Clinical Outcomes Over 3 Years of Once-Weekly Efanesoctocog Alfa Treatment in Adults and Adolescents from North America with Severe Hemophilia A in the Phase 3 XTEND-ed Long-Term Extension Study

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Introduction

- Efanesoctocog alfa is a first-in-class high-sustained factor VIII (FVIII) replacement therapy designed to decouple recombinant FVIII from endogenous von Willebrand factor (VWF) in circulation, thereby overcoming the VWF-imposed half-life ceiling[1,2]
- In previously treated adults and adolescents with severe hemophilia A (XTEND-1; NCT04161495), prophylactic treatment with once-weekly efanesoctocog alfa maintained normal to near-normal FVIII activity (>40%) for the majority of the week.
- Efanesoctocog alfa was well-tolerated and provided superior bleed protection compared with prior FVIII prophylaxis, with clinically meaningful improvements in physical health, pain, and joint health.[3]

Objective

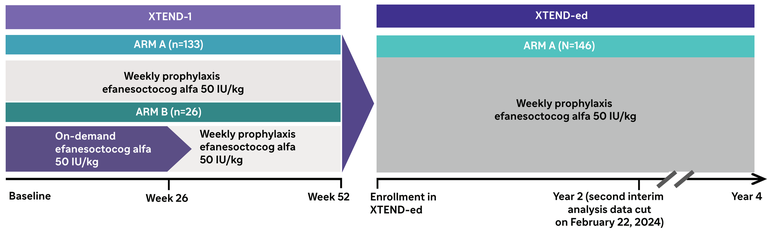
- To evaluate the safety and efficacy of efanesoctocog alfa in adults and adolescents with severe hemophilia A from North America in the Phase 3 long-term extension study, XTEND-ed (NCT04644575; second interim analysis).

Methods

Study design and patient selection:

- XTEND-ed (NCT04644575) is an ongoing, open-label, multicenter, multinational, Phase 3 long-term extension study.
- Arm A of XTEND-ed includes adults, adolescents, and children with severe hemophilia A (<1 IU/dL endogenous FVIII activity or a documented genotype known to produce severe hemophilia A) who completed XTEND-1 (NCT04161495) or XTEND-Kids (NCT04759131) and continued to receive once-weekly efanesoctocog alfa treatment for up to 4 years.
- Here, we present clinical outcomes from adults and adolescents (aged ≥12 years) from North America who completed XTEND-1 and rolled over to XTEND-ed Arm A **(Figure 1)**.
- Data cut for this second interim analysis was February 22, 2024.

Figure 1. XTEND-ed (Arm A) study design



Endpoint and statistics:

- The primary endpoint was the incidence of FVIII inhibitor development evaluated using the Nijmegen-modified Bethesda assay at the central laboratory.
  - Positive inhibitor titer was defined as ≥0.6 BU/mL and confirmed by a second test result from a separate sample drawn 2–4 weeks following the date of the original sample.
  - The incidence of inhibitor formation was reported with 95% confidence intervals (CI) as determined by the Clopper-Pearson exact method.
- Secondary endpoints include annualized bleed rates (ABRs), efficacy for bleed treatment, consumption, and safety.
  - The efficacy of efanesoctocog alfa in treating bleeding episodes was evaluated in terms of the number of injections and dose of efanesoctocog alfa required for bleed resolution. Percentages were calculated based on the total number of treated bleeding episodes.
  - The treatment response was reported per the International Society on Thrombosis and Haemostasis (ISTH) 4-point bleeding response scale of excellent, good, moderate, and none.
  - Safety outcomes were based on the number of patients in the safety analysis set.

RESULTS

Demographics

- Overall, there were 20 adults and adolescents from North America in Arm A of XTEND-ed (12 from the United States and 8 from Canada).
- Median age was 33 (13–74) years, and the majority (70.0%) were adults; there was one female participant **(Table 1)**.
- At the time of this interim data cut, a total of 9 (45.0%) participants remained in the study, as 8 (40.0%) have completed and 3 (15.0%) discontinued.
  - Reasons for discontinuation: adverse event (n=1), prohibited concomitant medication (n=1), and other (n=1).

Table 1. Demographics and baseline characteristics of participants from North America in XTEND-ed Arm A

Categories	N=20
Age at the enrollment of Arm A in years[a]	
Median (range)	33 (13–74)
12–17, n (%)	5 (25.0)
18–64, n (%)	14 (70.0)
≥65, n (%)	1 (5.0)
Sex, n (%)	
Male	19 (95.0)
Female	1 (5.0)
Ethnicity, n (%)	
Hispanic or Latino	2 (10.0)
Not Hispanic or Latino	17 (85.0)
Not Reported	1 (5.0)
Race, n (%)	
White	14 (70.0)
Black or African American	3 (15.0)
Asian	1 (5.0)
Not Reported	1 (5.0)
Other	1 (5.0)
Weight in kg, median (range)	74.2 (33.9–101.0)

Data cut: February 22, 2024.
Percentages are based on the number of participants with non-missing data in the Full Analysis Set. [a]Age = the year of informed consent - year of birth.

