ORIGINAL ARTICLE

Efanesoctocog Alfa Prophylaxis for Children with Severe Hemophilia A

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ABSTRACT

BACKGROUND

Once-weekly efanesoctocog alfa provides high sustained factor VIII activity with superior bleeding prevention as compared with prestudy factor VIII prophylaxis in previously treated patients 12 years of age or older with severe hemophilia A. Data on outcomes of efanesoctocog alfa treatment in children younger than 12 years of age with severe hemophilia A are limited.

METHODS

We conducted a phase 3, open-label study involving previously treated patients younger than 12 years of age with severe hemophilia A. Patients received prophylaxis with once-weekly efanesoctocog alfa (50 IU per kilogram of body weight) for 52 weeks. The primary end point was the occurrence of factor VIII inhibitors (neutralizing antibodies against factor VIII). Secondary end points included annualized rates of treated bleeding episodes, bleeding treatment, safety, and pharmacokinetics.

RESULTS

A total of 74 male patients were enrolled (38 with an age of <6 years and 36 with an age of 6 to <12 years). No factor VIII inhibitors developed. Most adverse events were nonserious. No serious adverse events that were assessed by the investigator as being related to efanesoctocog alfa were reported. In the 73 patients treated according to the protocol, the median and model-based mean annualized bleeding rates were 0.00 (interquartile range, 0.00 to 1.02) and 0.61 (95% confidence interval, 0.42 to 0.90), respectively. A total of 47 patients (64%) had no treated bleeding episodes, 65 (88%) had no spontaneous bleeding episodes, and 61 (82%) had no episodes of bleeding into joints. A total of 41 of 43 bleeding episodes (95%) resolved with one injection of efanesoctocog alfa. Mean factor VIII activity at steady state was more than 40 IU per deciliter for 3 days and more than 10 IU per deciliter for almost 7 days after dose administration. The geometric mean terminal half-life was 40.0 hours.

CONCLUSIONS

In children with severe hemophilia A, once-weekly prophylaxis with efanesoctocog alfa provided high sustained factor VIII activity in the normal to near-normal range (>40 IU per deciliter) for 3 days and more than 10 IU per deciliter for almost 7 days after administration, leading to effective bleeding prevention. Efanesoctocog alfa was associated with mainly nonserious adverse events. (Funded by Sanofi and Sobi; XTEND-Kids ClinicalTrials.gov number, NCT04759131.)

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Despite therapeutic advances in hemophilia A, life-threatening bleeding episodes and episodes of bleeding into joints occur with standard-care prophylactic treatment.[1-4] Maintaining high sustained coagulation factor levels in the normal to near-normal range (>40 IU per deciliter) improves protection from bleeding episodes[5-8]; however, the half-life of factor VIII replacement products is limited by interaction with von Willebrand factor (VWF; half-life of approximately 15 or 16 hours).[9,10] Hence, conventional standard half-life and extended half-life factor VIII concentrates require multiple injections weekly to manage hemophilia.[11-13] This burdensome regimen is difficult, particularly for children. Moreover, most standard and extended half-life products have shorter half-lives in children, necessitating more frequent injections, higher doses, or both, which can affect treatment adherence.[12,14,15] Until recently, once-weekly administration has not been a realistic option for highly effective factor VIII prophylaxis.[6,16,17]

Efanesoctocog alfa (ALTUVIIIO; formerly BIVV001) is a new class of high sustained factor VIII replacement therapy designed to decouple recombinant factor VIII from endogenous VWF and overcome the VWF-imposed half-life ceiling.[6,17-19] It is composed of a single recombinant factor VIII protein fused to the Fc domain of human IgG1, the D′D3 domain of VWF (factor VIII–binding domain), and two XTEN polypeptides.[18,19] These allow for a half-life that is four times as long as that with standard factor VIII therapies and three times as long as that with extended half-life factor VIII therapies.[20,21] This prolonged half-life allows for weekly administration of efanesoctocog alfa in adults and adolescents with severe hemophilia A.[6]

In the phase 3 XTEND-1 study, once-weekly efanesoctocog alfa at a dose of 50 IU per kilogram of body weight provided superior bleeding protection as compared with prestudy factor VIII prophylaxis and normal to near-normal factor VIII activity for most of the week in previously treated patients 12 years of age or older with severe hemophilia A.[6] Here, we report the results of the XTEND-Kids study, which evaluated the safety, efficacy, and pharmacokinetics of efanesoctocog alfa prophylaxis in previously treated children younger than 12 years of age with severe hemophilia A.

Methods

Study Population

XTEND-Kids was an open-label, international, single-group, phase 3 study involving previously treated children younger than 12 years of age with severe hemophilia A (<1 IU per deciliter [1%] endogenous factor VIII activity or documented genotype known to produce severe hemophilia A). Eligible patients had received recombinantor plasma-derived factor VIII or cryoprecipitate for at least 150 exposure days (in patients 6 to <12 years of age) or for more than 50 exposure days (in patients <6 years of age).

