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ADIS DRUG Q&A

Efanesoctocog alfa in hemophilia A: a profile of its use

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Abstract

Efanesoctocog alfa [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl; ALTUVIIIO®], indicated for routine prophylaxis, on-demand treatment of bleeding episodes, and perioperative management of bleeding, is a useful addition to the therapies available for the management of hemophilia A in adults and children. Its half-life is three- to four-fold longer than existing (standard and extended half-life) factor VIII replacement products, which enables once-weekly administration. In a phase 3 trial, pretreated adolescents and adults (aged ≥ 12 years) receiving efanesoctocog alfa prophylaxis had a low annualized rate of treated bleeding episodes, and in a subgroup of these patients, efanesoctocog alfa reduced the annualized bleeding rate compared with the rate in a pre-study, in which the same patients received standard-of-care factor VIII replacement product prophylaxis. A single dose of efanesoctocog alfa was also able to resolve nearly all bleeding episodes, with most responses being good or excellent. Additionally, hemostatic responses in patients receiving efanesoctocog alfa for perioperative management of bleeding were deemed excellent. Efanesoctocog alfa also had efficacy in preventing bleeding as prophylaxis and resolving bleeding episodes as on-demand treatment in pretreated children (aged < 12 years). Efanesoctocog alfa was well tolerated. No factor VIII inhibitors developed in patients receiving efanesoctocog alfa in patients of any age in these trials.

Plain Language Summary

Hemophilia A causes disability and even death if not adequately controlled. Replacement of deficient coagulation factor VIII is standard-of-care in managing severe hemophilia A; however, most factor VIII replacement products are rapidly cleared from the body, which necessitates frequent (2–3 times/week) intravenous injections of replacement product to maintain adequate bleed protection. Efanesoctocog alfa (ALTUVIIIO®) is a recombinant factor VIII replacement product which can sustain normal to near-normal levels (> 40 IU/dL) of factor VIII for the majority of the week with once-weekly administration in adolescents and adults with severe hemophilia A. In the XTEND-1 trial (in pretreated adolescents and adults), efanesoctocog alfa prophylaxis provided superior bleed prevention versus prior prophylaxis. Patients who received efanesoctocog alfa before surgery and, where necessary, after surgery also had excellent control of bleeding. In the XTEND-1 and XTEND-Kids (in pretreated children) trials, efanesoctocog alfa prophylaxis was associated with a low annualized bleeding rate; a single dose of efanesoctocog alfa was able to resolve almost all bleeding episodes. Efanesoctocog alfa was well tolerated. Patient did not develop antibodies that neutralize efanesoctocog alfa. Overall, efanesoctocog alfa is a useful addition to the treatment options available for the management of hemophilia A in adults, adolescents, and children.

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What is the rationale for developing efanesoctocog alfa in hemophilia A?

Hemophilia A is an X-linked congenital bleeding disorder characterized by a deficiency in coagulation factor VIII (FVIII) [1]. The severe form of the disorder predominantly occurs in men, with an estimated global incidence of 9.5 cases per 100,000. The severity of the disorder is related to the level of FVIII in the blood. Patients with severe hemophilia A have < 1 international unit (IU)/dL of FVIII (< 1% of the level of FVIII of a healthy individual) and have spontaneous bleeding episodes, predominantly in the absence of

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Adis evaluation of efanesoctocog alfa in the management of hemophilia A
Three- to four-fold longer half-life compared with existing standard and extended half-life factor VIII replacement products on the market
Low annualized bleeding rates when used as prophylaxis
Resolves bleeding episodes and provides excellent hemostatic control in patients undergoing major surgery
Well tolerated, with headaches and arthralgia being the most common adverse events

hemostatic challenge. Patients with moderate hemophilia A (1–5 IU/dL) have occasional spontaneous bleeding episodes and prolonged bleeding with minor trauma or surgery, while mild hemophilia A (> 5–40 IU/dL) is associated with rare spontaneous bleeding and heavy bleeding with major trauma or surgery. Bleeding episodes can have serious health consequences and may lead to disability (e.g., with bleeding into joints leading to progressive joint damage) or may even be life-threatening (e.g., with intracranial bleeding) [1].

Restoring FVIII activity is the main treatment strategy for severe hemophilia A [1]; hemostasis products (e.g., FVIII replacement products) are used in both preventative therapy (prophylaxis) and on-demand treatment of bleeding episodes, as well as prior to surgery to prevent excessive loss of blood [1].

For long-term management, the World Federation of Hemophilia (WFH) recommends prophylaxis over on-demand treatment in patients with severe hemophilia A [1]. The traditional goal of prophylaxis is to convert a patient with severe hemophilia A to a bleeding phenotype that is mild or moderate (i.e., maintain FVIII levels at > 1 IU/dL). More recently, however, it has been recognized that patients are still at risk of bleeding episodes with FVIII trough levels (concentrations at the end of a treatment cycle) of 1–3 IU/dL and maintaining higher trough levels (> 3–5 IU/dL, or higher) has become the new goal of treatment [1]. Most products on the market are able to adequately reduce the frequency of clinically apparent bleeding episodes; however, progressive joint damage can still occur with subclinical bleeds, and in the long term this can lead to pain, reduced function, and reduced quality of life [2]. Improving these long-term outcomes is a priority for new treatments of hemophilia A [2].

