

## Efanesoctocog alfa: a new standard for haemophilia A prophylaxis?

### Efanesoctocog alfa: ¿un nuevo estándar para la profilaxis en hemofilia A?

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#### Abstract

The arrival of new subcutaneous products for prophylaxis in hemophilia has focused on preventing bleeding by normalizing thrombin generation. Emicizumab has been a paradigm shift, and while some experts prefer prophylaxis with coagulation factor VIII (CFVIII), others consider emicizumab as the reference treatment due to its efficacy and safety. CFVIII extended half-life concentrates have improved previous treatments, but their effectiveness has been limited by their half-life, restricted by von Willebrand factor. New products, such as efanesoctocog alfa, approved in 2023, offer an ultra-long half-life, reducing the treatment burden. This recombinant product presents modifications that extend its plasma half-life and improve thrombin generation. The clinical efficacy of weekly prophylaxis has been demonstrated in the XTEND-1 and XTEND-Kids studies, showing good results in efficacy and tolerance, with a low incidence of inhibitors. Indirect comparisons suggest that efanesoctocog alfa could be superior to emicizumab in bleeding prophylaxis in adults and adolescents without inhibitors. In conclusion, efanesoctocog alfa inaugurates a new class of ultra-long half-life CFVIII, offering a significant therapeutic opportunity for hemophilia by normalizing thrombin generation in a physiological manner. However, more studies are needed to evaluate its efficacy and safety in different clinical scenarios.

**Keywords:** Prophylaxis. Ultra-long half-life. Von Willebrand factor. XTEN. Efficacy. Innovation.

#### Resumen

La incorporación de nuevos productos de administración por vía subcutánea para la profilaxis en la hemofilia se ha centrado en la prevención del sangrado mediante la normalización de la generación de trombina. El emicizumab ha sido un cambio de paradigma, y aunque algunos expertos prefieren la profilaxis con factor de coagulación VIII (CFVIII), otros lo consideran como el tratamiento de referencia debido a su eficacia y seguridad. Los concentrados de CFVIII de vida media extendida han mejorado los tratamientos previos, pero su semivida limitada por el factor Von Willebrand ha restringido su efectividad. Los nuevos productos, como el efanesoctocog alfa, aprobado en 2023, ofrecen una vida media ultralarga, reduciendo la carga de tratamiento. Este producto, de origen recombinante, presenta modificaciones que prolongan su semivida plasmática y mejoran la generación de trombina. La eficacia clínica de la profilaxis semanal se ha puesto de manifiesto en los estudios XTEND-1 y XTEND-Kids, mostrando buenos resultados en cuanto a eficacia y tolerabilidad, con una baja incidencia de inhibidores. Las comparaciones indirectas sugieren que el efanesoctocog alfa podría ser superior al emicizumab en la

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*profilaxis del sangrado en adultos y adolescentes sin inhibidor. En conclusión, el efanesoctocog alfa inaugura una nueva clase de CFVIII de vida ultra larga y ofrece una oportunidad terapéutica significativa para la hemofilia al normalizar la generación de trombina de manera fisiológica, aunque se requieren más estudios para evaluar su eficacia y seguridad en diferentes escenarios clínicos.*

**Palabras clave:** Profilaxis. Vida media ultralarga. Factor Von Willebrand. XTEN. Eficacia. Innovación.

## Introduction

The incorporation of new subcutaneous administration products into the arsenal of available therapies for prophylaxis has not only focused on maintaining minimum trough levels of factor VIII at 3% up to 5%<sup>1</sup>, which is important but also on preventing bleeding by normalizing thrombin generation in patients as an ideal goal. If the goal of hemostasis is to generate enough thrombin to form a stable clot, hemophilia results in reduced thrombin generation. Thrombin generation can be an accurate marker of patients' bleeding tendency<sup>2</sup>, which is highlighted with these new non-replacement factor therapies. For example, the impact of emicizumab on bleeding prophylaxis in hemophilia A (HA) with or without inhibitor is undeniable<sup>3</sup>. Emicizumab has represented a paradigm shift in prophylaxis and its definition. In the latest edition of the World Federation of Hemophilia (WFH) guidelines, prophylaxis is defined as "the administration of a hemostatic agent or agents to prevent bleeding"<sup>1</sup>, without specific reference to the administration of the deficient factor as in the second edition<sup>4</sup>. This has generated a debate between those who, like Collins et al.<sup>5</sup>, continue to consider prophylaxis with coagulation factor VIII (CF VIII) as the choice in hemophilia<sup>5</sup>, and others, like Parnes<sup>6</sup>, who argue that in light of the reported results with emicizumab, "its safety and efficacy profile are confirmed at the 2-year follow-up, and it should be considered the reference treatment for severe HA prophylaxis in patients with and without inhibitors."