Among the exclusion criteria were other known coagulation disorders, a history of hypersensitivity or anaphylaxis associated with any factor VIII product, a positive test for factor VIII inhibitor (≥0.6 Bethesda units [BU] per milliliter) at screening, or a history of a positive inhibitor test. Full enrollment criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The protocol is also available at NEJM.org.

Study Design and Treatment

Patients were assigned to receive once-weekly prophylactic doses of intravenous efanesoctocog alfa (50 IU per kilogram) for 52 weeks (Fig. S1 in the Supplementary Appendix). Patient- or caregiver-reported bleeding episodes were treated with one dose of efanesoctocog alfa (50 IU per kilogram), with additional doses of 30 or 50 IU per kilogram every 2 or 3 days if the episode did not resolve as judged by the caregiver in consultation with the investigator. Patients could resume routine prophylaxis after 72 hours if successfully treated with 50 IU per kilogram or without delay if successfully treated with 30 IU per kilogram. Patients undergoing major surgery during the study received a preoperative loading dose of efanesoctocog alfa (50 IU per kilogram) and could receive doses of 30 or 50 IU per kilogram every 2 or 3 days as needed.

End Points and Assessments

The primary end point was the occurrence of inhibitor development (neutralizing antibodies against factor VIII). Secondary end points included the annualized rate of treated bleeding episodes and annualized bleeding rate according to type

and location, the number of injections and doses of efanesoctocog alfa to treat a bleeding episode, the percentage of bleeding episodes treated with one injection, assessment of response to treatment of individual bleeding episodes, annualized consumption of efanesoctocog alfa, perioperative management, joint health, target-joint resolution, pharmacokinetics, and safety.

The presence of factor VIII inhibitors and antidrug antibodies were assessed by means of Nijmegen-modified Bethesda assay and validated efanesoctocog alfa–specific antidrug-antibody assay, respectively, performed by the central laboratory. Inhibitor development was defined as at least 0.6 BU per milliliter, confirmed by another positive sample obtained 2 to 4 weeks later.

Bleeding episodes were reported by patients or caregivers in an electronic patient diary, and adjudication by the investigator was not required. Caregivers were trained to enter bleeding location and type, symptoms, and response to treatment. A bleeding episode and bleeding resolution were defined according to International Society on Thrombosis and Hemostasis (ISTH) criteria.[22] Response to bleeding treatment was assessed by means of the ISTH 4-point response scale (excellent, good, moderate, or none) and was evaluated at the first injection to treat a bleeding episode.[23] Hemostatic response to treatment for surgery was assessed by means of the ISTH 4-point scale.

Joint health was assessed with the use of the Hemophilia Joint Health Score 2.1 (HJHS; range, 0 to 124, with lower scores indicating better joint health and a score of zero indicating no joint impairment) in patients 4 years of age or older. A target joint was defined as a major joint with at least three spontaneous bleeding episodes in a consecutive 6-month period before study entry, and target-joint resolution was assessed according to ISTH criteria at week 52. Quality of life was assessed with the use of the Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score (range, 0 to 100, with lower scores indicating better quality of life) in patients 4 years of age or older. Factor VIII activity was measured with the use of the activated partial thromboplastin time–based one-stage clotting assay with the Actin FSL reagent.

STUDY OVERSIGHT

The study was performed in accordance with the principles of the Declaration of Helsinki and local regulations. An independent external data monitoring committee monitored the safety and side-effect profile of efanesoctocog alfa during the study.

The study was funded by Sanofi and Sobi, which codeveloped efanesoctocog alfa. The authors had access to primary clinical study data and approved submission of the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the adherence of the study to the protocol. The manuscript was developed with medical writing support funded by Sanofi and Sobi.

STATISTICAL ANALYSIS

The analysis of inhibitor development was based on all treated patients who had at least one inhibitor test. A 95% confidence interval using the Clopper–Pearson method was calculated for inhibitor development.[24] Safety and efficacy were analyzed descriptively and based on the full analysis population (patients who received ≥1 dose of efanesoctocog alfa).

Primary analyses of bleeding end points were based on treated bleeding episodes consistent with ISTH criteria: an injection to treat a bleeding episode that was administered more than 72 hours after the preceding treatment of a bleeding episode was considered to be a first injection for a new bleeding episode in the same location.[22] Mean annualized bleeding rates and 95% confidence intervals were estimated with the use of a negative-binomial model that included the number of treated bleeding episodes during the efficacy period. Annualized bleeding rates were summarized descriptively according to type and location, and annualized bleeding rates for individual patients were calculated. Pharmacokinetic variables were analyzed in patients with postdose sampling available and summarized with geometric means and 95% confidence intervals (see the Supplementary Appendix for details). No adjustments were made for multiplicity.

