Clinical outcomes over 3 years of efanesoctocog alfa in adults and adolescents with severe haemophilia A: European results from the second interim analysis of XTEND-ed

Robert Klamroth,[1] Pratima Chowdary,[2] Toshko Lissitchkov,[3] Maria Teresa Alvarez-Román,[4] Umer Khan,[5] Linda Bystricka,[6] Elena Santagostino,[6] Sophie Susen[7]

[1]Vivantes Hospital, Friedrichshain, Berlin, Germany; [2]Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital, London, UK; [3]Specialized Hospital for Active Treatment of Hematological Diseases, Department of Chemotherapy, Hemotherapy and Hereditary Blood Diseases at Clinical Hematology Clinic, Sofia, Bulgaria; [4]Department of Hematology, University Hospital La Paz, Autonomous University of Madrid, Madrid, Spain; [5]Sanofi, Cambridge, MA, USA; [6]Sobi, Basel, Switzerland; [7]Lille University Hospital, Lille University, Lille, France.

PO109

Introduction

- Efanesoctocog alfa is a first-in-class high-sustained factor VIII (FVIII) replacement therapy, also known as ultra-long half-life FVIII, designed to overcome the half-life limitations caused by FVIII binding to endogenous von Willebrand factor.[1–3]
- In the completed Phase 3 XTEND-1 (NCT04161495) study, once-weekly efanesoctocog alfa was well tolerated and provided FVIII activity in the normal to near-normal range (>40%) for most of the week in patients ≥12 years of age with severe haemophilia A.[4]
- Participants completing XTEND-1 could continue efanesoctocog alfa in the long-term extension study XTEND-ed (NCT04644575); results of a second interim analysis (data cut-off: 22 February 2024) of the overall XTEND-ed population have previously been published.[5]

Objectives

- To assess long-term clinical outcomes in European adults and adolescents included in the XTEND-ed second interim analysis.

Methods

Study design

- XTEND-ed is an open-label extension study, evaluating long-term safety and efficacy of once-weekly efanesoctocog alfa (50 IU/kg) for the treatment of severe haemophilia A.
- Participants who completed XTEND-1 (or XTEND-Kids, a separate study that assessed once-weekly efanesoctocog alfa in patients <12 years of age) were eligible to enter into XTEND-ed (Arm A) (**Figure 1**).
- All those participants ≥12 years of age when entering XTEND-1 and enrolled at European sites, including Belgium, Bulgaria, France, Germany, Greece, Hungary, Italy, Netherlands, Spain and the United Kingdom, were included in the current XTEND-ed subanalysis.

Outcomes

- The primary endpoint was occurrence of FVIII inhibitors.
  - Inhibitor development was evaluated using the Nijmegen-modified Bethesda assay at a central laboratory and defined as an inhibitor result of ≥0.6 BU/mL, confirmed by a second test result from a separate sample 2–4 weeks later.
- Secondary endpoints included annualised bleed rates (ABRs), efficacy of bleed treatment and safety.
  - Mean (standard deviation [SD]) ABR values (treated bleeds) 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 Arm A of XTEND-ed to the day of the last dose of efanesoctocog alfa or the data cut-off date of 22 February 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).
  - Efficacy of bleed treatment was evaluated based on the number of injections required to treat a bleeding episode and patient assessment of treatment response (rated as 'excellent', 'good', 'moderate' or 'none').

Results

Patient population

- The patient population consisted of 76 male participants ≥12 years of age who were enrolled at European sites participating in the XTEND-ed study.
- Key patient demographics are shown in **Table 1**.

Treatment duration and factor usage

- Median (range) treatment duration in XTEND-ed was 123.6 (22.9–140.6) weeks (865.2 [160.3–984.2] days).
- Median (range) cumulative treatment duration, including XTEND-1, was 175.5 (46.3–192.6) weeks (1228.5 [324.1–1348.2] days).
- Median (range) weekly dose of efanesoctocog alfa was 51.3 (39.4–58.6) IU/kg.

FVIII inhibitor development

- No FVIII inhibitors were detected.