Extended half-life (EHL) CF VIII concentrates for HA have represented an advance over standard half-life concentrates, without achieving the results reported, for example, for their counterparts in hemophilia B. EHL CF VIII concentrates achieve plasma half-life extensions no more than 1.5-1.6 times vs the comparator, given the limitation imposed by the binding to von Willebrand factor (vWF), which transports FVIII in the blood, stabilizing it and preventing its rapid degradation. Additionally, reductions in the number of infusions, except for rare cases and depending on the products and patients, did not go beyond 30%, which allows reducing the treatment burden, but less than desirable<sup>7</sup>.

On the other hand, pegylated products do not have the approval of the European Medicines Agency for use in patients  $\leq 12$  years of age. While they achieved a reduction in the annualized bleeding rate (ABR) in prophylaxis, these range from 2 to 6 per year<sup>7</sup>, depending on the product. From the immunogenicity point of view, the results of 4<sup>th</sup> generation products obtained from a human cell line, such as efmoroctocog alfa, in previously untreated patients (PUP)<sup>8</sup>, show a high-titer inhibitor incidence of 15.6%, which is similar to the one found with plasma-derived products in the SIPPET study (18.6%)<sup>9</sup> and the lowest ever reported with recombinant products, comparable to simoctocog alfa.

## Efanesoctocog alfa: structure and clinical development

Regarding CF VIII concentrates, in February 2023, the U.S. Food and Drug Administration approved efanesoctocog alfa<sup>10</sup>, inaugurating a new class of ultra-long half-life CF VIII concentrates, which, while does not avoid the need for IV administration, significantly reduces the treatment burden and, therefore, the disease burden. It is a B-domain-depleted recombinant CF VIII concentrates, obtained from the HEK203 human cell line, with 3 key changes that allow extending its plasma half-life<sup>11,12</sup>. The use of Fc-fusion technology of immunoglobulins, successfully used in efmoroctocog alfa, prevents its rapid intracellular degradation. It incorporates a recombinant D'D3 domain of vWF, covalently linked to Fc-FVIII, allowing it to circulate in the blood regardless of the patient's native vWF. Finally, it is linked to 2 X-TEN polypeptide chains: one inserted in the B domain of the native FVIII sequence and another one located between the Fc region and the D'D3 domain. These polypeptides have larger hydrodynamic volumes than other typical globular proteins of similar mass and alter the hydrodynamic radius of the Fc-fusion protein, decreasing clearance and degradation rates, thereby improving pharmacokinetic properties<sup>12</sup>.

The clinical development program for efanesoctocog alfa began in 2018 and included 5 completed studies, of which XTEND-1 that evaluated the safety and efficacy

of the product in previously treated patients (PTP) aged  $\geq 12$  years with HA diagnosis, and XTEND-Kids, in PTPs aged  $< 12$  years, were the phase 3 clinical trials which led to the product regulatory approval. Currently, in relation to HA, the XTEND-ed (NCT04644645) phase 3 extension study in pediatric and adult patients, and the FREEDOM study<sup>13</sup>, which aims to evaluate joint health and physical activity outcomes in severe HA patients (F8 level  $< 1$ ) on efanesoctocog alfa prophylaxis, are ongoing.