RESULTS

PATIENT CHARACTERISTICS

Of 74 male patients (38 with an age of <6 years and 36 with an age of 6 to <12 years) who were enrolled, 72 (97%) completed the study (Fig. 1). Two patients (3%; both <6 years of age) discontinued the study: 1 owing to a positive inhibitor

test at baseline (result returned after 3 doses) and 1 owing to extreme fear of blood draws (after 44 doses).

All the patients received prophylaxis with a factor VIII replacement therapy before study entry, except 1 patient (6 to <12 years of age) who received on-demand treatment. Of the 73 patients receiving prophylaxis before the start of the study, most (51 [70%]) were using extended half-life products, with the majority receiving doses twice a week or every 3 days and ranging from every 2 days to every 7 days. For the 22 patients (30%) using standard half-life products, the dose regimens ranged from every 2 days to twice a week.

The demographic and clinical characteristics of the patients were representative of this age group with severe hemophilia A (Table 1 and Table S1). The overall median number of exposure days to efanesoctocog alfa was 53 (range, 3 to 72), and 66 of 74 patients (89%) had at least 50 exposure days.

IMMUNOGENICITY AND SAFETY

Factor VIII Inhibitors and Antidrug Antibodies

No inhibitors to factor VIII developed, with an overall incidence of 0% (95% confidence interval [CI], 0 to 5). Three patients tested positive for antidrug antibodies at screening or baseline (before administration of efanesoctocog alfa), which had no discernible effect on clinical efficacy, safety, or pharmacokinetics. No antidrug antibodies were observed in any patient after treatment.

Safety

Efanesoctocog alfa was associated with predominantly nonserious adverse events. A total of 62 patients (84%) had at least one adverse event that was reported after the start of treatment (Table 2). Of these, 3 patients (4%) had at least one adverse event that was assessed by the investigator as being related to efanesoctocog alfa, and 9 patients (12%) had at least one serious adverse event; none of the latter were assessed by the investigator as being related to efanesoctocog alfa. Common adverse events (occurring in ≥5% of the patients) are listed in Table 2, with the most common (occurring in ≥10% of the patients) being severe acute respiratory syndrome coronavirus 2 test positivity, upper respiratory tract infection, and pyrexia. No reports of grade 3 or higher allergic reaction or anaphylaxis and no reports of embolic or thrombotic events were noted. No

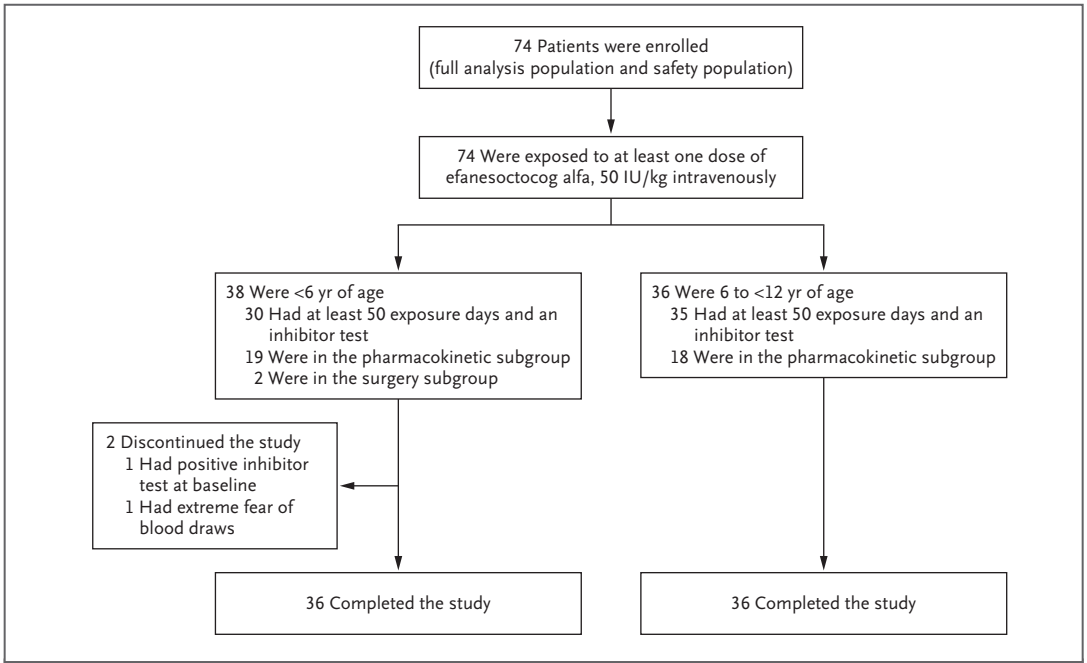


Figure 1. Patient Disposition and Exposure.

