Clinical Outcomes Over 2 Years of Once-Weekly Efanesoctocog Alfa Treatment in Children From North America With Severe Hemophilia A in the Phase 3 XTEND-ed Long-Term Extension Study

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Introduction

- Efanesoctocog alfa (ALTUVIIIO®; formerly BIVV001) 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]
- The Phase 3 XTEND-Kids (NCT04759131) study in children <12 years of age with severe hemophilia A demonstrated that once-weekly prophylaxis with efanesoctocog alfa (50 IU/kg):[3]
  - Was well tolerated, with no development of inhibitors.
  - Effectively treated and prevented bleeding episodes.
  - Maintained high sustained FVIII activity throughout the weekly dosing interval, remaining in the normal to near-normal range (>40 IU/dL for approximately 3 days and >10 IU/dL for nearly 7 days).

Objective

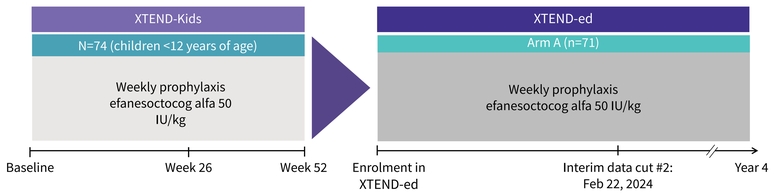
- To assess the long-term safety and efficacy of efanesoctocog alfa in North American children with severe hemophilia A, in the Phase 3 long-term extension study, XTEND-ed (NCT04644575; second interim analysis)

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 the respective parent studies where they received efanesoctocog alfa treatment up to 52 weeks.
- This analysis included the North American children under 12 years of age who completed the XTEND-Kids study and continued weekly prophylaxis with efanesoctocog alfa (50 IU/kg) in XTEND-ed (Arm A) (**Figure 1**).
- Exclusion criteria included a positive FVIII inhibitor test result (≥0.6 Bethesda units [BU]/mL) at screening or a history of positive inhibitor test, other known coagulation disorder(s), or a history of hypersensitivity with any FVIII product.
- Data cut for this second interim analysis of XTEND-ed was February 22, 2024.

Figure 1. Schematic of XTEND-ed study design for children



Outcome measures:

- 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 included annualized bleed rates (ABRs) for treated bleeds, efficacy for bleed treatment, 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 participant's assessment of response to treatment 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

- Of the 74 male children who participated in the XTEND-Kids study, 71 continued in the XTEND-ed study.
- Overall, 27 North American children were included in this sub-group analysis, of whom 19 were <6 years of age and 8 were between 6 –<12 years of age at the time of enrollment in the XTEND-Kids study (**Table 1**).
- Eight patients (29.6%) completed the study, whereas 18 (66.7%) are ongoing with treatment at the time of the interim analysis. One patient withdrew from the study due to the patient/guardian's decision.

Table 1. Demographics and baseline characteristics

	Age Cohort[a]		
	<6 years (n=19)	6 to <12 years (n=8)	Overall (N=27)
Age at enrollment in XTEND-ed, years[b]			
Median (range)	5.0 (2–8)	10.0 (7–13)	6.0 (2–13)
<12, n (%)	19 (100)	7 (87.5)	26 (96.3)
12–17, n (%)	0 (0)	1 (12.5)	1 (3.7)
Sex, n (%)			
Male	19 (100)	8 (100)	27 (100)
Ethnicity, n (%)			
Hispanic or Latino	2 (10.5)	0	2 (7.4)
Not Hispanic or Latino	17 (89.5)	8 (100)	25 (92.6)
Race, n (%)			
White	17 (89.5)	5 (62.5)	22 (81.5)
Black or African American	0	2 (25.0)	2 (7.4)
Asian	0	1 (12.5)	1 (3.7)
Not Reported	0	0	0
Other	2 (10.5)	0	2 (7.4)
Completion status, n (%)			
Ongoing	7 (36.8)	1 (12.5)	8 (29.6)
Completed	11 (57.9)	7 (87.5)	18 (66.7)
Discontinued	1 (5.3)[c]	0	1 (3.7)[c]

Data cut: February 22, 2024.
[a]Age cohort in the header refers to age at screening of parent study XTEND-Kids
[b]Age equals the year at point of informed consent for enrolment in Arm A of XTEND-ed, minus the patient's year of birth.
[c]One patient discontinued due to withdrawn consent.

Treatment duration:

- The median (range) treatment duration in XTEND-ed was 53.6 (36.3–96.6) weeks comprising a median (range) of 53.0 (11.0–96.0) exposure days.
- The median (range) cumulative treatment duration from XTEND-Kids baseline was 105.4 (88.1–148.6) weeks with median (range) 106.0 (65.0–149.0) exposure days (**Table 2**).
- Of the total 27 children from North America, 24 (88.9%) were both dose- and interval-compliant, whereas 3 (11.1%) were interval-compliant but not dose-compliant.

Table 2: Treatment duration and exposure days

	Through XTEND-ed interim analysis	During XTEND-ed
Treatment duration in weeks, median (range)	105.4 (88.1–148.6)	53.6 (36.3–96.6)
Exposure days, median (range)	106.0 (65.0–149.0)	53.0 (11.0–96.0)

Treatment duration refers to the total duration, including periods of pharmacokinetic evaluations, surgery/rehabilitation (major/minor), and large injection intervals (>28 days).
An exposure day refers to a 24-hour period in which ≥1 efanesoctocog alfa injections are given. All injections over the study course are counted.