Treatment duration:

- The median (range) treatment duration in XTEND-ed was 112.4 (44.1–136.6) weeks comprising a median (range) of 105.0 (45–143) exposure days (EDs).
- The median (range) cumulative treatment duration from XTEND-1 baseline was 164.0 (89.3–188.6) weeks with median (range) 157.0 (81–197) EDs.
- The median (range) number of prophylactic injections per patient in XTEND-ed was 104.5 (45–136); (mean [SD]: 97.0 [29.0]).
- All participants from North America were both dose and interval compliant.

Consumption:

- The median (Q1; Q3) total weekly efanesoctocog alfa consumption was 51.9 (51.1; 52.6) IU/kg.
- The median (Q1; Q3) average weekly prophylactic dose was 51.4 (50.1; 51.9) IU/kg.

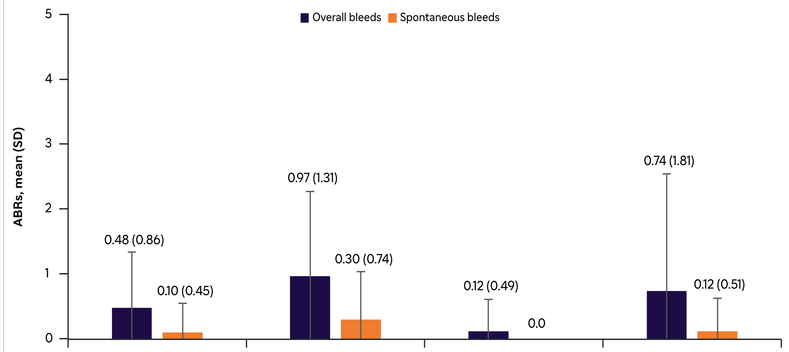
Inhibitor development:

- No FVIII inhibitors were detected in any of the participants during XTEND-ed or the parent studies (XTEND-1 or XTEND-Kids).
- The incidence of inhibitor formation in XTEND-ed at the time of the data cut was 0.0% (95% CI: 0.0–16.8).

Bleed protection:

- Over a median (range) efficacy period of 106.2 (44.1–132.7) weeks, the mean (95% CI) model-based ABR for overall treated bleeds was 0.60 (0.36–1.00), for spontaneous bleeds was 0.13 (0.05–0.34), and traumatic bleeds was 0.33 (0.15–0.73).
  - These results are consistent with the low ABRs reported in XTEND-1 — mean (95% CI) ABR for overall bleeds was 0.71 (0.52–0.97); spontaneous bleeds, 0.27 (0.18–0.41); and traumatic bleeds, 0.37 (0.25–0.54).
- Participants with zero overall bleeds over 2 years in XTEND-ed were 9 (45.0%); zero spontaneous bleeds were 16 (80.0%), and zero traumatic bleeds were 14 (70.0%).
- The ABRs for overall and spontaneous bleeds evaluated by 6-month intervals until Month 24 in XTEND-ed remained low **(Figure 2)**.

Figure 2. Summary of ABRs by 6-month intervals for treated overall and spontaneous bleeds in adults and adolescents from North America receiving once-weekly prophylaxis with efanesoctocog alfa (50 IU/kg) in XTEND-ed Arm A[a]

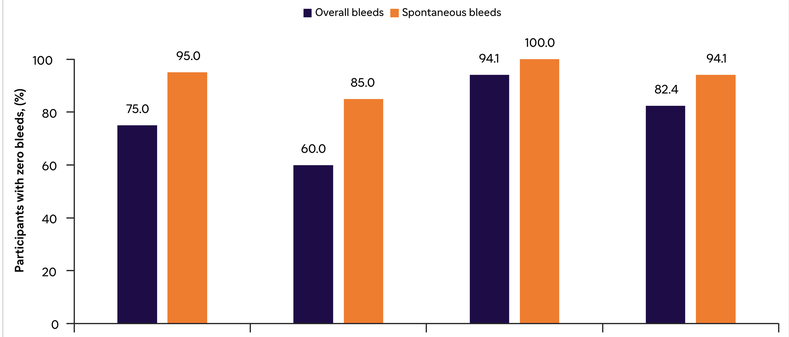


Duration	Day 1 – Month 6	Month 6 – 12	Month 12 – 18	Month 18 – 24
Evaluable participants, n (%)	20 (100.0)	20 (98.6)	17 (85.0)	17 (85.0)

Data cut: February 22, 2024.
ABR, annualized bleed rate; SD, standard deviation.
[a]Values are based on the number of participants with an evaluable efficacy period, defined as the treatment regimen period, from the first injection of efanesoctocog alfa in Arm A of XTEND-ed to the day of the last dose of efanesoctocog alfa or the second interim data cutoff date of February 22, whichever was first. The efficacy period excluded periods of surgery/rehabilitation (minor and major) and large injection intervals (>28 days).

- The percentage of participants with zero overall bleeds and zero spontaneous bleeds remained high, when evaluated by 6-month intervals until Month 24 in XTEND-ed **(Figure 3)**.

