Long-Term Clinical Outcomes of Efanesoctocog Alfa in Patients with Severe Haemophilia A: European Results from the Third Interim Analysis of XTEND-ed

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Introduction

- Efanesoctocog alfa is a first-in-class, high-sustained factor VIII replacement therapy (also known as ultra-long half-life FVIII) that has been designed to overcome the von Willebrand factor-imposed half-life ceiling.[1,2]
- The Phase 3 studies XTEND-Kids and XTEND-1 showed that once-weekly efanesoctocog alfa was highly efficacious, well tolerated and provided effective prevention and treatment of bleeds in patients with severe haemophilia A.[2,3]
- Moreover, prior analyses of the global cohort from the XTEND-ed long-term extension study showed that efanesoctocog alfa provided long-term bleed protection/treatment and was well tolerated.[4,5]

Aim

- To report data in a European subgroup of children, adolescents and adults with severe haemophilia A from XTEND-ed entry up to the third interim data cut-off.

Methods

Study design

- Patients who completed XTEND-Kids (<12 years of age; NCT04759131) or XTEND-1 (≥12 years of age; NCT04161495) could enter Arm A of XTEND-ed (NCT04644575) and continue to receive once-weekly prophylaxis with efanesoctocog alfa (50 IU/kg) for up to 4 years or until efanesoctocog alfa is commercially available in their country.[2–5]
- Patients from sites in the following European countries were included: Belgium, Bulgaria, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Outcomes

- The primary endpoint was the incidence of FVIII inhibitor development.
  - Inhibitor development was evaluated using the Nijmegen-modified Bethesda assay at a central laboratory (defined as an inhibitor result of ≥0.6 BU/mL and confirmed by a second test result from a separate sample 2–4 weeks later).
- Secondary endpoints included:
  - Overall annualised bleed rates (ABRs [as observed]; treated bleeds);
    - ABRs and the proportion of patients with zero treated bleeds are presented at 6-month intervals;
  - Number of injections required to treat bleeding episodes;
  - Patient-reported assessment of treatment response ('excellent', 'good', 'moderate' or 'none');
  - Treatment-emergent adverse events (TEAEs).
- All data are reported from XTEND-ed entry up to the data cut-off for the third interim analysis (21st February 2025).
- Baseline characteristics were summarised as mean (standard deviation [SD]) for continuous and n (%) for categorical characteristics. Treatment duration and factor usage were summarised as median (range). Observed ABRs overall and by 6-month intervals were summarised as mean (SD), and patients with zero treated bleeds were summarised as n (%) by 6-month intervals.
- Bleed data and treatment of bleeding episodes data are reported in patients with an evaluable efficacy period, defined as the period from the first injection of efanesoctocog alfa in Arm A of XTEND-ed to either the day of the last dose or the data cut-off for ongoing patients. The efficacy period excluded periods of surgery/rehabilitation (minor and major) and large intervals between injections (>28 days).

Results

Study population

- Overall, 109 male patients from 14 European countries in XTEND-Kids (n=33) and XTEND-1 (n=76) rolled over into Arm A of XTEND-ed.
- Baseline characteristics of these patients are shown in **Table 1**.

Treatment duration and factor usage

- Median (range) durations of treatment during XTEND-ed were:
  - Patients from XTEND-Kids: 120.7 (76.1–152.6) weeks.
  - Patients from XTEND-1: 173.1 (22.9–192.7) weeks.
- Median (range) cumulative durations of treatment from parent study through XTEND-ed were:
  - Patients from XTEND-Kids: 172.8 (128.2–204.7) weeks.
  - Patients from XTEND-1: 219.7 (46.3–244.8) weeks.
- Overall in XTEND-ed, the median (range) weekly efanesoctocog alfa dose was 51.4 (24.0–58.6) IU/kg.

