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ORIGINAL RESEARCH

Efanesoctocog Alfa versus Standard and Extended Half-Life Factor VIII Prophylaxis in Adolescent and Adult Patients with Haemophilia A without Inhibitors

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ABSTRACT

Introduction: In the Phase 3 XTEND-1 trial, (NCT04161495) efanesoctocog alfa prophylaxis provided superior bleed protection versus pre-study factor VIII (FVIII) replacement therapy in patients with severe haemophilia A. The aim of this study was to indirectly compare bleed outcomes between efanesoctocog alfa and standard/extended half-life (SHL and EHL) FVIII replacement therapies in adolescent and adult patients with severe haemophilia A without inhibitors.

Methods: A systematic literature review was conducted to identify Phase 3 trials of EHL and SHL FVIII replacement therapies for comparison with efanesoctocog alfa data from XTEND-1. Matching-adjusted indirect comparisons were used to compare annualised bleeding rates (ABRs) for any, treated, joint, and spontaneous bleeds between efanesoctocog alfa and comparators. The estimates from respective comparisons were pooled using random-effect meta-analyses to evaluate the overall difference between efanesoctocog alfa and comparator therapies.

Results: Four EHL therapies (rurioctocog alfa pegol, efmoroctocog alfa, turoctocog alfa pegol, damoctocog alfa pegol) and two octocog alfa SHL therapies were included. In meta-analyses, efanesoctocog alfa was associated

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with significantly lower ABRs for any [mean difference (95% CI) – 2.24 (– 3.24; – 1.25)], spontaneous [– 1.52 (– 2.33; – 0.72)], and joint bleeds [– 1.60 (– 2.32; – 0.88)] versus EHL therapies, and with significantly lower ABRs for any [– 3.61 (– 4.43; – 2.79)], treated [– 1.55 (– 1.89; – 1.20)], spontaneous [– 2.52 (– 3.31; – 1.72)], and joint bleeds [– 3.42 (– 4.77; – 2.08)] versus SHL therapies.
***Conclusion*:** Efanesoctocog alfa was associated with significantly lower ABRs (any, spontaneous and joint) compared with EHL or SHL prophylaxis therapies. Patients had, on average, 2.2 and 3.6 fewer bleeds per year versus EHL and SHL therapies, respectively.

PLAIN LANGUAGE SUMMARY

Factor VIII (FVIII) replacement therapies to prevent bleeding in people with haemophilia A are either standard half-life (SHL) or extended half-life (EHL), and injections may be given two to four times per week. Efanesoctocog alfa is a new FVIII replacement therapy, which only requires a once-weekly injection. In the XTEND-1 clinical trial, people receiving efanesoctocog alfa had fewer bleeds than they did before the trial when they were receiving a different FVIII replacement therapy. However, efanesoctocog alfa has not been compared with available SHL and EHL therapies. Researchers searched medical journals to identify clinical trials of SHL and EHL. They compared the number of bleeds with efanesoctocog alfa in the XTEND-1 trial with each SHL or EHL trial found in the literature search. The results were combined and analysed to find the overall difference between the results with efanesoctocog alfa and each other type of therapy. Compared with SHL and EHL therapy, once-weekly efanesoctocog alfa therapy reduced the rates of any bleeds, including spontaneous (that happen for no apparent reason) and joint bleeds. Overall, people who received efanesoctocog alfa had, on average, 3.6 fewer bleeds per year than those on SHL therapy and 2.2 fewer bleeds per year than those on EHL therapy. As well as reducing the number of injections needed per week, efanesoctocog alfa may work better at preventing bleeds than current SHL or EHL FVIII replacement therapies. This could have a large impact on the lives of people with severe haemophilia A.

Keywords: Annualised bleeding rate; Efanesoctocog alfa; Factor VIII replacement therapies; Haemophilia A; Indirect treatment comparison

Key Summary Points

Why carry out this study?

Several standard and extended half-life (SHL and EHL) factor VIII (FVIII) replacement therapies have been approved for the treatment of haemophilia. However, many of these are associated with significant burden given their frequent administrations, and bleeding into soft tissues and joints can still occur.

This study indirectly compared the efficacy of efanesoctocog alfa and approved standard/extended half-life (SHL and EHL) FVIII replacement therapies in adolescent and adult patients with severe haemophilia A without inhibitors.

What was learned from this study?

Once-weekly prophylaxis with efanesoctocog alfa high-sustained FVIII therapy was associated with superior efficacy over SHL and EHL FVIII replacement therapies, with significantly reduced rates of any bleeds, including spontaneous and joint bleeds.

In line with the higher FVIII activity levels and the longer half-life relative to SHL and EHL therapies, efanesoctocog alfa can provide meaningful improvements in the treatment landscape for haemophilia A.

