9.86)
Estimated mean (95% CI)	2.49 (1.21, 5.15)	8.45 (5.30, 13.46)	5.75 (3.75, 8.81)
Previously treated with on demand			
Median (Q1, Q3)	20.17 (5.14,28.88)	11.98 (.00,37.05)	18.18 (1.03,30.48)
Estimated mean (95% CI)	19.15 (12.91, 28.42)	18.64 (8.48, 40.96)	18.80 (12.41, 28.49)

Abbreviations: CI, confidence interval; N, number of patients; Q1, first quartile; Q3, third quartile; SD, standard deviation.

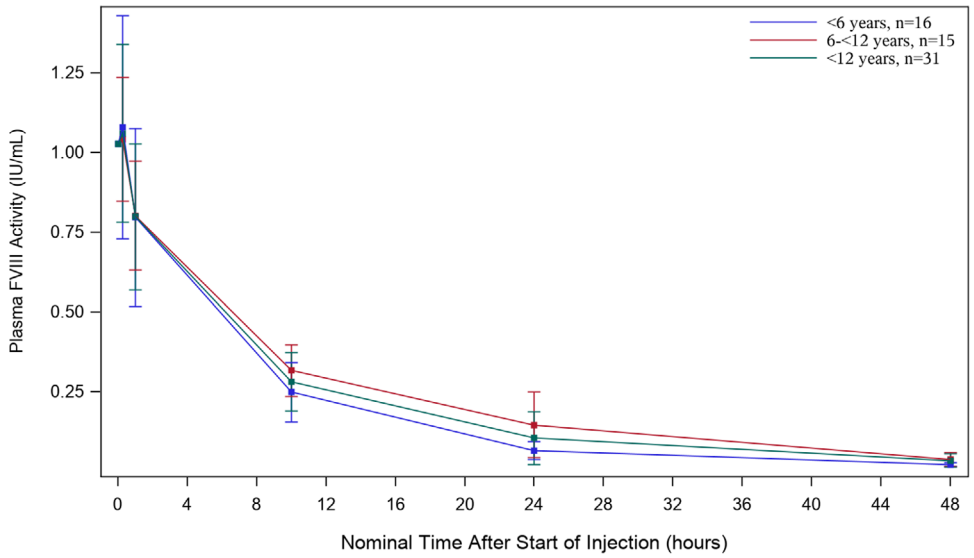

FIGURE 2 Plasma FVIII activity (IU/mL) versus time profiles of omfiloctocog alfa at nominal times. The one-stage clotting assay data shown represented means and standard deviations

trial with three times per week dosing, and fifteen (22.0%) changed dosing schedule from three times per week to every other day.

3.3.2 | Treatment of bleeding episodes

Of the 148 reported bleeds, 21 (14.2%) did not require additional omfiloctocog alfa on top of their regular prophylactic dose during the trial. A total of 127 (85.8%) bleeds were treated for 41 children, and most bleeding episodes were mild/moderate intensity (96.1%, 122/127), and trauma related (66.1%, 84/127). Joints (64.6, 82/127) were the most common location for bleeding episodes, particularly in the 6–12 years children (52 of 64 bleeds [81.3%] versus 30 of 63 bleeding episodes [47.6%] in the <6 years children). 39.7% of the 68 patients did not experience any bleeding episodes and the mean weekly dose of FVIII was 109.1 IU/kg for these patients.

TABLE 2 PK parameters for omfiloctocog alfa in children based on one stage assay

Parameters	<6 years (*N* = 16)	6–12 years (*N* = 15)	Total (*N*=31)
AUC_{inf} (IU*h/mL)	7.52 ± 2.08	10.61 ± 3.69	9.06 ± 3.33
C_{max} (IU/mL)	1.12 ± .37	1.02 ± .21	1.07 ± .30
IVR (IU/dL)/(IU/kg)	2.04 ± .67	1.90 ± .35	1.97 ± .54
$t_{1/2}$(h)	6.73 ± 1.70	10.20 ± 2.92	8.41 ± 2.92
CL (mL/h/kg)	7.78 ± 1.96	5.68 ± 1.71	6.73 ± 2.10
MRT (h)	9.37 ± 2.20	14.09 ± 3.77	11.73 ± 3.87
V_{SS} (mL/kg)	70.74 ± 16.50	75.44 ± 14.85	73.09 ± 15.61

Note: All data were indicated by mean ± SD.
Abbreviations: AUC_{inf}, area under the activity-time curve from time zero extrapolated to infinity; CL, plasma clearance rate; C_{max}, peak plasma drug concentration; IVR, ratio of the peak blood concentration to the actual dose; MRT, mean residence time; N, number of patients; $t_{1/2}$, terminal clearance half-life; V_{ss}, volume of distribution at steady-state.