The short half-life of FVIII necessitates frequent intravenous administration (two to three times a week) to maintain an acceptable FVIII trough level [3]. This high treatment burden impacts on treatment adherence [1]. Extended half-life FVIII products only provide modest (1.4- to 1.6-fold) improvements in half-life [4]. Plasma clearance of FVIII is coupled to its binding partner, endogenous von Willebrand factor (VWF), which has a half-life of ≈ 15–20 h [3–5]. Therefore, to overcome the half-life limit imposed by VWF and achieve high sustained FVIII levels, a replacement FVIII that is independent of its binding partner is required.

Efanesoctocog alfa [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl; ALTUVIIIO®] is a first-in-class high-sustained FVIII replacement product with pharmacokinetic parameters that are independent of VWF [6]. First approved in the USA in February 2023 [7], this recombinant DNA-derived FVIII concentrate is indicated for use in adults and children with hemophilia A [6]; it can be used for routine prophylaxis, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding [6]. A summary of the US prescribing information for efanesoctocog alfa is presented in Table 1. A dosing flow chart is presented in Fig. 1. Consult local prescribing information for more details [6].

How does efanesoctocog alfa work?

Efanesoctocog alfa is a FVIII analogue (B-domain deleted single chain FVIII) produced recombinantly in HEK293 cells as two polypeptide chains which are covalently linked by Fc hinge disulfide bonds [8]. It is used to replace lacking or deficient FVIII in patients with hemophilia A [8]. In vitro and in animal models, efanesoctocog alfa facilitated fibrin clot formation in plasma or platelet deposition and accumulation, with comparable dose-dependent kinetics to full-length recombinant human FVIII [9].

A number of modifications have been made to efanesoctocog alfa to extend its plasma half-life [8]. To decouple it from VWF and overcome the VWF-imposed half-life ceiling, a recombinant D'D3 domain of VWF was appended to efanesoctocog alfa. This stabilizes efanesoctocog alfa in the plasma and prevents its association with endogenous VWF. Additionally, efanesoctocog alfa features a dimeric Fc domain (for recovery from the lysosomal degradation pathway) and two XTEN polypeptide domains (which reduce renal clearance and shield the protein from proteolytic degradation [10]). In animal models of severe hemophilia A, efanesoctocog alfa provided three- to four-fold longer hemostatic control compared with full-length recombinant human FVIII [8].

These modifications may alter the behavior of efanesoctocog alfa in commercial FVIII assays, which are used for monitoring FVIII activity levels [11]. One study showed that most commercially available one-stage clotting assays were able to accurately and reliably measure FVIII activity (Table 1) [11]. However chromogenic substrate assays and

Table 1 Summary of the prescribing information of efanesoctocog alfa (ALTUVIIIO®) in hemophilia A in the USA [6]

What are the approved indications for efanesoctocog alfa?	
Adults and children with hemophilia A (congenital FVIII deficiency)	For routine prophylaxis to reduce the frequency of bleeding episodes
	For on-demand treatment and control of bleeding episodes
	For perioperative management of bleeding
How is efanesoctocog alfa available?	
Single-dose vials containing nominally 250 IU (cap color: yellow), 500 IU (red), 750 IU (garnet), 1000 IU (green), 2000 IU (royal blue), 3000 IU (mist grey), or 4000 IU (orange) of efanesoctocog alfa per vial as a white to off-white lyophilized powder for reconstitution	
How should efanesoctocog alfa be reconstituted and how should it be administered?	
Reconstitution	Allow the vial of drug and the prefilled dilutant syringe (containing 3 mL of sterile water for injection) to reach room temperature before use
	Puncture the vial stopper with the vial adapter and push until it is fully inserted; attach the prefilled syringe to the adapter; inject all of the liquid from the prefilled diluent syringe into the vial; gently swirl the vial until the powder is completely dissolved; do not use if the solution contains visible particles or is cloudy; once reconstituted do not refrigerate, store at room temperature (≤ 30°C), and use within 3 h
Administration	Adolescents and adults: intravenous injection at a rate of 1–2 min/vial
	Children (body weight ≥ 20 kg): intravenous injection at a rate of 2–3 min/vial
	Children (body weight < 20 kg): intravenous injection at a rate of 6 min/vial
What are the contraindications to the use of efanesoctocog alfa?	
Severe hypersensitivity reactions, including anaphylaxis, to the product or any of its excipients	
How should efanesoctocog alfa be used in special populations?	
Pregnancy and lactation	Lack of data
Patients aged < 12 years	Interim data suggest that no dosage adjustment is required
Patients aged ≥ 65 years	Insufficient data; however, clinical experience with other FVIII products has not identified a difference between elderly and younger patients
What other special warnings/precautions pertain to the use of efanesoctocog alfa?	
Hypersensitivity reactions	Inform patients of the signs of hypersensitivity reactions that may progress to anaphylaxis (including hives, shortness of breath, chest tightness, wheezing, hypotension, and itching); advise patients to discontinue treatment if symptoms occur and to contact a physician and/or seek immediate emergency care
Neutralizing antibodies	Monitor all patients for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests
Monitoring laboratory tests	Use a validated aPTT-based one-stage clotting assay to assess plasma FVIII activity

