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Two-Year Clinical Outcomes of Once-Weekly Efanesoctocog Alfa Prophylaxis in Children with Severe Hemophilia A: Second Interim Analysis of the XTEND-ed Phase 3 Study

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Disclosures for Dr Lynn Malec

In compliance with COI policy, EAHAD requires the following disclosures to the session audience:

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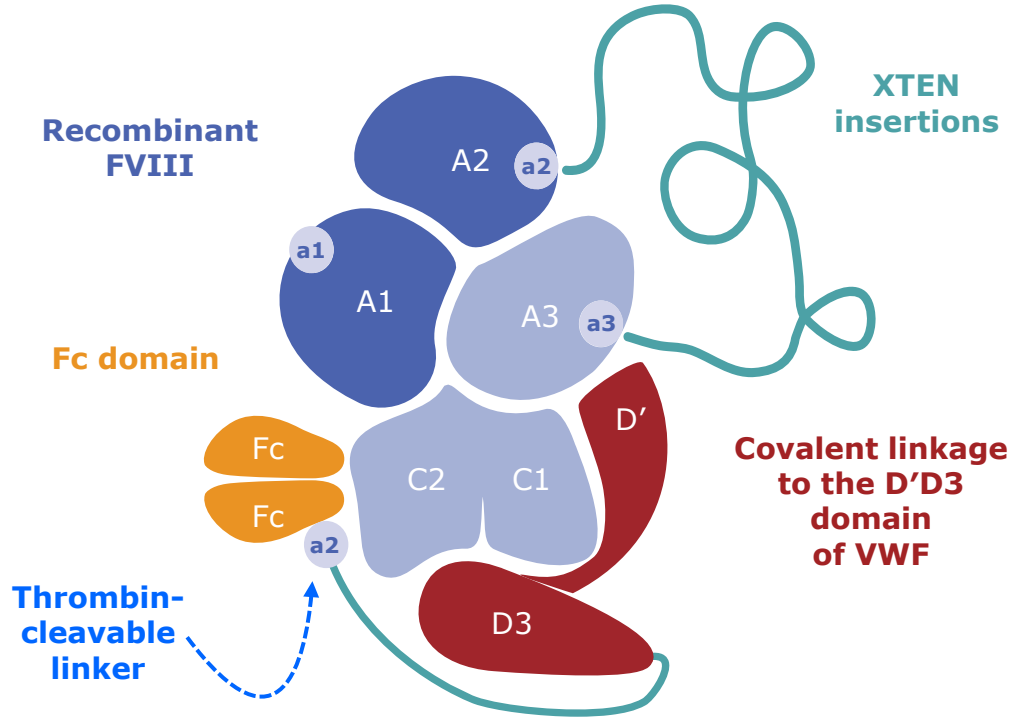
Other	No relevant conflicts of interest to declare

Efanesoctocog Alfa: A First-In-Class High-Sustained Factor Replacement Therapy Designed to Provide Higher FVIII Activity Levels for Longer

Efanesoctocog alfa is a novel fusion protein that **overcomes the VWF-imposed half-life ceiling**[1,2]



FVIII Replacement Therapy

- **Standard half-life (SHL) factor**
- **Extended half-life (EHL) factor**
- **High-sustained factor (HSF)**

In the XTEND-Kids study (NCT04759131), once-weekly efanesoctocog alfa 50 IU/kg prophylaxis[3]:

- Achieved **high-sustained factor levels in normal to near-normal range** (>40 IU/dL) for 3 days and >10 IU/dL for almost 7 days
- Was **well tolerated** and provided **highly effective bleed protection**

a1, a2, and a3, acidic region 1, 2, and 3; FVIII, factor VIII; VWF, von Willebrand factor; QoL, quality of life.

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. Malec L, et al. *N Engl J Med.* 2024;391(3):235-246.

