26 April 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Altuvoct (efanesoctocog alfa)
Treatment of haemophilia A
EU/3/19/2176

Sponsor: Swedish Orphan Biovitrum AB (publ)

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Recombinant human coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein
Other name(s)	--
International Non-Proprietary Name	Efanesoctocog alfa
Tradename	Altuvoct
Orphan condition	Treatment of haemophilia A
Sponsor's details:	Swedish Orphan Biovitrum AB (publ) 112 76 Stockholm Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Swedish Orphan Biovitrum AB (publ)
COMP opinion	23 May 2019
EC decision	28 June 2019
EC registration number	EU/3/19/2176
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus / Daniela Philadelphy
Applicant	Swedish Orphan Biovitrum AB (publ)
Application submission	25 April 2023
Procedure start	18 May 2023
Procedure number	EMA/H/C/005968
Invented name	Altuvoct
Therapeutic indication	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Altuvoct can be used for all age groups. Further information on Altuvoct can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/altuvoct
CHMP opinion	25 April 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Karri Penttila
Sponsor's report submission	27 November 2023
COMP discussion and adoption of list of questions	12-14 March 2024
COMP opinion (adoption via written procedure)	26 April 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2019 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing recombinant human coagulation factor VIII Fc – von Willebrand factor - XTEN fusion protein was considered justified based on non-clinical data in a valid model of condition showing better survival due to the improvement in coagulation;
- the condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or in surgery, which may also be life-threatening;
- the condition was estimated to be affecting approximately 0.8 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human coagulation factor VIII Fc – von Willebrand factor - XTEN fusion protein will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate better prolonged half-life than the currently authorised modified release factor VIIIs. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing recombinant human coagulation factor VIII Fc – von Willebrand factor - XTEN fusion protein as an orphan medicinal product for the orphan condition: treatment of haemophilia A.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor proposes that haemophilia A continues to be a distinct medical condition which meets the criteria for an orphan condition. Haemophilia A is a well describe X-linked genetic disorder that affects males exclusively with females being carriers of the gene mutation.

The condition is characterised by low or undetectable levels of the coagulating protein FVIII. FVIII activity as a consequence is low or undetectable and these patients will present with spontaneous and life-threatening bleeding events or excessive bleeding in response to trauma. Bleeds occur in muscle, central nervous system, organs, soft tissue, and more frequently in joints, which leads to progressive joint deformity, arthropathy, and severe disability.

The COMP continues to accept this as an orphan condition.

The approved therapeutic indication "Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Altuvoct can be used for all age groups" falls within the scope of the designated orphan condition "Treatment of haemophilia A"

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR. Chronically debilitating and/or life-threatening nature

The condition is chronically debilitating due to the complications associated with spontaneous and often excessive bleeding. The location and severity of the bleeding is associated with the morbidity of the condition with common problems associated with joint bleeding leading to joint deformity, arthropathy and physical disability. Bleeding can also occur in the central nervous system, organs and soft tissue leading to complications linked to the damage associated with the site of bleeding.

Life expectancy has been improving in these patients since the introduction of plasma-derived or recombinant factor VIIIs and generally it is accepted that only the very severe patients will have their life-expectancy shortened. It has however been reported by Eckhart C et al 2015 Journal of Thrombosis and Haemostasis, 13:1217-1225 2015 that patients with milder forms of haemophilia A were at risk of shortened life-expectancy. Indeed, it is reported that these patients had a life expectancy of 64 years which was less than the normal life-expectancy for males in Europe. The average life-expectancy for males across the European Union was 75 years for males and 81 years for females in 2022.