TABLE 3 Annualized bleeding rates

	<6 years (*N* = 34)	6–12 years (*N* = 34)	Total (*N* = 68)
All bleeds			
Median (Q1, Q3)	2.21 (0, 6.52)	2.17 (0, 4.35)	2.17 (0, 6.37)
Estimated mean (95% CI)	4.08 (2.75, 6.05)	4.03 (2.46, 6.62)	4.05 (2.96, 5.55)
Spontaneous bleeds			
Median (Q1, Q3)	.00 (2.15)	.00 (2.17)	.00 (2.15)
Estimated mean (95% CI)	1.24 (.67,2.29)	1.51 (.90,2.54)	1.38 (.93,2.05)
Traumatic bleeds			
Median (Q1, Q3)	2.15 (0, 4.30)	.00 (0, 4.20)	1.04 (0, 4.20)
Estimated mean (95% CI)	2.85 (1.80,4.51)	2.52 (1.41,4.49)	2.68 (1.87,3.86)
Joint bleeds			
Median (Q1, Q3)	.00 (0, 2.16)	2.09 (0, 4.35)	.00 (0, 3.22)
Estimated mean (95% CI)	1.56 (.84,2.90)	3.15 (1.91,5.21)	2.36 (1.59,3.52)

Abbreviations: CI, confidence interval; N, number of patients; Q1, first quartile; Q3, third quartile.

Hemostatic efficacy of omfiloctocog alfa was rated as excellent in 64 bleeding episodes (50.8%), good in 52 bleeding episodes (41.3%) and moderate in 10 bleeding episodes (7.9%). No bleeding episodes were reported as none response except one had no reported outcome. Thus, treatment success rate (i.e., ratings of "excellent" or "good") was 92.1% of all assessed bleeding episodes, which was similar in both age cohorts (Table 4). Most bleeding episodes (84.7%, 100/118) were controlled with ≤2 injections. Mean ± SD dose for treatment of bleeding episodes was 30.7 ± 6.7 IU/kg (median, 30.0 IU/kg) per injection and 57.7 ± 61.2 (median 35.7) per bleed in all patients.

One 9-year-old patient underwent a minor teeth extraction surgery, which required one prophylactic injection of omfiloctocog alfa before surgery. No bleeding episode occurred after the surgery. No hemostasis assessment was reported and this patient was excluded from perioperative analysis set.

3.3.3 | Joint function and quality of life

Improvement over baseline in the HJHS (Table 5) and CHO-KLAT (Figure 3) assessment were observed in both age cohorts. The mean total HJHS scores decreased by 3.4 (4.3 for <6 years and 2.8 for 6–12 years). The mean child-reported CHO-KLAT scores and the mean parent-reported CHO-KLAT scores were increased at last visit by 4.0 (4.0 for 6–12 years) and 1.5 (1.0 for <6 years and 2.0 for 6–12 years), respectively. Child-reported CHO-KLAT scores were not assessed for <6 years cohort. The most frequently improved item on the HJHS items was flexion loss in left ankle (11 [18.6%]). The minimal detectable change (MDC) of total HJHS scores was 5.70, and 21.05% patients showed a change > MDC. The MDC of CHOKLAT scores were 7.65 in child-reported score and 7.64 in parent-reported score. 35.29% patients showed a change >MDC in child-reported score, and 29.41% in parent-reported score.