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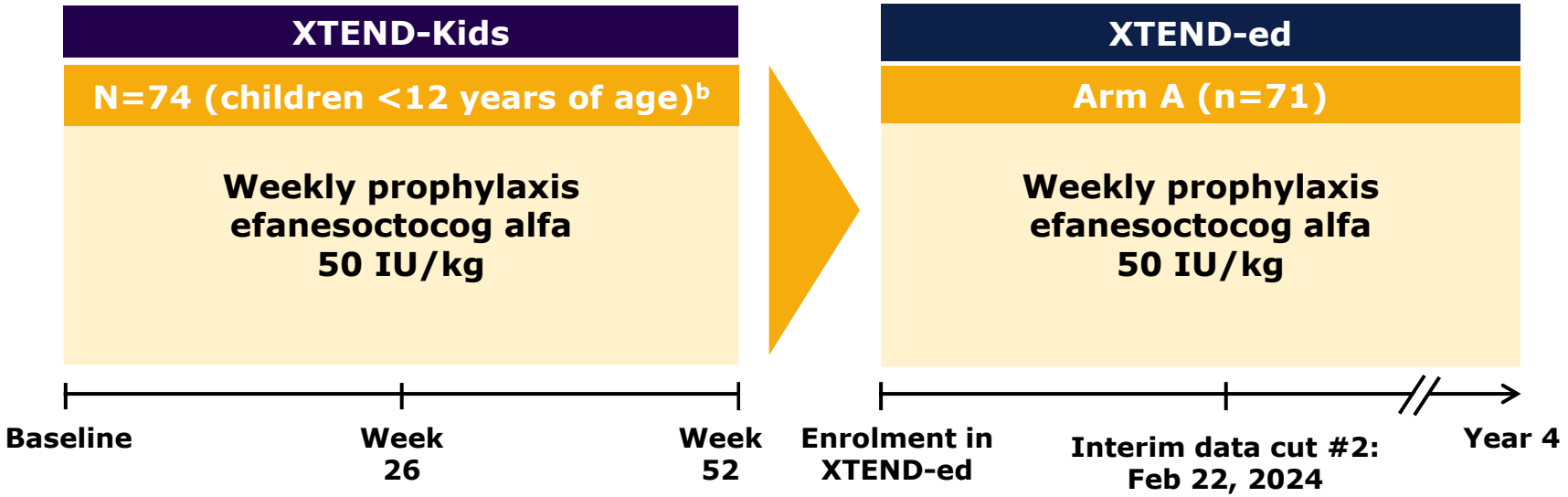
Aim

Evaluate long-term safety and efficacy of efanesoctocog alfa in **children with severe hemophilia A** in the Phase 3 long-term extension study (XTEND-ed): second interim analysis

XTEND-ed: An Ongoing, Multicentre, Open-Label Study of the Long-Term Safety and Efficacy of Efanesoctocog Alfa

- Previously treated patients (<12 years) with severe hemophilia A who completed XTEND-Kids were eligible to enroll into the long-term XTEND-ed study[a]



Primary endpoint

- The occurrence of inhibitor development[c]

Secondary endpoints

- Annualized bleed rates (ABRs)
- Treatment of bleeding episodes
- Safety and tolerability

This analysis: interim outcomes in children <12 years of age from XTEND-Kids (Data cut: February 22, 2024)

[a]Subjects >12 years who completed XTEND-1 could also enter XTEND-ed. Here we are only discussing the patients <12 years.
[b]Age at screening of parent study XTEND-Kids.
[c]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.

Data cut: February 22, 2024.
ABR, annualized bleed rate; BU, Bethesda Unit.