INTRODUCTION

Haemophilia A is a genetic disorder characterised by deficient or dysfunctional clotting factor VIII (FVIII) [1]. Prophylaxis with plasma-derived

or recombinant FVIII replacement therapy is recommended to prevent bleeding and chronic arthropathy in patients with severe haemophilia A [2]. Several standard and extended half-life (SHL and EHL) FVIII replacement therapies have been approved for the treatment of haemophilia [3]. However, while FVIII replacement therapies are effective, many are associated with significant burden given their frequent administrations [4], and bleeding into soft tissues and joints can still occur [5–7]. Previously, a trough factor level of 1 IU/dL (1%) was deemed an adequate goal, but there is now a recognition in the medical community that higher factor levels (> 3%) are needed to optimally reduce the risk of bleeds. However, achieving these levels would require higher doses or more frequent infusions of currently available clotting factor concentrates [2].

Efanesoctocog alfa (ALTUVIIIO®) is a first-in-class FVIII replacement therapy, uniquely designed to provide high sustained factor levels for longer by overcoming the von Willebrand factor-imposed half-life ceiling [8–10]. Once-weekly efanesoctocog alfa was approved in February 2023 by the United States Food and Drug Administration for adults and children with haemophilia A, based on results of the pivotal Phase 3 XTEND-1 trial (NCT4161495) and interim data from the Phase 3 XTEND-Kids trial (NCT04759131) [11–13]. The European Medicines Agency accepted the marketing authorisation application for efanesoctocog alfa in May 2023 [14]. XTEND-1 was a non-randomised trial in which patients who had previously received FVIII prophylaxis were allocated to receive efanesoctocog alfa prophylaxis for 52 weeks (Arm A), and those who had previously received on-demand treatment received on-demand efanesoctocog alfa for 26 weeks, followed by efanesoctocog alfa prophylaxis for 26 weeks (Arm B) [13]. Efanesoctocog alfa was well tolerated and provided highly effective prevention against bleeds, with a decrease in mean annualised bleeding rate (ABR) from 2.96 [95% confidence interval (CI) 2.00; 4.37] to 0.69 (95% CI 0.43; 1.11), demonstrating superiority over pre-study FVIII prophylaxis ($P < 0.001$) [13]. Significant improvements in physical health, pain intensity and joint health were also reported with efanesoctocog alfa [13]. In XTEND-1, switching from prior standard-of-care prophylaxis (56.4% SHL, 43.6% EHL) to efanesoctocog alfa resulted in a reduction in the number of weekly injections and mean factor consumption [15]. Significantly lower overall, joint, spontaneous, and spontaneous joint ABRs were observed, and the proportion of participants with zero bleeds increased from 42.3% to 64.1% [15].

While existing data support the use of efanesoctocog alfa as an effective option in haemophilia A, there are currently no head-to-head clinical trials directly comparing the efficacy of existing prophylaxis therapies. Indirect treatment comparisons (ITCs) can be used to compare treatment effects across trials with no common comparator arms, and may be used to help inform clinical decision making. The objective of this research was to compare efficacy outcomes between efanesoctocog alfa and approved SHL and EHL FVIII replacement therapies in adolescent and adult patients with severe haemophilia A without inhibitors.

METHODS

Literature Search and Study Selection

A systematic literature review (SLR) was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify Phase 3 clinical trials of FVIII replacement therapies and non-factor replacement therapies in patients with haemophilia A. This report focuses only on trials of efanesoctocog alfa and full-length FVIII SHL and EHL therapies identified in the SLR; results of non-factor therapies are presented elsewhere [16]. Details of the SLR are presented in the Supplementary Material.

Nine trials for six FVIII comparators met the inclusion criteria and were included in the analysis (Table 1). Two SHL therapies were identified: octocog alfa (Advate®; Tarantino 2004 [17] and Valentino 2012 [18]), and octocog alfa (Kovaltry®; and LEOPOLD I [19] and LEOPOLD II [20]). These were the two most prescribed full-length FVIII SHL therapies in the United States