Figure 3. Summary of percentage of adults and adolescents from North America with zero bleeds by 6-month intervals in XTEND-ed Arm A[a]



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[a]Values are based on the number of participants with an evaluable efficacy period, defined as the treatment regimen period, from the first injection of efanesoctocog alfa in Arm A of XTEND-ed to the day of the last dose of efanesoctocog alfa or the second interim data cutoff date of February 22, whichever was first. The efficacy period excluded periods of surgery/rehabilitation (minor and major) and large injection intervals (>28 days).

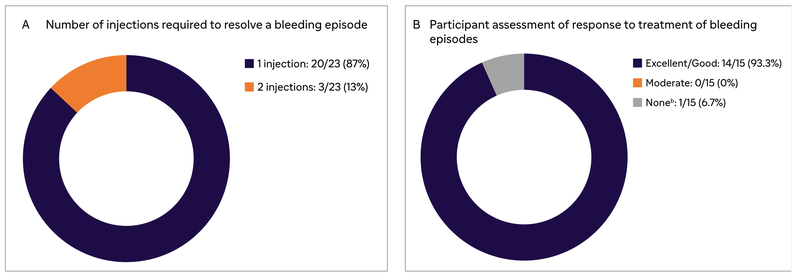
Efficacy for bleed treatment:

- There were 23 bleeding episodes reported in 20 participants.
- The majority (87%) of bleeds resolved with one injection of efanesoctocog alfa **(Figure 4A)**.
  - The median (range) dose per injection required to resolve a bleeding episode was 50.3 (30.5–71.1) IU/kg; (mean [SD]: 48.3 [8.78] IU/kg).
  - The median (range) total dose required to resolve a bleeding episode was 51.7 (30.5–82.7) IU/kg; (mean [SD]: 53.7 [14.10] IU/kg).
- Of 15 injections with an evaluation by participants, the hemostatic response was rated as excellent or good for 14 (93.3%) **(Figure 4B)**.

Conclusions

- FVIII inhibitors did not develop in adult and adolescent participants from North America in Arm A of XTEND-ed who rolled over from XTEND-1.
- ABRs remained low (<1), and the percentage of patients with zero bleeding episodes remained high over an additional 2 years of treatment with efanesoctocog alfa.
- Results from this second interim analysis of XTEND-ed North American participants (mean treatment duration: 101.2 weeks) show once-weekly efanesoctocog alfa prophylaxis (50 IU/kg) continues to be well-tolerated and highly effective in adults and adolescents.

Figure 4. Treatment of bleeding episodes with efanesoctocog alfa in participants from North America in XTEND-ed Arm A (A) Number of injections required to resolve a bleeding episode (B) Participants' assessment of response[a] to treatment of bleeding episodes



Data cut: February 22, 2024.
ISTH, International Society on Thrombosis and Haemostasis.
[a]Based on the ISTH 4-point response scale of excellent, good, moderate, and none. "None" means there was no improvement, not that the participant did not provide a response. [b]There was no reduction in elbow pain being experienced by a participant who received an injection to treat it assuming it was an elbow bleed. Subsequent clinical evaluation revealed that the participant was experiencing a gout flare in the elbow.

Safety:

- Overall, 19 (95.0%) participants reported at least 1 treatment-emergent adverse event and 4 (20.0%) participants reported at least 1 treatment-emergent serious adverse event **(Table 2)**.
- None were related to efanesoctocog alfa treatment.

Table 2. Overview of adverse events in participants from North America in XTEND-ed Arm A

	Participants (N=20)[a–c]
Total number of TEAEs	86
Participants with at least 1 TEAE, n (%)	19 (95.0)
Participants with at least 1 related TEAE, n (%)	0 (0.0)
TEAEs occurring in >10% of participants, n (%)[d,e]	
Upper respiratory tract infection	7 (35.0)
Nasopharyngitis	6 (30.0)
Back pain	5 (25.0)
Pain	4 (20.0)
Dizziness	4 (20.0)
Skin abration/laceration	4 (20.0)
Arthralgia	3 (15.0)
Total number of TESAEs	5
Participants with at least 1 TESAE, n (%)[f]	4 (20.0)
Participants with at least 1 related TESAE, n (%)	0 (0.0)
TEAEs leading to death, n (%)	0 (0.0)
TEAEs leading to treatment discontinuation, n (%)[g]	1 (0.0)

Data cut: February 22, 2024.
AE, adverse event; FVIII, factor VIII; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
[a]Percentages are based on the number of participants in the safety analysis set. [b]AEs with missing causality assessment are included in the related TEAE or related TESAE category. [c]AEs that occurred during a major surgical/rehabilitation period are excluded from this table, but AEs that occurred on the day the surgical/rehabilitation period started are included. [d]Events were coded using MedDRA version 26.1. [e]Participants were counted once if they reported multiple events in the same system organ class or preferred term. [f]There were no serious allergic/anaphylactic reactions. [g]One participant had a deep vein thrombosis following surgical correction of a femur fracture performed in the setting of another FVIII replacement product; therefore, discontinued treatment.

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