Efficacy period duration and bleeding rates

- Median (range) durations of efficacy periods during XTEND-ed were:
  - Patients from XTEND-Kids: 119.7 (34.2–152.6) weeks.
  - Patients from XTEND-1: 167.6 (19.0–192.7) weeks.
- Mean (SD) observed ABRs (treated bleeds) in XTEND-ed for patients who entered from XTEND-Kids and XTEND-1 were 0.62 (0.73) and 0.59 (1.03), respectively.
- Mean (SD) spontaneous/traumatic ABRs in XTEND-ed for patients who entered from XTEND-Kids and XTEND-1 were:
  - Spontaneous ABRs: 0.05 (0.14) and 0.23 (0.49), respectively.
  - Traumatic ABRs: 0.40 (0.51) and 0.21 (0.34), respectively.
- ABRs at 6-month intervals are presented in **Table 2**.
- Proportions of patients with zero treated bleeds during each 6-month interval are presented in **Figure 1**; the vast majority of patients experienced zero treated bleeds over each 6-month period.
  - In XTEND-ed, 78.8–87.9% of patients who entered from XTEND-Kids and 88.0–95.9% of patients from XTEND-1 had zero treated traumatic bleeds over each 6-month interval, respectively.

Treatment of bleeding episodes

- In patients with an evaluable efficacy period, the vast majority of bleeding episodes (92.8%) were resolved with a single injection of efanesoctocog alfa (**Figure 2A**).
  - The median (interquartile range) number of doses needed to resolve a bleeding episode was 1 (1–1).
- The vast majority of patients (93.0% of 129 evaluated injections) reported that the treatment of their bleeding episodes was 'excellent' or 'good' (**Figure 2B**).

Safety

- Efanesoctocog alfa was well tolerated with no unexpected safety findings (**Table 3**).
  - One patient had a treatment-related TEAE which resolved (isolated incident of low FVIII activity levels).
  - One patient had a TEAE leading to treatment discontinuation due to use of a prohibited medication (alternative FVIII product used for femur fracture surgery).
- No cases of FVIII inhibitor development were reported.

Conclusion

- **Once-weekly efanesoctocog alfa continued to provide highly effective bleed protection/treatment and remained well tolerated in European children, adolescents and adults through the third interim cut-off, consistent with the overall XTEND-ed population.**

Table 1 Baseline characteristics

	XTEND-ed European children (n=33)	XTEND-ed European adolescents and adults (n=76)
Age at XTEND-ed enrolment (years), mean (SD)	8.7 (2.8)	37.1 (15.0)
Age categories at XTEND-ed enrolment (years), n (%)		
<12	24 (72.7)	-
<6	11 (45.8)	-
6 to <12	13 (54.2)	-
12 to 17	9 (27.3)	10 (13.2)
18 to 64	0	63 (82.9)
≥65	0	3 (3.9)
Race, n (%)		
White	29 (87.9)	57 (75.0)
Black or African American	1 (3.0)	1 (1.3)
Asian	0	6 (7.9)
Not reported	3 (9.1)	12 (15.8)
Weight (kg), mean (SD)	30.1 (13.1)	79.5 (21.0)
BMI (kg/m²), mean (SD)	17.8 (3.6)	25.7 (5.2)

Patients were categorised into the XTEND-ed European children cohort and the XTEND-ed European adolescents and adults cohort based on their ages during screening for their parent study (XTEND-Kids or XTEND-1); therefore, some patients in the XTEND-ed European children cohort were aged ≥12 at the time of enrolment into XTEND-ed. Age at XTEND-ed enrolment was calculated by subtracting year of birth from year of informed consent. In XTEND-Kids and XTEND-1, 2 (6.1%) patients and 1 (1.3%) were of Hispanic/Latinx ethnicity, respectively.