Annualised bleed rates (ABR)

- The mean (SD) ABR was 0.64 (1.01) for adults and adolescents enrolled at European sites (n=76) of the XTEND-ed study; this is consistent with interim analysis data for the overall XTEND-ed adult and adolescent population (n=146; **Figure 2**). The model-based mean ABR (95% CI) for these patients was 0.63 (0.44; 0.90).
- Mean (SD) ABRs by 6-month period (n=76 in each period) were 0.69 (1.92), 0.66 (1.59), 0.56 (1.27) and 0.61 (1.91) for Day 1–Month 6, Months 6–12, Months 12–18 and Months 18–24, respectively (**Figure 2**).

Patients achieving zero bleeds

- The majority of patients did not experience bleeding episodes (**Figure 3**).
  - Specifically, 80%, 79%, 78% and 80% of participants (n=76) had zero bleeds of any type during the 6-month intervals of Day 1–Month 6, Months 6–12, Months 12–18 and Months 18–24, respectively.
  - Similarly, 91%, 91%, 90% and 86% of participants had zero spontaneous bleeds for the same intervals.

Treatment of bleeding episodes

- The majority of treated bleeds (102/109 [93.6%]) were resolved with a single dose of efanesoctocog alfa (**Figure 4a**).
- Response for treatment of bleeding episodes was rated 'excellent' or 'good' for 139/160 (86.9%) injections (**Figure 4b**).

Safety

- Efanesoctocog alfa was well tolerated with reported treatment-emergent adverse events (TEAEs) as expected for this population (**Table 2**).
  - 64 participants (84.2%) experienced ≥1 TEAE.
  - 13 participants (17.1%) had ≥1 treatment-emergent serious adverse event (TESAE).
  - 1 participant had a treatment-related TEAE (isolated incident of low FVIII activity levels).
  - 1 participant had a TEAE leading to discontinuation due to use of a prohibited medication (alternative FVIII concentrate used for femur fracture surgery).
  - 1 participant experienced a thromboembolic event (cerebral infarction [in the setting of chronic atrial fibrillation]) that was unrelated to efanesoctocog treatment. Anticoagulation was commenced and initially efanesoctocog alfa treatment was continued. The patient however subsequently discontinued the study due to use of anticoagulation.
  - There were no treatment-related TESAEs or TEAEs leading to death.

Conclusions

- **This subanalysis of interim data from adults and adolescents enrolled at European sites of the XTEND-ed study through 3 years of continuous treatment demonstrates that efanesoctocog alfa continues to be well tolerated and provide highly effective bleed protection, without FVIII inhibitor development, with long-term use.**