aPTT activated partial thromboplastin time, *FVIII* factor VIII, *IU* international units

one-stage clotting assays containing Actin FS reagent overestimated FVIII activity by 2.5- to 3.0-fold [11].

Anti-drug and neutralizing antibodies can develop after initial exposure to FVIII replacement products [3]. In clinical studies of efanesoctocog alfa ($n = 277$), four patients developed anti-drug antibodies and none developed neutralizing antibodies to FVIII [6]. Anti-drug antibodies did not impact bleeding episodes, the pharmacodynamic response, or the pharmacokinetic exposure parameters of efanesoctocog alfa [6].

What are the pharmacokinetic properties of efanesoctocog alfa?

Efanesoctocog alfa has a long half-life, which allows high levels of FVIII to be maintained with once-weekly administration (Table 2). Other key pharmacokinetic parameters are also summarized in Table 2. The accumulation of efanesoctocog alfa with once-weekly administration was minimal [12]. The pharmacokinetic profile of efanesoctocog alfa at week 26 (steady state) was similar to that after the first dose [6]. No clinically meaningful effects on its pharmacokinetic parameters were observed with age (1.4–72 years), sex, race (white, Asian), VWF antigen activity (40–339 IU/dL), hematocrit level (28–57%), blood type, hepatitis C virus status, or HIV status. Body weight of 12.5 to 133 kg altered the weight-normalized clearance by 79 to − 18% compared with a typical patient [6].

In a phase 1 comparison study in adults (18–65 years of age) with severe hemophilia A, efanesoctocog alfa had a three- and four-fold longer half-life compared with rurioctocog alfa pegol (an extended half-life recombinant FVIII) and octocog alfa (a recombinant FVIII), respectively [13]. The times until mean FVIII activity decreased to below 40 IU/dL and to ≈ 10 IU/dL

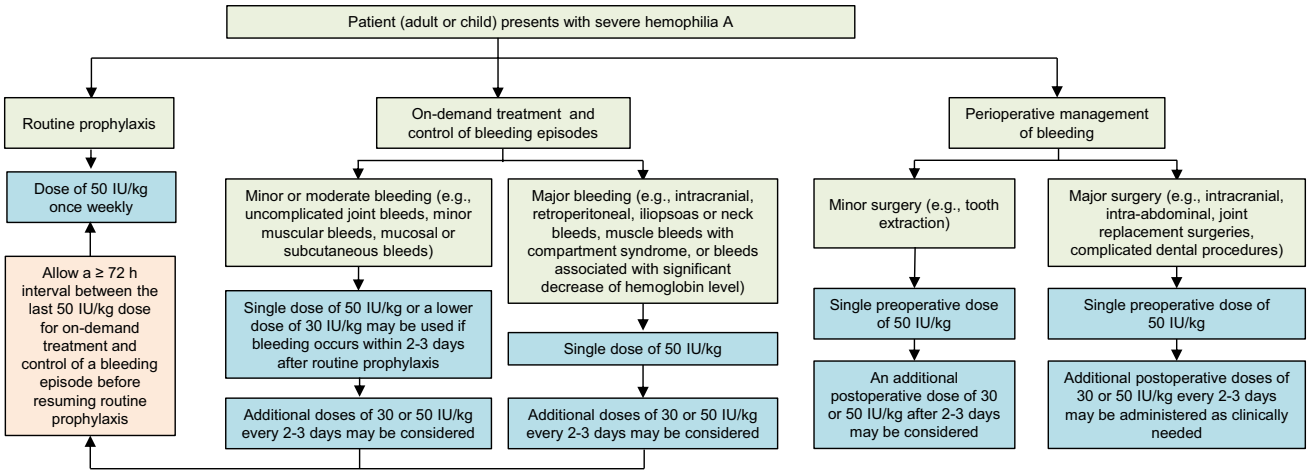

Fig. 1 Dosing recommendations for efanesoctocog alfa in hemophilia A in the USA [6]

were 4 days and 7 days in the efanesoctocog alfa group, 1 day and < 3 days in the rurioctocog alfa pegol group, and < 1 day and < 2 days in the octocog alfa group, respectively [13].