The XTEND-1 study included patients aged  $\geq 12$  years, with F8:C  $< 1\%$  or a documented genetic mutation consistent with severe HA and who had received prior CF VIII concentrates treatment, with a minimum of  $\geq 150$  exposure days (PTP). There were 2 groups of patients: group A came from previous CF VIII concentrates prophylaxis regimens, and group B were previously on-demand treated patients who must have had  $\geq 6$  hemorrhages within in the past 6 months or  $\geq 12$  within the past 12 months. The mean age at enrollment was 35.4 years, the median age at the start of the first prophylaxis was 1.0 years, and all but 1 patient were men<sup>12,14</sup>. Weekly prophylaxis with efanesoctocog alfa showed efficacy in preventing bleeds in PTPs with severe HA in the phase III XTEND-1 trial (NCT04161495)<sup>14</sup>. In group A, a total of 133 patients underwent weekly prophylaxis with efanesoctocog alfa (50 IU/kg) for 52 weeks, and in group B, 26 patients received on-demand treatment with the same product and dose for 26 weeks, followed by another 26 weeks of weekly prophylaxis with 50 IU/kg<sup>14</sup>. In group A, the median ABR was 0 (interquartile range [IQR], 0-1.04), with an estimated mean ABR of 0.71 (95% confidence interval [CI], 0.52-0.97); therefore, efanesoctocog was considered effective. A total of 65% of patients from group A (86 of 133) had no bleeds, 93% had between 0 and 2 bleeds, and 72% had no joint bleeds. 80% (107 of 133) had no spontaneous bleeds. A clinically significant variation in bleeding pattern was observed in patients in group A ( $n = 78$  evaluable), with a significant reduction in estimated mean ABR of 77% (from 2.96 to 0.69) (ABR ratio, 0.23; 95% CI, 0.13-0.42;  $p < 0.001$ ). The mean ABR from group B dropped from 21.42 down to 0.69 after switching from on-demand efanesoctocog alfa to prophylaxis<sup>14</sup>. Most bleeds (96.7% of 362 episodes), generally during on-demand treatment in group B, resolved with a single injection of efanesoctocog alfa (50 IU/kg)<sup>12,14</sup>. In 17 evaluable patients on weekly prophylaxis with 50 IU/kg, the steady-state F8 level was  $> 40\%$  (i.e., normal or near-normal activity) for a mean 4.1 days and 15.2% on day 7<sup>12,14</sup>. Additionally,

the area under the curve integrating real exposure and patient protection is much higher than other therapies, such as FVIII mimetics administered subcutaneously.

The XTEND-Kids pediatric trial (NCT04759131)<sup>15</sup> was presented in 2023 at the International Society on Thrombosis and Hemostasis congress held in Montreal, Canada. Its objective was to evaluate the safety, efficacy, and pharmacokinetics profile of efanesoctocog alfa in PTPs aged  $< 12$  years with severe HA. It included 74 boys (38  $< 6$  years and 36 aged 6 to  $< 12$  years) on a weekly prophylaxis regimen with 50 IU/kg efanesoctocog alfa for 52 weeks. No FVIII inhibitors were detected (0%; 95% CI, 0-4.9). The mean half-life was 40.2 hours, with a mean F8 level  $> 40\%$  for 3 days (vs. 4.1 days in adults and adolescents  $> 12$  years),  $> 15\%$  for approximately 5 days, and  $> 10\%$  for approximately 7 days (vs 15.2% in XTEND-1). The median ABR was 0 (IQR, 0-1.02), with a mean ABR of 0.89 (IQR, 0.56-1.42). Most bleeds resolved with a single 50 IU/kg dose, and the response to treatment was excellent or good in 98% of evaluated injections. Perioperative hemostasis was considered excellent in major surgeries performed, without relevant adverse events or treatment discontinuation. It was concluded that the product, in weekly prophylaxis, was well tolerated and provided protection against bleeds and highly effective treatment in children with severe HA, showing high and sustained FVIII activity at normal or near-normal levels ( $> 40\%$ ) for 3 days and around 10% on day 7, above the current trough levels recommended by WFH guidelines<sup>1</sup>. In pharmacokinetics terms, the only parameter that could alter efanesoctocog clearance in children appears to be body weight<sup>12</sup>. Regarding surgical procedures, due to its characteristics, it will allow major procedures without the need for continuous infusion.