(https://www.statista.com/statistics/274514/life-expectancy-in-europe/)

Number of people affected or at risk

The sponsor has provided a prevalence based the most recent World Federation of Haemophilia Annual Global Survey (WFH) (2020) and a recent meta-analysis (Iorio et al. 2019), the global prevalence at birth/100,000 males has been estimated to be 24.6 (95% CI 21.4–27.7) for all haemophilia A and 9.5 (95% CI 7.5–11.5) for severe haemophilia A. Although haemophilia A is expected to be equally distributed across the world (Skinner 2012, World Federation of Haemophilia 2021), differences in the observed prevalence reflect differences in diagnostic capability, in the reporting efficiency and effectiveness of national registries, and in economic capacity (Stonebraker et al. 2003, Stonebraker et al. 2010).

Mortality rates are higher in patients with haemophilia than in the general population, it is noted that the prevalence estimates for the current global population/100,000 males are lower than for those at birth: 17.1 (95% CI 14.8–19.3) for all haemophilia A and 6.0 (95% CI 5.8–6.1) for severe haemophilia A.

It is estimated that 1.125 million patients with haemophilia A exist in the global population, based namely on prevalence at birth estimates, however less than 200,000 (~18 %) have been identified and

reported globally, indicating a substantial need for more efficient diagnostic approaches especially in low to middle income countries (Iorio et al. 2019).

The sponsor notes that these estimates nevertheless confirm that hemophilia A is a rare disease globally, as well as in the EU by the EMA definition (< 5 cases per 10 000 persons) (Khosla et al. 2018, Iorio et al. 2019).

The sponsor should provide a clear final prevalence estimate for haemophilia A based on the World Federation of Haemophilia (WFH) publications as well as more current publications they may have sourced.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor has highlighted those two types of factor VIII products available in Europe; plasma derived and recombinant derived. Below is a non-exhaustive table provided by the sponsor:

Table 1. FVIII replacement products licensed for use in the EU

Tradename	**Active substance**
FVIII analogues	
Kogenate® FS, Helixate® NexGen, Advate®, Kovaltry®/Iblias®, Recombinate®	Octocog alfa
B-domain truncated/deleted FVIII	
ReFacto® AF	Moroctocog alfa
NovoEight®	Turoctocog alfa
Nuwiq®, Vihuma®	Simoctocog alfa
Afstyla®	Lonoctocog alfa
Obizur	Susoctocog alfa
FVIII – extended half-life	
Adynovi®[a]	Rurioctocog alfa pegol
FVIII – B domain truncated/deleted, extended half-life	
Elocta®	Efmoroctocog alfa
Jivi®[a]	Damoctocog alfa pegol
Esperoct®[a]	Turoctocog alfa pegol
Plasma-derived coagulation FVIII concentrate (non-inclusive list)	
Beriate®/Beriate P, Betafact®, Cluvot®, Haemoctin®, Haemonine®, Immunine®, Mononine®, Octanate®, Immunate®	
Plasma-derived human coagulation FVIII and human VWF concentrate (non-inclusive list)	
Optivate®, Wilate®, Voncento®, Fanhdi®, Haemate® P	

[a]This pegylated FVIII product is not authorized in the EU for patients <12 years of age.

There are currently several FVIII replacement products available for use in Europe so physicians have an extensive choice. The sponsor has discussed treatment modalities and articles available from the

World Federation of Haemophilia notably the most recent guidelines from 2020. WFH Guidelines for the Management of Hemophilia, 3rd edition (haemophilia.org.uk).

In the evaluation of this submission, it was noted that the indication being proposed is a "core indication" for all the possible indications available for the different Factor VIIIs available in the EEA. The proposed wording for the core indication has therefore been proposed to be applied to Altuvoct and is:

Altuvoct is indicated for "*Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). ALTUVOCT can be used for all age groups*".

The COMP considered that this wording constituted a complete overlap of all authorised Factor VIIIs, therefore significant benefit needs to be established for these products.

Emicizumab, sold under the brand name Hemlibra, is a humanized bispecific monoclonal antibody for the treatment of haemophilia A. Emicizumab binds to both the activated coagulation factor IX and to factor X, mediating the activation of the latter. This is normally the function of coagulation factor VIII, which is missing in haemophilia A patients.

