Bleed Treatment Outcomes with Efanesoctocog Alfa from the XTEND-ed Study in Patients Aged 50 Years and Older

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Conclusions

- **The results of this post hoc analysis of the XTEND-ed study confirm that prophylaxis treatment with once-weekly efanesoctocog alfa (50 IU/kg) provides highly effective bleed protection in patients aged ≥50 years**
- **The annualised bleed rate and safety profile in this population were comparable to those for the overall population**
- **Improvements in patient reported outcomes from XTEND-1 baseline for joint health, health-related quality of life, and pain outcomes were maintained through XTEND-ed**
- **No incidence of factor VIII inhibitors was detected**

Introduction

- Despite advances in treatment, people with severe haemophilia may still experience bleeding episodes, which affects their health and quality of life[1,2]
- Older adults with haemophilia A face complex medical challenges associated with age-related comorbidities, including atrial fibrillation and venous thromboembolic events requiring anticoagulant therapy; these are compounded by limited data regarding the use of factor therapy in this population[3]
- Efanesoctocog alfa is a first-in-class high-sustained factor VIII (FVIII) replacement therapy designed to decouple recombinant FVIII from endogenous von Willebrand factor to further extend its half-life[4–6]
- The phase 3 XTEND-1 (NCT04161495) study[7] showed that once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis in adult and adolescent patients (≥12 years) with severe haemophilia A:
  - Achieved high-sustained FVIII levels in the normal to near-normal range (>40%) for most of the week
  - Provided highly effective bleed protection with clinically meaningful improvements in physical health, pain intensity, and joint health
  - Was well tolerated with no development of inhibitors
- Patients completing XTEND-1 could continue weekly efanesoctocog alfa prophylaxis in the long-term extension study, XTEND-ed (NCT04644575)[8]

Objective

- To assess outcomes of patients aged ≥50 years treated with efanesoctocog alfa through the second interim analysis (Month 24) of XTEND-ed (data cut: February 22, 2024)

Methods

Study design and population

- The XTEND clinical trial programme is outlined in **Figure 1**
- This was a post hoc analysis of data from patients aged ≥50 years who entered XTEND-1 and rolled over into XTEND-ed

Figure 1. XTEND clinical trial programme

Patients provided informed consent; the study was approved by applicable review boards.
[a]Patients in Arm A will continue receiving efanesoctocog alfa prophylaxis for a cumulative total of ≥100 EDs; they can continue in XTEND-ed for up to 4 years, unless efanesoctocog alfa is commercially available in their participating country.
ClinicalTrials.gov. NCT04644575. Long-term safety and efficacy of efanesoctocog alfa (BIVV001) in previously treated patients with hemophilia A (XTEND-ed).
ED, exposure day; FVIII, factor VIII; IU, international unit; IV, intravenous.

- Bleeds were treated with a single injection of efanesoctocog alfa (50 IU/kg) with additional doses (30 or 50 IU/kg) administered as needed every 2–3 days
- Endpoints included the following:
  - Annualised bleed rates (ABRs)
  - Model-based ABRs (derived from a negative binomial model of treated bleeding episodes)
  - Numbers and locations of treated bleeds
  - Dose and number of efanesoctocog alfa administrations required to resolve bleeding episodes for 12-month efficacy periods
  - Haemophilia Joint Health Score (HJHS)
  - Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity 3a T-score
  - Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) physical health domain
  - Safety
- Data are based on bleeding episodes treated per protocol in the full analysis data set during the efficacy period (from first efanesoctocog alfa injection in XTEND-ed Arm A to the day of the last dose), excluding periods of surgery/rehabilitation

Results

- At enrolment of XTEND-ed, 32 patients (1 female) were aged ≥50 years; mean age (standard deviation [SD]; range) was 58.5 (6.6; 50.0–74.0) years (**Table 1**)
- The median (range) number of exposure days during XTEND-ed was 121.5 (30.0–146.0)
- The median (range) efficacy and treatment duration in XTEND-ed were 115.4 (31.3–136.6) and 120.1 (31.3–136.6) weeks, respectively
  - Cumulative median (range) treatment duration from XTEND-1 through XTEND-ed interim analysis 2 was 161.0 (46.3–187.6) weeks