Figure 1. XTEND-1 and XTEND-ed study design

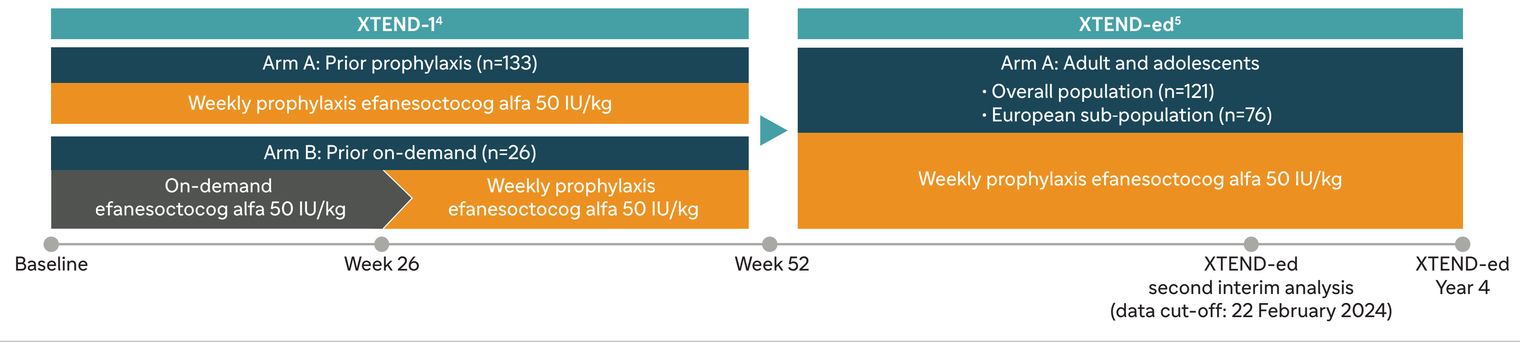
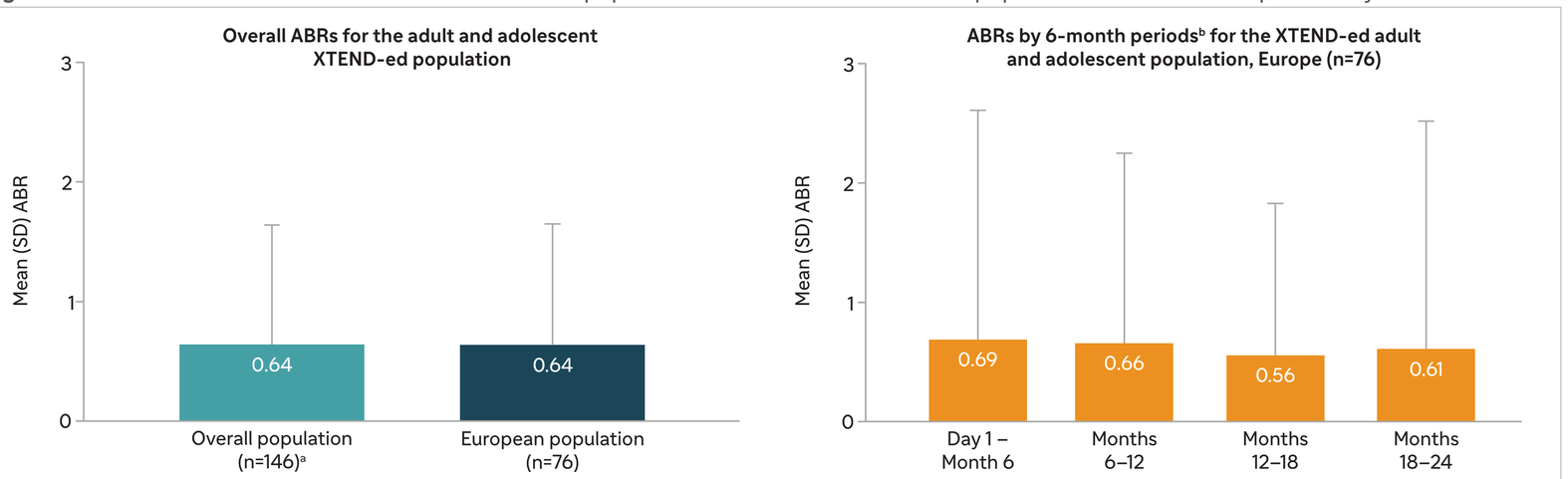
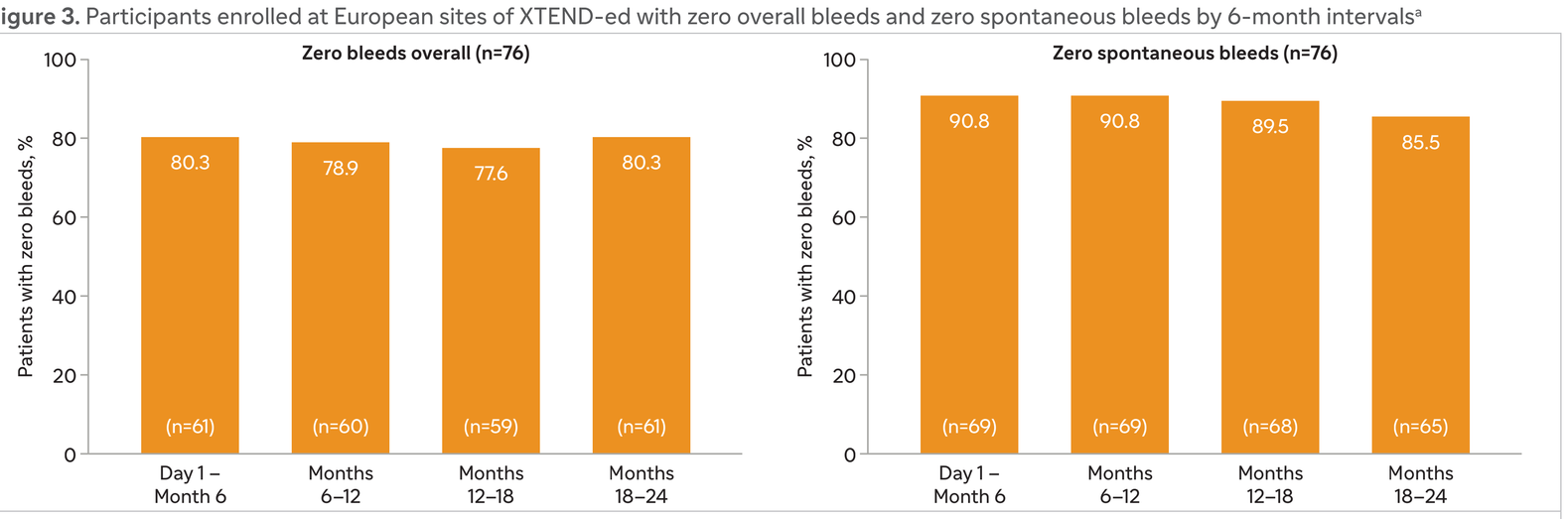