## Discussion

The XTEND-1 trial results in the  $\geq 12$  years population are really interesting, demonstrating that weekly infusions of 50 IU/kg of efanesoctocog are associated with trough levels  $\geq 15\%$  on day 7. It has long been recognized that joint bleeds would not be expected in patients with a baseline factor level  $\geq 15\%$ , with joint bleed reductions to nearly zero<sup>16</sup> when factor levels are  $> 12\%$ . As reported by Wang et al.<sup>17</sup>, the main independent prognostic factor affecting joint mobility in these patients is factor activity, especially in those with levels  $< 10\%$ . These *a priori* objectives can be met with the concentrate in question. It goes without saying that the main factor affecting the quality of life of hemophilia

patients is the severity of joint deterioration<sup>18</sup>, hence the need to emphasize the excellent results and degree of protection observed in the XTEND-1 trial, with 72% of patients without hemarthrosis and 80% without spontaneous bleeds.

The good results reported in the XTEND-1 trial led some authors<sup>19</sup> to conduct an adjusted indirect comparison of treatment with efanesoctocog alfa or emicizumab for bleeding prophylaxis in adults and adolescents with severe HA without inhibitor, using the results of the HAVEN-3 trial<sup>20</sup> on bleeding prophylaxis with emicizumab in PTPs adults and children  $\geq 12$  years as a reference. In general, it is concluded that prophylaxis with efanesoctocog alfa demonstrated superiority over emicizumab, with significantly reduced rates of any bleeding, treated bleeding, or treated joint bleeding. No significant difference was noted in the rate of treated spontaneous bleeds. An improvement in HJHS (Hemophilia Joint Health Score) score is observed, which is associated with the normal or near-normal F8 levels achieved with efanesoctocog alfa and the larger area under the curve. According to the authors, the higher efficacy and improved pharmacokinetic properties would make efanesoctocog an important addition to the hemophilia therapeutic landscape.

In the  $\leq 12$  years pediatric population, the results are not far from those reported, for example, for emicizumab, although they are not comparable due to the study design and included population. In 2019, the results of the phase III HOHOEMI trial<sup>21</sup>, evaluating weekly ( $n = 6$ ) or biweekly ( $n = 7$ ) prophylaxis with emicizumab in pediatric patients, aged 4 months to 10 years, previously on CF VIII concentrates prophylaxis (except the 4-month-old patient), over a 24-week period were presented. Two out of 6 and 5 out of 7 patients did not experience any treated bleeds, and the treated bleed ABRs were 1.3 (95% CI, 0.6-2.9) and 0.7 (95% CI, 0.6-2.9), respectively.

The interim analysis of the AOZORA trial<sup>22</sup> has been recently published. This study includes patients  $< 12$  years with severe HA without inhibitor who had either not previously received emicizumab or participated in the HOHOEMI study<sup>21</sup>. The study is expected to last 6 years from inclusion. The treated and treated joint bleed ABRs are evaluated. At 3 years, there is a reduction in the mean treated bleed ABR after starting emicizumab, from 3.7 (95% CI, 0.94-9.80) down to 0.7 (95% CI, 0.1-5.10); for treated joint bleeds, the ABR decreases from 0.4 (95% CI, 0.00-4.55) down to 0.2 (95% CI, 0-4.04).

The real-life experience reported by the PedNet group<sup>23</sup> included a total of 251 children (median age at

treatment initiation: 6.1 years; IQR, 2.1-12), 63% of whom had no anti-FVIII inhibitor. A total of 94% had severe HA, and 76% were  $< 12$  years old at emicizumab treatment initiation. The median follow-up time before emicizumab was 1.51 years and with emicizumab, 1.23 years. During emicizumab prophylaxis, a reduction in the mean ABR from 2.8 down to 1.1 ( $p < 0.001$ ) and joint bleeding from 0.8 down to 0.3 ( $p < 0.001$ ) is observed. Therefore, no significant differences are seen in the reported mean ABR results: 0.89 in XTEND-Kids and 1.1 in PedNet with emicizumab.