TABLE 4 Bleeding episodes and hemostatic efficacy of omfiloctocog alfa

	<6 years (*N* = 22)	6–12 years (*N* = 19)	Total (*N* = 41)
Number of bleeds	63	64	127
Site of bleeds, *n* (%)			
Joint	30 (47.6)	52 (81.3)	82 (64.6)
Subcutaneous	17 (27.0)	0	17 (13.4)
Soft tissues	11 (17.5)	5 (7.8)	16 (12.6)
Muscular	6 (9.5)	5 (7.8)	11 (8.7)
Mucosal	5 (7.9)	3 (4.7)	8 (6.3)
Others[a]	3 (4.8)	1 (1.6)	4 (3.1)
Severity of bleeds, *n* (%)			
Mild/moderate	59 (93.7)	63 (98.4)	122 (96.1)
Severe	4 (6.3)	1 (1.6)	5 (3.9)
Cause of bleeds, *n* (%)			
Spontaneous	19 (30.2)	24 (37.5)	43 (33.9)
Traumatic	44 (69.8)	40 (62.5)	84 (66.1)
Hemostatic response, *n* (%)			
Missing	1 (1.6)	0	1 (.8)
n	62	64	126
Excellent	37 (59.7)	27 (42.2)	64 (50.8)
Good	22 (35.5)	30 (46.9)	52 (41.3)
Moderate	3 (4.8)	7 (10.9)	10 (7.9)
None	0	0	0
Success rate, *n* (%)	59 (95.2)	57 (89.1)	116 (92.1)
Injections to treat the bleeding episodes (from start to stop of bleed)[b]			
1 injection	35 (64.8)	36 (56.3)	71 (60.2)
2 injections	10 (18.5)	19 (29.7)	29 (24.6)
3 injections	5 (9.3)	5 (7.8)	10 (8.5)
≥4 injections	4 (7.4)	4 (6.3)	8 (6.8)

Abbreviations: N, number of bleeding patients; n, number of bleeding episodes.
[a]The category 'other' included pharynx, toe, and finger.
[b]The time on bleeding episodes was missing in nine patients.

TABLE 5 HJHS at baseline and 24-week follow-up

HJHS Total[a]	<6 years (*N* = 34)	6-12 years (*N* = 34)	Total (*N* = 68)
Baseline			
Mean (SD)	7.0 (7.5)	7.7 (7.3)	7.4 (7.3)
Median (Q1, Q3)	4.0 (.5,13.0)	5.5 (1,12)	5.0 (1,13.0)
V7/EOT			
Mean (SD)	3.8 (4.0)	4.9 (5.7)	4.4 (5.0)
Median (Q1, Q3)	2.0 (0,7)	3.0 (0,9)	3.0 (0,7.5)
Change			
Mean (SD)	-4.3 (6.2)	-2.8 (3.5)	-3.4 (4.8)
Median (Q1, Q3)	-2.0 (-9.0,0)	-2.0 (-4,0)	-2.0 (-4.0,0)

Abbreviations: HJHS, hemophilia joint health score; Q1, first quartile; Q3, third quartile; SD, standard deviation.
[a]Assessment of HJHS: Total: 0 (best) to 124 (worst).

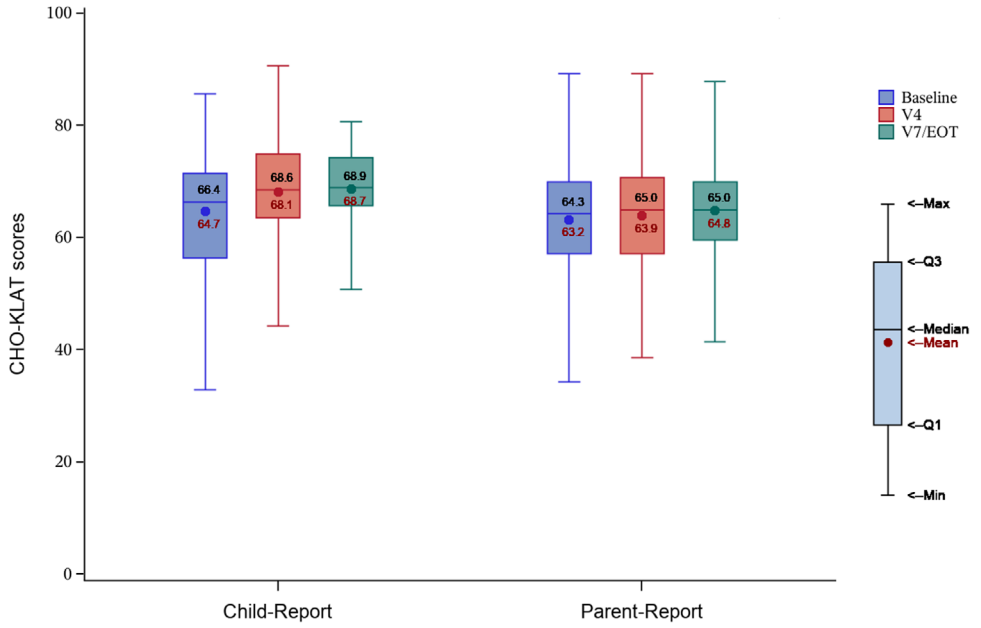

FIGURE 3 Distribution of Canadian Hemophilia Outcomes-Kids Life Assessment Tool (CHO-KLAT scores) by respondent

