Single Technology Appraisal

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

Contents:

The following documents are made available to stakeholders:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 10 June 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Swedish Orphan Biovitrum Ltd (“Sobi”)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

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Background

Sobi would like to thank the committee for their consideration of efanesoctocog alfa for the treatment of severe haemophilia A. Efanesoctocog alfa is the first and only chronic therapy for haemophilia A to be granted orphan drug designation that has demonstrated significant benefit over approved therapies (1). Sobi also acknowledges the concerns of the committee and has sought to provide certainty on the issues raised throughout the draft guidance response document.

Despite improvements in haemophilia management over the last 50 years, people living with haemophilia A continue to experience life-threatening bleeds and joint bleeding resulting in pain, loss of function, and impaired work and societal participation (2). Regular prophylaxis fails to prevent joint bleeds in the real-world setting (3, 4), with recent evidence suggesting that sustained clotting factor VIII (FVIII) levels of 15–50% are necessary to achieve a near-zero joint bleed rate (5).

Efanesoctocog alfa offers the opportunity of being the first once-weekly FVIII replacement therapy by maintaining FVIII levels in the near-normal to normal range (>40%) for 4 days in adults and for 3 days in children. At 7 days, FVIII levels were 15% in adults and 10% in children (6, 7).

In previously treated adults and adolescents aged ≥12 years with severe haemophilia, a once-weekly fixed prophylactic dose of efanesoctocog alfa 50 IU/kg demonstrated effective bleed protection with a mean annualised bleed rate (ABR) of 0.71 (6). Superior bleed protection was also demonstrated versus pre-study FVIII prophylaxis, with a 77% reduction in mean annualised bleeding rate from 2.96 to 0.69 ($p<0.001$) (6). Similar results were seen in previously treated children aged <12 years, with a mean ABR of 0.89 (6, 7) Collectively, these results illustrate that efanesoctocog alfa has the potential to provide significant improvements in clinical outcomes for people living with haemophilia A, demonstrating sustained FVIII activity with once-weekly dosing.

Historically, treatments for haemophilia have gone through a national tender process with National Health Service (NHS) England. Since its inception, the tender has resulted in a significant reduction in the unit price of recombinant factor VIII (rFVIII; almost half within 6 years) (8). These price reductions have continued through subsequent tender cycles, and the new tender (1st July 2024 to 30th April 2027) is structured so that competitive pricing is maintained for the standard half-life (SHL) and extended half-life (EHL) lots (75% of the scoring based on price to win the rank one position in a lot) (9). There is a third lot entitled, “emicizumab” (given patent protections this means that one branded product is applicable).

Although it is welcome that new technologies for haemophilia A, through NICE evaluation, are able to demonstrate value beyond a one-dimensional pricing measure, Sobi feel that there is an inherent disadvantage for new innovations (such as efanesoctocog alfa) when there is a requirement to demonstrate cost-effectiveness against older technologies where price has been significantly eroded due to successive national tender exercises. Where a technology such as emicizumab did not have to proceed through the same process and has been of significant value to patients, caregivers and clinicians alike, it is concerning that the haemophilia community may be deprived of a further innovation that would make an important impact on the condition. Indeed, issues with funding meant that, it was not until the 2004 that all patients had access to recombinant Factor despite the first being available to UK in 1994 (10). This comes at a time when the systemic, collective and individual failures to support the haemophilia community over the years has never been more prominent.

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Sobi's opinion remains that emicizumab is the key comparator for efanesoctocog alfa in this appraisal. Sobi has obtained the latest data from the National Haemophilia Database (NHD) which further emphasises the consideration of emicizumab as the key comparator in this appraisal. Data shows that [redacted]% of patients with severe haemophilia A 12 years and older without inhibitors are treated with emicizumab nationally (11). This figure is higher in patients under 12 years old with [redacted]% treated with emicizumab (11). SHL products are used prophylactically in [redacted]% and [redacted]% of under 12s and over 12s, respectively (11).

While Sobi still consider SHLs to be an inappropriate comparator due to a significant and ongoing decline in their usage, their minimal market share is acknowledged. Despite this, efanesoctocog alfa remains cost-effective versus more than [redacted]% and [redacted]% of the market[a] in <12 year and ≥12-year-olds, respectively.

Ultimately, efanesoctocog alfa is an innovative, high-sustained FVIII replacement therapy that provides effective bleed protection both prophylactically and on-demand, whilst demonstrating sustained factor levels in the normal to near-normal range with a single weekly dose. Efanesoctocog alfa has the potential to improve patient outcomes and provides a meaningful alternative to existing therapies.

We kindly request consideration of the aforementioned factors, and the updated PAS (patient access scheme; new economic model result are presented in Appendix C) when assessing efanesoctocog alfa for the treatment of people with severe haemophilia A.

[a] Market share in <12 years calculated as total of emicizumab + efmoroctocog alfa + simoctocog alfa. Market share in ≥12 years calculated as total of emicizumab + half of EHLs (i.e. assuming a 50% split between turoctocog alfa and efmoroctocog alfa)