Table 1 Trials and regimens included in analysis

Trial	Product	Dosing frequency	Study arms	Included patients
High sustained FVIII				
XTEND-1 [13]	Efanesoctocog alfa (ALTUVIIIO®)	Q1W	Arms A (n = 133) and B (n = 26) as relevant to match	≥ 12 years; previous prophylaxis (Arm A) or on-demand treatment (Arm B)
Standard half-life (SHL)				
Valentino 2012 [18]	Octocog alfa (Advate®)[a]	Q2D	Standard prophylaxis arm (n = 32)	> 7–64 years; previous on-demand treatment
		Q3D	PK-driven prophylaxis arm (n = 34)	
LEOPOLD I [19]	Octocog alfa (Kovaltry®)	BIW/ TIW	Prophylaxis (n = 62)	12–65 years; previous prophylaxis or on-demand treatment
LEOPOLD II [20]	Octocog alfa (Kovaltry®)	BIW	BIW arm (n = 28)	12–65 years; previous on-demand treatment
		TIW	TIW arm (n = 31)	
Extended half-life (EHL)				
PROLONG-ATE [21]	Rurioctocog alfa pegol (Adynovate®)	BIW	Prophylaxis (n = 120)	12–65 years; previous prophylaxis or on-demand treatment
PROPEL [22]	Rurioctocog alfa pegol (Adynovate®)	Variable	Target FVIII 1–3% (n = 57)	12–65 years; previous prophylaxis or on-demand treatment
		Variable	Target FVIII 8–12% (n = 58)	
A-LONG [23–25]	Efmoroctocog alfa (Eloctate®/Elocta®)	BIW	Individual prophylaxis (n = 118)	≥ 12 years; previous prophylaxis or on-demand treatment
PATHFINDER 2 [26, 27]	Turoctocog alfa pegol (Esperoct®)	Q4D	Prophylaxis (n = 175)	≥ 12 years; previous prophylaxis or on-demand treatment

Table 1 continued

Trial	Product	Dosing frequency	Study arms	Included patients
PROTECT VIII [28]	Damoctocog alfa pegol (Jivi®)	BIW	BIW, > 1 breakthrough bleed[b] (*n* = 13)	12–65 years; previous prophylaxis or on-demand treatment
		BIW	BIW, ≤ 1 breakthrough bleed[b] (*n* = 11)	12–65 years; previous prophylaxis or on-demand treatment
		BIW	BIW, pooled (*n* = 24)	12–65 years; previous prophylaxis or on-demand treatment
		Q5D	Q5D arm, ≤ 1 breakthrough bleed[b] (*n* = 43)	12–65 years; previous prophylaxis or on-demand treatment
		Q7D	Q7D arm, ≤ 1 breakthrough bleed[b] (*n* = 43)	12–65 years; previous prophylaxis or on-demand treatment

[a]An additional study, Tarantino et al. 2004, was identified; the publication did not contain sufficient detail to be included in the analysis

[b]Joint or muscle bleeds and no identified trauma during 10-week run-in period on BIW regimen

BIW twice weekly, *FVIII* clotting factor VIII, *PK* pharmacokinetic, *Q2D* every 2 days, *Q3D* every 3 days, *Q4D* every 4 days, *Q5D* every 5 days, *Q7D* every 7 days, *Q1W* once-weekly, *TIW* three times weekly

at the time of the analysis and deemed representative; other SHL therapies were available but were not included in the SLR as most SHLs are deemed to be generally equivalent in efficacy. The Tarantino 2004 study met inclusion criteria [17]; however, the publication did not contain sufficient detail to be included in the analysis. All four EHL therapies available in the United States were included: rurioctocog alfa pegol (Adynovi/Adynovate®; PROLONG-ATE [21] and PROPEL [22]); efmoroctocog alfa (Elocta/Eloctate®; A-LONG [23–25]); turoctocog alfa pegol (Esperoct®; PATHFINDER 2 [26, 27]); and damoctocog alfa pegol (Jivi®; PROTECT VIII [28]).

Characteristics for Comparator Trials are Presented in the Supplementary Material, Table S1

This is a post hoc analysis and modelling of data already collected and/or published data. Original studies were all approved by the relevant institutional review boards at each study site and were carried out in accordance with the International Conference on Harmonisation good clinical practice guidelines and the Declaration of Helsinki.

Efficacy Outcomes

For the included studies, information on study design and data on all available baseline characteristics and outcomes of interest were extracted from the selected treatment arms. Outcomes of interest assessed included: ABRs (any, treated, joint, spontaneous) and the proportion of patients with zero bleeds (any, treated, joint, spontaneous). The definition or calculation of treated and any bleed may have differed between trials; however, all efforts were made to identify the exact definition of each for proper classification. Where a classification was unclear, the conservative assumption was made that bleed rates reported in comparator arms referred to any bleed. Definitions for bleed outcomes are presented in the Supplementary

Material, Table S2. Outcomes assessed in each trial were summarised for patients with prior on-demand regimens and for a mixed population of patients with prior prophylaxis and/or on-demand regimen (Supplementary Material, Tables S3 and S4, respectively).