Consumption:

- The median (Q1–Q3) total weekly efanesoctocog alfa consumption was 55.9 (54.3–58.1) IU/kg.
- The median (Q1–Q3) average weekly prophylactic dose was 54.5 (52.8–57.0) IU/kg.

No inhibitors developed during the study

- **No FVIII inhibitors developed**
- **Incidence of inhibitor formation (%)[a–c]: 0.0 (95% CI, 0.0–60.2)**

CI, confidence interval; FVIII, Factor VIII.
[a]Inhibitor development was evaluated using the Nijmegen-modified Bethesda assay at the central laboratory. Inhibitor development was defined as an inhibitor result of ≥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.
[b]All patients had previously received treatment with recombinant and/or plasma-derived FVIII, or cryoprecipitate at the start of the observation period.
[c]95% CI calculated using the Clopper-Pearson exact method.

Bleed protection:

- The mean (95% CI) model-based ABR was 0.77 (0.50–1.18) for overall treated bleeds, 0.03 (0.00–0.24) for spontaneous bleeds, and 0.60 (0.33–1.10) for traumatic bleeds.
- The mean (SD) ABRs for overall and spontaneous bleeds evaluated by 6-month intervals in XTEND-ed remained low (**Figure 2A**).
- The percentage of participants with zero overall bleeds and zero spontaneous bleeds remained high, when evaluated by 6-month intervals in XTEND-ed (**Figure 2B**).

Figure 2. Summary of (A) annualized bleed rates and (B) participants with zero bleeds, by 6-month intervals for treated overall and spontaneous bleeds.

Data cut: February 22, 2024.
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).

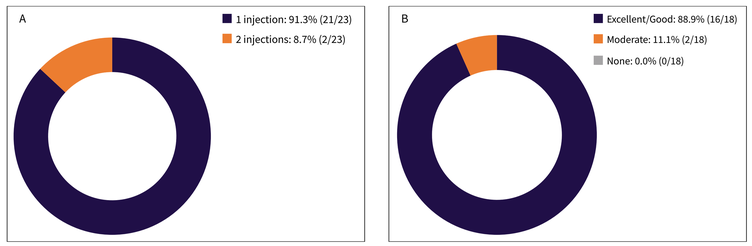
Efficacy for bleed treatment:

- Overall, 23 bleeding episodes were reported in 27 children of which 91.3% (21/23) were resolved with one injection of efanesoctocog alfa **(Figure 3A)**.
- The median (range) dose per injection required to resolve a bleeding episode was 55.3 (30.2–66.2) IU/kg (mean [SD]: 52.8 [8.08] IU/kg).
- The median (range) total dose required to resolve a bleeding episode was 55.3 (30.2–113.6) IU/kg (mean [SD]: 59.9 [20.9] IU/kg).
- Of the 18 injections with an evaluation, the hemostatic response was rated as excellent or good for 16 (88.9%) **(Figure 3B)**.

Conclusions

- No FVIII inhibitors developed in previously treated children from North America treated with efanesoctocog alfa who rolled over from XTEND-Kids
- ABRs remained low, and the percentage of patients with zero bleeding episodes remained high over an additional 1 year of treatment with efanesoctocog alfa.
- Outcomes for the North American subset of pediatric participants in the long-term XTEND-ed extension study are similar to those observed for the overall population.
  - Efanesoctocog alfa continues to be well-tolerated and highly effective in children (<12 years of age).

Figure 3. Summary of treatment of bleeding episodes (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.

Safety:

- Overall, 22 (81.5%) participants experienced ≥1 treatment-emergent adverse event (TEAE), with 1 participant experiencing ≥1 treatment-related TEAE. Two participants (7.4%) experienced ≥1 treatment-emergent serious adverse event (TESAE); neither of the TESAE was related to treatment. **(Table 3)**.
- None of the TEAEs resulted in death or required treatment discontinuation. Additionally, no thrombotic events occurred.

Table 3. Overview of adverse events in children from North America in XTEND-ed Arm A

	Age Cohort[a]		
	<6 years (n=19)	6 to <12 years (n=8)	Overall (N=27)
Total number of TEAEs[b–d]	97	25	122
Participants with ≥1 TEAE, n (%)	16 (84.2)	6 (75.0)	22 (81.5)
Participants with ≥1 related TEAE, n (%)	0 (0.0)	1 (12.5)[e]	1 (3.7)
Total number of TESAEs	1	1	2
Participants with ≥1 TESAE, n (%)	1 (5.3)	1 (12.5)	2 (7.4)
Participants with ≥1 related TESAE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to treatment discontinuation or death	0	0	0

Data cut: February 22, 2024.
AE, adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
[a]Age cohort on the header refers to age at screening of parent study XTEND-Kids. [b]Percentages are based on the number of participants in the Safety Analysis Set. [c]AEs with missing causality assessment are included in the related TEAE or related TESAE. [d]AEs that occur during a major surgical/rehabilitation period are excluded from this table, but adverse events that occur on the day the surgical/rehabilitation period starts will be included. [e]One participant reported two TEAEs related to treatment: headache and left arm pain following injection (both events resolved).

Disclosures
LM - Consultative/Advisory Board: CSL Behring, Novo Nordisk, Pfizer, Sanofi, Sobi, Spark Therapeutics, Takeda, Genetech, and Biomarin; Speakers Bureau: CSL Behring, Sanofi. **MS** - Consultant/Advisory Board: Bayer, CSL Behring, Genentech, Medexus, Novo Nordisk, Pfizer, Sanofi. **CT** - Honoraria for advisory boards for Takeda and Sanofi. **UK, GN,** and **LM** - Employees of Sanofi and may hold shares and/or stock options in the company.
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