Clinical outcomes over 2 years of efanesoctocog alfa in children with severe haemophilia A: European results from the second interim analysis of XTEND-ed

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Introduction

- Efanesoctocog alfa is a first-in-class high-sustained factor VIII (FVIII) replacement therapy, also known as ultra-long half-life FVIII, designed to overcome the half-life limitations caused by FVIII binding to endogenous von Willebrand factor.[1–3]
- In the completed Phase 3 XTEND-Kids (NCT04759131) study, once-weekly efanesoctocog alfa was well tolerated and provided FVIII activity in the normal to near-normal range (>40%) for three days, and activity of ~10% for seven days, in patients <12 years of age with severe haemophilia A.[4]
- Participants completing XTEND-Kids could continue efanesoctocog alfa in the long-term extension study XTEND-ed (NCT04644575); results of a second interim analysis (data cut-off: 22 February 2024) of the overall XTEND-ed population have previously been published.[5]

Objectives

- To assess long-term clinical outcomes in European children included in the XTEND-ed second interim analysis.

Methods

Study design

- XTEND-ed is an open-label extension study, evaluating long-term safety and efficacy of once-weekly efanesoctocog alfa (50 IU/kg) for the treatment of severe haemophilia A.
- Participants were aged <12 years when entering XTEND-Kids. Those who completed XTEND-Kids (or XTEND-1, a separate study that assessed once-weekly efanesoctocog alfa in patients ≥12 years of age) were eligible to enter into XTEND-ed (**Figure 1**).
- All those participants <12 years enrolled at European sites, including France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, Turkey and the United Kingdom, were included in the current XTEND-ed subanalysis.

Outcomes

- The primary endpoint was occurrence of FVIII inhibitors.
  - Inhibitor development was evaluated using the Nijmegen-modified Bethesda assay at a central laboratory and defined as an inhibitor result of ≥0.6 BU/mL, confirmed by a second test result from a separate sample 2–4 weeks later.
- Secondary endpoints included annualised bleed rates (ABRs), participants with zero bleeds, efficacy of bleed treatment and safety.
  - Mean (standard deviation [SD]) ABR values (treated bleeds) 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 data cut-off date of 22 February 2024 (the date of the second interim data cut), whichever was first. The efficacy period excluded periods of surgery/rehabilitation (minor and major) and large injection intervals (>28 days).
  - Efficacy of bleed treatment was evaluated based on the number of injections required to treat a bleeding episode and patient assessment of treatment response (rated as 'excellent', 'good', 'moderate' or 'none').

Results

Patient population

- The patient population consisted of 33 male paediatric participants <12 years of age who were enrolled at European sites participating in the XTEND-ed study.
- Key patient demographics are shown in **Table 1**.

Treatment duration and factor usage

- Median (range) treatment duration in XTEND-ed was 69.0 (53.1–100.6) weeks (483 [371.7–704.2] days).
- Median (range) cumulative treatment duration, including XTEND-Kids, was 120.6 (101.3 –152.6) weeks (844.2 [709.1–1068.2] days).
- Median (range) weekly dose of efanesoctocog alfa was 52.3 (29.6–55.6) IU/kg.

FVIII inhibitor development

- No FVIII inhibitors were detected.

Annualised bleed rates (ABR)

- The mean (SD) ABR was 0.70 (0.85) for European paediatric patients <6 years, and 0.78 (1.06) for those 6 to <12 years; this is consistent with interim analysis data for the entire XTEND-ed paediatric population <12 years of age (n=71; **Figure 2**). The model-based mean ABR (95% CI) was 0.66 (0.32; 1.36) and 0.79 (0.42; 1.48) for patients aged <6 years and 6 to <12 years, respectively.
- Mean (SD) ABRs for the overall European paediatric population <12 years of age by 6-month period (n=33 in each period) were 0.78 (1.66), 0.82 (1.85), 0.82 (2.97) and 0.15 (0.60) for Day 1–Month 6, Months 6–12, Months 12–18 and Months 18–24, respectively; data for populations <6 and 6–12 years of age are presented in **Figure 2**.