The primary outcome of XTEND-1 trial was assessed at 52 weeks, which was similar to four other studies (LEOPOLD I, LEOPOLD II, A-LONG, and Valentino 2012) that had efficacy periods of around 1 year. In the PATHFINDER 2 trial, the mean duration of treatment was almost 43 weeks (range 1–84 weeks). In three studies, the efficacy duration was shorter compared with XTEND-1 [PROLONG-ATE (24 ± 2 weeks for the prophylaxis arm); PROPEL (24 weeks); PROTECT VIII (10-week run-in period followed by randomisation to prophylaxis arms for 10–36 weeks)]. The estimated ABR for any bleed observed in Arm A of XTEND-1 at 26 weeks was non-significantly higher than that for the full treatment period of 52 weeks; therefore, the ITC used the ABRs from the 52-week time point for all comparisons, based on the assumption that treatment effect is constant over time [29]. All comparisons were based on ABRs, rather than absolute numbers of bleeds over a specific time period. The comparison of the proportion of patients without bleeds during follow-up was not attempted between XTEND-1 and comparator trials except the A-LONG trial, due to different observation periods.

Matching-Adjusted Indirect Comparison (MAIC)

As recommended in NICE TSD 18 guidelines, unanchored MAIC was used to compare efanesoctocog alfa and interventions assessed in disconnected studies and control for population differences [30]. For each comparator trial, the baseline range for age and/or body weight and/or prior bleeds was applied to patients in XTEND-1, prior to inclusion in the MAIC. Participants in XTEND-1 with age and/or body weight and/or prior bleeds outside the ranges reported in the corresponding comparator cohorts were excluded from the analysis (Supplementary Material, Table S5). Further details on the MAIC methodology are in the Supplementary Material.

Statistical Analysis

For consistency, the new effects were estimated using the same statistical methods as adopted in the comparator trial; therefore, ABRs were calculated using either arithmetic mean or using regression analysis such as negative binomial regression models. For SHL therapies, results were analysed as mean number of bleeds per year and the between-treatment effects as mean difference (MD; 95% CI) of annual number of bleeds. For EHL therapies, results were presented as MD (95% CI) of annual number of bleeds or incidence rate ratios (IRRs; 95% CI).

Estimated effects from each study comparison were pooled using random-effect meta-analyses to evaluate the overall difference between bleed outcomes in efanesoctocog alfa and comparator trials. Availability of individual patient data from the A-LONG trial allowed for bleed rate comparison between efanesoctocog alfa and efmoroctocog alfa using a negative-binomial regression model (main scenario) and an MD model, thus the comparison can be used in meta-analysis for both scenarios (ABR [IRR] and ABR [MD]). All statistical analyses and meta-analyses were conducted using the R statistical software version 4.2.1® Core Team, Vienna, Austria) [31].

RESULTS

Patient Populations

Baseline characteristics of the included XTEND-1 participants (pooled arms or individual arms) were adequately matched to aggregated data from each comparator study, so that there were no differences between populations on these baseline characteristics. Baseline characteristics before and after matching are presented in the Supplementary Material, Tables S6–S11; the effective sample size (ESS) of the XTEND-1 population after matching is shown for each comparison.

SHL Therapies

The trial arms used for comparisons between efanesoctocog alfa and the two SHL comparators, octocog alfa (Advate) and octocog alfa (Kovaltry), are shown in Table 1.

Efanesoctocog alfa was associated with a significantly lower frequency of any bleeds (treated and untreated) compared with both octocog alfa (Advate) regimens in the Valentino 2012 trial (Table 2) [18–28]. Efanesoctocog alfa was also associated with a significantly lower frequency of any, spontaneous, and joint bleeds versus all three octocog alfa (Kovaltry) regimens in the LEOPOLD I and LEOPOLD II trials (Table 2).

EHL Therapies

The trial arms used for comparisons between efanesoctocog alfa and the four EHL comparators, rurioctocog alfa pegol, turoctocog alfa pegol, damoctocog alfa pegol, and efmoroctocog alfa, are shown in Table 1.

A significantly lower frequency of any (treated and untreated), spontaneous, and joint bleeds was associated with efanesoctocog alfa compared with twice-weekly rurioctocog alfa pegol in the PROLONG-ATE trial, and in the regimen targeting FVIII level of 1 to 3% in the PROPEL trial (Table 2). Efanesoctocog alfa was also associated with a non-statistically significant lower mean frequency of bleeds versus rurioctocog alfa pegol targeting serum FVIII level of 8–12% in PROPEL (Table 2). Efanesoctocog alfa was associated with a significantly lower rate of any bleeds and lower frequency of any treated bleeds, spontaneous treated bleeds, and joint treated bleeds compared with turoctocog alfa pegol every 4 days in the PATHFINDER 2 trial (Table 2). Compared with all damoctocog alfa pegol regimens in PROTECT VIII, efanesoctocog alfa was associated with a significantly lower mean ABR for any bleeds, spontaneous bleeds, and joint bleeds (Table 2).

Efanesoctocog was associated with a significantly lower incidence of any, spontaneous, and joint treated bleeds compared with individualised efmoroctocog alfa prophylaxis in the A-LONG trial (Table 2). The proportion of patients with zero bleeds was significantly higher for efanesoctocog alfa versus efmoroctocog alfa for any treated bleeds [odds ratio (OR): 1.99 (95% CI 1.20; 3.30)), spontaneous treated bleeds [OR: 2.06 (95% CI 1.21; 3.52)], and joint treated bleeds [OR: 1.73 (95% CI 1.12; 2.67)].