What is the efficacy of efanesoctocog alfa in adolescents and adults with hemophilia A?

Efanesoctocog alfa as prophylaxis adequately reduces the frequency of bleeding episodes in previously treated adolescents and adults with severe hemophilia A. This was demonstrated in the open-label, multinational, phase 3 XTEND-1 trial [12]. In this trial, patients were aged ≥ 12 years with endogenous FVIII activity of < 1 IU/dL or a documented genotype associated with severe hemophilia A, and had ≥ 150 exposure days to recombinant or plasma-derived FVIII concentrates or cryoprecipitate prior to trial initiation. Key exclusion criteria included clinical signs or symptoms of a decreased response to FVIII, other known coagulation disorders, positive test result for FVIII inhibitor (or history of) at screening (≥ 0.6 Bethesda units/mL), or major surgery ≤ 8 weeks before screening [12].

Table 2 Pharmacokinetic parameters of efanesoctocog alfa in patients with severe hemophilia A [6]

	Pediatric pts		Adolescent and adult pts	
PK parameters	1 to < 6 years	6 to < 12 years	12 to < 18 years	≥ 18 years
Single dose (50 IU/kg)				
No. of pts	14	18	25	134
Mean Vss (mL/kg)	38.0	38.1	34.9	31.0[a]
MRT (h)	51.9	56.3	60.0	63.9[a]
Mean AUC (IU × h/dL)	6710	7190	8350	9850
Mean $t_{1/2}$ (h)	39.9	42.4	44.6	48.2[a]
Mean CL (mL/h/kg)	0.740	0.681	0.582	0.493[a]
Steady state (50 IU/kg once weekly)				
No. of pts	20	35	24	124
Mean peak (IU/dL)	113	121	124	150
Mean IR (kg × IU/dL/IU)	2.10	2.17	2.25	2.64
Mean time to 40 IU/dL (h)[b]	59.2	72.2	81.7	97.0
Mean time to 10 IU/dL (h)[b]	139	163	179	200
Mean trough levels (IU/dL)	6.75	9.77	9.23	18.0

PK parameters based on factor VIII activity in a one-stage clotting assay

AUC area under the activity-time curve over the dosing interval, *CL* clearance, *IR* incremental recovery, *MRT* mean residence time, *PK* pharmacokinetic, *pts* patients, $t_{1/2}$ half-life, *Vss* volume of distribution at steady state

[a]Calculated based on 128 profiles

[b]Predicted using a population PK model

Patients who previously received prophylaxis with FVIII replacement products received prophylaxis with intravenous efanesoctocog alfa 50 IU/kg once weekly for 52 weeks (group A; $n=133$) [12]. Patients who previously received on-demand treatment with FVIII replacement products and had ≥6 bleeding episodes within the previous 6 months or ≥12 bleeding episodes in the previous 12 months received on-demand intravenous efanesoctocog alfa 50 IU/kg for 26 weeks, followed by prophylaxis with intravenous efanesoctocog alfa 50 IU/kg once weekly for a further 26 weeks (group B; $n=26$). Bleeding episodes during the trial were treated with a single dose of efanesoctocog alfa 50 IU/kg, with additional doses of 30 or 50 IU/kg every 2–3 days, as needed, if the bleeding did not resolve. Patients who had surgery during the trial were included in the surgery subgroup, and received preoperative efanesoctocog alfa 50 IU/kg, with additional doses of 30 or 50 IU/kg every 2–3 days, as needed [12].

The primary endpoint was the mean annualized bleeding rate (ABR) in the full analysis set (i.e., all patients in group A who received ≥1 dose of efanesoctocog alfa) and was analyzed by a negative-binomial regression model [12]. The primary endpoint was considered met if the upper limit of the 1-sided 97.5% confidence interval (CI) for mean ABR in group A was ≤6 (based on published historical data of marketed FVIII replacement products). Key secondary endpoints were non-inferiority and superiority of efanesoctocog alfa prophylaxis (data from XTEND-1) compared with standard-of-care FVIII prophylaxis (data from a prospective, observational pre-study of XTEND-1), as measured by intra-patient ABRs in group A. Non-inferiority (assessed in patients with ≥6 months of efficacy data in XTEND-1 and the pre-study) and superiority (assessed in the full analysis set) were assessed sequentially using a negative-binomial regression model. Efanesoctocog alfa was considered non-inferior to standard-of-care FVIII prophylaxis if the upper limit of the 1-sided 97.5% CI of the paired ABR difference was <4. Efanesoctocog alfa was considered superior to standard-of-care FVIII prophylaxis if the upper limit of the 1-sided 97.5% CI of the paired ABR ratio was <1 [12].