3.4 | Safety

Out of 69 treated patients, 53 (76.8%) patients reported 182 treatment-emergent AEs and majority of them were mild or moderate. The most common AEs were respiratory tract infection (31 patients [44.9%]), respiratory tract infection and bronchitis (7 patients [10.1%]) and diarrhea (4 patients [5.8%]). One patient temporarily discontinued treatment because of upper respiratory tract infection. Per Investigator's assessment, two adverse reactions (2.9%) occurred: one was considered to be possibly related (urticaria; moderate intensity and resolved) and the other one was deemed to be probably related (FVIII inhibitor). The estimated rate of FVIII inhibitor development was 1.4%. A FVIII inhibitor development (≥5 BU/mL) was reported in a 2-year-old patient with an exon 21 deletion genotype of F8 gene. This patient started the first FVIII treatment at 9 months of age. Prior to enrollment, the patient was on prophylaxis with a Pd FVIII product for 138 EDs two times per week at 25 IU/kg, and received a live attenuated Encephalitis B vaccine. During the trial the patient received 21 IU/kg omfiloctocog alfa three times per week for prophylaxis, and reported an AE of upper respiratory tract infection during the treatment. After 12 EDs of omfiloctocog alfa, the patient showed positive for a high-titer FVIII inhibitor for the first time (47.3 BU/ml). Five doses of omfiloctocog alfa had been administered to the patient before the first test result was available. The result of a second sample (drawn 12 days after the first sample) was still positive (72.1 BU/ml). The patient was subsequently withdrawn from the trial immediately, followed by treatment of immune tolerance induction (ITI) with omfiloctocog alfa at a dose of 200 IU/kg/d and was recovering at the last follow up visit. A reduced titer of FVIII inhibitor (1.9 BU/mL) was detected in the 4th month following treatment, which reduced further to .3 BU/mL with lower FVIII recovery (58.2%) and reduced half-life (4.8 h) at the 6th month. The outcome was considered as partial response[16] to the ITI treatment.

Five AESIs in <6 years cohort were reported in 5 (7.2%) patients. Two (2.9%) of the AESIs were drug related AE: urticaria and the persistence of high FVIII inhibitor as described above. The remaining three AESIs (dermatitis contact, rash and hypersensitivity) were mild/moderate and did not recur during continued exposure to omfiloctocog alfa.

Two (2.9%) SAEs (bronchitis and FVIII inhibitor) were recorded in 2 patients. The bronchitis was severe in intensity, possibly not related to omfiloctocog alfa, and recovered. The FVIII inhibitor was already mentioned above. No other safety-related concerns were identified.

4 | DISCUSSION

In this phase III study, omfiloctocog alfa was efficacious for prophylaxis and treatment of bleeding episodes in previously treated patients (PTPs) aged <12 years with severe hemophilia A.

An age-dependent effect of omfiloctocog alfa PK was observed, and the clearance of omfiloctocog alfa tended to decrease with age when comparing- both pediatric and adult patients. This observation most likely reflects physiologic differences between different age cohorts (0-6 years, 6–12 years, and ≥12 years[7]) and highlights the significance of assessing dose and frequency in both pediatric and adult patients. During the prophylactic period, IVR was >1.7 (IU/dL)/(IU/kg) in <12 years patients and similar in both age cohorts, and remained stable over time.

The terminal half-life of NovoEight® is 7.7 and 8.0 h for children <6 and 6–12 years, respectively, which is consistent with omfiloctocog alfa (6.7 and 9.9 h).[17] The median half-life of FVIII of all patients in this study (7.5 h) is lower than that in WAPPS database[18] for children ≤17 years (9.3 h). The shorter median half-life of omfiloctocog alfa might be due to more young patients recruited. The median age of the study participants is much lower compared with the WAPPS data[18] (5.8 years

versus 8.6 years; 50% patient <6 years in this study vs 13.7% in the WAPPS database).