Hemlibra is indicated for: *routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency):*

- with factor VIII inhibitors
- without factor VIII inhibitors who have:
  - severe disease (FVIII < 1%) - moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.

Hemlibra can be used in all age groups.

Valoctocogene roxaparvovec, sold under the brand name Roctavian, is a gene therapy used for the treatment of hemophilia A. Valoctocogene roxaparvovec is made of a virus (AAV5) that has been modified to contain the gene for factor VIII, which is lacking in people with hemophilia A. It is an adeno-associated virus vector-based gene therapy. It has also been authorised in Europe for use in the condition.

ROCTAVIAN is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

As the indications of Hemlibra and Roctavian are restricted to certain patients with haemophilia A and the indication for Altuvoct is not, significant benefit doesn't need to be shown versus these two products.

Significant benefit

The sponsor is claiming a clinically relevant advantage of using their product in patients with haemophilia A. The sponsor came from protocol assistance for significant benefit on 19 July 2021.

- To support their claim for significant benefit the sponsor has submitted data from their pivotal Phase III study EFC16293.

This was a Phase 3, open-label, multinational, multicenter study of the safety, efficacy, and PK of IV efanesoctocog alfa (Altuvoct) in PTPs ≥12 years of age with severe hemophilia A (defined as <1 IU/dL

[<1%] endogenous FVIII or a documented genotype known to produce severe hemophilia A). A total of approximately 150 participants were planned to be enrolled and treated with efanesoctocog alfa.

The study was comprised of 2 arms:

- Arm A included participants who were on a prophylaxis treatment regimen with FVIII prior to the study. Participants in Arm A were to receive efanesoctocog alfaat a dose of 50 IU/kg IV once weekly on a prophylaxis treatment regimen for up to 52 weeks. Approximately 124 participants were planned to be enrolled in Arm A including at least 75 participants with at least 6 months of participation in Study 242HA201/OBS16221 (hereafter referred to as OBS16221) prior to baseline. Study OBS16221 was a global, multicenter, prospective study of up to 12 months' duration conducted in participants ≥12 years of age with severe hemophilia A who were receiving a marketed FVIII product; the aim of this study was to collect retrospective data from participants' medical records as well as prospective clinical data (eg, ABR, HJHS, PRO measures of general health-related and disease-specific QoL etc) in order to enhance knowledge on the current care and treatment of severe hemophilia A. Data from Study OBS16221 were used to perform an intra-participant comparison of ABR between weekly prophylactic treatment with efanesoctocog alfa and prestudy prophylactic treatment with a marketed FVIII product.
- Arm B included participants who were on an on-demand treatment regimen prior to the study. Approximately 26 participants were planned to be enrolled in Arm B and receive efanesoctocog alfa as:
  - On-demand regimen: Participants in Arm B received efanesoctocog alfa at a dose of 50 IU/kg IV as on-demand treatment of bleeding episodes for the first 26 weeks followed by:
  - Prophylaxis regimen: Participants in Arm B switched to receive efanesoctocog alfa at a dose of 50 IU/kg IV once weekly as a prophylaxis treatment regimen for another 26 weeks.

Throughout their lives, study participants had been exposed to different haemophilia treatments. FVIII products included plasma derived FVIII, recombinant FVIII, and FVIII cryoprecipitate in 107 (69.9%), 114 (74.5%) and 41 (26.8%) of participants, respectively.

Severe hemophilia diagnosis had to be documented by FVIII activity (defined as <1 IU/dL [<1%] endogenous FVIII activity) or genotype. In addition, participants on pre-study on-demand treatment had to have at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrollment, which provided additional confirmation of a severe bleeding phenotype prior to enrollment in EFC16293.A total of N=159 participants were enrolled:

- Arm A: N=133 participants (including N=82 participants rolled over from observational study OBS16211)
- Arm B: N=26 participants (including N=10 participants rolled over from observational study OBS16221)

Primary efficacy end-point data is summarised in the table below.