Regarding inhibitor development, no FVIII inhibitor antibodies were detected in the efanesoctocog alfa clinical program, even in patients  $< 12$  years in XTEND-Kids<sup>12,14,15</sup>. Transient antibodies against the drug were detected in 2.2% of patients (4/277) during treatment (up to 49.64 weeks) in clinical studies, without impacting FVIII activity-time profiles, pharmacokinetic parameters, bleeding, or pharmacodynamic response<sup>12,14</sup>. In any case, product switching is not considered a risk factor for developing anti-FVIII antibodies<sup>24</sup>, and the overall de novo inhibitor incidence in PTPs with HA is as low as 3 per 1000 person-years<sup>25</sup>.

For the final efanesoctocog molecule, amino acid sequences with potential to bind to type II major histocompatibility complex (MHC) receptors were modified. The R1680 site (both wild-type and mutated) had potential to bind to MHC, so 9 amino acid residues from the B domain were removed, generating a final molecule with only 5 amino acids from this domain (SFSQN) to reduce the immunogenic risk. Efanesoctocog has endogenous protein domains (D'D3 and Fc) to which people have shown good tolerance and a FVIII sequence, which is similar to other rFVIII products<sup>26</sup>. The XTEN polymers are created as non-immunogenic polypeptides formed by 6 hydrophilic and chemically stable amino acids (A, E, G, P, S, and T). They have been used to extend the half-life of various peptide and protein-based therapies. To date, clinical data suggest that their immunogenicity in humans is very low or null<sup>27</sup>.

Regarding the inconvenience of IV product administration, sometimes requiring the placement of an intravascular device like a Port-a-Cath, the weekly regimen could almost completely resolve it, as reported in the literature. A Swedish study<sup>28</sup> concluded that age at prophylaxis initiation was an independent predictive factor for developing arthropathy, being more important than the regimen. Assuming early prophylaxis initiation (before age 2 or before the first hemarthrosis), regimens could be individualized to reduce venous access problems at the start of prophylaxis at a very young

age<sup>29</sup>, which is an approach reinforced with the advent of EHL-CF VIII concentrates. The original goal of starting prophylaxis with a weekly infusion was to “train the vein” and avoid the use of an intravascular device. Stepped regimens reduced intravascular device use from 88% down to 27% and achieved better acceptance of CF VIII concentrates prophylaxis, with its associated burden, by both parents and caregivers. In the PedNet publication<sup>30</sup>, it is reported that weekly CF VIII concentrates prophylaxis was the most common form of initiation, increasing from 49% of children from 2000 through 2009 up to 68% from 2010 through 2019, and at an earlier age (median, 13.1 vs. 17.6 months). Additionally, FVIII doses were reduced, from a mean of 43.5 IU/kg (IQR, 34.6-49.0) down to 30.9 IU/kg (IQR, 26.3-46.3). After 2010, a total of 60% of severe HA patients started prophylaxis before experiencing any bleeding, except for sporadic cases diagnosed significantly later (median, 8.3 months; IQR, 3.7-11.9) who also had more bleeding before prophylaxis initiation<sup>30</sup>. Weekly prophylaxis is the most common initiation form (68%), and there is a trend to start it at an earlier age (13.1 months). Efanesoctocog will likely facilitate this earlier initiation than reflected in the PedNet publication<sup>30</sup>. Prophylaxis could be complete, weekly, without the need for an intravascular device, improving its tolerability and efficacy. More studies are needed to corroborate this hypothesis, as body weight may alter efanesoctocog alfa clearance in children<sup>12</sup>.

For the lack of studies evaluating the safety and efficacy profile in PUP, especially in those < 12 months of age, it is not possible to make indirect comparisons with emicizumab as done in adults. The HAVEN 7 study<sup>31</sup> results on emicizumab prophylaxis safety and efficacy in children < 12 months are very good, with an intracerebral hemorrhage incidence rate of 0 in 56 patients. A 2017 PedNet publication<sup>32</sup> on the incidence rate of intracerebral hemorrhages in children and adolescents with severe hemophilia A or B reported that, for children aged 0 to 12 months on complete prophylaxis (i.e., 3 times/week) on CF VIII concentrates, the intracerebral hemorrhage incidence rate was 0, the same as for the partial prophylaxis group, estimating a risk of intracerebral hemorrhage for the former of 0.00033/child-year, almost nil. Efanesoctocog will likely change the concept of complete prophylaxis, *a priori*, to a weekly infusion, and the intracerebral hemorrhage risk will remain the same or even lower. At a time when there is controversy on whether tolerate FVIII<sup>33,34</sup>, efanesoctocog could address both issues: tolerization and bleeding protection; moreover,

prophylaxis would be “more physiological,” replenishing the deficient protein.