Patients younger than 6 years of age and those 6 to younger than 12 years of age may have been included in multiple subgroups. One patient younger than 6 years of age had a positive test for factor VIII inhibitor at baseline. However, the positive result was returned after the patient had initiated efanesoctocog alfa prophylaxis, and the patient was subsequently withdrawn from the study after receiving three doses.

adverse events led to treatment discontinuation, and no deaths occurred.

EFFICACY

The median annualized rate of treated bleeding episodes was 0.00 (interquartile range, 0.00 to 1.02), and the model-based estimated mean overall annualized rate of treated bleeding episodes was 0.89 (95% CI, 0.56 to 1.42) among all enrolled patients (Table S2). The estimated mean annualized rate of bleeding into joints was 0.59 (95% CI, 0.27 to 1.28), the annualized rate of spontaneous bleeding was 0.16 (95% CI, 0.08 to 0.30), and the annualized rate of traumatic

Table 1. Key Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	<6 Yr of Age (N=38)	6 to <12 Yr of Age (N=36)	Overall (N=74)
Median age (range) — yr	4 (1.4–5.0)	8 (6.0–11.0)	5 (1.4–11.0)
Weight — kg	17.9±3.5	35.8±12.9	26.6±12.9
Race — no. (%)†			
Asian	4 (11)	4 (11)	8 (11)
Black	1 (3)	2 (6)	3 (4)
White	30 (79)	25 (69)	55 (74)
Not reported	0	4 (11)	4 (5)
Other	3 (8)	1 (3)	4 (5)
Geographic region — no. (%)			
Asia–Pacific	11 (29)	8 (22)	19 (26)
Europe	7 (18)	20 (56)	27 (36)
North America	20 (53)	8 (22)	28 (38)
Median age at start of prophylaxis (range) — yr	1.0 (0–4)	1.0 (0–5)	1.0 (0–5)
Factor VIII genotype — no. (%)			
Intron 22 inversion	7 (18)	9 (25)	16 (22)
Frameshift	4 (11)	4 (11)	8 (11)
Missense	2 (5)	5 (14)	7 (9)
Nonsense	4 (11)	0	4 (5)
Large structural change: >50 bp	5 (13)	6 (17)	11 (15)
Small structural change: <50 bp	0	1 (3)	1 (1)
Splice-site change	1 (3)	1 (3)	2 (3)
Other	2 (5)	1 (3)	3 (4)
Unknown	13 (34)	9 (25)	22 (30)
Family history of factor VIII inhibitor — no. (%)			
Yes	7 (18)	1 (3)	8 (11)
No	26 (68)	31 (86)	57 (77)
Unknown	5 (13)	4 (11)	9 (12)
No. of episodes of bleeding into joints in the past 12 mo	0.8±2.1	1.3±5.1	1.1±3.9
≥1 Target joint — no. (%)‡			
Yes	1 (3)	1 (3)	2 (3)
No	37 (97)	35 (97)	72 (97)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race was reported by the patient's parent or legal guardian.
‡ A target joint was defined as a major joint with at least three spontaneous bleeding episodes in a consecutive 6-month period before study entry.

Table 2. Safety Results.*

End Point	<6 Yr of Age (N=38)	6 to <12 Yr of Age (N=36)	Overall (N=74)
Primary end point			
Occurrence of neutralizing antibodies to factor VIII (95% CI) — %	0 (0–9)	0 (0–10)	0 (0–5)
Secondary safety end points			
Total no. of adverse events	146	108	255 †
Patients with ≥1 adverse event — no. (%)	33 (87)	29 (81)	62 (84)
Most common adverse events — no. (%)‡			
SARS-CoV-2 test positivity	7 (18)	4 (11)	11 (15)
Upper respiratory tract infection	6 (16)	5 (14)	11 (15)
Pyrexia	8 (21)	1 (3)	9 (12)
Asymptomatic Covid-19	2 (5)	5 (14)	7 (9)
Viral gastroenteritis	5 (13)	1 (3)	6 (8)
Head injury	1 (3)	5 (14)	6 (8)
Nasopharyngitis	3 (8)	3 (8)	6 (8)
Arthralgia	0	5 (14)	5 (7)
Pain in arms or legs	2 (5)	3 (8)	5 (7)
Vomiting	4 (11)	1 (3)	5 (7)
Viral infection	3 (8)	1 (3)	4 (5)
Viral upper respiratory tract infection	3 (8)	1 (3)	4 (5)
Diarrhea	3 (8)	1 (3)	4 (5)
Contusion	1 (3)	3 (8)	4 (5)
Patients with ≥1 adverse event assessed by the investigator as being related to efanesoctocog alfa — no. (%)	3 (8)	0	3 (4)
Adverse events assessed by the investigator as being related to efanesoctocog alfa — no. (%)			
Hematochezia	1 (3)	0	1 (1)
Alanine aminotransferase increased	1 (3)	0	1 (1)
Aspartate aminotransferase increased	1 (3)	0	1 (1)
Coagulation factor VIII level increased on chromogenic assay	1 (3)	0	1 (1)
VWF antigen increased	1 (3)	0	1 (1)
Patients with ≥1 serious adverse event — no. (%)	5 (13)	4 (11)	9 (12)
Patients with ≥1 serious adverse event assessed by the investigator as being related to efanesoctocog alfa — no. (%)	0	0	0
Patients with ≥1 adverse event of special interest — no. (%)§	1 (3)	0	1 (1)
Adverse event leading to treatment discontinuation — no. (%)	0	0	0