Table 2. Summary of annualized bleeding rates

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Number of participants with an efficacy period	133	26	26
Total number of treated bleeding episodes	86	268	8
Total participant-years followed	121.2	12.5	11.4
Duration of efficacy period (weeks)			
Number	133	26	26
Mean (SD)	47.55 (8.77)	25.12 (1.07)	22.89 (6.00)
Median	50.09	25.00	25.08
Q1 ; Q3	48.06 ; 51.09	24.72 ; 25.02	22.07 ; 27.06
Min ; Max	0.1 ; 54.1	23.9 ; 29.3	1.1 ; 27.1
Annualized bleeding rate (ABR)			
Number	133	26	26
Mean (SD)	0.71 (1.43)	21.42 (7.41)	0.69 (1.35)
Median	0.00	21.13	0.00
Q1 ; Q3	0.00 ; 1.04	15.12 ; 27.13	0.00 ; 0.00
Min ; Max	0.0 ; 11.0	8.3 ; 33.4	0.0 ; 4.1
0	86 (64.7)	0	20 (76.9)
>0-5	45 (33.8)	0	6 (23.1)
>5-10	1 (0.8)	1 (3.8)	0
>10-20	1 (0.8)	10 (38.5)	0
>20	0	15 (57.7)	0
ABR, model based[a]			
Mean (95% CI)	0.71 (0.52; 0.97)		

Note: 1: Summaries are based on treated bleeds.
2: Percentages are based on the number of participants in each study arm and treatment regimen with an evaluable efficacy period.
3: The efficacy period reflects the sum of all intervals of time during which participants are treated with efanesoctocog alfa according to the study arms and treatment regimens excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
4: Participants are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen.
a 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.
Source: CSR EFC16293 Table 13

Study EFC16293, once-weekly prophylaxis with efanesoctocog alfa at a dose of 50 IU/kg conferred highly effective protection against treated bleeds, as demonstrated by low mean ABRs of 0.71 (95 % CI: 0.52 to 0.97) in adults and adolescents and 0.89 (95% CI 0.56; 1.42).

Efanesoctocog alfa also demonstrated superior protection against bleeds in intra-patient (adult and adolescent) comparisons with historical pre-study prophylaxis with an authorized FVIII replacement product: mean ABR (95 % CI) decreased from 2.99 (2.03; 4.42) with prestudy prophylaxis to 0.69 (0.43; 1.12) with efanesoctocog alfa prophylaxis, for a mean ABR difference (95 % CI) of –2.30 (3.49; –1.11) and a statistically significant rate reduction of 77 % (58% to 87%; $p < 0.0001$).

Table 3. Key secondary endpoint: intra-participant comparison of ABR between efanesoctocog alfa PPX treatment vs. historical PPX treatment in Study EFC16293 in adults and adolescents.

	Arm A	
	Historical Prophylaxis (OBS16221) (N=77)	**BIVV001 Prophylaxis (EFC16293) (N=77)**
Number of participants with an observation or efficacy period	77	77
Total number of treated bleeding episodes	212	51
Total participant-years followed	69.7	73.5
Duration of observation or efficacy period (weeks)		
Number	77	77
Mean (SD)	47.26 (6.72)	49.80 (2.47)
Median	50.15	50.09
Q1 ; Q3	43.86 ; 52.10	49.07 ; 51.18
Min ; Max	27.4 ; 54.0	39.1 ; 54.1

