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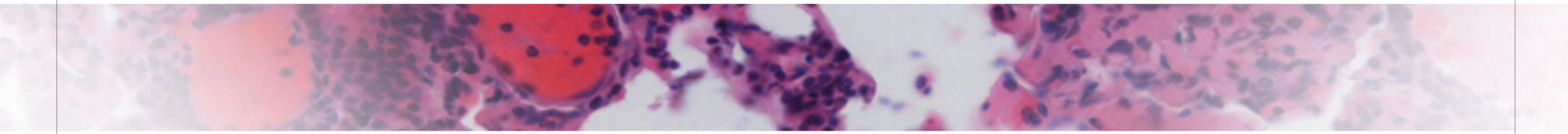

Once-Weekly Efanesoctocog Alfa Prophylaxis Provided High-Sustained Factor VIII Activity Levels, Independent of Blood Group, in Children <12 Years of Age with Severe Hemophilia A

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Efanesoctocog Alfa: A First-in-Class High-Sustained FVIII Replacement Therapy[1,2]

Efanesoctocog alfa is a **first-in-class high-sustained FVIII replacement** therapy **uniquely designed to overcome the von Willebrand factor-imposed FVIII half-life ceiling**[1,2]

Compared to standard and extended half-life FVIII comparators, efanesoctocog alfa has a **3- to 4-fold longer half-life**[3]

In the Phase 3 XTEND-Kids study (NCT04759131) in previously treated **children <12 years of age with severe hemophilia A**, efanesoctocog alfa was **well tolerated** and **FVIII inhibitor development was not detected**[4]

FVIII, factor VIII.

1. Chhabra ES, et al. *Blood*. 2020;135:1484-1496; 2. Konkle BA, et al. *N Engl J Med*. 2020;383:1018-1027; 3. Lissitchkov T, et al. *Res Pract Thromb Haemost*. 2023;7:100176; 4. Malec L, et al. ISTH 2023. LB 01.1.

Objective

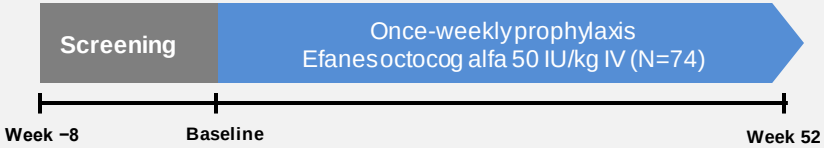
To characterize the **pharmacokinetics of efanesoctocog alfa in children <12 years of age with severe hemophilia A** in the XTEND-Kids study

XTEND-Kids: Open-Label, Multicenter, Phase 3 Study of Efanesoctocog Alfa in Previously Treated Children

Key eligibility criteria

- Children with severe hemophilia A[a]
- Previous treatment with any recombinant and/or plasma-derived FVIII, or cryoprecipitate
  - ≥150 EDs for patients 6 to <12 years of age
  - ≥50 EDs for patients <6 years of age

Study design



Pharmacokinetic assessments

Peak (15 minutes post-dose) and **trough** (pre-dose) sampling was performed in the **overall study population** at **all scheduled visits**

A **subgroup of participants** (n=37) underwent PK sampling **after the first dose of efanesoctocog alfa** (at baseline)

FVIII activity levels were assessed using the activated partial thromboplastin time -based one-stage clotting assay with the reagent Actin FSL

ED, exposure days; FVIII, factor VIII; IV, intravenous; PK, pharmacokinetic.
[a]Endogenous FVIII activity <1 IU/dL or a documented genotype known to produce severe hemophilia A. [b]Pre-dose samples were collected within 30 minutes prior to dosing.

Methods: Time to FVIII Activity Levels and Pharmacokinetic Analyses

Time to FVIII activity levels:

- A PopPK model was developed using data from Phase 1/2a and Phase 3 studies in adults, adolescents, and children
- The PopPK model can be described as a one-compartment model with linear clearance. Bodyweight and Asian race were identified as covariates which impacted the PK variabilities
- This model was then used to simulate FVIII activity to determine time to certain pre-defined FVIII activity levels at steady state (Week 26) in the overall population and PK subgroup

Pharmacokinetic analyses in the overall population (N=74):

- All participants had trough and peak sampling at all scheduled visits including Day 1

Pharmacokinetic analyses in the PK subgroup (n=37):

- Pre-dose FVIII activity was used to calculate baseline-corrected trough FVIII activity levels for each participant
- PK parameters after the first dose were estimated for participants in the PK subgroup using non-compartmental analysis

FVIII, factor VIII; PK, pharmacokinetic; PopPK, population pharmacokinetic.