Table 2 ABRs at 6-month intervals (treated bleeds)

	XTEND-ed European children (n=33)			XTEND-ed European adolescents and adults (n=76)		
Mean (SD) observed ABRs	n[a]	Overall bleeds	Spontaneous bleeds	n[a]	Overall bleeds	Spontaneous bleeds
Day 1–Month 6	33	0.91 (1.82)	0.06 (0.35)	76	0.69 (1.93)	0.26 (0.89)
Months 6–12	33	0.73 (1.65)	0.06 (0.35)	75	0.67 (1.59)	0.21 (0.71)
Months 12–18	33	0.44 (1.01)	0.07 (0.38)	74	0.58 (1.28)	0.27 (0.84)
Months 18–24	32	0.57 (1.05)	0	73	0.63 (1.86)	0.30 (0.72)
Months 24–30	-	-	-	73	0.56 (1.27)	0.17 (0.65)
Months 30–36	-	-	-	73	0.54 (2.61)	0.06 (0.33)

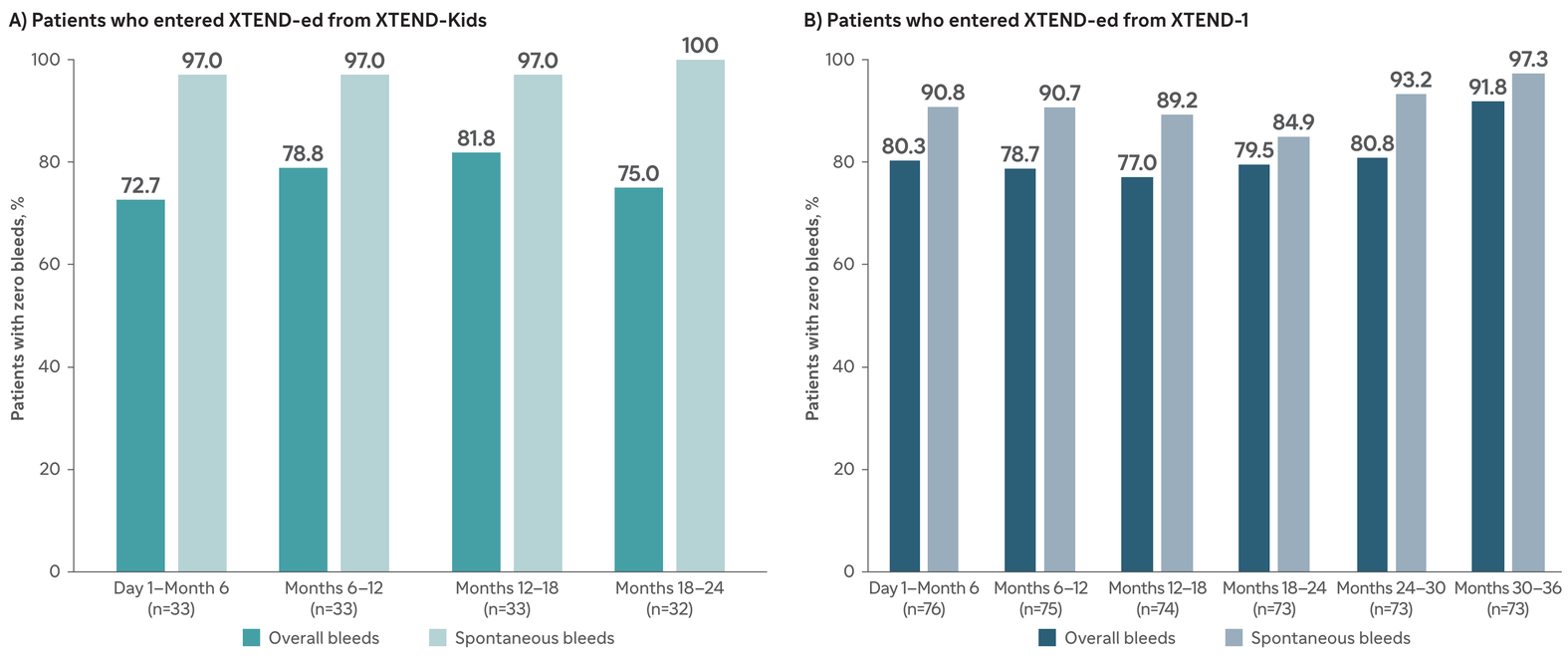
Six-month intervals had a fixed length of 182 days. **[a]** n values refer to the number of patients who started each 6-month interval; these patients may not have completed the full 6-month interval.