Key Patient Demographics and Disease Characteristics in Children <12 Years

	Age Cohort[a]		
	<6 years (n=35)	6 to <12 years (n=36)	Overall (N=71)
Age at enrollment in XTEND-ed, years[b]			
Median (range)	6.0 (2–8)	10.0 (7–13)	7.0 (2–13)
<12, n (%)	35 (100)	23 (63.9)	58 (81.7)
12–17, n (%)	0 (0)	13 (36.1)	13 (18.3)
Median weight, kg (range)	17.5 (11.4–25.7)	32.9 (17.2–66.5)	22.1 (11.4–66.5)
Sex, n (%)			
Male	35 (100)	36 (100)	71 (100)
Race, n (%)			
Asian	4 (11.4)	4 (11.1)	8 (11.3)
Black or African American	1 (2.9)	2 (5.6)	3 (4.2)
White	25 (71.4)	27 (75.0)	52 (73.2)
Not reported	2 (5.7)	3 (8.3)	5 (7.0)
Other	3 (8.6)	0 (0)	3 (4.2)
Completion status, n (%)			
Ongoing	23 (65.7)	29 (80.6)	52 (73.2)
Completed	11 (31.4)	7 (19.4)	18 (25.4)
Discontinued	1 (2.9)[c]	0	1 (1.4)[c]

Second Interim Analysis Data Cut Feb 22, 2024

- Overall, **71 participants** from XTEND-Kids **rolled over to XTEND-ed**
- Median (range) age was **7.0 (2.0–13.0) years**
- A total of **52 participants (73.2%) remain in the study[d]** as of the second interim data cut

[a]Age cohort on 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. [d]18 subjects completed the study and 1 subject discontinued from the study.

Data cut: February 22, 2024.
Percentages are based on the number of patients in the full analysis set.

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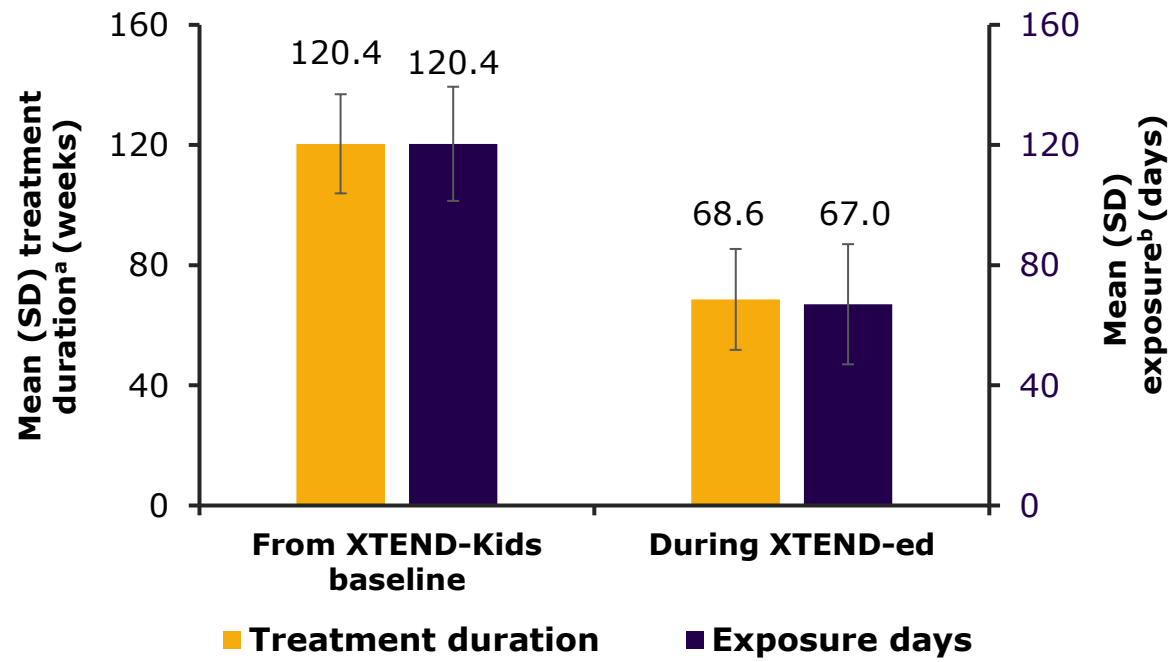
No FVIII Inhibitors Developed During the XTEND-ed Study

Treatment duration and exposure days



No FVIII inhibitors developed[c]

Incidence of inhibitor formation:
0.0 (95% CI, 0.0–5.1)[d]