At baseline, the mean age of patients was 35.4 years, with 16%, 81%, and 3% of patients between the ages of 12–17 years, 18–64 years, and ≥65 years, respectively [12]. The majority (99%) of patients were male. The median age at the start of first prophylaxis was 1.0 years. The majority (79%) of patients had no known family history of FVIII inhibitors, but almost half had a genotype associated with an increased risk of developing FVIII inhibitors. In the 12 months prior to the trial, the mean number of bleeding episodes was 3.2 in group A and 35.7 in group B. The mean number of bleeding episodes into joints was 2.3 in group A and 27.4 in group B. Overall, ≥1 target joints (≥3 spontaneous bleeds into a major joint in a consecutive 6-month period) were reported in 31% of patients (20% in group A and 88% in group B). In the patients evaluated for joint health ($n=116$ in group A; $n=25$ in group B), the mean Hemophilia Joint Health Score (HJHS; scores range from 0–124, with higher scores indicating worse joint health) was 18.1 in group A and 26.3 in group B [12].

Efanesoctocog alfa prophylaxis was associated with low bleeding rates (Table 3). The primary endpoint of XTEND-1 was met, with the upper limit of the 1-sided 97.5% CI for the mean ABR being ≤6 in group A (Table 3) [12]. Almost two-thirds of patients in group A experienced zero bleeding episodes over the course of the trial (Table 3) and the majority (93%) of patients experienced ≤2 bleeding episodes. The mean annualized rate of spontaneous bleeding in group A was 0.29, with 80% of patients experiencing zero spontaneous bleeding episodes. For bleeding into joints, the mean ABR in group A was 0.52, with 72% of patients experiencing zero bleeds into joints. Mean ABRs for all treated bleeds (0.69), spontaneous bleeds (0.45), and bleeds into joints (0.61) in the prophylaxis period of group B further support the efficacy of efanesoctocog alfa prophylaxis in severe hemophilia A [12].

In XTEND-1, patients receiving efanesoctocog alfa had a reduced ABR compared with their previous treatment [12]. Efanesoctocog alfa prophylaxis was considered superior to standard-of-care FVIII in intra-patient comparisons of group A (key secondary endpoint), with a significant reduction of 77% in the mean ABR in group A when the value in XTEND-1 was compared with that in the pre-study (Table 3). In 29 patients who had exit interviews, all preferred efanesoctocog alfa prophylaxis to their previous hemophilia treatment. In group B, the mean ABR decreased from 21.42 to 0.69 when patients switched from on-demand treatment to prophylaxis with efanesoctocog alfa [12].

Efanesoctocog alfa was efficacious in resolving bleeding episodes [12]. Of the 362 bleeding episodes that occurred during the study, 97% were resolved [as assessed by a 4-point International Society on Thrombosis and Haemostasis (ISTH) response scale] following a single injection of efanesoctocog alfa 50 IU/kg, with 95% of 334 evaluated episodes having a good or excellent response [12]. During the on-demand period in group B ($n=26$) there were 268 bleeding episodes; 74% were due to spontaneous bleeding, 23% were due to trauma, and 3% were of unknown cause [14].

Perioperative efanesoctocog alfa was efficacious in achieving hemostasis in patients undergoing surgery [12]. During the trial, there were 14 major surgeries. Two of these surgeries occurred after the final dose of efanesoctocog alfa and were not assessed. In the 12 assessed surgeries in which efanesoctocog alfa was prescribed for perioperative management of bleeding, all patients had hemostatic responses (assessed with the ISTH response scale) that were deemed excellent by the investigator or surgeon [12]. Median blood loss during surgery ($n=6$) was 75 mL (range of 0–500 mL), and no patients required blood transfusion during surgery [15].

Table 3 Efficacy of efanesoctocog alfa in adolescents and adults with severe hemophilia A in the phase 3 XTEND-1 trial [12]

Endpoint	Key results
ABR (group A)	
No. of pts	133
Mean (95% CI), model-based[a,b]	0.71 (0.52–0.97)
Median (IQR)	0 (0–1.04)
Zero bleeding episodes (% of pts)	65
Intra-patient ABR (group A)	
No. of pts[c]	78
Mean of EFS[d] vs Std (95% CI), model-based[b]	0.69 (0.43–1.11) vs 2.96 (2.00–4.37)
Rate ratio (95% CI)[d]	0.23 (0.13–0.42)*
Median of EFS vs Std (IQR)	0 (0–1.04) vs 1.06 (0–3.74)

ABR annualized bleeding rate, *EFS* efanesoctocog alfa, *IQR* interquartile range, *pts* patients, *Std* standard-of-care factor VIII replacement prophylaxis

*$p < 0.001$ vs Std

[a]Primary endpoint

[b]Estimated with negative-binomial regression model

[c]Includes patients with ≥6 months of data on both pre-study (Std) and trial treatment (EFS)

[d]Assessed in the full analysis set

Additionally, efanesoctocog alfa improved several long-term outcomes, including patient health-related quality of life (HRQoL), symptoms of pain, and joint health [12]. At week 52, compared with baseline, patients receiving efanesoctocog alfa in group A had:

- A significant ($p < 0.0001$) improvement in HRQoL, with a least-squares mean change of −4.25 in the total Haemophilia Quality of Life Questionnaire for Adults score (Haem-A-QoL; scores range from 0–100, with higher scores representing greater impairment) and a significant ($p < 0.02$) improvement in 7 out of 10 domains of the Haem-A-QoL [16];
- A significant ($p = 0.0276$) and clinically relevant reduction in pain, with a least-squares mean change of −0.21 in the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity-Short Form 3a (scores range from 1–5, with higher scores indicating worse pain); pain intensity at its worst was improved or unchanged in 81.5% of patients [17];
- A significant ($p = 0.0101$) improvement in joint health, with a least-squares mean change of −1.54 in HJHS; the greatest improvements were in the swelling, muscle atrophy, crepitus motion, and flexion loss HJHS domains [18];
- Improved (41% of patients), unchanged (27%), or worsened (32%) joint health in the 22 participants whose joint health was further assessed with the assistance of ultrasound [19];
- All target joints (45 among 14 patients) resolved (≤2 bleeding episodes in the target joint over 12 months) among those who received ≥12 months of prophylaxis [12].

What is the efficacy of efanesoctocog alfa in children with hemophilia A?

Efanesoctocog alfa provides effective protection from and treatment of bleeding in previously treated children with severe hemophilia A [20]. The open-label, multinational, phase 3 XTEND-Kids trial [21] enrolled patients aged <6 years ($n = 38$) or 6 to <12 years ($n = 36$) [20]. Patients weighed ≥ 10 kg and had endogenous FVIII activity of <1 IU/dL or a documented genotype known to produce severe hemophilia A [21]. All patients received prophylaxis with intravenous efanesoctocog alfa 50 IU/kg once weekly for 52 weeks [20] The primary endpoint was the incidence of FVIII inhibitor development; the ABR was a secondary endpoint [21].

At week 52, the mean ABR was 0.89 (95% CI 0.56–1.42) and the median ABR was 0.00 (95% CI 0.00–1.02). Most bleeds resolved following a single dose of efanesoctocog alfa and the majority of responses to treatment were good or excellent [20].

What is the tolerability profile of efanesoctocog alfa?

Efanesoctocog alfa was well tolerated in previously treated adults, adolescents, and children with severe hemophilia A and there were no reports of FVIII inhibitors developing in these patients. In XTEND-1, the safety of efanesoctocog alfa was assessed in 159 adults and adolescents who had ≥1 dose of the study drug; 96% of these patients had ≥25 exposure-days to efanesoctocog alfa and 72% had ≥50 exposure-days [6]. Treatment-emergent adverse events (TEAEs) were reported in 77% of patients, with the most common (occurring in ≥5% of patients) being headache (20% of patients) arthralgia (16%), fall (6%), and back pain (6%) [12]. Adverse drug reactions were reported in 36% of patients [6]. One or more serious TEAEs occurred in 9% of patients; these included hemophilic arthropathy in two (1%) patients [12]. Two (1%) patients discontinued treatment due to adverse events; one patient with a history of HIV discontinued due to a decreased CD4 lymphocyte count, and one patient who had received another FVIII product during the study (which was prohibited) had a combined tibia-fibula fracture. A single death occurred during the trial due to metastatic pancreatic carcinoma, which was deemed not treatment-related by the investigator [12].

In XTEND-Kids, the safety of efanesoctocog alfa was evaluated in 74 children ($n = 38$ aged <6 years; $n = 36$ aged 6 to <12 years), with a mean exposure to efanesoctocog alfa of 49.81 weeks. Nine children had ≥1 serious TEAE; no adverse event led to treatment discontinuation [20].

FVIII inhibitor development, thrombotic events, serious allergic reactions, and anaphylaxis are adverse events that

can occur with coagulation factor replacement products (Table 1) [1, 6]. However, there were no reports of these adverse events in XTEND-1 [12]. Of note, all patients in the trial had prior exposure to FVIII replacement products, and inhibitors to coagulation factor typically develop during initial exposure. Additionally, patients with inhibitors to FVIII at screening or with a history of a positive inhibitor test were excluded from the trial, as were patients who had previously experienced allergic reactions or anaphylaxis with FVIII replacement products [12]. FVIII inhibitors were not detected in any patients in XTEND-Kids [20]. In a phase 1/2a trial (EXTEN-A; $n = 16$) [21], asymptomatic increases in the level of thrombin–antithrombin III complex with no associated clinical sequelae were reported in two patients who received efanesoctocog alfa [22]. No development of FVIII inhibitors, no hypersensitivity reactions or anaphylaxis were reported in this trial [22].

What is the current clinical role of efanesoctocog alfa in hemophilia A?

Efanesoctocog alfa is a useful addition to the therapies available for routine prophylaxis, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding in adults and children with hemophilia A. It has efficacy in preventing and treating bleeding episodes, is well tolerated, and has a prolonged plasma half-life compared with standard and extended half-life factor FVIII replacement products.