Patients achieving zero bleeds

- The majority of patients did not experience bleeding episodes (**Figure 3**).
  - Specifically, 76%, 79%, 82% and 94% of participants <12 years of age (n=33) had zero bleeds of any type during the 6-month intervals of Day 1–Month 6, Months 6–12, Months 12–18 and Months 18–24, respectively.
  - Over the 2-year period analysed, 91% of participants had zero spontaneous bleeds.

Treatment of bleeding episodes

- The majority of bleeds (30/35 [85.7%]) were resolved with a single dose of efanesoctocog alfa (**Figure 4a**).
- Response for treatment of bleeding episodes was rated 'excellent' or 'good' for 42/44 (95.5%) injections (**Figure 4b**).

Safety

- Efanesoctocog alfa was well tolerated with reported treatment-emergent adverse events (TEAEs) being as expected for this population (**Table 2**).
  - 26 participants (78.8%) experienced ≥1 TEAE.
  - 2 participants (6.1%) had ≥1 treatment-emergent serious adverse event (TESAEs).
  - There were no treatment-related TESAEs or TEAEs leading to death.

Conclusions

- **This subanalysis of interim data for paediatric patients <12 years of age enrolled at European sites of the XTEND-ed study through 2 years of continuous treatment demonstrates that efanesoctocog alfa continues to be well tolerated and provide highly effective bleed protection, without FVIII inhibitor development, with long-term use.**