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Comparator treatments** The draft guidance states that it is not possible to estimate the cost-effectiveness of efanesoctocog alfa, partially because evidence comparing it with all relevant clotting factor VIII (FVIII) replacement therapies was not provided. Specifically, the committee requested comparisons with: ***Previously untreated patients (PUP)*** • Emicizumab • Standard half-life (SHL) FVIII (octocog alfa, simoctocog alfa, or morcotocog alfa) • Efmoroctocog alfa ***Previously treated patients (PTP)*** • Emicizumab • SHL FVIII (octocog alfa, simoctocog alfa, or morcotocog alfa) • Extended half-life (EHL) FVIII (efmoroctocog alfa, turoctocog alfa pegol, or rurioctocog alfa pegol) The Company have provided comparisons with other FVIIIs for PUPs and PTPs, but maintain the original position that emicizumab for PTPs and emicizumab and efmoroctocog alfa for PUPs are the most appropriate comparators based on current treatment patterns and clinical advice. [redacted] ***<u>Positioning and comparators of efanesoctocog alfa</u>*** In the company submission, efanesoctocog alfa was positioned as an alternative treatment for PUPs and PTPs relative to EHLs and emicizumab, whenever its use was being considered. This is equivalent to considering an optimised use of efanesoctocog alfa, precedents for which exist in other Technology Appraisals. For example, in TA858, the Appraisal Committee recommended the use of lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma for people with intermediate- and poor-risk metastatic renal cell carcinoma scores only if nivolumab plus ipilimumab would otherwise be offered (12). While a comparison with other FVIIIs for PUPs and PTPs has been included in this response (Appendix A), we maintain our original position that comparisons with SHL FVIII replacement therapies are inappropriate as they do not represent the standard of care in the National Health Service (NHS). For this reason, Sobi has obtained the latest data from the National Haemophilia Database (NHD) which further emphasises that emicizumab is the key comparator in this appraisal with data showing that [redacted]% of patients with severe haemophilia A aged 12 years and older without inhibitors are treated with emicizumab nationally (11). This figure is higher in patients under 12 years old with [redacted]% treated with emicizumab (11). Moreover, SHL products are only used prophylactically in [redacted]% and [redacted]% of under 12s and over 12s, respectively (11), with clinical advice suggesting that these proportions will continue to decline and be negligible in 5-years' time (12). These findings show that nationally SHL use is minimal and declining, as evidenced by the fact that SHL use is lower in those under 12 years old versus those aged 12 and over. Furthermore, clinical opinion

suggests that older patients that remain on SHLs are unlikely to switch (due to indifference or reluctance; please see Comment 9). SHLs are therefore not a relevant comparator – this is similar to the Company positioning that efanesoctocog alfa should be considered as an alternative treatment to emicizumab in PTPs, and an alternative to emicizumab and EHLs in PUPs.

Figure 1: Proportion of replacement therapies used prophylactically in severe haemophilia A (baseline factor VIII <1%) and no current inhibitor, in the UK, 2023

Abbreviations: EHL, extended half-life; SHL, standard half-life; UK, United Kingdom.

Previously untreated patients (PUPs)

As previously stated, NHD data obtained by Sobi indicates that the vast majority of patients under 12 with severe haemophilia A are treated with emicizumab or efmoroctocog alfa ([redacted]% and [redacted]%, respectively) (11). Only [redacted]% of patients in this group are treated with SHLs (11). Please note that whilst these data include both PUPs and PTPs, the data can be extrapolated to highlight the low use of SHLs in this patient cohort.

Furthermore, the draft guidance states that one clinical expert noted that SHLs are still used but was not specific about the choice of products. Clinical advice from two major paediatric treatment centres following the draft guidance has indicated that SHLs, and specifically simoctocog alfa, are only routinely considered when a patient is at high risk of inhibitor development (e.g. specific genetic mutations or known family history) or presents with a central nervous system (CNS) bleed (combined incidence of around 5% of all PUPs). This is because it is produced in a human cell line and has theoretical advantages with respect to a lower risk of inhibitor development (13). Therefore, although we have provided an analysis comparing efanesoctocog alfa with simoctocog alfa for PUPs, this comparison is not relevant for PUPs and under 12s in the vast majority of cases as evidenced by the NHD data. For these people, the appropriate comparators are efmoroctocog alfa and emicizumab.

Previously treated patients (PTPs)

In the PTP population, Sobi maintain that emicizumab represents the most relevant comparator as it is now standard of care in England and Wales. Although no formal treatment pathway exists, clinical advice indicates that if patients switch it is most commonly to emicizumab. This is also evidenced by significant market share growth of emicizumab and flat/declining share for factor replacement

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	therapies. [redacted] [redacted]. Data from the NHD reinforces emicizumab's position as standard of care in the NHS. The latest data cut highlights that in patients 12 years and older with severe haemophilia A, [redacted]% are prescribed emicizumab with [redacted]% and [redacted]% receiving EHL and SHL therapies, respectively (11). The proportion of severe haemophilia A patients without an inhibitor using emicizumab has increased from [redacted]% in 2019 to [redacted]% in 2023 (11). As highlighted above, the proportion of patients aged under 12 treated with emicizumab is [redacted]% (11). This further reinforces that emicizumab is the treatment of choice in people with severe haemophilia A, with many younger patients being commenced on it. These data, alongside clinical expert feedback, indicate that clinicians are increasingly focused on prescribing emicizumab due to its improved clinical outcomes over earlier generation factor replacement therapies. This trend is likely to continue and by comparing efanesoctocog alfa with emicizumab Sobi has sought to focus on the only relevant comparator based on clinical outcomes. In indirect treatment comparison (ITC) analyses submitted to NICE and from clinical and patient feedback, it is a reasonable assumption that efanesoctocog alfa is at least as effective as emicizumab.
2	**Indirect treatment comparison** In the draft guidance, the committee concludes that the results of the Company's ITC were not appropriate for decision making, due to concerns with the methodology and face validity of the results. To address these concerns, the ITCs have been updated, with alternative approaches explored, as discussed below. ***Matching adjusted indirect comparison (MAIC) adjusting both the A-LONG and XTEND-1 populations to the aggregate data from HAVEN 3*** The company base-case analysis has been updated to address concerns that the committee had around the factors adjusted for in the ITC. The committee noted that people in HAVEN 3 had a higher bleeding rate at study entry than people in XTEND-1, which may indicate that patients in HAVEN 3 had more severe disease, and this is a potential prognostic factor that had not been adjusted for. While it is informative to consider intra-patient comparisons when assessing the efficacy of a treatment, as has been done in XTEND-1 and HAVEN 3, comparing pre-study bleed rates across trials is not a suitable indicator of severity, as the bleed rates will be driven by the treatment patients were receiving at the time. Both pre-studies drew data from a mixture of medical records and electronic case report forms. HAVEN 3 began enrolment in 2016 and completed in 2017. During this time, United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) data indicates that 90% of people with severe haemophilia A in the UK were treated with SHLs and 7% with EHLs. Of the patients treated prophylactically in the HAVEN-3 pre-study, 83.7% were treated with SHLs and 18.4% were treated with EHLs, although the exact proportion of patients using SHLs and EHLs that then enrolled on to HAVEN 3 has not been reported (14). In comparison, amongst patients enrolled from the observational pre-study for XTEND-1, 56% were using SHL as their pre-study prophylaxis and 44% were using EHLs. Differences in the prophylactic regimen will influence the bleed rate in the pre-study period, and clinicians indicated that they expect annualised bleed rates (ABRs) to fall over time, as management of severe haemophilia A has improved. However, the choice of pre-study prophylaxis is not expected to influence the bleed rate for patients treated with efanesoctocog alfa or emicizumab.