Table 1. Patient demographics and baseline disease characteristics

	Participants aged ≥50 years (N=32)[a]
Age at enrolment in XTEND-ed, years[a]	
Mean (SD)	58.5 (6.6)
XTEND-1 arm patient carried over from, n (%)	
Arm A	23 (71.9)
Arm B	9 (28.1)
Sex, n (%)	
Male	31 (96.9)
Female	1 (3.1)
Race, n (%)	
White	23 (71.9)
Black/African American	1 (3.1)
Asian	6 (18.8)
NR	2 (6.3)
BMI, kg/m²	
Mean (SD)	26.4 (4.3)
Relevant medical history in patients at XTEND-ed baseline[b]	
Haemophilic arthropathy	23 (71.9)
Hypertension	19 (59.4)
HCV	16 (50.0)
HIV	14 (43.8)
Chronic HCV	6 (18.8)
Arthralgia	4 (12.5)
Type 2 diabetes	4 (12.5)
Arthropathy	2 (6.3)
Dyslipidaemia	2 (6.3)
Haemarthrosis	2 (6.3)
Hypercholesterolaemia	2 (6.3)
Hyperlipidaemia	2 (6.3)
Arrhythmia	1 (3.1)
Atrial fibrillation	1 (3.1)
Relevant surgical history in patients at XTEND-ed baseline[b]	
Knee arthroplasty	12 (37.5)
Hip arthroplasty	5 (15.6)
Joint arthroplasty	2 (6.3)
Shoulder arthroplasty	1 (3.1)
Synovectomy	1 (3.1)

[a]There were an additional 3 patients who were aged ≥50 years at XTEND-ed baseline versus XTEND-1 baseline.
[b]Any condition accruing in >10% of the cohort.
BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NR, not reported, SD, standard deviation.

FVIII consumption

- Total mean (SD) and median (Q1: Q3) annualised efanesoctocog alfa consumption in XTEND-ed was 2673.9 (71.2) IU/kg and 2681.2 (2659.2: 2713.7) IU/kg, respectively
  - The mean (SD) weekly consumption was 56.4 (18.2) IU/kg
- The mean (SD) weekly routine prophylaxis dose was 50.9 (1.1) IU/kg
- The median (range) number of all injections per patient in the XTEND-ed study period was 121.5 (30.0–146.0) and the median (range) cumulative number of injections since the first dose received in XTEND-1 was 165.0 (47.0–199.0)

Annualised bleed rates and treatment of bleeds

- ABRs are reported in **Table 2**

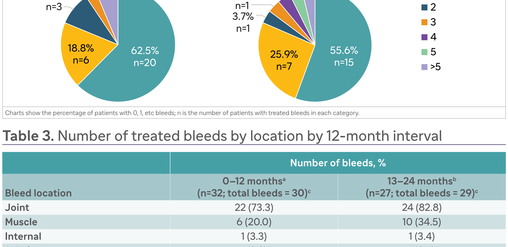
Table 2. Annualised bleed rates

ABRs during efficacy period	Participants aged ≥50 years (N=32)
Overall	
Mean (95% CI), model-based	0.92 (0.54–1.55)
Median (range)	0.45 (0–4.8)
Spontaneous	
Mean (95% CI), model-based	0.38 (0.19–0.75)
Median (range)	0 (0–3.3)
Traumatic	
Mean (95% CI), model-based	0.29 (0.15–0.54)
Median (range)	0 (0–1.8)

ABR, annualised bleed rate; CI, confidence interval.

- There were 32 and 27 patients in the 0- to 12-month and 13- to 24-month efficacy periods, respectively
- The mean and median number of bleeding episodes per patient for the 2 efficacy periods in XTEND-ed were as follows:
  - **0–12 months:** mean (SD), 0.94 (1.90); median (range), 0 (0–8)
  - **13–24 months:** mean (SD), 1.07 (1.90); median (range), 0 (0–8)
- Most patients had 0 (62.5% and 55.6% at 0–12 and 13–24 months, respectively) or 1 (18.8% and 25.9% at 0–12 and 13–24 months, respectively) treated bleeding episode (**Figure 2**)
  - Most bleeds occurred in joints and muscle (**Table 3**)
  - Treated bleeds according to type are shown in **Figure 3**
- The median (range) number of injections administered for bleed resolution was 1 (1–2) (**Figure 4**)

Figure 2. Number of bleeding episodes per participant by 12-month interval



Charts show the percentage of patients with 0, 1, etc bleeds; n is the number of patients with treated bleeds in each category.

Table 3. Number of treated bleeds by location by 12-month interval

	Number of bleeds, %	
Bleed location	0–12 months[a] (n=32; total bleeds = 30)[c]	13–24 months[b] (n=27; total bleeds = 29)[c]
Joint	22 (73.3)	24 (82.8)
Muscle	6 (20.0)	10 (34.5)
Internal	1 (3.3)	1 (3.4)
Skin/mucosa	1 (3.3)	1 (3.4)
Unknown	0	0

[a]Data were not captured for 2 bleeds.
[b]Concurrent bleeding episodes in >1 location are included in each location; 7 bleeds occurred in more than 1 location.
[c]n = number of participants with an efficacy period

Figure 3. Treated bleeds by type by 12-month interval

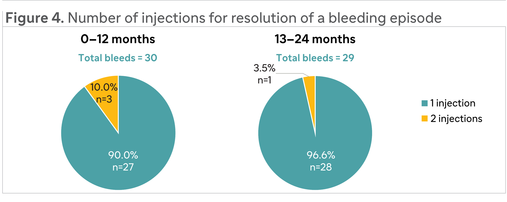
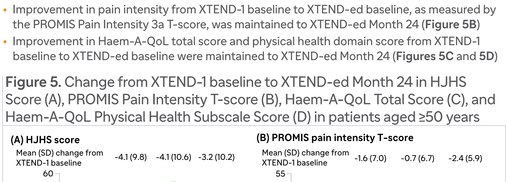