Figure 1. XTEND-Kids and XTEND-ed study design

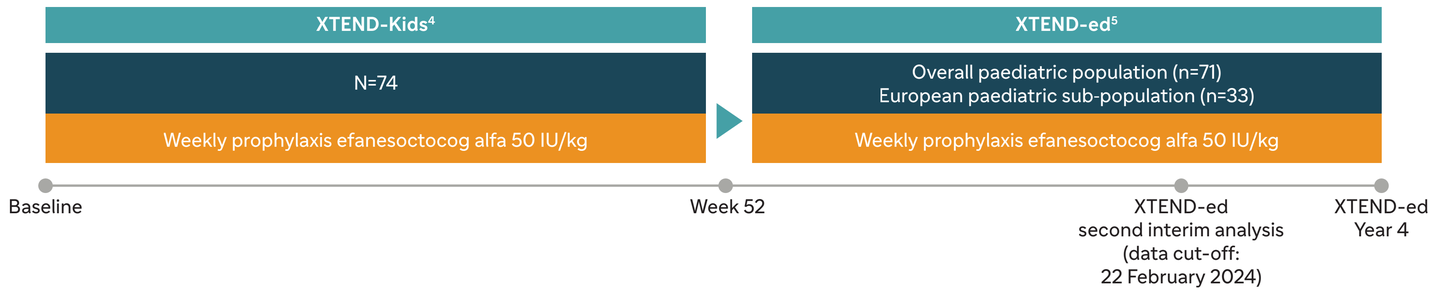
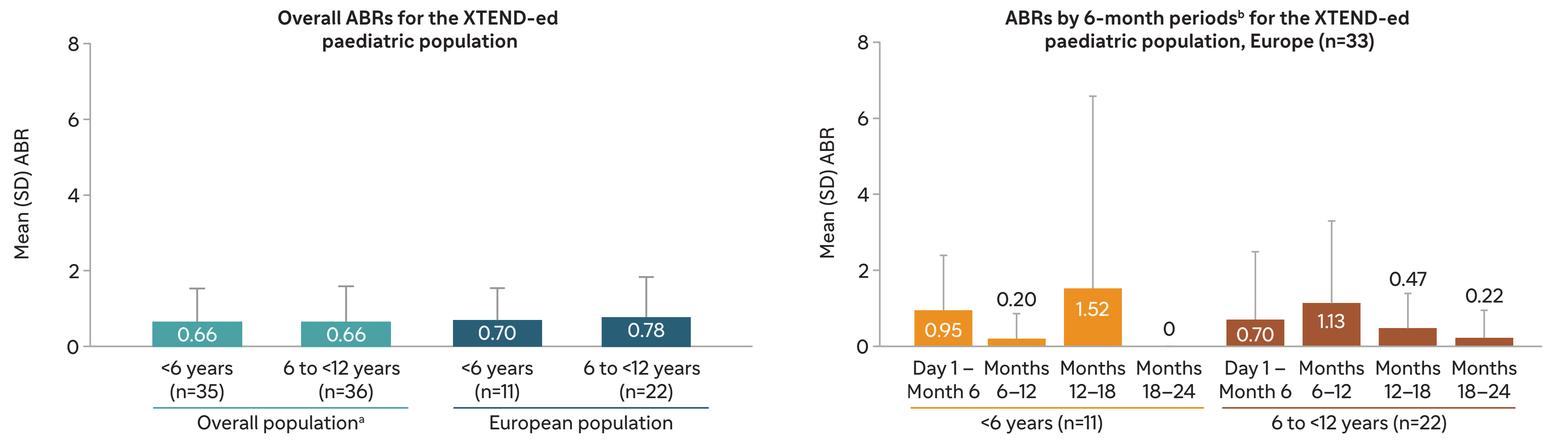
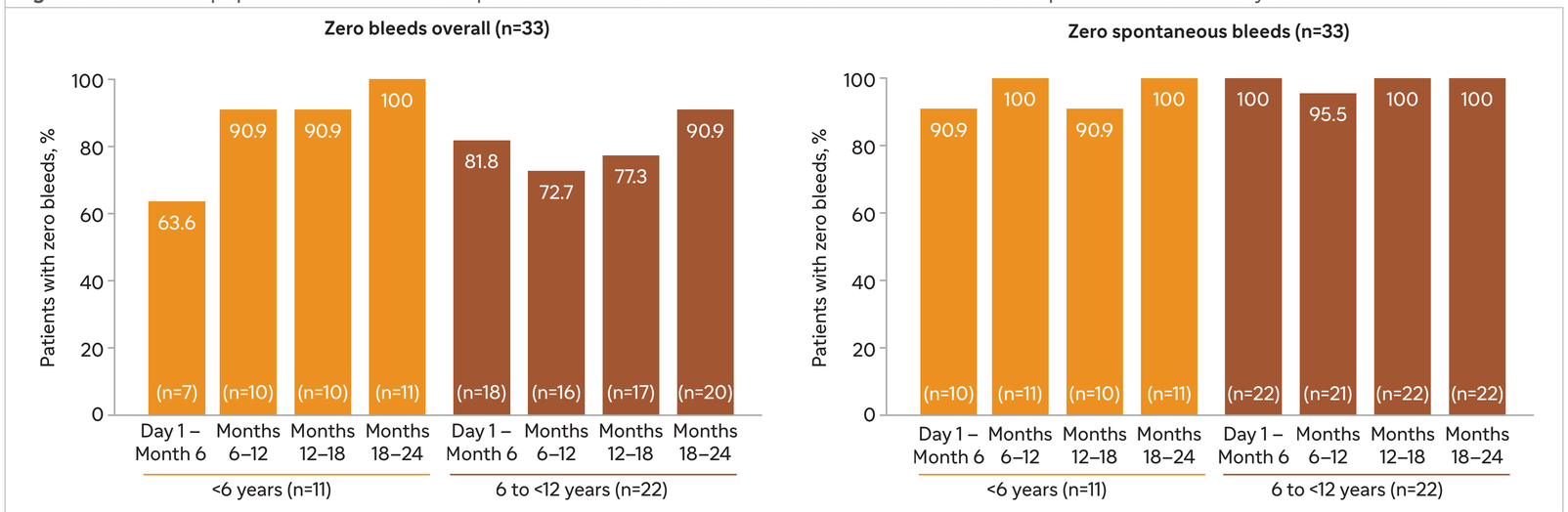


Figure 2. ABRs in the XTEND-ed overall paediatric population and paediatric population enrolled at European study sites



[a]Published previously;[5] [b]Six-month intervals are based on individuals' scheduled visits. In case of an intermediate missing visit date, the target date per protocol was used.

Figure 3. Paediatric population enrolled at European sites of XTEND-ed with zero overall bleeds and zero spontaneous bleeds by 6-month intervals[a]



[a]Six-month intervals are based on individuals' scheduled visits. In case of intermediate missing visit date, the target date per protocol was used.