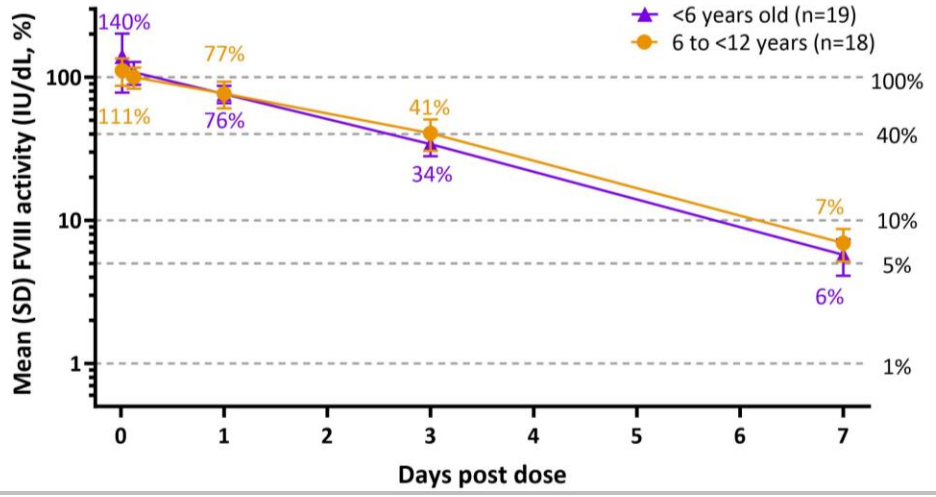
XTEND-Kids Overall Study Population and PK Subgroup: Key Participant Demographics

	Overall study population (N=74)	PK subgroup (n=37)		
		<6 years (n=19)	6 to <12 years (n=18)	Overall (n=37)
Median (range) age, years	5.0 (1.4–11.0)	4.0 (2.0–5.0)	7.5 (6.0–11.0)	5.0 (2.0–11.0)
Median (range) BMI, kg/m^2	16.9 (13.2–31.0)	16.5 (14.0–21.0)	17.6 (13.0–28.0)	17.0 (13.0–28.0)
Race, n (%)				
Asian	8 (10.8)	0	1 (5.6)	1 (2.7)
Black or African American	3 (4.1)	0	0	0
White	55 (74.3)	16 (84.2)	14 (77.8)	30 (81.1)
Not reported or Other	8 (10.8)	3 (15.8)	3 (16.7)	6 (16.2)

BMI, body mass index; PK, pharmacokinetic.

Mean FVIII Activity After the First Dose of Efanesoctocog Alfa

Baseline-corrected FVIII activity levels based on the OSC assay in the PK subgroup (n=37)



Mean FVIII activity-time profiles after the first dose of efanesoctocog alfa were similar between age groups

FVIII, factor VIII; OSC, activated partial thromboplastin time-based one-stage clotting; PK, pharmacokinetic; SD, standard deviation.
Malec L, et al. ISTH 2023. LB 01.1.

PK Parameters After the First Dose of Efanesoctocog Alfa

Summary of PK parameters by age for baseline-corrected FVIII activity based on OSC assay after the first dose of efanesoctocog alfa (50 IU/kg) in the PK subgroup[a]

Mean (SD)	<6 years of age (n=19)	≥6–<12 years of age (n=18)	Overall (N=37)
$t_{½}$, h[b]	38.0 (3.72)	42.4 (3.70)	40.2 (4.29)
CL, mL/h/kg[b]	0.742 (0.121)	0.681 (0.139)	0.711 (0.132)
C_{max}, IU/dL	143 (57.8)	113 (22.7)	128 (46.4)
$AUC_{0–tau}$, h*IU/dL[c]	6800 (1120)	7190 (1450)	7000 (1300)
IR, kg*IU/dL/IU	2.81 (1.10)	2.24 (0.437)	2.53 (0.880)
V_{ss}, mL/kg[b]	36.6 (5.59)	38.1 (6.80)	37.3 (6.19)