Table 3 Safety outcomes

n (%)	Overall (N=109)
Patients with ≥1 TEAE	101 (92.7)
Patients with ≥1 related TEAE	1 (0.9)[a]
Patients with ≥1 TESAE	21 (19.3)
Patients with ≥1 related TESAE	0
Patients with TEAEs leading to death	1 (0.9)[b]
Patients with TEAEs leading to treatment discontinuation	1 (0.9)[c]

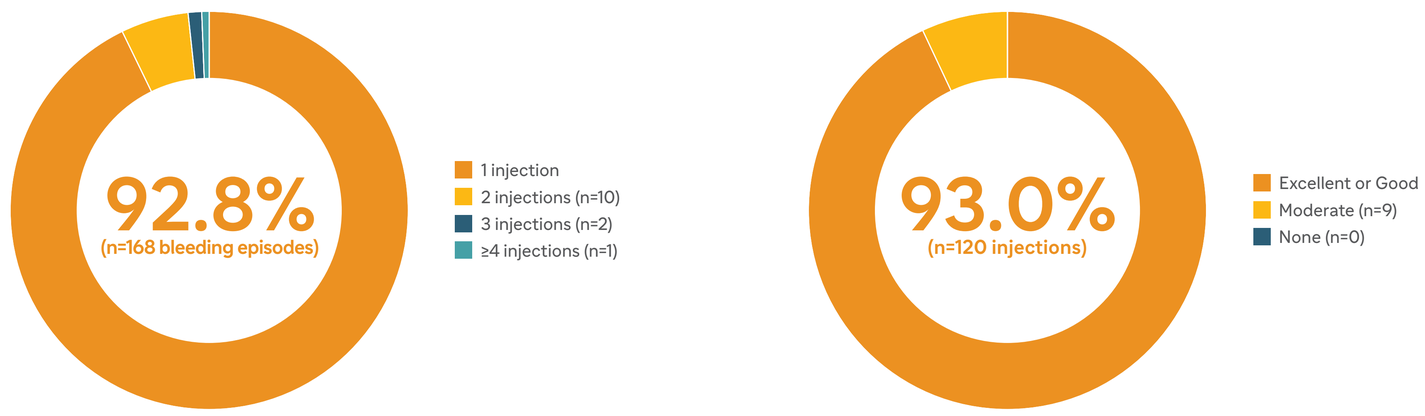
Included patients received ≥1 dose of efanesoctocog alfa. **[a]** One patient had a treatment-related TEAE which resolved (isolated incident of low FVIII activity levels observed prior to next dose of efanesoctocog alfa); **[b]** one death occurred which was unrelated to efanesoctocog alfa; **[c]** one patient had a TEAE leading to treatment discontinuation due to use of a prohibited medication; they received an alternative FVIII product used for femur fracture surgery while in hospital and subsequently discontinued efanesoctocog alfa.

Figure 1 Patients with zero treated bleeds at 6-month intervals



Six-month intervals had a fixed length of 182 days. n values refer to the number of patients who started each 6-month interval; these patients may not have completed the full 6-month interval at the time of the data cut-off.

Figure 2 Treatment of bleeding episodes



[a] All injections given from the initial sign of a bleed until the last date/time within the bleed window were counted; **[b]** 'None' means that there was no improvement and not that the patient did not provide a response.

References: 1. Konkle BA, et al. N Engl J Med 2020;383:1018–27; **2.** Malec L, et al. N Engl J Med 2024;391:235–46; **3.** von Drygalski A, et al. N Engl J Med 2023;388:310–8; **4.** Klamroth R, et al. Blood 2024;144:717–8; **5.** Malec L, et al. Blood 2024;144:5495–6.

Abbreviations: ABR: annualised bleeding rate; **BMI:** body mass index; **BU:** Bethesda unit; **FVIII:** factor VIII; **IU:** International Unit; **SD:** standard deviation; **TEAE:** treatment-emergent adverse event; **TESAE:** treatment-emergent serious adverse event.

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