Table 1. Baseline characteristics of paediatric patients enrolled at European XTEND-ed study sites

	<6 years[a] (n=11)	6 to <12 years[a] (n=22)	Overall (N=33)
Age at enrolment of XTEND-ed (years)[a]			
Median (min; max)	6.0 (4; 7)	10.0 (7; 13)	8.0 (4; 13)
<12, n (%)	11 (100)	13 (59.1)	24 (72.7)
12–17, n (%)	0	9 (40.9)	9 (27.3)
Sex, n (%)			
Male	11 (100)	22 (100)	33 (100)
Race, n (%)			
White	8 (72.7)	21 (95.5)	29 (87.9)
Black or African American	1 (9.1)	0	1 (3.0)
Asian	0	0	0
Not reported	2 (18.2)	1 (4.5)	3 (9.1)
Ethnicity, n (%)			
Hispanic or Latino	0	2 (9.1)	2 (6.1)
Not Hispanic or Latino	10 (90.9)	20 (90.9)	30 (90.9)
Not reported	1 (9.1)	0	1 (3.0)
Weight (kg)			
Median (min; max)	19.60 (12.7; 25.7)	31.45 (20.7; 66.5)	26.00 (12.7; 66.5)

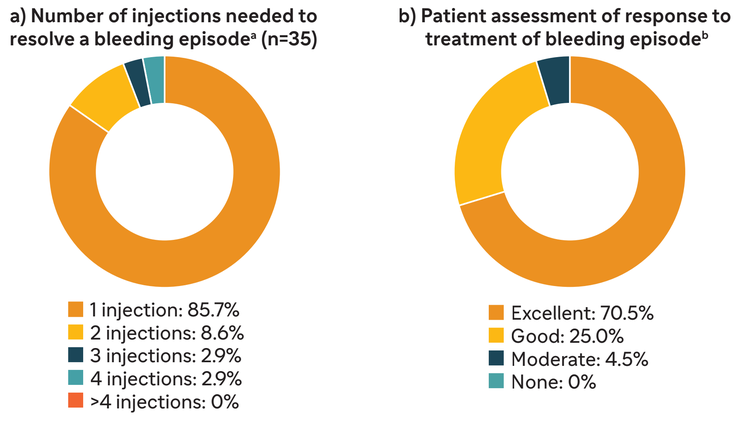
[a]Age = year of informed consent minus year of birth.

Table 2. Safety data for paediatric patients enrolled at European XTEND-ed study sites

	<6 years[a] (n=11)	6 to <12 years[a] (n=22)	Overall (N=33)
Total number of TEAEs	30	99	129
Participants with ≥1 TEAE, n (%)	7 (63.6)	19 (86.4)	26 (78.8)
Participants with ≥1 treatment-related TEAE, n (%)	0	0	0
Total number of TESAEs	1	1	2
Participants with ≥1 TESAE, n (%)	1 (9.1)	1 (4.5)	2 (6.1)
Participants with ≥1 treatment-related TESAE, n (%)	0	0	0
TEAEs leading to death	0	0	0
TEAEs leading to treatment discontinuation	0	0	0

[a]Age = year of informed consent minus year of birth.

Figure 4. Number of injections needed to resolve a bleeding episode[a] and response rating in paediatric population enrolled in European sites of XTEND-ed



[a]All injections given from the initial sign of a bleed, until the last date/time within the bleed window were counted; [b]Based on 44 injections with an evaluation. 'None' means that there was no improvement, not that the participant did not provide a response.

References: 1. Chhabra ES, et al. *Blood* 2020;135(17):1484–1496; **2.** Konkle BA, et al. *N Engl J Med* 2020;383(11):1018–1027; **3.** Lissitchkov T, et al. *Blood Adv* 2022;6(4):1089–1094; **4.** Malec L, et al. *N Engl J Med* 2024;391(3):235–246; **5.** Malec L, et al. ASH 2024, 07–10 December, San Diego, California, USA.

Abbreviations: ABR: annualised bleed rate; **BU:** Bethesda unit; **CI:** confidence interval; **FVIII:** factor VIII; **IU:** international units; **SD:** standard deviation; **TEAE:** treatment-emergent adverse event; **TESAE:** treatment-emergent serious adverse event.

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