Note: 1: Summaries are based on treated bleeds.
2: Percentages are based on the number of participants in the prophylaxis treatment regimen of each study with an evaluable observation or efficacy period.
3: The analysis is based on the Per Protocol Set and including participants in Arm A who have at least 6 months of efficacy period in the EFC16293 study and at least 6 months of observation period on prophylaxis collected in Study OBS16221.
4: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 according to the study arms and treatment regimens excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
[a] Estimated using a negative binomial regression model with treatment (BIVV001 prophylaxis vs historical prophylaxis) as covariate.
[b] P-value relates to the null hypothesis: rate ratio (BIVV001 prophylaxis/historical prophylaxis) =1.
[c] Estimated using the Hodges-Lehmann method. [d]P-value relates to the null hypothesis: median of paired difference (BIVV001 prophylaxis - historical prophylaxis) =4 based on Wilcoxon Signed Rank test.
PGM=PRODOPS/BIVV001/EFC16293/CSR_01/REPORT/PGM/intra_abr_eff_t.sas OUT=REPORT/OUTPUT/intra_abr_eff_t_x.rtf (05MAY2022 15:33)
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Table 4. Key secondary endpoint: intra-participant comparison of ABR between efanesoctocog alfa PPX treatment vs. historical PPX treatment

	Arm A	
	Historical Prophylaxis (OBS16221) (N=77)	**BIVV001 Prophylaxis (EFC16293) (N=77)**
Annualized bleeding rate (ABR)		
Number	77	77
Mean (SD)	2.98 (5.21)	0.69 (1.51)
Median	1.07	0.00
Q1 ; Q3	0.00 ; 3.74	0.00 ; 1.04
Min ; Max	0.0 ; 35.6	0.0 ; 11.0
0	32 (41.6)	49 (63.6)
>0-5	28 (36.4)	27 (35.1)
>5-10	11 (14.3)	0
>10-20	5 (6.5)	1 (1.3)
>20	1 (1.3)	0

Note: 1: Summaries are based on treated bleeds.
2: Percentages are based on the number of participants in the prophylaxis treatment regimen of each study with an evaluable observation or efficacy period.
3: The analysis is based on the Per Protocol Set and including participants in Arm A who have at least 6 months of efficacy period in the EFC16293 study and at least 6 months of observation period on prophylaxis collected in Study OBS16221.
4: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 according to the study arms and treatment regimens excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
[a] Estimated using a negative binomial regression model with treatment (BIVV001 prophylaxis vs historical prophylaxis) as covariate.
[b] P-value relates to the null hypothesis: rate ratio (BIVV001 prophylaxis/historical prophylaxis) =1.
[c] Estimated using the Hodges-Lehmann method. [d]P-value relates to the null hypothesis: median of paired difference (BIVV001 prophylaxis - historical prophylaxis) =4 based on Wilcoxon Signed Rank test.
PGM=PRODOPS/BIVV001/EFC16293/CSR_01/REPORT/PGM/intra_abr_eff_t.sas OUT=REPORT/OUTPUT/intra_abr_eff_t_x.rtf (05MAY2022 15:33)
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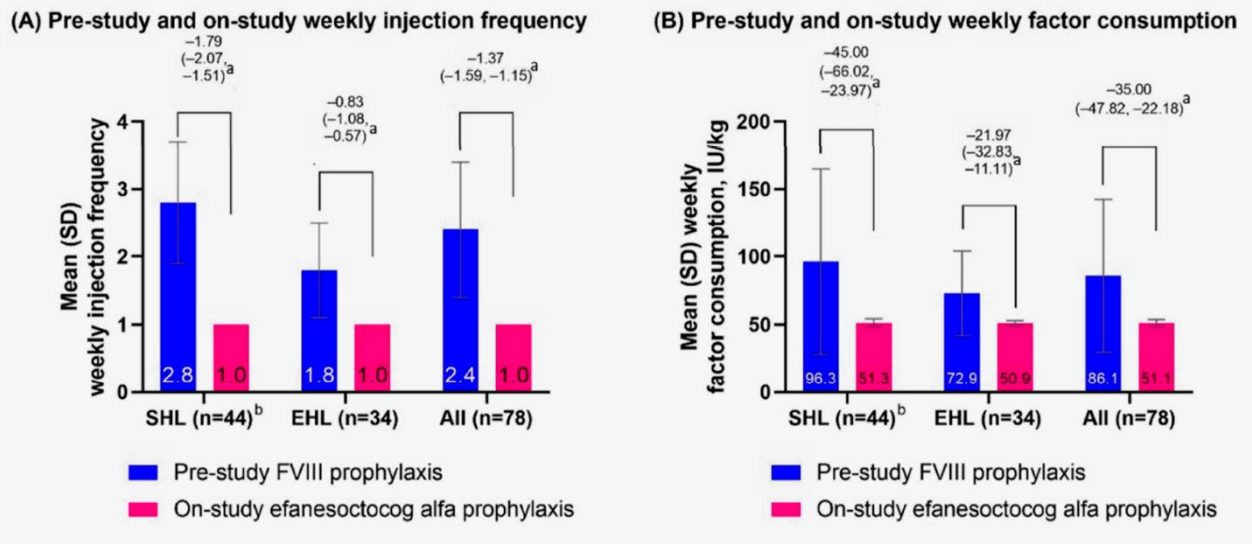
A post-hoc analysis was performed to compare weekly FVIII consumption and injection frequency during pre-study prophylaxis and during efanesoctocog alfa prophylaxis in 78 participants who had received ≥6 months standard-of-care FVIII prophylaxis (SHL FVIII [recombinant or plasma-derived FVIII; n=44] or EHL rFVIII [n=34]) in the observational Study OBS16221 and were then enrolled in Arm A to receive weekly efanesoctocog alfa prophylaxis.