None-the-less, an updated MAIC adjusting for pre-study bleed rates has been performed, comparing Arm A of XTEND-1 to Arm D of HAVEN 3, per the committee's preference. The updated MAIC adjusts for age, weight, race, presence of target joints and the average number of bleeds at baseline. In addition, the base-case and updated MAICs have also been run comparing the A-LONG individualised prophylaxis to HAVEN 3 Arm D, to allow for a comparison of efanesoctocog alfa, efmoroctocog alfa, and emicizumab in the same population (i.e. all matched to the HAVEN 3 population). Details of each analysis can be found in Appendix A.

Table 1 presents the results of the base-case MAICs. Table 2 presents the outputs of the updated MAIC with adjustment for pre-study ABR. When adjusting for the number of bleeds at baseline, there is a [redacted] in the point estimates in the efanesoctocog alfa vs emicizumab comparisons, however outputs are [redacted] across analyses. The ABR for treated joint bleeds is [redacted] in the updated MAIC analysis. Estimates of efficacy for efmoroctocog alfa compared with emicizumab show it to [redacted] at preventing treated bleeds. These analyses have been incorporated into the economic model, with details and results presented in Appendix A.

Table 1: Base-case MAIC outputs

Efficacy outcome	EFA *(XTEND-1)*	Efmo *(A-LONG)*	Emi (HAVEN 3)	EFA vs efmo	EFA vs emi	Efmo vs emi
	IR (SE)	IR (SE)	IR (SE)	IRR (95%CI)	IRR (95%CI)	IRR (95%CI)
ABR any	[redacted]	–	[redacted]	–	[redacted]	–
ABR any treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABR spontaneous (treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABR joint (treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Statistically significant comparisons are in bold.
Abbreviations: ABR, annualised bleed rate; CI, confidence interval; efa, efanesoctocog alfa; efmo, efmoroctocog alfa, emi, emicizumab; IR, incidence rate; IRR, incidence rate ratio; MAIC, matching adjusted indirect comparison; SE, standard error.

Table 2: Updated MAIC with adjustment for pre-study ABR

Efficacy outcome	EFA *(XTEND-1)*	Efmo *(A-LONG)*	Emi (HAVEN 3)	EFA vs efmo	EFA vs emi	Efmo vs emi
	IR (SE)	IR (SE)	IR (SE)	IRR (95%CI)	IRR (95%CI)	IRR (95%CI)
ABR any	[redacted]	–	[redacted]	–	[redacted]	–
ABR any treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABR spontaneous (treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABR joint (treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Statistically significant comparisons are in bold.
Abbreviations: ABR, annualised bleed rate; CI, confidence interval; efa, efanesoctocog alfa; efmo,

efmoroctocog alfa, emi, emicizumab; IR, incidence rate; IRR, incidence rate ratio; MAIC, matching adjusted indirect comparison; SE, standard error.

Table 3 presents the estimated ABRs from the updated analyses, where ABRs from Arm D of HAVEN 3 have been used for the baseline rates of bleeding, with treatment effects applied for efanesoctocog alfa and efmoroctocog alfa. In both analyses the ABRs for both treated and any bleeds are [redacted].

Table 3: Estimated ABRs from the updated MAIC analyses

	EFA	Efmo	Emi
Base-case MAIC matched to HAVEN 3			
All bleeds	[redacted]	[redacted]	[redacted]
Treated bleeds	[redacted]	[redacted]	[redacted]
MAIC with adjustment for pre-study ABRs			
All bleeds	[redacted]	[redacted]	[redacted]
Treated bleeds	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, annualised bleed rate; EFA, efanesoctocog alfa; efmo, efmoroctocog alfa; emi, emicizumab; MAIC, matching-adjusted indirect comparison.

The draft guidance states that "multiple alternative approaches should be explored to estimate the effectiveness of efanesoctocog alfa versus the relevant comparators, either directly or indirectly through an indirect comparison". Each alternative approach is discussed below.

Analyses using outcomes from the pre-study period and intra-patient comparisons directly

This section groups together two sets of analyses proposed by the committee, as they are used in conjunction in the economic model:

1. Using evidence from the intra-patient analysis directly to inform outcomes for SHLs and EHLs

2. Using the intra-patient comparisons in XTEND-1 and HAVEN 3 to produce an anchored ITC using prior SHL and EHL factor VIII therapy as the common comparator.

After providing informed consent, 78 patients (12–69 years old) who had received ≥6 months standard-of-care (SoC) FVIII prophylaxis (SHL [n=44] or EHL [n=34]) in the observational study, prior to enrolling in Arm A of XTEND-1. This data was used to inform a post-hoc intra-patient comparison. This analysis considered treated bleeds only. Patients using SHL FVIII prophylaxis are expected to have higher bleed rates than those using EHL FVII prophylaxis, so in order to populate the model it was necessary to look at a subgroup analysis, to avoid assuming equivalent efficacy for SHLs and EHLs (15). The outputs of the intra-patient comparison are presented in Table 4.