Figure 2. ABRs in XTEND-ed overall adult and adolescent population and adult and adolescent population enrolled at European study sites



[a]Published previously;[5] [b]Six-month intervals are based on individuals' scheduled visits. In case of an intermediate missing visit date, the target date per protocol was used.

Figure 3. Participants enrolled at European sites of XTEND-ed with zero overall bleeds and zero spontaneous bleeds by 6-month intervals[a]



[a]Six-month intervals are based on individuals' scheduled visits. In case of intermediate missing visit date, the target date per protocol was used.

Table 1. Baseline characteristics of adults and adolescents enrolled at European XTEND-ed study sites

	XTEND-ed European adults and adolescents (n=76)
Age at enrolment of XTEND-ed (years)[a]	
Median (min; max)	37.5 (13; 71)
12–17, n (%)	10 (13.2)
18–64, n (%)	63 (82.9)
≥65, n (%)	3 (3.9)
Sex, n (%)	
Male	76 (100)
Race, n (%)	
White	57 (75.0)
Black or African American	1 (1.3)
Asian	6 (7.9)
Not reported	12 (15.8)
Ethnicity, n (%)	
Hispanic or Latino	1 (1.3)
Not Hispanic or Latino	69 (90.8)
Not reported	6 (7.9)
Weight (kg)	
Median (min; max)	78.0 (35.9; 132.8)

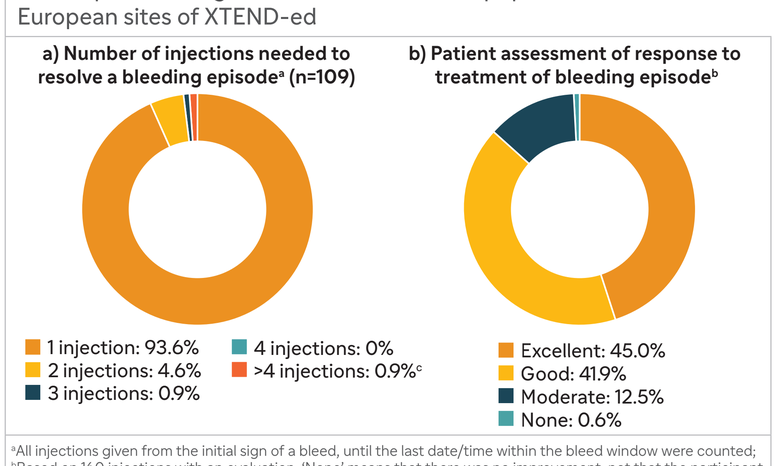
[a]Age = year of informed consent minus year of birth.