* Covid-19 denotes coronavirus disease 2019, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, and VWF von Willebrand factor.
† Included are adverse events that occurred during the major surgical or rehabilitation period; these adverse events are excluded from each age cohort column but are included in the overall column. Each patient is counted only once in the overall column.
‡ Shown are events that occurred in at least 5% of the overall population.
§ Adverse events of special interest included serious or nonserious events of symptomatic overdose; inhibitor development; a grade 3 or higher allergic reaction according to Common Terminology Criteria for Adverse Events, version 5.0; an anaphylactic reaction associated with administration of the study drug; or an embolic or thrombotic event (except injection-site thrombophlebitis). One patient younger than 6 years of age had urticaria after eating chocolate.

bleeding was 0.44 (95% CI, 0.27 to 0.70). A total of 47 patients (64%) had no bleeding episodes, 65 (88%) had no spontaneous bleeding episodes, and 61 (82%) had no episodes of bleeding into joints.

Data on annualized bleeding rates for individual patients are shown in Figure S2. An 11-year-old patient with a history of traumatic bleeding into the hip joint (no target joints at baseline) reported 2 such episodes and did not receive weekly prophylaxis for an extended period, as specified by the protocol. After initial doses and strict bed rest to treat the bleeding into the hip (response to the first injection rated as "good" after treatment of the first episode and "excellent" after treatment of the second episode), the investigator continued treatment with an intensive consolidation regimen of follow-up injections (efanesoctocog alfa, 52.6 IU per kilogram) two or three times per week for approximately 4 months. Consequently, the patient received 33 injections of efanesoctocog alfa between day 48 and day 169. Although the patient reported 3 episodes of traumatic bleeding into the joints (2 in the same hip and 1 in the wrist), the final analysis reported 21 treated episodes of bleeding into the joints (annualized bleeding rate, 21.4) according to the ISTH definition that injections to treat a bleeding episode more than 72 hours after preceding bleed treatment are considered to be a first injection for a new bleeding episode in the same location (i.e., the occurrence of a new bleeding episode was imputed if >72 hours lapsed between 2 consecutive injections administered).[22] Intensive consolidation therapy resulted in classification of 18 derived "new treated bleeding episodes of unknown type." Magnetic resonance imaging was performed on the affected hip on day 142 and did not show effusion, hemosiderin deposition, cartilaginous damage, or cortical bony abnormality suggestive of acute bleeding or hemophilic arthropathy. After resumption of once-weekly prophylaxis, the patient reported 1 episode of traumatic bleeding into the wrist. The patient had no antidrug antibodies. More details are provided in the Supplementary Appendix.

The ad hoc sensitivity analysis including 73 patients treated according to the protocol showed an estimated mean annualized bleeding rate of 0.61 (95% CI, 0.42 to 0.90) and median annualized bleeding rate of 0.00 (interquartile range, 0.00 to 1.02) (Table 3). The overall estimated mean annualized rate of bleeding into joints was 0.30 (95% CI, 0.16 to 0.57), and the percentage of patients with no episodes of bleeding into joints was 84% (61 patients). The estimated mean annualized rate of spontaneous bleeding was 0.16 (95% CI, 0.08 to 0.31), and the annualized rate of traumatic bleeding was 0.40 (95% CI, 0.24 to 0.65).

Among patients in the sensitivity analysis, 43 treated bleeding episodes occurred (17 in patients <6 years of age and 26 in patients 6 to <12 years of age). A total of 41 of 43 bleeding episodes (95%) resolved with 1 injection of efanesoctocog alfa. Furthermore, 36 of 37 evaluable first injections (97%) were assessed as leading to excellent or good responses (Table 3).