PK parameters after the first dose of efanesoctocog alfa were similar for the two age cohorts

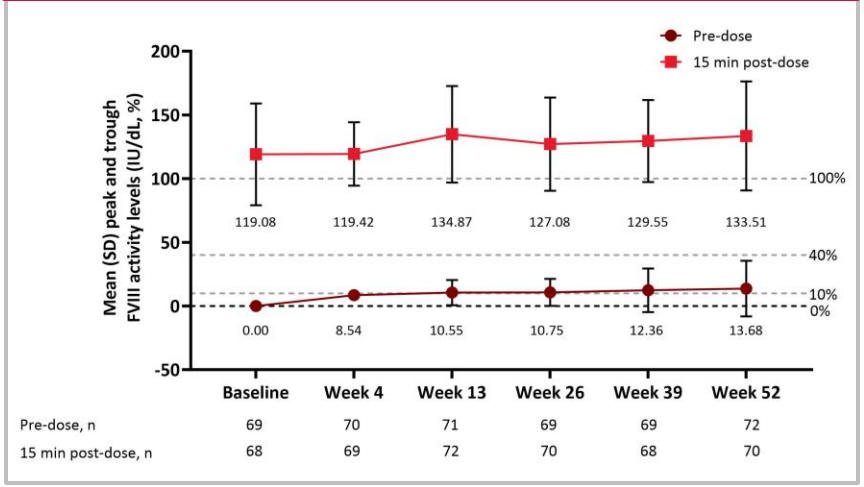
AUC_{0-tau}, area under the activity-time curve over the dosing interval; CL, clearance; C_{max}, maximum activity; FVIII, factor VIII; IR, incremental recovery; OSC, activated partial thromboplastin time-based one-stage clotting; PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal half-life; t_{max}, time to reach maximum concentration; V_{ss}, volume of distribution at steady state.

[a]Mean (SD) t_{max} was 0.793 (1.06) hours for the overall cohort (n=37), 0.593 (0.844) hours for participants ≥6–<12 years of age (n=18), and 0.983 (1.22) hours for participants <6 years of age (n=19). [b]CL and $t_{½}$ could not be calculated for 1 participant in the <6 years cohort, data reported for 18 participants in <6 years cohort and 36 participants in overall cohort. [c]AUC_{0-tau} could not be calculated for 2 participants in the <6 years cohort; data reported for 17 participants in <6 years cohort and 35 participants in overall cohort.

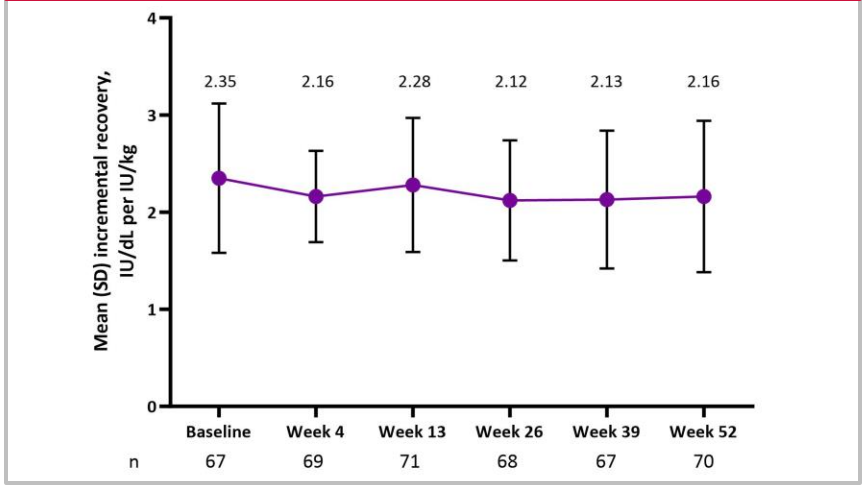
Malec L, et al. ISTH 2023. LB 01.1.

Mean FVIII Activity Levels Were Stable Throughout the Study

Peak (15-min post-dose) and trough (pre-dose) FVIII activity levels throughout the study in the overall study population[a]



Summary of incremental recovery by visit in the overall study population[b]



After weekly dosing of 50 IU/kg, incremental recovery was constant, and troughs and peaks were stable

FVIII, factor VIII; SD, standard deviation.

