Treatment of Bleeding Episodes With Efanesoctocog Alfa in Adults, Adolescents, and Children With Severe Haemophilia A: Third Interim Analysis of the XTEND-ed Long-term Extension Study

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Conclusions

- Long-term data in XTEND-ed show that in previously treated patients with severe haemophilia A, the overall annualised bleed rate remains consistently below 1 in patients of all ages after a median of 3 years' treatment
- A single 50 IU/kg dose of efanesoctocog alfa continues to provide highly effective treatment of bleeds regardless of age, bleed type, or location

Introduction

- Efanesoctocog alfa is a first-in-class high sustained factor VIII replacement therapy that overcomes the von Willebrand factor–imposed half-life ceiling[1,2]
- The XTEND-1 (NCT04161495)[3] and XTEND-Kids (NCT04759131)[4] studies demonstrated that once-weekly efanesoctocog alfa was well tolerated and provided highly effective protection from bleeds in previously treated patients with severe haemophilia A
- XTEND-ed (NCT04644575) is a long-term study of patients who rolled over from XTEND-1 and XTEND-Kids; prior interim analyses confirmed the long-term efficacy and safety of efanesoctocog alfa
- Here, we follow up on the treatment of bleeds with efanesoctocog alfa after a median of 3 years in XTEND-ed

Methods

- Patients who completed XTEND-1 and XTEND-Kids could continue once-weekly efanesoctocog alfa prophylaxis (50 IU/kg) in XTEND-ed
- Single-dose efanesoctocog alfa (50 IU/kg) was recommended for the initial treatment of bleeds; further doses (30 or 50 IU/kg) were allowed as needed every 2–3 days
- Data cutoff date for this analysis was 21 February 2025
- Annualised bleed rate (ABR; model-based, derived from a negative binomial model of treated bleeds), the number of treated bleeds with locations, and the dose and number of efanesoctocog alfa administrations required to resolve bleeds are presented descriptively
  - Data are based on treated bleeds in the full analysis data set during the efficacy period (first efanesoctocog alfa injection in XTEND-ed Arm A to the day of the last dose); periods of surgery/rehabilitation and long (>28 days) injection intervals are excluded
- At 72 hours after the initial treatment, patients evaluated response to treatment using the 4-point International Society on Thrombosis and Haemostasis (ISTH) scale[5]
- Safety was assessed in the safety analysis population, which was identical to the full analysis set

Results

Patient population

- A total of 217 patients rolled over to XTEND-ed (age group at parent study baseline: <6 years, n=35; 6–<12 years, n=36; ≥12 years, n=146); at data cutoff, 146 patients were ongoing (**Table 1**)

Table 1. Patient baseline demographics and study completion status

	Patients (N=217)
Age, years[a]	
Mean (SD)	27.4 (18.6)
<6 years, n (%)	35 (16.1)
6–<12 years, n (%)	36 (16.6)
≥12 years, n (%)	146 (67.3)
Sex, n (%)	
Male	216 (99.5)
Female	1 (0.5)
Race, n (%)	
White	152 (70.0)
Black/African American	7 (3.2)
Asian	35 (16.1)
Other	5 (2.3)
NR	18 (8.3)
BMI, kg/m²	
Mean (SD)	23.0 (5.9)
Median (min–max)	22.8 (13.2–40.8)
Completion status, n (%)	
Ongoing	146 (67.3)
Completed	55 (25.3)
Discontinued	16 (7.4)

Percentages are based on the number of patients with non-missing data in the full analysis set.
[a]Reported at screening of parent study (XTEND-1/XTEND-Kids). BMI, body mass index; NR, not reported; SD, standard deviation.

- Mean (standard deviation [SD]) treatment duration in XTEND-ed was 139.1 (43.3) weeks
- The median (range) efficacy period was 154.6 (8.1–192.7) weeks

Annualised bleed rates

- After a median of 3 years in XTEND-ed, the mean (95% CI) model-based ABR for all treated bleeds was 0.61 (0.50–0.74)
  - ABRs by age group, bleed type, and bleed location are reported in **Table 2**

Table 2. Summary of ABRs by age group, bleed type, and bleed location after a median of 3 years in XTEND-ed