Table 4: Summary of the intra-patient comparison

	Mean ABR (95% CI)	Mean difference (95% CI)	Rate ratio (95% CI)
Pre-study SHL FVIII prophylaxis (n=44)	3.23 [redacted]	–2.44 (–4.31, –0.57)	[redacted]
On-study efanesoctocog alfa prophylaxis (n=44)	0.79 [redacted]		
Pre-study EHL FVIII prophylaxis (n=34)	2.61 [redacted]	–2.06 (–3.23, –0.89)	[redacted]

On-study efanesoctocog alfa prophylaxis (n=34)	0.55 [redacted]		
Pre-study SHL and EHL FVIII prophylaxis (n=78)	2.96 [redacted]	–2.27 (–3.44, –1.10)	[redacted]
On-study efanesoctocog alfa prophylaxis (n=78)	0.69 [redacted]		

Abbreviations: ABR, annualised bleed rate; CI, confidence interval; EHL, extended half-life; FVIII, factor VIII; SHL, standard half-life.

These bleed rates have been incorporated in the economic model directly, with the ABR for emicizumab then informed by an ITC comparing the rate ratio in the intra-patient comparisons performed for HAVEN 3 and XTEND-1, using prior FVIII prophylaxis as a common comparator. As highlighted above, the assumption that the prior FVIII prophylaxis forms a common comparator may not hold, as the treatments that formed SoC would be different between HAVEN 3 and XTEND-1 due to increased use of EHL therapies in the time between the two studies. As such, an analysis comparing the rate ratios should adjust prior therapy. However, no baseline characteristics for the pre-study population in HAVEN 3 have been identified, beyond the ABR and it was only possible to assign weights based on the ABR. Table 5 summarises the outputs of the ITC used in the model, with full details of the ITC are presented in Appendix A. The results of the ITC show a [redacted] in treated bleeds with efanesoctocog alfa, with a rate ratio of [redacted]. This is [redacted] with the MAIC, which shows rate ratios on treated bleeds between [redacted].

Table 5: Outputs of the ITC using intra-patient comparisons

			Pre-study	On-study
XTEND-1	N		78	78
	Unweighted ABR		[redacted]	[redacted]
	Rate ratio versus pre-study (unweighted)	Negative binomial regression	[redacted]†	
	Weighted ABR		[redacted]	[redacted]
	Rate ratio versus pre-study (weighted)	Negative binomial regression	[redacted]†	
HAVEN 3	N		48	48
	ABR [95%CI]		[redacted]	[redacted]
	Rate ratio versus pre-study	Negative binomial regression	[redacted]	
Weighted rate ratio between XTEND-1 and HAVEN 3			[redacted]	

†Due to convergence issues, the effect of random intercept was omitted; however, this had [redacted] on the estimate for unweighted comparison, which were the [redacted] compared with those presented in the XTEND-1 manuscript (0.23 [0.13; 0.42]).
Abbreviation: ABR, annualised bleed rate.

Anchoring the ITC by using the on-demand arms of each trial

The committee proposed an additional analysis anchoring the ITC by using the on-demand arms of each trial, in line with the incremental cost-effectiveness ratio (ICER) and Canadian Agency for Drugs and Technologies in Health (CADTH) reviews of emicizumab, then using a PSM between Arm A and Arm B of XTEND-1 to provide a relative effect adjusted for confounders.

Reyes et al. 2019 (16) conducted an network meta analysis (NMA) to compare emicizumab versus FVIII prophylaxis through no-prophylaxis/on demand (OD) arm based on RCTs. This approach was possible only using trials recruiting patients receiving OD before enrolment, who were assigned

either to prophylaxis or OD regimens. This is because patients who were receiving FVIII prophylaxis before enrolment cannot be offered OD during the trial, which is a less effective treatment.

The method proposed by the committee is not applicable, since patients assigned to Arm A and Arm B of the XTEND-1 trial were recruited from different and non-overlapping sub-populations: previously treated with prophylaxis and OD, respectively. Since the populations were non overlapping, propensity score matching (PSM) cannot balance the populations regarding prior therapy and thus would not be balanced on prior rate of bleed and prior risk of target joints, which are tightly correlated with the treatment received by patients. PSM could only adjust for such sociodemographic factors as age, body weight/BMI, ethnicity/race, which have rather limited impact on the results. Therefore, it is not possible to use PSM to balance Arm A and Arm B for important confounders. In addition, Arm D of HAVEN 3 was the only arm that included patients previously receiving prophylaxis and was not part of the randomisation and does not have an overlapping population, so cannot be directly compared to Arms A, B, and C. Therefore, this analysis would not be able to provide a reliable estimate of relative effect between Arm A of XTEND-1 and Arm D of HAVEN 3.

This analysis would also assume that the OD arms of each trial are equivalent, however this may not be true. On-demand treatments for haemophilia have different pharmacokinetic profiles, affecting the duration and intensity of their action. For example, efanesoctocog alfa, efmoroctocog alfa, and SHL factor VIII therapies vary in how long they maintain factor VIII levels in the bloodstream, influencing their efficacy. Efanesoctocog alfa has a longer half-life than the comparators, which may confer additional benefit and reduce ABRs compared with comparator trials. The pre-study ABR in Arm B was 35.7, but was 21.4 during the OD period of Arm B, suggesting that OD treatment with efanesoctocog alfa was more effective than the patients prior OD regimen.

Given these limitations, an analysis using the OD arms was not considered appropriate and has not been performed.

Summary of new analyses included in the cost-effectiveness analysis

The updated analyses include the following data and assumptions for each comparator:

- Efanesoctocog alfa
  - Scenarios using the updated MAIC analyses matching to the HAVEN 3 study, where emicizumab outputs from HAVEN 3 Arm D inform the baseline ABRs
  - Data from the intra-patient comparison used directly to inform ABRs
- Emicizumab
  - HAVEN 3 Arm D inform the baseline ABRs
  - Data from the intra-patient comparison applied to the baseline ABR from the XTEND-1 pre-study observational period
- EHLs/efmoroctocog alfa
  - For comparisons with EHLs, it has been assumed that they are all equally effective. This is based on inputs from clinical experts, who have stated that they view each as being equally effective
  - Scenarios using the updated MAIC analyses matching to the HAVEN 3 study, where emicizumab outputs from HAVEN 3 Arm D inform the baseline ABRs
  - Scenarios using a subgroup of the pre-study population to inform ABRs
- SHLs
  - For comparisons with SHLs, it has been assumed that they are all equally effective. This is based on inputs from clinical experts, who have stated that they view each as being equally effective in terms of ABRs
  - Scenarios using a subgroup of the pre-study population to inform ABRs
  - A MAIC comparing to SHLs has also been performed to inform the model, with details presented in Appendix A.