With efanesoctocog alfa prophylaxis, mean overall weekly injection frequency decreased from 2.4 to 1.0 injections per week and weekly FVIII consumption decreased from 86.1 to 51.1 IU/kg per week, compared to pre-study prophylaxis. Mean (95% CI) changes in weekly injection frequency and in

weekly consumption were −1.37 (−1.59, −1.15) injections per week and −35.00 (−47.82, −22.18) IU/kg per week, respectively.

Figure 1. Pre-study and on-study weekly injection frequency and FVIII consumption



Abbreviations: CI, confidence interval; EHL, extended half-life; FVIII, factor VIII; SD, standard deviation; SHL, standard half-life.
a. Mean difference, 95% CI.
b. Pre-study SHL includes SHL rFVIII and plasma-derived FVIII.

The sponsor has provided data in their maintenance report and in the appendices of the clinical study report EFC16293 in adolescents and adults which would support a clinically relevant advantage when treatment from available Factor VIII products is switched to Altuvoct. In particular, a lower annualised bleeding rate (ABR) was reported. Data also showed a significant reduction in injection frequency and Factor VIII consumption in the pre-study Factor FVIII group compared to the on-study group with Altuvoct.

The sponsor also submitted data supporting that efanesoctocog alfa demonstrated superior protection against bleeds in intra-patient (adult and adolescent) comparisons with historical prestudy prophylaxis with an authorized FVIII replacement product: mean ABR (95 % CI) decreased from 2.99 (2.03; 4.42) with prestudy prophylaxis to 0.69 (0.43; 1.12) with efanesoctocog alfa prophylaxis, for a mean ABR difference (95 % CI) of –2.30 (3.49; –1.11) and a statistically significant rate reduction of 77 % (58% to 87%; p < 0.0001).

The non-inferiority of prophylaxis treatment with efanesoctocog alfa over historical prophylaxis on the key efficacy endpoint was tested as part of the prespecified hierarchical step-down testing procedure. The superiority of efanesoctocog alfa prophylaxis compared with pre-study prophylaxis in the FAS was also achieved by the prespecified hierarchical step-down testing procedure, as the upper limit of the 1-sided 97.5% CI was less than the prespecified value of 1 (rate ratio: 0.23 [95% CI: 0.13 to 0.42]; p<0.0001).