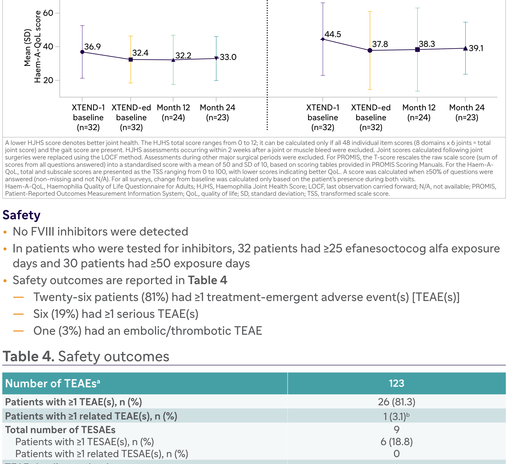
Figure 4. Number of injections for resolution of a bleeding episode



Joint health, health-related quality of life, and pain outcomes

- For patients aged ≥50 years, the mean (SD) change in HJHS score from XTEND-1 baseline was -4.1 (10.6) and -3.2 (10.7) points to XTEND-ed Months 12 and 24, respectively (**Figure 5A**)
- Improvement in pain intensity from XTEND-1 baseline to XTEND-ed baseline, as measured by the PROMIS Pain Intensity 3a T-score, was maintained to XTEND-ed Month 24 (**Figure 5B**)
- Improvement in Haem-A-QoL total score and physical health domain score from XTEND-1 baseline to XTEND-ed baseline were maintained to XTEND-ed Month 24 (**Figures 5C** and **5D**)

Figure 5. Change from XTEND-1 baseline to XTEND-ed Month 24 in HJHS Score (A), PROMIS Pain Intensity T-score (B), Haem-A-QoL Total Score (C), and Haem-A-QoL Physical Health Subscale Score (D) in patients aged ≥50 years



A lower HJHS score denotes better joint health. The HJHS total score ranges from 0 to 12; it can be calculated only if all 48 individual item scores (8 domains x 6 joints + total joint score) and the gait score are present. HJHS assessments occurring within 2 weeks after a joint or muscle bleed were excluded. Joint scores calculated following joint surgeries were replaced using the LDCF method. Assessments during other major surgical periods were excluded. For PROMIS, the T-score rescales the raw scale score (sum of scores from all questions answered) into a standardised score with a mean of 50 and SD of 10, based on scoring tables provided in PROMIS Scoring Manuals. For the Haem-A-QoL, total and subscale scores are presented as the TSS ranging from 0 to 100, with lower scores indicating better QoL. A score was calculated when ≥50% of questions were answered (non-missing and not N/A). For all surveys, change from baseline was calculated only based on the patient's presence during both visits.
Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; HJHS, Haemophilia Joint Health Score; LDCF, last observation carried forward; N/A, not available; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; SD, standard deviation; TSS, transformed scale score.

Safety

- No FVIII inhibitors were detected
- In patients who were tested for inhibitors, 32 patients had ≥25 efanesoctocog alfa exposure days and 30 patients had ≥50 exposure days
- Safety outcomes are reported in **Table 4**
  - Twenty-six patients (81%) had ≥1 treatment-emergent adverse event(s) [TEAE(s)]
  - Six (19%) had ≥1 serious TEAE(s)
  - One (3%) had an embolic/thrombotic TEAE

Table 4. Safety outcomes

Number of TEAEs[a]	123
Patients with ≥1 TEAE(s), n (%)	26 (81.3)
Patients with ≥1 related TEAE(s), n (%)	1 (3.1)[b]
Total number of TESAEs	9
Patients with ≥1 TESAE(s), n (%)	6 (18.8)
Patients with ≥1 related TESAE(s), n (%)	0
TEAEs leading to death	0
TEAEs leading to treatment discontinuation	0
Number of embolic and thrombotic TEAEs	1
Patients with ≥1 embolic and thrombotic TEAE(s), n (%)[b]	1 (3.1)

[a]AEs with missing causality assessment were included in related TEAE or related TESAE. AEs that occurred during the major surgical/rehabilitation period were excluded from this table, but AEs that occurred on the day the surgical/rehabilitation period started were included. Events were coded using MedDRA version 26.1. Patients were counted once if they reported multiple events in the same system organ class or preferred term.
[b]Embolic and thrombotic AEs were medically adjudicated using the Embolic and Thrombotic Events SMQ. The TEAE was a cerebral infarction in a patient with a medical history of chronic atrial fibrillation who was not receiving antithrombotic prophylaxis therapy.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Events Standard MedDRA Query; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

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