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3	**Utilities** The draft guidance states the utility values used by the Company are uncertain. The committee's objections to the utility analyses and the Company's concerns are summarised below. ***Extending efanesoctocog alfa data to other FVIII or emicizumab*** The committee raised concerns that it may not be possible to extend efanesoctocog alfa data to other FVIII therapies or emicizumab, due to the differences in dose frequency and the mode of administration. While research has been conducted into patient preference on mode and frequency of administration in severe haemophilia A, there was little in the literature that isolated the impact of intravenous (IV) vs subcutaneous (SC) injections when using the same treatment schedule – the majority of the research has compared IV treatments more than once per week (SHLs and EHLs) to less frequent SC administration (emicizumab). One publication was identified that varied both mode and frequency of administration together and this suggests that the mode of administration is not important for weekly treatments, with no significant difference in preference weights (17). This was validated by clinicians consulted by the Company whilst preparing to respond to the draft guidance, who indicated that preference is down to individual patients, with some preferring one mode of administration over another, particularly in haemophilia, where many patients are used to receiving injections. In addition, emicizumab is not a monotherapy and patients treated with emicizumab will still require IV injections to treat bleeds, prior to physical activities and prior to surgery. UKHCDO data indicates that in 2023, [redacted]% and [redacted]% of patients treated with emicizumab in the under 12 years and 12 years and older age groups, respectively, were also issued an SHL (11). IV infusions may have a larger impact on quality of life (QoL) for these patients as they may not be used to this mode of administration, as highlighted in the draft guidance. The publication does however highlight that frequency of administration has a larger impact on preference than mode of administration. The impact of treatment frequency on EQ-5D utilities has previously been explored using data from the CHESS II study (18), with an analysis considering the impact of weekly vs more frequent infusions. The study showed that increased infusion frequency was associated with reduced QoL, with a decrement for more frequent infusions between –0.027 and –0.107, depending on the model specification selected. Though the utility analysis used in the model has been updated to include data from the A-LONG and ASPIRE studies, it was not possible to estimate an impact of more frequent administration from the trial data and the impact of more frequent administration has been excluded from the company base-case. This is expected to be conservative, as EHLs and SHLs all have more frequent administration that efanesoctocog alfa. Scenario analyses applying disutilities associated with more frequent administration have been presented in Appendix A. While emicizumab may be administered less frequently, the difference between administration weekly and every other week is expected to be small. The patient expert at the committee meeting highlighted that the issues they had with more frequent administration had resolved with efanesoctocog alfa. ***The assumption that the type, severity, and location of bleeds were identical for the different treatments under evaluation*** The committee raised concerns that the utility analysis does not differentiate between the type, severity, or location of bleeds, and that these had been assumed to be identical between treatments. The utility analysis was conducted based on studies assessing very effective therapies and the collected number of events was very low. Additionally, there was a limited number of EQ-5D measurements. Given the limited number of observations corresponding to dependent and independent variables the data does not allow for a higher granularity of the investigation, e.g. by bleed location.

Previous studies have included a difference in utility for joint and non-joint bleeds, for example Cook et al. 2020(19) had differences in utility between 0.10 and 0.12, depending on Petterson score (Company Submission, Appendix H). However, the outputs of the ITC indicate that the assumption that the location of bleeds is identical between therapies may be reasonable. Across the three sets of results presented in Table 1 and Table 2, the impact of efanesoctocog alfa on treated bleeds and treated joint bleeds is similar, indicating that the proportion of treated bleeds that are joint bleeds is comparable across treatments. Therefore, it is not expected that modelling different utility values for joint and non-joint bleeds will lead to a difference in cost-effectiveness results.

Very little evidence was identified comparing the impact of spontaneous and traumatic bleeds. One study (20) included a utility of 0.44 for moderate haemophilia A with a trauma bleed and 0.68 for moderate haemophilia A with a spontaneous bleed. However, this study used utility analyses derived from a vignette study, rather than using data collected in people with severe haemophilia A and does not meet the NICE reference case. No other studies considered any difference due to bleed type.

The disutilities did not capture the impact of chronic pain from subclinical bleeds

The impact of chronic pain due to subclinical bleeds is captured implicitly in the utility analysis through the correlation of both factors with FVIII, though it has not been captured explicitly. For comparisons with other FVIII therapies this is expected to be a conservative approach for efanesoctocog alfa. XTEND-1 included the change from baseline to Week 52 in Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity 3a past 7 days, intensity of pain at its worst score (PAINQU6, referred to as PROMIS Pain Intensity first item) as a secondary endpoint. A significant difference was found in Arm A (p=0.0276), indicating that patients treated with efanesoctocog alfa are expected to have less pain than those treated with prophylactic FVIII therapies. However, XTEND-1 is the only trial that has included pain specific outcomes. While some studies (21) have quantified the impact of emicizumab on chronic pain, HAVEN 3 did not include any specific measures of pain in its primary or secondary outcomes and no comparable outcomes for emicizumab were identified. As such, no direct comparison of efanesoctocog alfa with emicizumab for the reduction of chronic pain has been possible, and a direct link between pain, treatment and utility cannot be incorporated into the model.