Meta-Analyses of SHL and EHL Therapies

The individual estimates for the comparisons between efanesoctocog alfa and SHL or EHL therapies were pooled using random-effects model meta-analyses to obtain common estimates for each comparison (Fig. 1). Compared with SHL therapies [octocog alfa (Advate) and octocog alfa (Kovaltry)], efanesoctocog alfa was associated with significantly lower frequencies of any (treated and untreated), spontaneous, and joint bleeds (Fig. 1). Compared with EHL therapies (rurioctocog alfa pegol, turoctocog alfa pegol, damoctocog alfa pegol, and efmoroctocog alfa), efanesoctocog alfa was associated with significantly lower frequencies of any, spontaneous, and joint bleeds (Fig. 1). The rate of any bleeds was significantly reduced by 77% in those receiving efanesoctocog alfa compared with EHL therapies (Fig. 2). Summary results of the meta-analyses are presented in the Supplementary Material, Tables S12 and S13.

DISCUSSION

The present analysis compared the efficacy of efanesoctocog alfa, a first-in-class, high-sustained FVIII therapy, with available SHL and EHL FVIII replacement therapies. As a result of the absence of direct comparisons in head-to-head clinical trials, the comparative efficacy of efanesoctocog alfa prophylaxis and other FVIII replacement therapies was assessed using MAICs. The findings from these analyses demonstrate that once-weekly efanesoctocog alfa prophylaxis, as assessed in XTEND-1, was associated with improved bleed prevention compared with SHLs and EHLs.

The frequency of any (treated and untreated), any treated, spontaneous, and joint bleeds was

Table 2 Summary of the results for the comparison between efanesoctocog alfa and FVIII factor comparators

Study, arm	ABR (MD) (95% CI)		ABR (IRR) (95% CI)	AsBR (MD) (95% CI)	AjBR (MD) (95% CI)
	All	Treated			
Comparison with SHL					
Efanesoctog alfa versus Octocog alfa (Advate®)					
Valentino 2012 [18], Q2D (standard prophylaxis arm)	**– 2.89 (– 4.91; – 0.87)**	**– 1.35 (– 1.81; – 0.89)**	N/A	N/A	N/A
Valentino 2012 [18], Q3D (PK-driven PPX arm)	**– 3.99 (– 5.72; – 2.26)**	**– 1.70 (– 2.08; – 1.32)**	N/A	N/A	N/A
Efanesoctog alfa versus Octocog alfa (Kovaltry®)					
LEOPOLD I [19], Arms A and B	**– 2.97 (– 4.28; – 1.67)**		N/A	**– 2.23 (– 3.10; – 1.35)**	**– 2.67 (– 3.85; – 1.49)**
LEOPOLD II [20], BIW (Arm B)	**– 5.70 (– 8.37; – 3.03)**		N/A	**– 4.52 (– 7.14; – 1.90)**	**– 5.16 (– 7.72; – 2.60)**
LEOPOLD II [20], TIW (Arm C)	**– 4.30 (– 6.59; – 2.01)**		N/A	**– 2.62 (– 4.34; – 0.90)**	**– 3.53 (– 5.69; – 1.37)**
Comparison with EHL					
Efanesoctog alfa versus Rurioctocog alfa pegol (Adynovate®)					
PROLONG-ATE [21] BIW (SAS)	N/A		**0.20[a] (0.12; 0.31)**	N/A	N/A
PROLONG-ATE [21] BIW (PPAS)	**– 2.89[a] (– 3.82; – 1.96)**		N/A	**– 1.79[a] (– 2.48; – 1.10)**	**– 1.49[a] (– 2.08; – 0.90)**
PROPEL [22] (FVIII target 1–3%)	**– 2.63[b] (– 4.60; – 0.66)**		N/A	**– 2.14[b] (– 3.86; – 0.42)**	**– 2.11[a] (– 4.04; – 0.17)**
PROPEL [22] (FVIII target 8–12%)	*– 0.24[b] (– 1.22; 0.74)*		N/A	*– 0.09[b] (– 0.61; 0.42)*	*– 0.49[b] (– 1.20; 0.21)*
Efanesoctog alfa versus Turoctocog alfa pegol (Esporoct®)					
PATHFINDER 2 [26, 27]	N/A	**– 2.50 (– 3.20; – 1.80)**	**0.24 (0.15; 0.37)**	**– 1.46[c] (– 1.99; – 0.93)**	**– 1.90[c] (– 2.51; – 1.29)**