Efanesoctocog alfa inaugurates a new class of ultra-long plasma life CF VIII concentrates, bridging the physiological limitation that vWF imposed on extending the plasma half-life of these agents. This, along with the safety and efficacy profile demonstrated in the XTEND clinical trials, suggests that CF VIII concentrates prophylaxis may likely resume its leading role by allowing thrombin generation to be normalized or near-normalized physiologically. More studies are needed to evaluate the safety and efficacy profile in other scenarios, such as PUP, and in preventing intracranial hemorrhage at an early age. However, it represents a therapeutic opportunity and a significant step toward mental and physical liberation from hemophilia and its treatment<sup>35</sup>.

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## Conflicts of interest

None declared.

## Ethical considerations

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

## References

1. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe WS, et al. WFH Guidelines for the Management of Hemophilia, 3<sup>rd</sup> edition. *Haemophilia*. 2020;26(Suppl 6):1-158.
2. Sidonio RF, Hoffman M, Kenet G, Dargaud Y. Thrombin generation and implications for hemophilia therapies: a narrative review. *Res Pract Thromb Haemost*. 2022;7:100018.
3. Callaghan MU, Negrier C, Paz-Priel I, Chang T, Chebon S, Lehle M, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. *Blood*. 2021;137:2231-42.
4. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1-47.
5. Collins PW, Obaji SG, Roberts H, Gorsani D, Rayment R. Clinical phenotype of severe and moderate haemophilia: who should receive prophylaxis and what is the target trough level? *Haemophilia*. 2021;27:192-8.