Insufficient justification of the Company's preferred model or parameter set, and use of the Tobit model

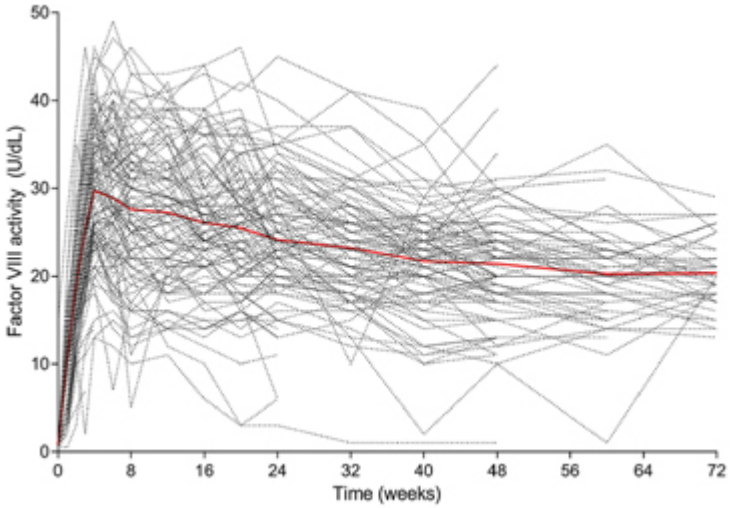
Tobit regression is a potential solution to model outcome variables with floor and ceiling effects (22) such as EQ-5D data. The utility analysis are interpretable in the range -infinity to 1, where 1 indicates perfect health, 0 indicates death and negative values correspond to states worse than death. Therefore, the ceiling effect at 1 cannot be excluded during the estimation of the utility values when applying country-specific tariffs to EQ-5D data. Moreover, the utility analysis using linear regression can also lead to predictions greater than 1 for selected patients. The Tobit model allows to account for the potential ceiling effect and prevents from estimations greater than 1, thus it was preferred for the utility analysis. Of the four models presented in Company submission, models 1 and 2 including time from study initiation showed the best statistical fit; however the difference in fit between these models was minimal. Model 1, which includes a coefficient for FVIII <20% was selected for the base-case, as this aligned with input from clinicians that people would modify their behaviour once they no longer had peak protection (23).

The utility analysis has been updated, to include data from A-LONG and ASPIRE and to test additional parameters in the modelling, and both Tobit and linear models have been explored. In general, the results from Tobit and the linear regressions are quite consistent. Tobit models have been retained in the base case analysis, however scenarios using linear models have also been explored and provide similar results.

	Previously, the implementation in the model had assumed people with FVIII above 50% would have QoL similar to the general population and had used the utility models solely to estimate the impact of bleeds and FVIII levels. However, in the updated analysis the baseline utility value has been taken from the clinical trial data, with decrements for bleeds and FVIII levels applied to this. In the base case, utility values are assumed to decline proportionally with the general population values. A sensitivity analysis uses the age coefficients from the utility models to predict how utility declines over time. The updated utility models predict changes in utility value with each additional year of age between –0.0029 and –0.0053, depending on the model specification. This is above the change for the age and sex-matched general population, where the average decrement in each year is -0.0020. However, this value may not reflect how utility changes over time for patients treated with efanesoctocog alfa or other effective prophylaxis, instead it may be due to a correlation between age and lower QoL at baseline. Older patients will have spent more of their lifetime without access to highly effective treatment, and are likely to have had a higher bleed rate and more damage to joints.
4	**The link between FVIII and QoL** The relationship between FVIII and QoL was included based on clinical advice that patients with higher FVIII levels are more able to undertake their usual activities, due to the better protection from bleeds. Furthermore, analyses have found a strong correlation between FVIII and QoL (24). While patients do not regularly monitor their FVIII levels, as the patients' experts in the committee meeting highlighted, they are aware of how they change over time. They are also aware of how this impacts their ability to perform certain activities, especially when considering the time since their last infusion. For example, a patient may only engage in sporting activity or higher risk activities immediately following their dose, when they have 'peak protection', and avoid such activities beyond this (25, 26). This sentiment was captured in exit interviews performed as part of XTEND-1. Exit interviews were performed with 29 individuals, 17 of whom were enrolled in Arm A and were receiving prophylactic treatment prior to enrolling in the trial. Thirteen of the 17 (76.5%) had reported "wearing off" with prior prophylactic treatment, including more pain, stiffness, feeling unprotected, breakthrough bleeds, and limited physical activities (27). *"It's almost like you can feel that you need an injection… I don't know how to describe it. I was aware…I felt different immediately after you know, the hours after an injection, compared to say, 4 days later before I did an injection. I was aware that I needed to [infuse]."* Participants also noted changes in their physical functioning after receiving efanesoctocog alfa, noting a reduction in pain and improved ability to exercise and perform other usual activities (28). *"I'm not getting the increased achiness on the day before or the day of my infusion. Generally, the achiness has gone from my life. I still have arthritic pain, but I can tell you that those moments where I sit down and can't walk anymore are fewer than they were before."* *"The thing that has changed most in my daily life, that improved [is]… exercising… before the injections I would not do it. Because if I do it without receiving injections, it strains the joints a little, but nowadays the status is maintained to a degree, and because it is maintained, I do exercise, light work outs, and there is no specific strains on my body."* *"The effect would last only about two days when I received the injections before, but now I can feel the effects lasting throughout the week. That is what the numbers also say, and what I feel in my daily life. So, in those ways, there is much improvement."* In total, 92% (142/155) of patients preferred efanesoctocog alfa over their previous treatment. One of the most common reasons given for this preference was that they 'felt better protected' (64% [91/142]).

Patients treated with emicizumab do not experience the same fluctuation in protection over time, as emicizumab concentrations are well maintained between doses, however this does not mean they always have 'peak protection'. For some patients, their ability to carry out their usual activities will still be impacted by the risk of bleeds. In the economic analysis, this was reflected through FVIII equivalence, using the assumption that patients treated with emicizumab have protection equivalent to FVIII between 10% and 20% (29). This range is consistent with reported FVIII-like activity from HAVEN-1, which stabilised around 20%, with mean activity of 20.2 IU/dL at Week 72.

Figure 2: FVIII-like activity in HAVEN-1



However, the Company acknowledge that this is based on animal models and may overstate the impact on QoL. There has been little research to estimate the FVIII equivalence in humans, however one study (30) identified by the company did estimate the FVIII equivalence in 10 people with severe haemophilia A. They found that all patients had FVIII above 10%, with 3 patients falling into the 10–20% category. In the updated economic analysis, it has been assumed that 30% of emicizumab patients would have FVIII in the range 10–20%, however scenarios have also been explored in which no disutility is applied based on FVIII levels in the emicizumab arm.