In adults and adolescents (≥12 years of age), Altuvoct prophylaxis demonstrated a significantly low ABR, that was reduced in comparison to other rFVIII products, for a prolonged dosing regimen of once weekly. Efficient treatment of bleeding events and excellent haemostatic response during perioperative management have been shown. Similar efficacy was shown in the paediatric population (<12 years of age). The extended half-life of efanesoctocog alfa allows a once-weekly administration of prophylactic FVIII replacement in patients with severe haemophilia A patients and represents an acknowledge

benefit. This reduced administration frequency may also positively impact treatment compliance in some patients.

Major Contribution to Patient Care

In study EFC16293, participants were assessed at baseline for joint health (Hemophilia Joint Health Score), quality of life (Haem-A-QoL), and pain intensity (PROMIS Pain Intensity). At Week 52, all scores were significantly lower than at baseline, showing improvements in joint health, quality of life, and pain intensity. These results mirror the results seen for the efficacy endpoints and were considered supportive of the sponsor's claim for major contribution to patient care. They indicate that efanesoctocog alfa could provide additional benefits beyond effective control of bleeding helping distinguish it from all other prophylaxis treatment options, enabling it to significantly improve the health, well-being, and quality-of-life in people with haemophilia of all ages. While a positive trend throughout these results is recognized, the outcomes are not considered robust enough support the significant benefit.

The COMP considered that the above-mentioned aspect is of significant benefit in the management of Haemophilia A patients. The Committee therefore agreed that significant benefit had been met for the purpose of maintaining the orphan designation.

Comments on sponsor's response to the COMP list of issues

Sponsor has provided a more complete prevalence estimate for the EU based on the recent WFH Annual Global Survey for 2022 (World Federation of Hemophilia 2023). The prevalence of persons with hemophilia A (PwH A) in each EU member state with reported data is provided in Table 5.

From these data, there are approximately 31 365 PwH A in the EU, with an overall prevalence of 0.723/10 000 inhabitants. There is a wide range in the reported prevalence of PwH A in individual countries, from a low of 0.246/10 000 inhabitants in Luxemburg to a high of 1.382/10 000 in Ireland. Since hemophilia A is expected to be equally distributed across the world (Skinner 2012, World Federation of Hemophilia 2023), such differences in the observed prevalence likely reflect differences in diagnostic capability, in the reporting efficiency and effectiveness of national registries, in healthcare infrastructure, and in economic capacity (Stonebraker et al. 2003, Stonebraker et al. 2010)

Table 5. Distribution of people with hemophilia A (reported) in EU member states by country – WFH 2022[a]

Country	Population	PwH A	Prevalence per 10,000 persons
Austria	9,042,528	716	0.792
Belgium	11,669,446	1077	0.923
Bulgaria		No data	--
Croatia	3,854,000	280	0.727
Cyprus		No data	--
Czech Republic	10,526,073	919	0.873
Denmark		No data	--
Estonia	1,344,768	102	0.758
Finland	5,556,880	180	0.324
France	67,935,660	7893	1.162
Germany	84,079,811	4245	0.505
Greece	10,566,531	835	0.790
Hungary	9,683,505	910	0.940
Ireland	5,086,988	703	1.382
Italy	58,856,847	2944	0.500
Latvia	1,883,379	96	0.510
Lithuania	2,833,000	178	0.628
Luxembourg	650,774	16	0.246
Malta		No data	--
Netherlands	17,703,090	1535	0.867
Poland	37,561,599	2754	0.733
Portugal	10,379,007	818	0.788
Romania	18,956,666	1615	0.852
Slovakia	5,431,752	622	1.145
Slovenia	2,108,732	241	1.143
Spain	47,615,034	1842	0.387
Sweden	10,486,941	844	0.805
Total, w/data	433,813,011	31,365	0.723

[a] WFH Annual Report for 2022 (World Federation of Hemophilia 2023)