	ABR, mean (95% CI)[a]			
	Age at screening of parent study			Overall (N=217)
	<6 years (n=35)	6–<12 years (n=36)	≥12 years (n=146)	
Overall	0.57 (0.35–0.93)	0.70 (0.49–1.00)	0.60 (0.47–0.76)	0.61 (0.50–0.74)
Type				
Spontaneous	0.08 (0.03–0.20)	0.08 (0.03–0.22)	0.20 (0.15–0.28)	0.17 (0.13–0.22)
Traumatic	0.39 (0.20–0.75)	0.51 (0.35–0.74)	0.29 (0.22–0.39)	0.33 (0.27–0.42)
Location				
Joint	0.18 (0.09–0.34)	0.43 (0.29–0.63)	0.42 (0.31–0.56)	0.38 (0.30–0.48)
Muscle	0.05 (0.02–0.15)	0.09 (0.03–0.28)	0.14 (0.09–0.22)	0.12 (0.08–0.18)
Internal	0.08 (0.02–0.29)	0.03 (0.01–0.11)	0.04 (0.03–0.08)	0.05 (0.03–0.08)
Skin/mucosa	0.18 (0.09–0.38)	0.16 (0.06–0.41)	0.05 (0.03–0.08)	0.08 (0.05–0.13)

[a]Model-based mean was estimated using a negative binomial model with the total number of treated bleeds during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable. ABR, annualised bleed rate; CI, confidence interval.

Summary of bleeding episodes

- There were 341 treated bleeds during the efficacy period, most commonly in joints, muscles, and skin/mucosa (**Tables 3 and 4**)
- Mean (SD) time to spontaneous bleed from last prophylactic injection was similar between age groups:
  - <6 years: 4.8 (2.3) days
  - 6–<12 years: 4.2 (1.7) days
  - ≥12 years: 5.0 (2.3) days

Table 3. Summary of bleeding episodes in XTEND-ed by 12-month periods in patients aged ≥12 years (N=146)

	0–12 months	13–24 months	25–36 months[a]
Number of patients	146	141	132
Patients with 0 bleeds, n (%)	96 (65.8)	96 (68.1)	103 (78.0)
Treated bleeds per patient, n (%)			
1	23 (15.8)	26 (18.4)	17 (12.9)
2	18 (12.3)	10 (7.1)	6 (4.5)
3	3 (2.1)	4 (2.8)	5 (3.8)
4	3 (2.1)	1 (0.7)	0
5	1 (0.7)	2 (1.4)	0
>5	2 (1.4)	2 (1.4)	1 (0.8)
Treated bleeds by type,[b] n (%)			
Spontaneous	35 (35.0)	32 (37.6)	16 (29.1)
Traumatic	49 (49.0)	41 (48.2)	26 (47.3)
Treated bleeds by location,[b] n (%)			
Joint	71 (71.0)	63 (74.1)	33 (60.0)
Muscle	19 (19.0)	24 (28.2)	14 (25.5)
Internal	6 (6.0)	7 (8.2)	6 (10.9)
Skin/mucosa	8 (8.0)	3 (3.5)	6 (10.9)

[a]The majority, but not all, patients have completed the full 12-month period. [b]Percentages are based on total treated bleeds.

Table 4. Summary of bleeding episodes in XTEND-ed by 12-month periods in patients aged <12 years (N=71)