In the pivotal XTEND-1 trial, once-weekly efanesoctocog alfa prophylaxis was associated with low bleeding rates (primary endpoint), with almost two-thirds of patients experiencing zero annualized bleeding episodes (Table 3). Efanesoctocog alfa prophylaxis was superior in preventing bleeding episodes compared with prophylaxis with standard-of-care FVIII replacement products used by patients in a pre-study (Table 3). XTEND-1 also supported the use of efanesoctocog alfa in on-demand treatment and control of bleeding episodes as well as for perioperative management of bleeding. Furthermore, efanesoctocog alfa significantly improved patient HRQoL, pain, and joint health compared with baseline measurements [12]. In XTEND-Kids, children with hemophilia A receiving efanesoctocog alfa prophylaxis had low annualized bleeding rates; efanesoctocog alfa was also effective for treating and controlling bleeding episodes [20]. Efanesoctocog alfa was well tolerated in children and adults [6]. Inhibitor development was not observed in clinical trials [12, 20, 22].

The WFH does not currently recommend any FVIII replacement product over another and the choice of treatment should take into consideration availability, cost, and patient preferences [1]. In meta-analyses, efanesoctocog alfa significantly decreased ABRs (including any bleeding, spontaneous bleeding, and bleeding into joints) compared with approved standard half-life FVIII replacement products [23] and extended half-life FVIII replacement products [24], and significantly decreased ABRs (any bleeding and bleeding into joints, but not spontaneous bleeding) compared with the non-factor replacement product emicizumab [25]. However, due to limitations of indirect comparisons, these results should be interpreted with caution. Head-to-head trials including data relating to long-term outcomes (e.g., joint health) with efanesoctocog alfa and its competitors would be of interest.

Treatment adherence to prophylaxis can be a significant problem for management of severe hemophilia [1]. One of the main barriers to adherence is the requirement for frequent intravenous administration of FVIII replacement products, which results in issues of venous access, timing of treatments, and places a large treatment burden on patients [1]. The main advantage of efanesoctocog alfa prophylaxis over other FVIII replacement products is its three- to four-fold extended half-life [13], which permits once-weekly administration (instead of two to three times a week) and enables the maintenance of high trough levels of FVIII (Table 2). The improved pharmacokinetics of efanesoctocog alfa allow for adequate hemostasis to be achieved with a once-weekly dosing regimen, with normal or near-normal (> 40 IU/dL) levels of FVIII for 4 days after administration and FVIII levels consistent with a mild hemophilia phenotype (> 5–40 IU/dL) at trough concentrations in patients ≥ 18 years of age (Table 2). Although the clearance of efanesoctocog alfa appears to be more rapid in children, a FVIII level consistent with a mild hemophilia phenotype can still be maintained at trough concentrations in most children with once-weekly administration of this agent (Table 2). This reduces the treatment burden on patients compared with standard and extended half-life factor FVIII replacement products. Among the treatments approved for routine prophylaxis in hemophilia A, emicizumab is the only other treatment available that is amenable to a once-weekly (or less) dosing regimen and has the additional advantage of being subcutaneously administered [26]. However, emicizumab prophylaxis is unable to reliably achieve bleed protection equivalent to normal or near-normal levels of FVIII [27].