If the global prevalence estimate of 1.71/10 000 males (Iorio et al. 2019) is extrapolated across the EU 2022 population of 446 820 419, of which 49% is male (Eurostat), the overall prevalence of males with hemophilia A is 0.84/10 000 EU inhabitants (Table 6). However, hemophilia A is also present in the female population in a range of severities, albeit at a much lower frequency than in males. Female carriers of a defective *F8* gene may present with lower-than-normal levels of FVIII activity, producing a mild (>5 to <40 IU/dL) to moderate (1 to 5 IU/dL) phenotype, or even severe hemophilia (<1 IU/dL) in cases of X chromosome inactivation (Garagiola et al. 2021, van Galen et al. 2021). Females with 2 copies of a defective *F8* gene acquired either through inheritance or *de novo* mutation may present with a moderate to severe phenotype.

Table 6. Estimated prevalence of male and female PwH A in the EU

				Male:Female 1:0[b]		**Male:Female 26.3:1[c]**		**Male:Female 7.7:1[d]**	
	EU Population 2022[a]	Percent	Ratio	HA prevalence per 10 000	No. of PwHA in EU	HA prevalence per 10 000	No. of PwHA in EU	HA prevalence per 10 000	No. of PwHA in EU
Male	218,406,986	49	1	1.71	37348	1.71	37348	1.71	37348
Female	228,413,433	51	1.046	0	0	0.065	1485	0.22	5073
Total	446,820,419				37348		38833		42421
Overall prevalence				0.84		0.87		0.95	

[a] Eurostat (https://ec.europa.eu/eurostat/en/)
[b] Iorio et al (Iorio et al. 2019)
[c] WFH Annual Report for 2022 (World Federation of Hemophilia 2023)
[d] UKHCDO Annual Report 2022/2023 (United Kingdom Haemophilia Centre Doctors' Organisation 2023)

In the WFH annual report, among the global total of 208 957 persons known to have hemophilia A, 189 750 are male (91%), 7225 (3%) are female, and 9754 (5%) are of unknown sex. Thus, the global ratio of known males to known females is 26.3:1. The sponsor thinks that this is likely a substantial underestimate of female prevalence due to widespread difficulties in capturing persons with mild to moderate hemophilia who may not seek or have access to treatment. If this low ratio is used to estimate prevalence in the EU, an estimated 1485 females with hemophilia A are added to the EU population for an overall prevalence of 0.87/10 000 (Table 6).

Another estimate of the prevalence of female PwH A is available from the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Annual Report for 2023 (United Kingdom Haemophilia Centre Doctors' Organisation 2023). This data was used as supportive data for the final estimate. Among a total of 7244 people with congenital hemophilia A registered and treated in the UK with a FVIII activity level <40 IU/dL (i.e., at least mild hemophilia), 6412 are male and 832 are female, 9 of whom have severe hemophilia A. Thus, the ratio of male to female PwH A in the UK is 7.7:1. If this higher ratio is used to estimate prevalence in the EU, an estimated 5073 females with hemophilia A are added to the EU population for an overall prevalence of 0.95/10 000 (Table 2). This estimate is perhaps the most precise given the extensive health care system in the UK, which is likely to identify most patients with hemophilia A, including females.

COMP conclusions

In conclusion, all of these estimates, including the most liberal result of 0.95/10 000, confirm that hemophilia A is a rare disease in the EU by the EMA definition of < 5 cases per 10 000 persons. The COMP accepted the most liberal result of 0.95 in 10,000 as the final estimate for haemophilia A.

4. COMP position adopted on 26 April 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of haemophilia A (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or associated with surgery, which may also be life-threatening;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Altuvoct, the claim that Altuvoct is of significant benefit to those affected by the orphan condition is established. Altuvoct prophylaxis once weekly demonstrated a significantly lowered annual bleeding rate, compared to other Factor VIII products. The COMP considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Altuvoct, recombinant human coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein, efanesoctocog alfa, for Treatment of haemophilia A (EU/3/19/2176) is not removed from the Community Register of Orphan Medicinal Products.