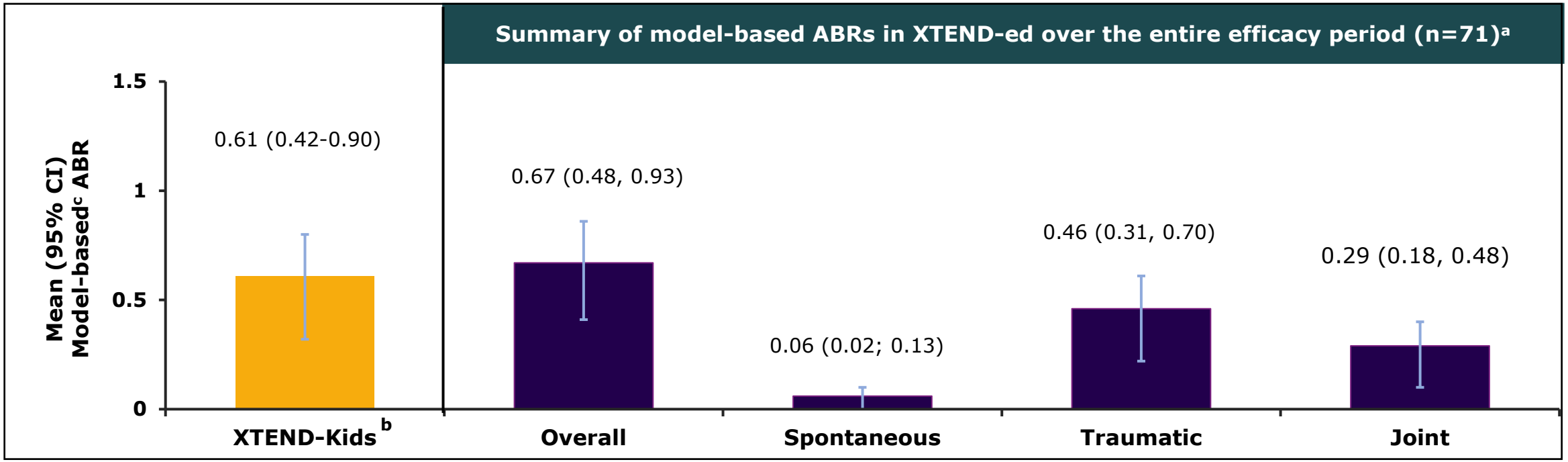
Total weekly consumption of efanesoctocog alfa: Median (Q1–Q3)

Prophylactic weekly dose: 53.6 (52.3–56.0) IU/kg)
Prophylaxis and bleed treatment: 54.0 (52.3–56.0) IU/kg

[a]Duration defined as the time period from the start of the treatment regimen to the end of that treatment regimen; [b]Exposure day defined as a 24-hour period in which ≥1 injections of efanesoctocog alfa are given, all injections over the study course are counted. [c]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. [d]95% CI calculated using the Clopper-Pearson exact method.

Data cut: February 22, 2024.
CI, confidence interval; FVIII, Factor VIII; SD, standard deviation; Q1, first quartile; Q3, third quartile.

Low Bleed Rates Were Maintained With Weekly Efanesoctocog Alfa Prophylaxis in Children



- Mean (95%CI) **overall model-based ABR** during **XTEND-ed** was **0.67 (0.48, 0.93),** maintaining the low ABR of 0.61 observed in XTEND-Kids (n=73)
- **Median ABR was zero** for all bleed types

[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 XTEND-ed to the day of the last dose of efanesoctocog alfa or the data cutoff date of February 22, 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). [b]During XTEND-Kids, participants received once-weekly efanesoctocog alfa 50 IU/kg prophylaxis for 52 weeks. [c]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.

Data cut: February 22, 2024.
ABR, annualized bleed rate; SD, standard deviation.