In the full analysis population (74 patients), the mean (±SD) annualized consumption of efanesoctocog alfa per patient was 3003.2±394.0 IU per kilogram. The mean annualized consumption was 3115.6±488.6 IU per kilogram in patients younger than 6 years of age and 2884.7±207.9 IU per kilogram in those 6 to younger than 12 years of age. The mean weekly prophylaxis dose was 56.7±5.1 IU per kilogram in patients younger than 6 years of age and 53.2±2.0 IU per kilogram in those 6 to younger than 12 years of age.

Two major surgeries occurred in patients younger than 6 years of age: a dental restoration including tooth extraction in one patient and circumcision in the other. A single loading dose of efanesoctocog alfa maintained hemostasis during surgery in each instance, with a mean total dose of 61.1±1.1 IU per kilogram. Both hemostatic responses were deemed by the investigator or surgeon as being excellent.

JOINT HEALTH

The mean overall HJHS improved from baseline to week 52 (baseline, 2.2±5.5 points; week 52, 1.6±4.8 points; change, −0.6±6.0 points). The mean change was more pronounced in 33 patients 6 to younger than 12 years of age (baseline, 2.1±4.5 points; week 52, 1.1±2.5 points; change, −1.1±4.3 points) than in 18 patients 4 to younger than 6 years of age (baseline, 2.4±7.1 points; week 52, 2.4±7.1 points; change, 0.2±8.3 points). Two patients had at least one target joint at baseline. One of the two patients had resolution of his target joints; the other patient did not have at least 12 months of exposure to efanesoctocog alfa prophylaxis to allow for assessment.

Table 3. Estimated Model-Based Annualized Bleeding Rates and Treatment of Bleeding Episodes (Sensitivity Analysis).*

Variable	<6 Yr of Age (N=38)	6 to <12 Yr of Age (N=35)	Overall (N=73)
Overall bleeding			
Mean ABR (95% CI)†	0.48 (0.30–0.77)	0.75 (0.41–1.40)	0.61 (0.42–0.90)
Median ABR (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.05)	0.00 (0.00–1.02)
Patients with no bleeding episodes — no. (%)	24 (63)	23 (66)	47 (64)
Spontaneous bleeding			
Mean ABR (95% CI)†	0.17 (0.08–0.38)	0.15 (0.04–0.55)	0.16 (0.08–0.31)
Median ABR (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Patients with no bleeding episodes — no. (%)	32 (84)	32 (91)	64 (88)
Bleeding into joints			
Mean ABR (95% CI)†	0.19 (0.06–0.62)	0.41 (0.19–0.89)	0.30 (0.16–0.57)
Median ABR (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Patients with no bleeding episodes — no. (%)	34 (89)	27 (77)	61 (84)
Traumatic bleeding			
Mean ABR (95% CI)†	0.28 (0.14–0.55)	0.52 (0.26–1.04)	0.40 (0.24–0.65)
Median ABR (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.98)	0.00 (0.00–0.00)
Patients with no bleeding episodes — no. (%)	30 (79)	25 (71)	55 (75)
No. of injections to treat a bleeding episode			
Total no. of treated bleeding episodes	17	26	43
1 injection — no. (%)	15 (88)	26 (100)	41 (95)
2 injections — no. (%)	2 (12)	0	2 (5)
>2 injections — no. (%)	0	0	0
Response to treatment of bleeding episodes‡			
No. of first injections evaluated	16	21	37
Excellent or good response — no. (%)	15 (94)	21 (100)	36 (97)
Moderate response — no. (%)	1 (6)	0	1 (3)
No response — no. (%)	0	0	0

* The sensitivity analysis included patients who were treated according to the protocol. ABR denotes annualized bleeding rate, and IQR interquartile range.
† The mean ABR was estimated with the use of a negative-binomial model, with the total number of treated bleeding episodes during the efficacy period as the response variable and the log-transformed duration of the efficacy period (in years) as an offset variable.
‡ Data are for the first injection for each bleeding episode and are based on injections with an evaluation.