Table 2 continued

Study, arm	ABR (MD) (95% CI)		ABR (IRR) (95% CI)	AsBR (MD) (95% CI)	AjBR (MD) (95% CI)
	All	Treated			
Efanesoctog alfa versus Damoctocog alfa pegol (Jivi®)					
PROTECT VIII [28] BIW (> 1 bleeds)	**– 5.42 (– 9.52; – 1.32)**		N/A	N/A	N/A
PROTECT VIII [28] BIW (≤ 1 bleeds)	**– 1.72 (– 3.33; – 0.11)**		N/A	N/A	N/A
PROTECT VIII [28] BIW (pooled arms)	N/A		N/A	**– 2.31 (– 3.79; – 0.83)**	**– 3.36 (– 5.04; – 1.68)**
PROTECT VIII [28] Q5D	**– 2.16 (– 3.47; – 0.85)**		N/A	**– 1.47 (– 2.27; – 0.67)**	**– 2.05 (– 3.09; – 1.01)**
PROTECT VIII [28] Q7D	**– 5.37 (– 8.38; – 2.36)**		N/A	**– 5.04 (– 7.97; – 2.11)**	**– 4.06 (– 6.80; – 1.32)**
PROTECT VIII [28] (pooled arms)	**– 3.79[a] (– 5.22; – 2.36)**		N/A	**– 3.05[a] (– 4.32; – 1.79)**	**– 3.18[a] (– 4.39; – 1.97)**
Efanesoctog alfa versus Efmoroctocog alfa (Eloctate®/Elocta®)					
A-LONG [23–25] individualised prophylaxis[d]	N/A	**– 1.71 (– 2.93; – 0.49)**	**0.29[c] (0.17; 0.51)**	**– 1.30[c] (– 2.42; – 0.18)**	**– 1.06[c] (– 2.03; – 0.10)**

Bold text significantly favours efanesoctocog alfa; italicised text favours efanesoctocog alfa, but not significantly

[a]Due to limited reporting presence of untreated bleeds could not be ruled out, thus XTEND-1 total bleeds were used for comparison

[b]'All bleeds' (treated or not treated) was assumed based on definition from primary outcome

[c]Treated bleeds

[d]The propensity score matching analysis between efanesoctocog alfa and efmoroctocog alfa allowed for estimation of both IRR and MD for incidence rates, due to availability of IPD from both studies

ABR annualised bleeding rate, *AjBR* annualised joint bleeding rate, *AsBR* annualised spontaneous bleeding rate, *BIW* twice weekly, *CI* confidence interval, *FVIII* factor VIII, *IPD* individual patient data, *IRR* incidence rate ratio, *MD* mean difference, *PPAS* per protocol analysis set, *Q2D* every 2 days, *Q3D* every 3 days, *Q5D* every 5 days, *Q7D* every 7 days, *SAS* safety analysis set, *TIW* three times a week

significantly reduced with efanesoctocog alfa versus the SHL octocog alfa (Kovaltry) in patients with prior prophylaxis or on-demand treatment. Significantly lower mean ABRs for all bleeds were also reported with efanesoctocog versus octocog alfa (Advate) in patients with prior on-demand treatment (no patients with prior prophylaxis were included in the octocog alfa trials). Individual patient data were not available for SHL therapies; thus, it was only possible to calculate the mean difference for efanesoctocog alfa versus SHL therapies, and not the IRR.

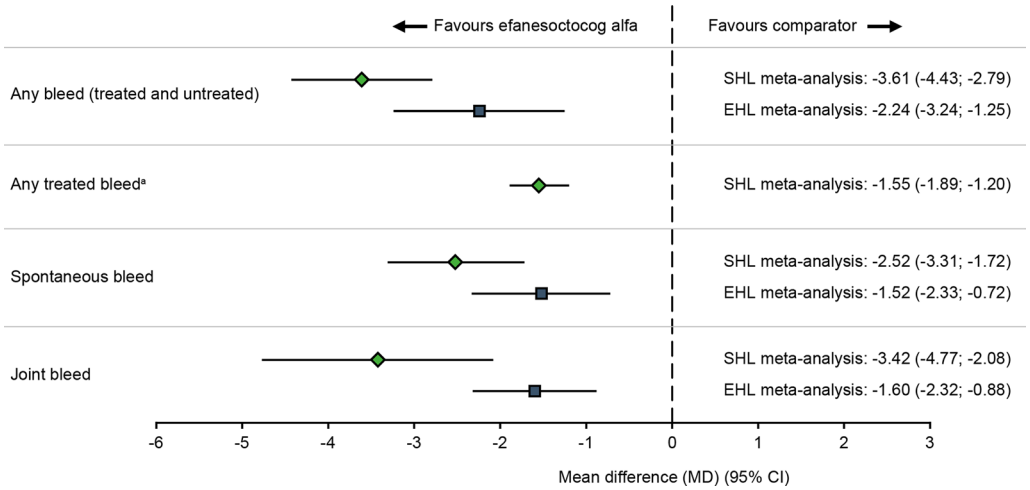

Fig. 1 Overall summary plot of meta-analyses of MDs for efanesoctocog alfa versus SHL and EHL therapies. [a]EHL comparator studies, except for efmoroctocog alfa, did not differentiate between treated and any bleed, in conservative methodology all EHL reported bleed data was assumed to be any bleed. *ABR* annualised bleeding rate, *CI* confidence interval, *EHL* extended half-life, *MD* mean difference, *SHL* standard half-life