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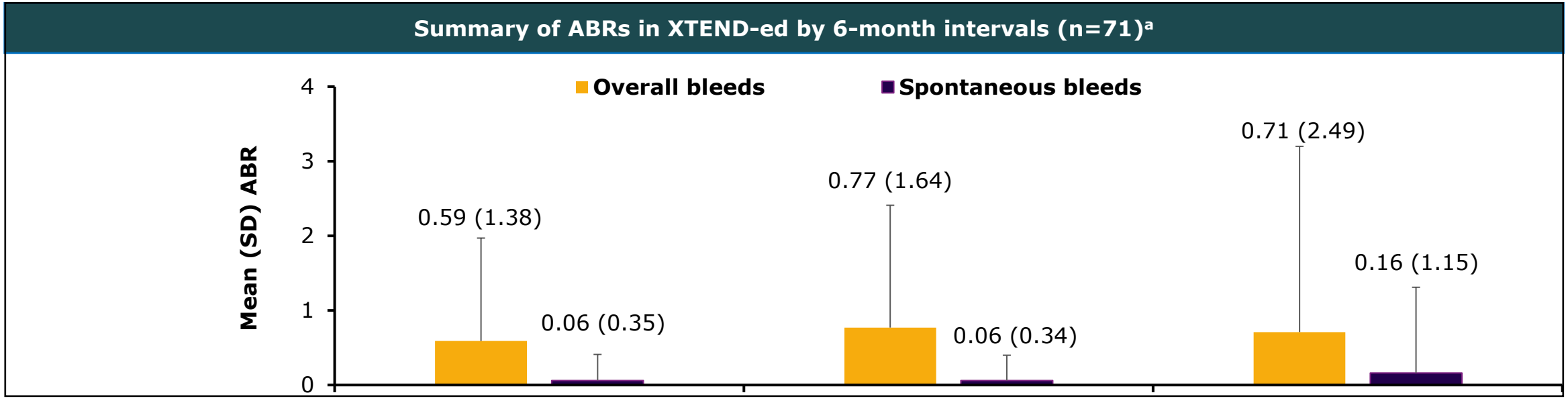
Low Bleed Rates Were Consistently Maintained Over 6-Month Intervals in Children

Summary of ABRs in XTEND-ed by 6-month intervals (n=71)[a]



Duration	Day 1 – Month 6	Month 6–12	Month 12–18
Evaluable participants, n (%)	71 (100.0)	71 (100.0)	53 (74.6)

Median ABR was 0 across all 6-month intervals for overall and spontaneous bleeds

[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 XTEND-ed to the day of the last dose of efanesoctocog alfa or the data cutoff date of February 22, 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).

Data cut: February 22, 2024.
ABR, annualized bleed rate; SD, standard deviation.

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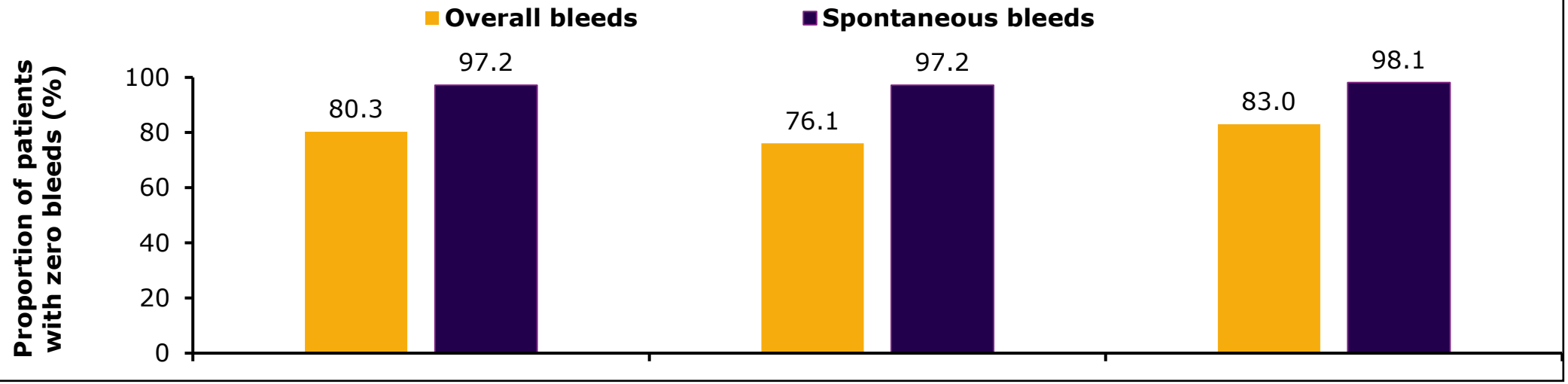
Percentage of Participants With Zero Bleeds Remained High Over 6-Month Intervals in Children