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References

1. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia. 3rd edition. Haemophilia. 2020;26(Suppl 6):1–158.
2. Manco-Johnson MJ, Warren BB. Long-term prophylaxis: what are our options and how to define success? Hematology (United States). 2022;2022(1):579–85.
3. Cho S, Perry AM, Cheng AM, et al. Advances in hemophilia A management. Adv Pediatr. 2022;69(1):133–47.
4. Sarafanov AG. Plasma clearance of coagulation factor VIII and extension of its half-life for the therapy of hemophilia A: a critical review of the current state of research and practice. Int J Mol Sci. 2023;24(10):1–20.
5. Pipe SW, Montgomery RR, Pratt KP, et al. Life in the shadow of a dominant partner: the FVIII-VWF association and its clinical implications for hemophilia A. Blood. 2016;128(16):2007–16.
6. Bioverativ Therapeutics Inc. ALTUVIIIO™ [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl], lyophilized powder for solution, for intravenous use: US prescribing information. 2023. https://dailymed.nlm.nih.gov/. Accessed 16 Jan 2024.
7. Keam SJ. Efanesoctocog alfa: first approval. Drugs. 2023;83(7):633–8.
8. Seth Chhabra E, Liu T, Kulman J, et al. BIVV001, a new class of factor VIII replacement for hemophilia A that is independent of von Willebrand factor in primates and mice. Blood. 2020;135(17):1484–96.
9. Demers M, Aleman MM, Kistanova E, et al. Efanesoctocog alfa elicits functional clot formation that is indistinguishable to that of recombinant factor VIII. J Thromb Haemost. 2022;20(7):1674–83.
10. Podust VN, Balan S, Sim BC, et al. Extension of in vivo half-life of biologically active molecules by XTEN protein polymers. J Control Release. 2016;240:52–66.
11. Pipe S, Sadeghi-Khomami A, Konkle B, et al. Efanesoctocog alfa activity assessment with one-stage clotting (OSA) and chromogenic substrate (CSA) factor VIII assays [abstract no. POO18 plus poster]. In: 16th Annual Congress of the European Association for Haemophilia and Allied Disorders. 2023.
12. von Drygalski A, Chowdary P, Kulkarni R, et al. Efanesoctocog alfa prophylaxis for patients with severe hemophilia A. N Engl J Med. 2023;388(4):310–8.
13. Lissitchkov T, Willemze A, Jan C, et al. Pharmacokinetics of recombinant factor VIII in adults with severe hemophilia A: fixed-sequence single-dose study of octocog alfa, rurioctocog alfa pegol, and efanesoctocog alfa. Res Pract Thromb Haemost. 2023;7(e100176):1–7.
14. Weyand AC, Meunier S, Amano K, et al. Treatment of bleeding episodes with efanesoctocog alfa in patients with severe haemophilia A in the phase 3 XTEND-1 study [abstract no. PO202]. Haemophilia. 2023;29(Suppl 1):136–7.
15. Klamroth R, von Drygalski A, Hermans C, et al. Perioperative management with efanesoctocog alfa in patients with hemophilia A in the phase 3 XTEND-1 study [abstract no. PO122]. Haemophilia. 2023;29(Suppl 1):87–8.
16. Wilson A, Nemes L, Quon D, et al. Efanesoctocog alfa prophylaxis improves health-related quality of life in patients with hemophilia A: results from the XTEND-1 phase 3 study [abstract no. PO150]. Haemophilia. 2023;29(Suppl 1):105.
17. Wilson A, Kragh N, Mshijid J, et al. Efficacy of efanesoctocog alfa on pain in patients with hemophilia A: results from the XTEND-1 phase 3 clinical trial in previously treated patients with hemophilia A [abstract no 322]. Blood. 2022;140(Suppl 1):5610–1.
18. von Drygalski A, Königs C, Nagae C, et al. Change in Hemophilia Joint Health Score (HJHS) during the phase 3 XTEND-1 study of efanesoctocog alfa in patients with severe hemophilia A [abstract no. OR02]. Haemophilia. 2023;29(Suppl 1):14–5.
19. Susen S, Konkle B, Hermans C, et al. Changes in anatomical structural joint health assessed by ultrasound in the phase 3 XTEND-1 study of efanesoctocog alfa in patients with severe haemophilia A [abstract no. PP-TH-030(1462067) plus poster]. Haemophilia. 2023;29(Suppl. 2):31–3.
20. Malec L, Peyvandi F, Chan A, et al. Efanesoctocog alfa prophylaxis for previously treated patients <12 years of age with severe hemophilia A [abstract no. LB 01.1]. In: International Society on Thrombosis and Haemostasis 2023 Congress. 2023.
21. US National Institute of Health. ClinicalTrials.gov (NCT04759131). 2023. http://www.clinicaltrials.gov/. Accessed 16 Jan 2024.
22. Konkle BA, Shapiro AD, Quon DV, et al. BIVV001 fusion protein as factor VIII replacement therapy for hemophilia A. N Engl J Med. 2020;383(11):1018–27.
23. Tosetto A, Arnaud A, Kragh N, et al. Efanesoctocog alfa vs. standard half-life (octocog alfa) FVIII therapies for prophylaxis in adolescents and adults with severe hemophilia A: a matching-adjusted indirect comparison and meta-analysis [abstract no. PB0213]. In: International Society on Thrombosis and Haemostasis 2023 Congress. 2023.
24. Klamroth R, Guyot P, Arnaud A, et al. Efanesoctocog alfa versus extended half-life factor VIII therapies for prophylaxis in adolescents and adults with severe hemophilia A: a matching-adjusted indirect comparison and meta-analysis [abstract no. PB0201]. In: International Society on Thrombosis and Haemostasis 2023 Congress. 2023.
25. Alvarez-Román M, Kragh N, Guyot P, et al. Efanesoctocog alfa versus emicizumab in the prophylactic treatment of adolescents and adults with severe hemophilia A without inhibitors: a matching-adjusted indirect comparison [abstract no. PB0195]. In: International Society on Thrombosis and Haemostasis 2023 Congress. 2023.
26. Blair HA. Emicizumab: a review in haemophilia A. Drugs. 2019;79(15):1697–707.
27. Kizilocak H, Marquez-Casas E, Malvar J, et al. Determining the approximate factor VIII level of patients with severe haemophilia A on emicizumab using in vivo global haemostasis assays. Haemophilia. 2021;27(5):730–5.