6. Parnes A. In hemophilia, it just keeps getting better. *Blood*. 2021;137:2135-6.
7. Young G. Nonfactor therapies for hemophilia. *Hemasphere*. 2023;7:e911.
8. Konigs C, Ozelo MC, Dunn A, Kulkarni R, Nolan B, Brown S, et al. First study of extended half-life rFVIIIc in previously untreated patients with hemophilia A: PUPs A-LONG final results. *Blood*. 2022;139:3699-707.
9. Peyvandi F, Cannavò A, Garagiola I, Palla R, Manucci PM, Rosendaal FR, et al. Timing and severity of inhibitor development in recombinant versus plasma-derived factor VIII concentrates: a SIPPET analysis. *J Thromb Haemost*. 2018;16:39-43.
10. Altuviiiio. Ficha técnica. Disponible en: [altuviiiio-prescribing-information.pdf](https://www.altuviiiio.com/prescribing-information.pdf).
11. Seth Chhabra E, Liu T, Kulman J, Patarroyo-White S, Yang B, Lu QJ, 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;135:1484-96.
12. Bioverativ Therapeutics Inc. Efanesoctocog alfa [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl]: US prescribing information. 2023. (Consultado el 7 de marzo de 2023.) Disponible en: <https://www.altuviiiio.com/>.
13. A Study Evaluating Physical Activity and Joint Health in Severe Haemophilia A Patients ≥12 Years Treated Once Weekly With Efanesoctocog Alfa (FREEDOM) ClinicalTrials.gov ID NCT05817812; disponible en: <https://clinicaltrials.gov/study/NCT05817812>
14. von Drygalski A, Chowdary P, Kulkarni R, Susen S, Konkle BA, Oldenburg J, et al. Efanesoctocog alfa prophylaxis for patients with severe hemophilia A. *N Engl J Med*. 2023;388:310-8.
15. Malec L, Peyvandi F, Chan A, Koenigs C, Zulfikar B, Yuan H, et al. Efanesoctocog alfa prophylaxis for previously treated patients <12 years of age with severe hemophilia A. *Res Pract Thromb Haemost*. 2023;7(Suppl 2):1-290.
16. Den Uijl IEM, Fischer K, van der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. *Haemophilia*. 2011;17:41-4.
17. Wang M, Recht M, Iyer NN, Cooper D, Soucie JM. Hemophilia without prophylaxis: assessment of joint range of motion and factor activity. *Res Pract Thromb Haemost*. 2020;4:1035-45.
18. Coppola A, Cerbone AM, Mancuso G, Mansueto MF, Mazzini C, Zanon E. Confronting the psychological burden of haemophilia. *Haemophilia*. 2011;17:21-7.
19. Álvarez Román MT, Kragh N, Guyot P, Wilson A, Wojciechowski P, Margas W, 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. ISTH Congress, Montreal, 2023; PB0195. Presented at ISTH Congress 24-28 June 2023 Montréal. Access available: <https://isth2023.eventscribe.net/fsPopup.asp?PresentationID=1255728&mode=presInfo>
20. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379:811-22.
21. Shima M, Nogami K, Nagami S, Yoshida S, Yoneyama K, Ishiguro A, et al. A multicentre, open-label study of emicizumab given every 2 or 4 weeks in children with severe haemophilia A without inhibitors. *Haemophilia*. 2019;25:979-87.
22. Shima M, Takedani H, Kitsukawa K, Taki M, Ishiguro A, Nagae C, et al. Three-year interim analysis results of the AOZORA study to evaluate the long-term safety and joint health in children with hemophilia A without factor VIII inhibitors receiving emicizumab. *Blood*. 2023;142:3991-2.
23. Van der Zwet K, Marloes de Kovel, Motwani J, Van Geet C, Nolan B, Glosli H, et al. The emicizumab switch: real-world data of 251 pediatric patients from the Pednet Registry. *Blood*. 2022;140(Suppl 1):8442-3.
24. Hay C, Palmer B, Chalmers E, Liesner RJ, Maclean R, Rangarajan S; United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Incidence of factor VIII inhibitors throughout life in severe hemophilia A in the United Kingdom. *Blood*. 2011;117:6367-70.
25. Xi M, Makris M, Marcucci M, Santagostino E, Mannucci PM, Iorio A. Inhibitor development in previously treated hemophilia A patients: a systematic review, meta-analysis and meta-regression. *J Thromb Haemost*. 2013;11:1655-62.
26. Seth Chhabra E, Liu T, Kulman J, Patarroyo-White S, Yang B, Lu Q, 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;135:1484-96.
27. Podust VN, Balan S, Sim BC, Coyle MP, Ernst U, Peters RT, et al. Extension of in vivo half-life of biologically active molecules by XTEN protein polymers. *J Control Release*. 2016;240:52-66.
28. Astermark J, Petrini P, Tengborn L, Schulman S, Ljung R, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. *Br J Haematol*. 1999;105:1109-13.
29. Coppola A, Franchini M. Target of prophylaxis in severe haemophilia: more than factor levels. *Blood Transfus*. 2013;11:327-9.
30. Ljung R, de Kovel M, van den Berg HM; PedNet study group. Primary prophylaxis in children with severe haemophilia A and B – Implementation over the last 20 years as illustrated in real-world data in the PedNet cohorts. *Haemophilia*. 2023;29:498-504.
31. Pipe SW, Collins P, Dhalluin C, Kenet G, Schmitt G, Buri M, et al. Emicizumab prophylaxis in infants with hemophilia A (HAVEN 7): primary analysis of a phase 3b, open-label trial. *Blood*. 2024;143:1355-64.
32. Andersson NG, Auerswald G, Barnes C, Carcao M, Dunn AL, Fijnvandraat K, et al. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B – the impact of prophylactic treatment. *Br J Haematol*. 2017;179:298-307.
33. López M, Vázquez RJN, Román MTA. FVIII tolerance in the emicizumab era: why yes? *Hematol Transfus Int*. 2024;12:19-20.
34. Ranta S, Motwani J, Blatny J, Bühlren M, Carcao M, Chambost H, et al. Dilemmas on emicizumab in children with haemophilia A: a survey of strategies from PedNet centres. *Haemophilia*. 2023;29:1291-8.
35. Hermans C, Pierce GF. Ultra-long FVIII: a major step forward to a hemophilia-free mind. *J Thromb Haemost*. 2024 Apr 27;S1538-7836(24)00228-9. doi: 10.1016/j.jtha.2024.04.010. Online ahead of print.