The committee also noted that one clinical expert estimated that people were unlikely to have spontaneous bleeds with factor VIII activity levels of over 10% or bleeds with minor trauma with levels of over 15% and the draft guidance highlights that people with a factor VIII activity level of 20% were classed as having mild haemophilia A, so would have a relatively low risk of bleeding. They go on to request a scenario considering a disutility applied to patients with FVIII below 15%.

FVIII levels of 15 and 20% are both considered mild haemophilia, and would be associated with a lower risk of bleeding. In a recent publication (31), FVIII levels of both 15 and 20% were considered important. Healthcare professionals (HCPs) agreed that the aim of prophylaxis should be to achieve a trough FVIII level ≥15 IU/dL and maintain a longer period with FVIII levels of ≥20–30 IU/dL to provide better bleed protection. Similar findings were reported in an elicitation study carried out by the Company, where clinicians stated that FVIII levels of 15–25% were appropriate (32). The aspirational goal for people with haemophilia A is to prevent all joint bleeds, which may be achieved by maintaining normalised (50–150 IU/dL) FVIII levels. However, the disutility associated with FVIII levels does not need to be exactly aligned with thresholds linked to bleeding, but rather it should be linked to the threshold at which patients might start to limit their behaviour and start experiencing the symptoms associated with lower FVIII. This is likely to be highly individualized, however in the

	updated utility analysis, significant disutilities were found for FVIII levels below 5%, 15% and 20% in different models. To address the uncertainty around utility linked to FVIII levels, the following scenarios have been included in the updated analysis: • No disutility linked to FVIII • Disutilities at 5%, 15% and 20% • A disutility for FVIII below 5%, with a separate disutility for FVIII between 5% and 20% • Disutilities for FVIII therapies, but no disutilities for patients treated with emicizumab.
5	**Wastage costs** The draft guidance states that the wastage costs for efanesoctocog alfa and efmoroctocog alfa are uncertain and requests the economic model be updated to account for vial wastage associated with prophylactic treatment. This has been incorporated for all prophylactic treatments for adult patients, however in people under 18 costs are assigned without wastage. Weight is more variable amongst under 18s, especially in very young children, and as patients grow it is likely that the dose, they receive will at different times be varied up or down. This was confirmed by a clinical expert consulted by the company. In their paediatric practice patients come into clinic every 6 months and are likely to have gained weight, however they do not always increase the dose used for prophylaxis. Incorporating vial wastage in population whose weight changes from cycle to cycle would be complicated to implement in the model and is not expected to have a large impact on cost-effectiveness estimates, as all comparators use weight-based dosing schedules. Wastage of SHL for patients treated with emicizumab is still included in the base case, however the approach has been updated. The dose of SHL wastes assumes that patients would have enough SHL on had to treat a bleed, using 2 doses of 25 IU/kg. This is a dose of 4,175 units for an average patient, and the average cost per unit for SHLs is applied. This cost is then applied to the proportion of patients that don't experience a bleed in 2 years, which is calculated as the probability of not experiencing a bleed in a 6-month cycle to the power of 4. The uncertainty associated with this assumption is explored in 2 scenarios, one without any SHL wastage, and one where the wastage is halved.
6	**Resource cost and use for managing bleeds** The draft guidance states that the resource use and costs for managing bleeds are uncertain. The Company submission assumes that patients who experience a bleed would have 1.11 contact with a haematologist on average, with 6% of bleeds requiring an Accident and Emergency (A&E) visit and this was confirmed to be a reasonable assumption during discussions with clinical experts. The External Assessment Group (EAG) noted that bleeds were likely to be mild to moderate and could be managed on the phone and often by specialist nurses, also highlighting that there were more up-to-date costs that could be applied. The company has sought further clinical input on how bleeds are managed. The clinical experts consulted stated that for a typical bleed, patients would phone a nurse, then administer treatment at home. There would be a follow-up with the centre which would include a multi-disciplinary team (MDT) review for joint bleeds. For bleeds outside of work hours, patients would get to A&E for treatment and then follow-up with the specialist centre the following day. They also highlighted that patients using emicizumab are 'deskilled' with IV and are more likely to require assistance with treating their bleeds. To reflect the critique from the EAG and committee and additional input from the clinical experts consulted, the cost of bleed management in the model base-case has been updated and additional sensitivity analyses performed. The cost per visit used in the base case is the weighted cost across Service Code 309 using the 2021/22 NHS reference costs (£512.74), which includes face-to-face

	and non-face-to-face outpatient contacts, both consultant-led and non-consultant led. This will reflect bleeds that can be resolved over the phone and those that do not require a consultant contact but will also reflect requirement for MDT meeting associated with joint bleeds. This retains the assumption of 1.11 contacts per bleed, plus 6% requiring an A&E visit. A scenario has also been included that uses the average cost of a single non-consultant-led, non-face-to-face contacts (£345.90), assuming all bleeds can be resolved over the phone with a single contact. A scenario without resource use for bleeds has also been included. The clinical experts also highlighted that patients using emicizumab are 'deskilled' with IV and are more likely to require assistance with treating their bleed, indicating that the assumption of equal costs for each arm may be conservative.
7	**The indirect comparison of efanesoctocog alfa with emicizumab** The draft guidance states that the results of an indirect comparison of efanesoctocog alfa with emicizumab are unreliable, so whether one works better than the other is unknown. Although the indirect comparison is based on a small amount of data, this is a common issue in a rare disease setting. In this analysis, the effective sample size (ESS) for most of the analyses did not drop below 50% of the initial sample, which can be considered as acceptable compared with other published analyses, in which an 80% drop of ESS was not infrequent (33). The ITC showed that compared with emicizumab, efanesoctocog alfa was associated with reduced incidence of any bleeds (treated and untreated) as well as with lower rate of bleeds when compared specifically with once weekly (QW) regimen in patients with prior prophylaxis and with every 4 weeks (Q4W) regimen. Moreover, efanesoctocog alfa tends to improve Hemophilia Joint Health Score (HJHS) assessment compared with emicizumab.
8	**The impact of a new treatment option with a less frequent dosing schedule** The draft guidance notes that the committee recognised that severe haemophilia A is a chronic condition that has a significant impact on the lives of people affected by it. The committee also concluded that a new treatment option with effective bleeding control and a less frequent dosing schedule would be welcomed by people with haemophilia A. This suggests that innovation in the field is needed, and the Company are disappointed with the Committee's draft position not to recommend efanesoctocog alfa for the treatment of severe haemophilia A. We believe that efanesoctocog alfa, as a clinically- and cost-effective therapy, would serve to address not only the substantial unmet need for a therapy with a less frequent dosing schedule, but also with the potential to decrease the burden of disease through improved outcomes due to maintained FVIII levels within the normal to near-normal range. In addition, given that it can be used prophylactically and on demand, this removes the need for multiple treatments associated with non-factor therapy. The innovation of efanesoctocog alfa has been recognised by the European Medicines Agency (EMA) Committee for Orphan Medicinal Products. Efanesoctocog alfa was awarded orphan status by the EMA in 2019, and this status was reviewed in April 2024. The COMP concluded that "*…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."*(1).
9	**Switching treatments** In Section 3.14 the committee notes that people with haemophilia A switch treatments regularly. However, switching treatment regimens for patients with haemophilia is not a common practice.