[a]Data during surgical/rehabilitation period (major and minor) are excluded. Values below the lower limit of quantification were imputed as zero. [b]Incremental recovery was calculated as (peak activity – trough activity/actual dose). Peak activity at each visit was the highest activity after dosing. Trough activity at each visit was the activity level prior to dosing. Data during surgical/rehabilitation periods (major and minor) were excluded.

Time to Pre-defined FVIII Activity Levels at Steady State

Mean (SD)	<6 years of age (n=37)[a]	≥6–<12 years of age (n=36)[a]	PK subgroup, all ages (N=37)[b]
Time to 40 IU/dL, h	68 (10.5)	81 (12.3)	72 (12.5)
Time to 15 IU/dL, h	126 (15.7)	146 (15.6)	134 (16.7)
Time to 10 IU/dL, h	150 (18.2)	173 (17.1)	160 (18.7)
Time to 5 IU/dL, h	192 (22.6)	219 (20.0)	203 (22.3)

At steady state, mean FVIII activity levels remained in the normal to near-normal range, or >40%, for 3 days and >10% for ~7 days

FVIII, factor VIII; PK, pharmacokinetic; SD, standard deviation.
[a]Data presented for the overall study population. [b]Data presented for the PK subgroup.

Blood Group O and Non-O Participant Demographics and PK Parameters

Participant demographics for those included in the blood group analysis subgroup[a]

	Blood group O (n=12)	Blood group non-O (n=19)
Median (range) age, years	5.0 (3.0–11.0)	6.0 (2.0–11.0)
Median (range) BMI, kg/m²	17.2 (14.0–19.0)	16.8 (13.0–28.0)
Race, n (%)		
Asian	0	1 (5.3)
Black or African American	0	0
White	11 (91.7)	14 (73.7)
Not reported or Other	1 (8.3)	4 (21.1)

Summary of PK parameters by blood group after the first dose of efanesoctocog alfa (50 IU/kg)[a]

Mean (SD)	Blood group O (n=12)	Blood group non-O (n=19)
$t_{½}$, h	40.2 (4.45)	40.0 (4.17)[b]
CL, mL/h/kg	0.76 (0.12)	0.68 (0.15)[b]
C_{max}, IU/dL	123 (52.0)	130 (41.3)
$AUC_{0–tau}$, h*IU/dL	6515 (873)	7259 (1574)[b]

PK parameters after the first dose were similar in participants with blood group O and non-O

AUC_{0-tau}, area under the activity-time curve over the dosing interval; BMI, body mass index; CL, clearance; C_{max}, maximum activity; FVIII, factor VIII; PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal half-life.
[a]Six participants with unknown blood group are not included in this analysis. [b]Reported for only 18 participants.

Immunogenicity

No inhibitors to FVIII were detected among participants in XTEND-Kids[1]

There were no treatment-emergent or treatment-induced anti-drug antibodies

Three (4%) participants were positive for anti-drug antibodies at screening/baseline which had no impact on clinical efficacy, safety, or PK

- All 3 participants tested negative for anti-drug antibodies at later timepoints in the study

FVIII, factor VIII; PK, pharmacokinetic.
The presence of FVIII inhibitor and anti-drug antibodies was assessed by the Nijmegen-modified Bethesda assay and a validated efanesoctocog alfa-specific antidrug-antibody assay, respectively, performed by the central laboratory. Inhibitor development was defined as ≥0.6 BU/mL confirmed by another positive sample drawn 2–4 weeks later.
1. Malec L, et al. ISTH 2023. LB 01.1.

Conclusions

PK parameters and the mean FVIII activity-time profile were similar for participants <6 years and ≥6–<12 years of age

No relevant differences in PK parameters were observed between participants with blood group O and non-O

In both age cohorts, mean FVIII activity levels at steady state were maintained in the **normal to near-normal range,** above 40 IU/dL, for 3 days and remained above 10 IU/dL for approximately 7 days following a **once-weekly regimen of 50 IU/kg efanesoctocog alfa**

Once-weekly prophylaxis with efanesoctocog alfa provided high-sustained FVIII levels across the week for children <12 years of age in the XTEND-Kids study

FVIII, factor VIII; PK, pharmacokinetic.

Thank you

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and the study investigators