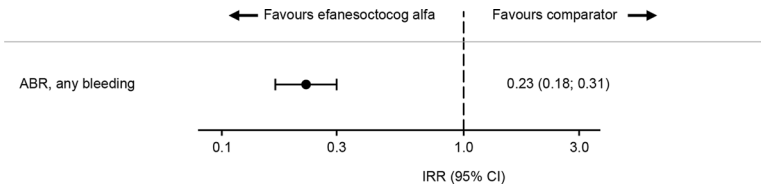

Fig. 2 Summary plot for meta-analysis of IRRs for efanesoctocog alfa versus EHL therapies. *ABR* annualised bleeding rate, *CI* confidence interval, *EHL* extended half-life, *IRR* incidence rate ratio

Similar results were observed compared with EHL therapies; efanesoctocog alfa was associated with significantly lower mean ABRs (any, spontaneous, and joint bleeds) versus damoctocog alfa pegol, rurioctocog alfa pegol, and turoctocog alfa pegol in patients with prior prophylaxis or on-demand treatment. Significantly lower incidences of any, spontaneous, and joint treated bleeds were also observed with efanesoctocog alfa compared with efmoroctocog alfa individualised prophylaxis in patients with prior prophylaxis or on-demand treatment. Bleed outcomes significantly favoured efanesoctocog alfa versus all comparator arms except the elevated rurioctocog alfa pegol arm in PROPEL (targeting FVIII level of 8% to 12% in patients previously treated with on-demand or prophylaxis regimens), where it was numerically favourable for efanesoctocog alfa. To achieve trough factor levels of 8–12% compared with 1–3%, a 75% increase in prophylaxis injection frequency (3.5 compared with 2.0 injections per week) and a 94% increase in mean weekly consumption was required [22]. Such elevated dosing is not typically seen outside of the PROPEL study; for example, efanesoctocog alfa is given as a once-weekly therapy.

This improvement in bleed outcomes with efanesoctocog alfa is expected considering its enhanced pharmacokinetic properties compared with available SHL or EHL products. Efanesoctocog alfa provides high-sustained levels of FVIII within normal to near-normal levels (> 40%) for most of the week and 15% at Day 7 [13], and has a 3- to 4-fold longer elimination half-life and 3- to 6-fold greater exposure (area under the FVIII activity-time curve, > 3.5- to 6-fold) than octocog alfa and

rurioctocog alfa pegol [32]. These high factor levels are expected to correlate with improved bleed control and improved quality of life [2].

Meta-analyses for EHL and SHL therapies supported the individual comparisons and demonstrated that, overall, efanesoctocog alfa was associated with significantly lower rates of any, spontaneous, and joint bleeds versus the selected comparators. In this analysis, efanesoctocog alfa was associated with superior efficacy over available FVIII replacement therapies for the treatment of adolescents and adults with severe haemophilia A without inhibitors. Prevention of bleeding and joint damage is one of the key priorities in haemophilia treatment and care [2].

MAICs of efanesoctocog alfa compared with the non-factor replacement therapy emicizumab have also been conducted, with results demonstrating a significantly lower incidence of any bleeds (treated and untreated) and joint bleeds favouring efanesoctocog alfa [16]. Taken together, these results demonstrate that efanesoctocog may be associated with a significant clinical benefit over existing haemophilia therapies in terms of bleeding prevention, and thus should be considered by healthcare professionals during clinical decision making as a preferred option for prophylactic treatment of adults and adolescents. Moreover, efanesoctocog alfa prophylaxis is less burdensome to patients due to the once-weekly dosing regimen compared with the more frequent dosing typically required for SHLs and EHLs [33].

The comparative efficacy of efanesoctocog alfa versus FVIII replacement therapies in other patient populations or over a longer time frame has not yet been assessed. However, data from two further Phase 3 trials of efanesoctocog alfa, including the ongoing long-term XTENDed trial (NCT04644575) and the completed XTEND-Kids (NCT04759131) trial in children under 12 years of age, may in the future be able to confirm and expand upon the current findings. Consistent with the findings of XTEND-1, the latter study showed that efanesoctocog alfa prophylaxis was well tolerated and provided highly effective bleed protection in children with severe haemophilia A [12].