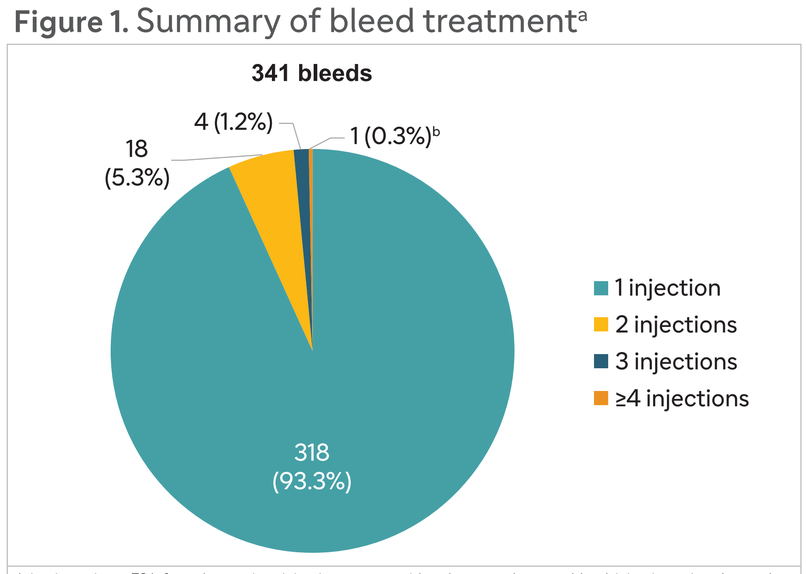
	0–12 months	13–24 months[a]
Number of patients	71	62
Patients with 0 bleeds, n (%)	46 (64.8)	41 (66.1)
Treated bleeds per patient, n (%)		
1	13 (18.3)	15 (24.2)
2	4 (5.6)	3 (4.8)
3	7 (9.9)	3 (4.8)
4	0	0
5	1 (1.4)	0
>5	0	0
Treated bleeds by type,[b] n (%)		
Spontaneous	4 (8.5)	2 (6.7)
Traumatic	34 (72.3)	20 (66.7)
Treated bleeds by location,[b] n (%)		
Joint	23 (48.9)	12 (40.0)
Muscle	5 (10.6)	4 (13.3)
Internal	3 (6.4)	5 (16.7)
Skin/mucosa	14 (29.8)	6 (20.0)

[a]The majority, but not all, patients have completed the full 12-month period. [b]Percentages are based on total treated bleeds.

Treatment of bleeding episodes

- A single efanesoctocog alfa injection resolved 93.3% (318/341) of bleeds (**Figure 1**)
- Median (Q1–Q3) efanesoctocog alfa total dose for resolution was 50.8 (45.5–52.4) IU/kg
- Responses were rated excellent/good or moderate for 89.4% and 10.1% of bleeds, respectively

Figure 1. Summary of bleed treatment[a]



[a]Injections given ≤72 h from the previous injection were considered to treat the same bleed; injections given beyond 72 h were considered to treat new bleeds. All injections (including routine prophylaxis) given from the initial sign of a bleed until the last date/time within the bleed window are counted. [b]Seven injections were recorded to treat an exercise-induced traumatic haematoma within the right iliopsoas muscle of a patient with poor compliance regarding treatment and completion of the ePD. Doses of 50 IU/kg were administered every other day, and the patient resumed routine prophylaxis 18 days after the first injection. ePD, electronic patient diary; IU, international unit.

Safety

- No factor VIII inhibitors developed with efanesoctocog alfa during the XTEND-ed study
- Treatment-related adverse events occurred in 4 patients (1.8%) (**Table 5**)
- No treatment-related serious adverse events were detected (**Table 5**)

Table 5. Summary of safety over a median of 3 years in XTEND-ed

	<6 years (n=35)	6–<12 years (n=36)	≥12 years (n=146)	Overall (N=217)
≥1 TEAE, n (%)	30 (85.7)	30 (83.3)	126 (86.3)	186 (85.7)
≥1 related TEAE, n (%)[a]	1 (2.9)	1 (2.8)	2 (1.4)	4 (1.8)
≥1 TESAE, n (%)	4 (11.4)	3 (8.3)	29 (19.9)	36 (16.6)
≥1 related TESAE, n (%)	0	0	0	0
TEAEs leading to death, n (%)[b]	0	0	2 (1.4)	2 (0.9)
TEAEs leading to discontinuation, n (%)[c]	0	0	3 (2.1)	3 (1.4)

The table includes adverse events that occurred on the day the surgical/rehabilitation period started but not those that occurred during a major surgical/rehabilitation period.
[a]Treatment-related TEAEs in children: asthma; post-infusion pain and headache. Treatment-related TEAEs in adults/adolescents: facial paralysis; coagulation FVIII level decreased. All treatment-related TEAEs were resolved.
[b](1) Unknown cause in a patient with metastatic lung cancer who died at home; (2) type A aortic dissection; none was treatment related. [c]TEAEs leading to treatment discontinuation: (1) femur fracture (patient received an alternative FVIII product in hospital and was discontinued from the study); (2) deep vein thrombosis after surgical correction of a femur fracture (in the setting of treatment with another FVIII product); (3) subarachnoid hemorrhage following aortic dissection repair (treatment discontinued because of necessary use of anticoagulant therapy, prohibited medication). All events were unrelated to efanesoctocog alfa.
FVIII, factor VIII; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

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