Prophylaxis with omfiloctocog alfa resulted in low ABRs. The overall estimated mean ABR during prophylaxis was 4.05, which was similar in both age cohorts. In the study of omfiloctocog alfa prophylaxis in adults,[7] the estimated mean ABR was 2.82 for overall bleeding episodes. Higher ABRs in children compared with adults was mainly due to a higher incidence of traumatic bleeding episodes, which is consistent with published data.[7]This difference likely reflects a higher physical activity level in children, which suggests that physical activity needs to be considered when determining appropriate prophylaxis dosing. More joint bleeding episodes occurred in 6–12 years, which probably related to the deteriorated joint health with age increasing. The estimated mean ABR (95% CI) with omfiloctocog alfa in children was similar with those of other FVIII products, including Nuwiq® (4.0, 95 CI%: 3.30, 5.28)[19] and NovoEight® (5.3, 95% CI: 3.90, 7.28)[20] although the direct comparison was hampered by the different trial design (including dose/dosing schedules, age and methodologies).

The recommended prophylactic dosing regimen of omfiloctocog alfa was 25–50 IU/kg every other day or three times per week, with actual average dose level of 34.1 IU/kg per prophylaxis injection, which is comparable to those of BDD rFVIII[19,20] at the same dosing frequency.

Omfiloctocog alfa was efficacious for the treatment of bleeding episodes. The overall success rate was 92.1%, with similar success rates in both age cohorts, which was consistent or better than those reported in Nuwiq®[19] (82.4%) and NovoEight®[20] (92%) studies. Furthermore, a total of 100 (84.7%) of the bleeding episodes were resolved with 1–2 injections of omfiloctocog alfa. Mean dose of omfiloctocog alfa was 30.7 IU/kg per injection and 57.7 IU/kg per bleeding episodes, which was similar or lower than those of BDD rFVIII.[21]

There is a limitation of this study. A bleed was treated and managed at home, so patients had to inform the investigators during bleeding episodes. The investigators verified the severity based on the signs of bleeds, and could perform imaging scan (e.g., ultrasound) if they thought it necessary. In this regard, the likelihood of misclassification and under/over-reporting of bleeds could not be excluded.

Prophylaxis with omfiloctocog alfa improved joint function and quality of life. The observed changes in the HJHS and CHO-KLAT scores in both age cohorts were as a result of a combined effect of omfiloctocog alfa treatment and change of treatment mode from irregular prophylaxis or on-demand treatment prior to the study.

Overall, treatment with omfiloctocog alfa was safe and well tolerated with a low incidence of drug related AEs. Both the frequency and types of AE were considered similar to that of other FVIII products.[19–20,22] The safety profile of omfiloctocog alfa in both age cohorts was consistent with what was documented in our previous pivotal study in adults.[7] There was no new or unexpected safety concern identified. One 2-year old patient with 138 EDs prior to enrollment developed inhibitory antibodies against FVIII after 12 EDs of omfiloctocog alfa. The patient had several risk factors, including a young age, deletion of exon 21 of F8 gene, less than 150 EDs, receiving vaccine immunisation and viral infection. Taken together, of 60 patients who received on demand treatment (internal data) and 73 patients who received prophylactic treatment,[7] the estimated mean (95% CI) overall rate of FVIII inhibitor development was .45% (.01%, 2.47%) of all the PTPs (222 cases) who received omfiloctocog alfa, which was within the range of inhibitor occurring rates as reported in other studies of PTPs with hemophilia A.[23]

5 | CONCLUSION

Omfiloctocog alfa demonstrated to be safe and efficacious for bleeding prophylaxis in pediatric patients <12 years with severe hemophilia A.

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CONFLICTS OF INTEREST

Renchi Yang has received speaker/consultancy fees from Bayer, Novo Nordisk, Pfizer, Roche, Sinocelltech, and Takeda. This study was sponsored by Sinocelltech Ltd. Chuanrong Ma, Wenlin Gai and Liangzhi Xie are employed by Sinocelltech Ltd., and have an ownership in the company. The other authors declare no conflict of interests.

AUTHORS CONTRIBUTION

Renchi Yang, Runhui Wu, Liangzhi Xie, and Wenlin Gai conceived the study design. Xiaoling Wang, Xielan Zhao, Yanli Cheng, Zeping Zhou, Jing Sun, Ming Xu, Wenqian Li, Jianwen Xiao, Fenge Yang, Yun Chen, Weiqun Xu, Jing Huang, and Renchi Yang contributed to the acquisition and interpretation of data. Wenlin Gai, Chuanrong Ma, and Liangzhi Xie participated in the trial management. Renchi Yang, Chuanrong Ma, Wenlin Gai, and Liangzhi Xie wrote the manuscript. All authors critically reviewed and revised the manuscript. The final version of this manuscript was approved by all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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