Summary of percentage of participants from XTEND-ed (n=71) with zero bleeds by 6-month intervals[a]



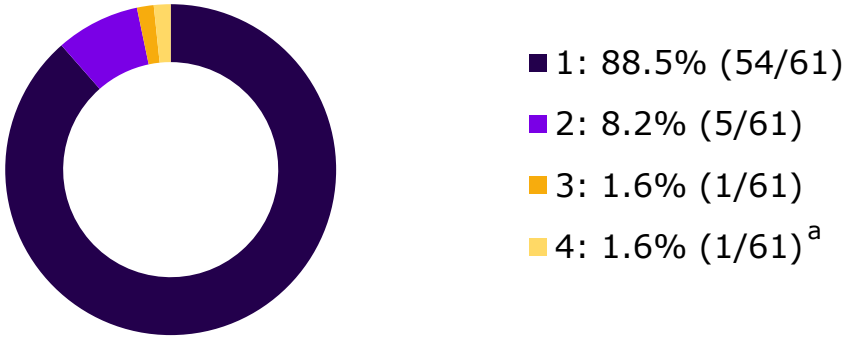
Duration	Day 1 – Month 6	Month 6–12	Month 12–18
Evaluable participants, n (%)	71 (100.0)	71 (100.0)	53 (74.6)

The percentage of pediatric participants with overall zero bleeds remained approximately 80% evaluated over 6-month intervals through the first 18 months of XTEND-ed

[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 XTEND-ed to the day of the last dose of efanesoctocog alfa or the data cutoff date of February 22, 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).

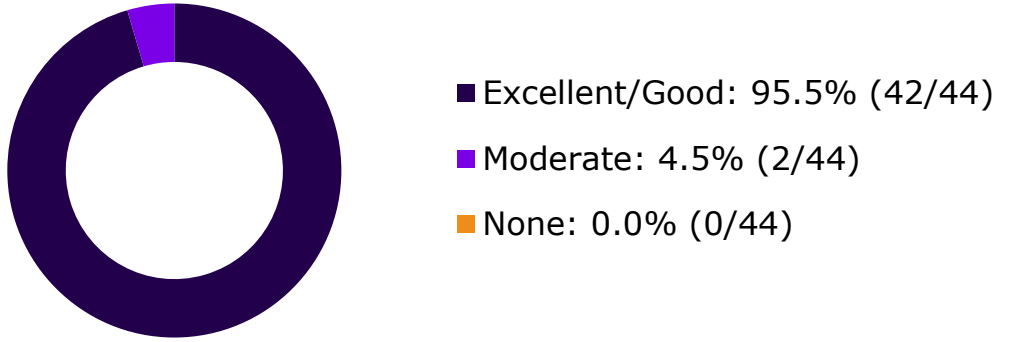
Efanesoctocog Alfa Remains Highly Effective for the Treatment of Bleeding Episodes in Children

Number of injections required to resolve a bleeding episode



88.5% of bleeding episodes (54/61) resolved with **a single injection** of efanesoctocog alfa

Participant assessment of response to efanesoctocog alfa treatment of bleeding episodes[b]:



Of the **44 injections**[c] with an evaluation**, 95.5% (42/44)** were assessed as **excellent** or **good**

Dose of efanesoctocog alfa required for resolution of a bleeding episode	Dose per injection (IU/kg)	Total dose (IU/kg)
Mean (SD)	50.84 (7.59)	59.24 (23.33)
Median (range)	51.83 (30.0–66.2)	53.35 (30.0–145.2)

[a]Subject requiring 4 injections: Two injections were given as pre-emptive treatment for head trauma following a motor vehicle accident, however, each injection was recorded in duplicate and the error not noted prior to the data cut (this will be rectified for the final data set); [b]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. [c]The injections are 'first' injections to treat a bleeding with evaluation.