Table 2. Safety data for adult and adolescent patients enrolled at European XTEND-ed study sites

	XTEND-ed European adults and adolescents (n=76)
Total number of TEAEs	373
Participants with ≥1 TEAE, n (%)	64 (84.2)
Participants with ≥1 treatment-related TEAE, n (%)[a]	1 (1.3)[b]
Total number of TESAEs	22
Participants with ≥1 TESAE, n (%)	13 (17.1)
Participants with ≥1 treatment-related TESAE, n (%)	0
Participants with TEAEs leading to death	0
Participants who discontinued (use of prohibited medications)	2 (2.6)[c]

[a]Adverse events with missing causality assessment are included in the treatment-related TEAE; [b]Coagulation FVIII level decreased (isolated incident of low FVIII activity levels observed prior to next dose of efanesoctocog alfa; FVIII activity levels were measured locally). This event resolved; [c]One participant received an alternative FVIII product in hospital after a femur fracture and subsequently discontinued efanesoctocog alfa. A second patient experienced a thromboembolic event (cerebral infarction [in the setting of chronic atrial fibrillation]). Anticoagulation was commenced and initially efanesoctocog alfa treatment was continued. However, the patient subsequently discontinued the study due to use of anticoagulation.

Figure 4. Number of injections needed to resolve a bleeding episode[a] and response rating in adult and adolescent population enrolled at European sites of XTEND-ed



[a]All injections given from the initial sign of a bleed, until the last date/time within the bleed window were counted; [b]Based on 160 injections with an evaluation. 'None' means that there was no improvement, not that the participant did not provide a response; [c]The participant requiring >4 injections was an adult with a history of significant non-compliance during the trial. The patient recorded 7 injections to treat an exercise-induced traumatic haematoma within the right iliopsoas muscle. Doses of 50 IU/kg were administered every other day and the participant resumed routine prophylaxis 18 days after the first injection.

References: 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.** Lissitchkov T, et al. *Blood Adv* 2022;6(4):1089–1094; **4.** von Drygalski A, et al. *N Engl J Med* 2023;388(4):310–318; **5.** Klamroth R, et al. ASH 2024, 07–10 December, San Diego, California, USA.

Abbreviations: ABR: annualised bleed rate; **BU:** Bethesda unit; **CI:** confidence interval; **FVIII:** factor VIII; **IU:** international units; **SD:** standard deviation; **TEAE:** treatment-emergent adverse event; **TESAE:** treatment-emergent serious adverse event.

Funding: This trial was funded by Sobi and Sanofi. Sobi and Sanofi reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content.

Acknowledgements: Medical writing assistance was provided by Helen Stanford and Steven Barberini of The Salve Health Ltd, UK, funded by Sobi. Design assistance was provided by Jenna Zan, Zed. Coordination of the development of this poster was provided by Nick Fulcher, PhD (Sobi) and Alicia Mack, PharmD (Sanofi).

Disclosures: RK: Received honoraria and/or been a member of advisory committees for Bayer, BioMarin, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Sobi and Shire/Takeda. **PC:** Advisor for Bayer, Boehringer Ingelheim, ApcinteX, CSL Behring, Chugai, Freeline, Novo Nordisk, Pfizer, Roche, Sanofi, Spark, Sobi and Takeda. **TL:** Principal investigator of clinical trial for Sanofi and Sobi. **MTA-R:** Received honoraria for speaking, honoraria for consulting, and/or funds for research from Takeda, Bayer, CSL Behring, Grifols, Novo Nordisk, Sobi, Octapharma, LFB, Roche, Amgen, Novartis and Pfizer. **UK:** Employee of Sanofi; may hold shares and/or stock options in the company. **LB:** Employee of Sanofi; may hold shares and/or stock options in the company. **ES:** Employee of Sanofi; may hold shares and/or stock options in the company. **SS:** Research support from CSL Behring, Roche/Chugai, Stago and Siemens Healthineers, and honoraria for lectures or consultancy from BioMarin, Bioverativ, CSL Behring, HemoSonics, LFB, Novo Nordisk, Roche/Chugai, Sanofi, Siemens Healthineers, Shire/Takeda and Sobi.

Access poster via the Sobi Science Library

Access poster via the Sanofi Library of Congresses

Presented at the 18th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) | Milan, Italy | 4–7 February 2025