Limitations

Unanchored comparisons are limited due to necessity of making several assumptions including conditional constancy of the absolute effects, under which all prognostic variables and effect modifiers were matched [30, 34]. Here, MAIC comparisons were limited by the quality and precision of the reporting of baseline characteristics in the comparator trials, since the matching could only be carried out against reported aggregated data, potentially leaving some covariates unbalanced. The strength of MAIC also depends on the similarity of populations across trials, as insufficient overlap of baseline characteristics can lead to loss of information expressed by a big drop in ESS. Consequently, estimates based on small amounts of data indicate smaller overlap between cohorts and may be less reliable. In other published MAIC analyses, a drop of 80% in ESS is not infrequent [30]. There was also a high degree of heterogeneity for spontaneous and any bleeds in the meta-analysis of EHL therapies, suggesting differences in reported ABRs between the different products. This heterogeneity was likely the result of the inclusion of two regimens with different dosing intensities in the PROPEL trial. However, the consistent finding of lower ABRs for any bleeds with efanesoctocog alfa compared with EHL and SHL therapies across multiple regimens and patients with different baseline characteristics makes it unlikely that the statistical superiority of efanesoctocog alfa is a chance finding. In addition, there was no substantial heterogeneity in the meta-analysis of SHL therapies.

Only three studies reported data for patients on prior on-demand regimens only (and none with prior prophylaxis), thus comparison by subgroups for prior regimen was limited. The description of bleeding type (treated or any) was insufficient in three studies (PROLONGATE, PROPEL, PROTECT VIII), so, in these cases, a conservative assumption that these bleeds were any bleeds was made when comparing with efanesoctocog alfa, meaning the true magnitude of bleed reduction of efanesoctocog alfa could be greater than reported.

The incidence of bleeding was analysed using various methodologies, including regression models, for which structures were not fully described. Furthermore, some studies reported incidence as arithmetic mean with the associated standard deviation, which seems inappropriate considering skewness of bleeding distributions, and the LEOPOLD I study did not report the method of ABR estimation. In this case, the analysis was made under the assumption of the same method as used in LEOPOLD II.

Regarding whether FVIII levels account for any ABR differences between studies, correlation of factor levels with bleed rates and according to treatment type would require patient-level data for EHL and SHL. Given the lack of access to such data, except for the A-LONG trial, it was not feasible to conduct these analyses. Moreover, it was not feasible to determine whether FVIII troughs were similar throughout the course of the studies; that is, whether lower initially (after initiating the respective therapies), compared with terminally (the end of the studies). Data showing bleed incidence rates at the beginning or end of each study are only available for the XTEND-1 study [13], but such a comparison would be complicated by the fact that the study time periods varied.

Because of the small sample size of adolescents in XTEND-1, and the lack of consistency across EHL and SHL clinical trials in reporting data for the adolescent population, it was deemed unfeasible to conduct a treatment comparison in this subpopulation. It was also not possible to conduct an indirect comparison for female patients with mild/moderate disease, since XTEND-1 only included patients with severe haemophilia. However, it may be possible to make comparisons with other important groups in the future, such as those using real-world evidence among patients receiving EHL, SHL, and efanesoctocog alfa.

CONCLUSIONS

In this MAIC, once-weekly prophylaxis with efanesoctocog alfa high-sustained FVIII therapy was associated with superior efficacy over SHL and EHL FVIII replacement therapies, with significantly reduced rates of any bleeds, including spontaneous and joint bleeds. In line with the high FVIII activity levels and the longer half-life relative to SHL and EHL therapies, efanesoctocog alfa can provide a meaningful improvement in the treatment landscape for haemophilia A.

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Data Availability. Qualified researchers may request access to patient-level data and related study documents. Patient-level data will be anonymised, and study documents will be redacted, including to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org.

Declarations

Conflict of Interest. Alix Arnaud, Amanda Wilson, and Patricia Guyot are Sanofi employees and may hold stock/stock options in Sanofi. Nana Kragh and Linda Bystrická are employees of Sobi and may hold stock/stock options in Sobi. Piotr Wojciechowski is co-founder at Assignity and an external consultant at Putnam PHMR. Marlena Wdowiak and Wojciech Margas are employees of Putnam PHMR. Robert Klamroth has received honoraria and/or been a member of advisory committees for Bayer, Biomarin, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Sobi, and Takeda. Alberto Tosetto has no relevant conflicts of interest. Piotr Wojciechowski's and Wojciech Margas' affiliation Assignity is now called Clever-Access.

Ethical Approval. This is a post hoc analysis and modelling of data already collected and/or published data. Original studies were all approved by the relevant institutional review boards at each study site and were carried out in accordance with the International Conference on Harmonisation good clinical practice guidelines and the Declaration of Helsinki.

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