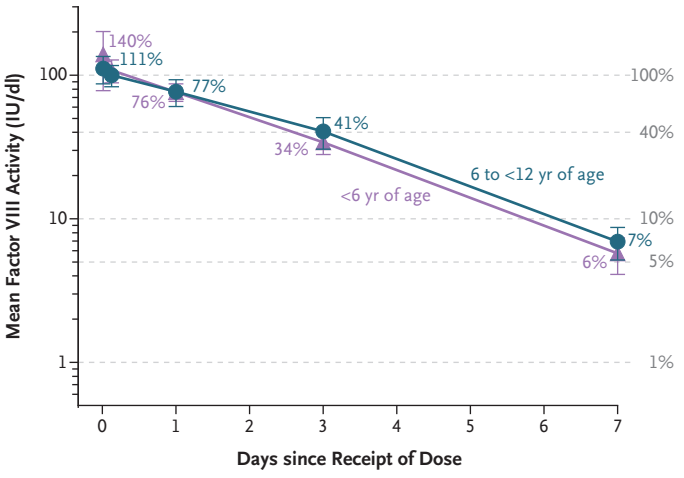
QUALITY OF LIFE

The mean Haemo-QoL score at baseline was 23.8±14.3 in 21 patients 4 to 7 years of age; the mean change in the Haemo-QoL total score from baseline to week 52 was –2.5±10.5 in 14 patients with available data. Among 14 patients 8 to younger than 12 years of age, the mean Haemo-QoL score at baseline was 22.1±13.7, with a mean change from baseline to week 52 of –9.8±12.2 in 10 patients with available data. Both age groups had a mean decrease in the Haemo-QoL score, which is in the direction of improvement in quality of life; the clinical meaningfulness of the change in the Haemo-QoL score has not yet been rigorously defined among children with hemophilia.

PHARMACOKINETICS

A total of 37 patients (19 with an age of <6 years and 18 with an age of 6 to <12 years) underwent pharmacokinetic assessment after the first dose of efanesoctocog alfa (Fig. 2). The mean age was

3.79±1.18 years among patients younger than 6 years of age and 8.11±2.05 years among those 6 to younger than 12 years of age. After the first dose of efanesoctocog alfa, the mean factor VIII activity was in the normal to near-normal range (>40 IU per deciliter) for up to 3 days. Mean factor VIII activity was sustained above 40 IU per deciliter for 3.0 days, above 15 IU per deciliter for 5.6 days, and above 10 IU per deciliter for 6.7 days (Table S3). The geometric mean terminal half-life was 40.0 hours (95% CI, 38.5 to 41.5) overall, 37.8 hours (95% CI, 36.0 to 39.7) in patients younger than 6 years of age, and 42.3 hours (95% CI, 40.5 to 44.2) in those 6 to younger than 12 years of age. The geometric mean incremental recovery (i.e., the increase in plasma level per IU per kilogram of efanesoctocog alfa administered) was 2.42 IU per deciliter per IU per kilogram of efanesoctocog alfa (95% CI, 2.19 to 2.67) overall, 2.63 IU per deciliter per IU per kilogram of efanesoctocog alfa (95% CI, 2.22 to 3.12) in patients younger than 6 years of age, and 2.21 IU per deciliter per IU per kilogram of efanesoctocog alfa (95% CI, 2.01 to 2.42) in those 6 to younger than 12 years of age. The patient with an annualized bleeding rate of 21.4 who was excluded from the sensitivity analysis was included in the pharmacokinetics subgroup and had a factor VIII trough value of 9.4 IU per deciliter after the first dose (Table S4).



Pharmacokinetic Variable	<6 Yr of Age (N=19)	6 to <12 Yr of Age (N=18)	Overall (N=37)
	geometric mean (95% CI)		
Half-life — hr	37.8 (36.0–39.7)	42.3 (40.5–44.2)	40.0 (38.5–41.5)
C_{max} — IU/dl	134 (113–160)	111 (100–122)	122 (110–135)
T_{max} — hr	0.51 (0.30–0.86)	0.38 (0.26–0.56)	0.44 (0.32–0.61)
AUC_{0-tau} — hr×IU/dl	6720 (6190–7300)	7060 (6380–7810)	6890 (6470–7340)
Clearance — ml/hr/kg	0.73 (0.67–0.80)	0.67 (0.61–0.74)	0.70 (0.66–0.74)
Incremental recovery — IU/dl per IU/kg	2.63 (2.22–3.12)	2.21 (2.01–2.42)	2.42 (2.19–2.67)

Figure 2. Factor VIII Activity over Time and Pharmacokinetic Variables.
The graph shows plasma factor VIII activity levels that have been corrected for baseline factor VIII activity levels at each time point among 37 patients who underwent pharmacokinetic assessment after the first dose of efanesoctocog alfa. I bars indicate standard deviations. The tabular data show the results of pharmacokinetic variables. Incremental recovery is the increase in plasma level per IU per kilogram of efanesoctocog alfa administered. AUC_{0-tau} denotes area under the activity–time curve over the administration interval, C_{max} maximum concentration, and T_{max} time to reach maximum concentration.