Data cut: February 22, 2024.
ISTH, International Society on Thrombosis and Haemostasis; SD, standard deviation.

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Treatment With Efanesoctocog Alfa was Well-Tolerated in Children

	XTEND-ed participants from XTEND-Kids (N=71)		
	<6 years (n=35)	6 to <12 years (n=36)	Overall (N=71)
Total number of TEAEs, n[a–c]	130	159	289
Patients with ≥1 TEAE, n (%)	25 (71.4)	30 (83.3)	55 (77.5)
Patients with ≥1 related TEAE, n (%)	0 (0.0)	1 (2.8)[d]	1 (1.4)[d]
Total number of TESAEs, n	2	2	4
Patients with ≥1 TESAE, n (%)	2 (5.7)	2 (5.6)	4 (5.6)
Patients with ≥1 related TESAE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to treatment discontinuation or death, n (%)	0	0	0
TEAEs leading to treatment discontinuation, n (%)	0	0	0

[a]Percentages based on the number of patient in the safety analysis set.
[b]AEs with missing causality assessment are included as related TEAE or related TESAE.
[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]A participant experienced two related TEAEs: a headache and left arm pain. The headache occurred after the left arm pain on the same day. Both events were resolved.

Data cut: February 22, 2024.
AE, adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Treatment With Efanesoctocog Alfa was Well-Tolerated in Children (cont'd)

	<6 years (n=35)	6 to <12 years (n=36)	Overall (N=71)
TEAEs occurring in >5% of patients overall, n (%)[a-e]			
Cough	3 (8.6)	7 (19.4)	10 (14.1)
Arthralgia	2 (5.7)	7 (19.4)	9 (12.7)
Pyrexia	6 (17.1)	2 (5.6)	8 (11.3)
Upper respiratory tract infection	2 (5.7)	5 (13.9)	7 (9.9)
Headache	0 (0.0)	7 (19.4)	7 (9.9)
Nasopharyngitis	3 (8.6)	3 (8.3)	6 (8.5)
Viral upper respiratory tract infection	3 (8.6)	3 (8.3)	6 (8.5)
Influenza	1 (2.9)	4 (11.1)	5 (7.0)
Joint injury	1 (2.9)	4 (11.1)	5 (7.0)
Skin laceration	3 (8.6)	2 (5.6)	5 (7.0)
Conjunctivitis	3 (8.6)	1 (2.8)	4 (5.6)
Ear infection	4 (11.4)	0 (0.0)	4 (5.6)
Oropharyngeal pain	3 (8.6)	1 (2.8)	4 (5.6)
Pain in extremity	1 (2.9)	3 (8.3)	4 (5.6)
Head injury	1 (2.9)	3 (8.3)	4 (5.6)
Limb injury	1 (2.9)	3 (8.3)	4 (5.6)

	<6 years (n=35)	6 to <12 years (n=36)	Overall (N=71)
Participants with TESAE, n (%)			
Partial seizures	0 (0.0)	1 (2.8)	1 (1.4)
Hematoma muscle	1 (2.9)	0 (0.0)	1 (1.4)
Head injury	0 (0.0)	1 (2.8)	1 (1.4)
Thermal burn	1 (2.9)	0 (0.0)	1 (1.4)

[a]Percentages based on the number of patient in the safety analysis set.
[b]AEs with missing causality assessment are included as related TEAE or related TESAE.
[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 26.0.
[e]Patients are counted once if they report multiple events in the same system organ class or preferred term.

Data cut: February 22, 2024.
AE, adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Conclusions

FVIII inhibitors did not develop

Mean ABRs remained low (<1)

The percentage of patients with zero bleeding episodes remained high

Results from over 2 years in previously treated children with severe hemophilia A demonstrate that once-weekly efanesoctocog alfa continues to be **well tolerated** and **provides highly effective bleed protection**.

Data cut: February 22, 2024.
ABR, annualized bleed rate; FVIII, factor VIII.

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