DISCUSSION

The XTEND-Kids study assessed efanesoctocog alfa in children younger than 12 years of age. Once-weekly prophylaxis with intravenous efanesoctocog alfa (50 IU per kilogram) provided highly effective bleeding prevention, with a median annualized bleeding rate of 0.00 (interquartile range, 0.00 to 1.02) and an estimated mean annualized bleeding rate of 0.89 (95% CI, 0.56 to 1.42) in the full analysis population. Most patients (47 of 74 [64%]) had no bleeding episodes. In the sensitivity analysis including patients treated according to the protocol, the mean annualized bleeding rate was 0.61 (95% confidence interval, 0.42 to 0.90), and the annualized rate of bleeding into joints was 0.30 (95% CI, 0.16 to 0.57). Efanesoctocog alfa also provided effective treatment of bleeding episodes, with a single injection of 50 IU per kilogram resolving most episodes. No inhibitors to factor VIII developed, most adverse events were not serious, and no adverse events led to discontinuation of efanesoctocog alfa. Comparing bleed prevention provided by efanesoctocog alfa with other factor VIII products in previously treated children, we noted that in the PROTECT VIII Kids study of damoctocog alfa pegol, the median annualized bleeding rate was 2.9 (interquartile range, 1.1 to 6.1) and 23% of the patients had no bleeding episodes in Part 1 of the study.[25] In a phase 3 study of rurioctocog alfa pegol, the median annualized bleeding rate was 2.0 (interquartile range, 0.0 to 3.9) and 38% of the patients had no bleeding episodes.[26] Finally, the Kids A-LONG study of efmoroctocog alfa showed a median annualized bleeding rate of 1.96 (interquartile range, 0.00 to 3.96) and

46% of the patients had no bleeding episodes.[27] Although these clinical study results cannot be directly compared because of the differences in patient populations and study designs, the XTEND-Kids study showed favorable bleeding protection with efanesoctocog alfa prophylaxis as compared with these extended half-life factor VIII products.

Even though data from large clinical trials of emicizumab are limited in children younger than 12 years of age with severe hemophilia A without factor VIII inhibitors, our finding of a mean annualized bleeding rate of 0.61 (95% CI, 0.42 to 0.90) with efanesoctocog alfa suggests improved bleeding protection as compared with that in a small Japanese study involving 13 children who received emicizumab prophylaxis every 2 weeks or every 4 weeks. That study showed annualized rates of treated bleeding episodes of 1.3 (95% CI, 0.6 to 2.9) and 0.7 (95% CI, 0.2 to 2.6) with the respective emicizumab regimens.[28]

The results of the XTEND-Kids study were consistent with those of XTEND-1, a phase 3 study of efanesoctocog alfa in previously treated adults and adolescents (≥12 years of age) with severe hemophilia A, in which the same weekly dose of 50 IU per kilogram was used, except for the 11-year-old outlier patient who was removed for ad hoc sensitivity analyses. Of note, the prolonged and intense treatment did not raise safety concerns. In hindsight, the definition used for treatment of a new bleeding episode was derived during the development of standard and extended half-life therapies with half-lives of 9 to 18 hours and may have been too strict for studying a factor VIII product with a half-life of 38 to 42 hours. The mean annualized consumption (on a per-weight basis) was somewhat higher in patients younger than 6 years of age than in those 6 to younger than 12 years of age, possibly related to the recommendation of rounding to the nearest whole vial, which could have affected younger patients' consumption.

As expected, the terminal half-life of efanesoctocog alfa was lower in children (geometric mean of 37.8 hours in those <6 years of age and 42.3 hours in those 6 to <12 years of age) than in adults and adolescents (47.0 hours).[6] This difference has been reported for other factor VIII replacement therapies and is due to an age-related reduction in clearance.[14,29] Nonetheless, factor VIII levels remained above 10 IU per deciliter for nearly 7 days across the two age cohorts. Shortening the weekly administration interval was not deemed to be necessary in any patient during this study.

Primary prophylaxis is key to prevent bleeding into joints and subsequent hemophilic arthropathy and to maintain joint health throughout life.[30,31] In our study, prophylaxis with efanesoctocog alfa resulted in a low annualized rate of bleeding into joints. Given the effect that poor joint health can have on quality of life, early prevention of bleeding into joints may contribute to improved quality of life and greater health equity in this age group, especially over a lifetime.[30,32]

One limitation of our study is that a larger sample of previously treated patients followed over a longer period and assessments of previously untreated patients would be useful in understanding immune response and the potential immunogenicity of efanesoctocog alfa. The XTEND-ed study (ClinicalTrials.gov number, NCT04644575) is currently ongoing, which will provide longer-term safety and efficacy data for efanesoctocog alfa in the previously treated patients who completed the XTEND-1 or XTEND-Kids studies. It should also be noted that registry studies are planned for efanesoctocog alfa in previously untreated patients with severe hemophilia A (e.g., as part of the ATHN [American Thrombosis and Hemostasis Network] Transcends study [NCT04398628]).

In this study, once-weekly efanesoctocog alfa (50 IU per kilogram) provided high sustained factor VIII activity and highly efficacious protection against bleeding episodes in children with severe hemophilia A, a population in which this goal has been difficult to achieve without burdensome treatment regimens. No factor VIII inhibitors developed. Weekly prophylaxis with efanesoctocog alfa has the potential to provide long-term preservation of joint health.[33]

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APPENDIX

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