	There are several factors that contribute to this infrequency, including the theoretical risk of inhibitor development, guidelines and policies that limit switching, and the stability of patients on long-term prophylaxis (34, 35). There may also be a reluctance to switch where patient preferences and lifestyle choices are important considerations. In addition, some patients with haemophilia often develop a strong psychological link with their current product (36). Indeed, the complex, multi-generational impact of the contaminated blood scandal means that many patients are firm in their reluctance to change their current product (37). One of the reasons for the reluctance to switch treatments is the theoretical risk of developing inhibitors (37). Inhibitors are antibodies that neutralise the effectiveness of the treatment, making it significantly harder to manage bleeding episodes. Research indicates that the likelihood of developing inhibitors is highest during the initial exposures to factor VIII concentrates, usually within the first 10 to 15 exposures, and typically occurs in childhood (38). This risk of inhibitors is lower after the first 50 exposure days (38), but it may make healthcare providers cautious about switching treatments if the patient is stable on their current regimen. People with severe haemophilia usually develop inhibitors early during childhood, whilst people with mild or moderate conditions tend to develop them later in life (39). The UKHCDO treatment guidelines specifically address scenarios where a switch might occur, such as lack of anticipated clinical benefits, increased bleeding episodes, reduced trough levels of blood factors, non-adherence to the prescribed regimen, and non-compliance with Haemtrack™ (35). With the exception of non-compliance with Haemtrack™, these are aligned with the proposed reasons for switching in the company submission. In conclusion, treatment switching in haemophilia is an infrequent occurrence. The most likely time for a switch is early in a patient's life, after the initial exposures to treatment. Beyond this period, switches are typically driven by specific clinical indications and patient preferences rather than routine practice. This careful approach ensures that patients maintain stability and effective management of their condition, thereby minimising risks associated with treatment changes.
10	**Textual clarifications, factual inaccuracies, and typographical errors** ***Randomisation in XTEND-1*** The draft guidance states that a limitation of XTEND-1 is that there was no randomisation between on-demand and prophylactic efanesoctocog alfa for people having on-demand therapy when they entered the study. We are concerned that this is a misunderstanding of the trial design; in XTEND-1, patients in Arm B who were on an on-demand treatment regimen prior to the study received an on-demand regimen for the first 26 weeks, and then switched to a prophylaxis treatment regimen for another 26 weeks. Therefore, these patients did not need to be randomised. Note, there was no randomisation between patients in Arm A (receiving prophylaxis for 52 weeks) and Arm B (receiving on-demand treatment for 26 weeks followed by prophylaxis for 26 weeks) as the two arms enrolled patients with different pre-study regimens (Arm A: pre-study prophylaxis regimen; Arm B: pre-study on-demand regimen). ***Missing dosing regimen*** The draft guidance states that the Company also presented data from XTEND-Kids, a single-arm study in which 74 PTPs under 12 years had 50 IU/kg of efanesoctocog alfa for 52 weeks. Please clarify that dosing in this trial was once-weekly.

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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	Emicizumab wash-out period The draft guidance states that the trial excluded people who had emicizumab within the last 6 months. According to the trial eligibility criteria, the wash-out period for emicizumab was 20 weeks.
11	**Long-term benefits not captured by the quality-adjusted life years (QALY)** ***Improvements in joint damage*** Efanesoctocog alfa provides clinically meaningful disease control in patients with haemophilia A. In the short-term, this translates to fewer bleeds. In the long-term, better disease control means slower progression of joint damage, leading to improvements in quality of life and reduced requirement for surgical joint replacements. While this link is well-established, data quantifying how reducing the number of bleeds translates into slower progression of joint damage is not available for inclusion in the economic model, and so this impact will not be reflected in the ICER. ***Near-normal FVIII levels*** In patients aged 12 years and over, once-weekly prophylaxis with efanesoctocog alfa 50 IU/kg provided mean FVIII activity of >40 IU/dL for approximately 4 days after administration and >15 IU/dL at Day 7 (40). Mild haemophilia A is defined as FVIII activity of >5–<40 IU/dL (6), and more recently, near-normal FVIII levels have been defined as >40–<50 IU/dL (5). Therefore, patients aged ≥12 years treated with efanesoctocog alfa can be considered as having near-normal FVIII levels for 4 days of the week, and equivalent to having mild disease for the remaining 3 days. In comparison, patients treated with emicizumab have trough levels of plasma emicizumab expected to correspond to FVIII concentrations of at least 10–15 IU/dL, though this cannot be determined for certain (41). ***FVIII tolerance*** Clinicians have stated that children with severe haemophilia A being treated with emicizumab will inevitably still require treatment with rFVIII to cover bleeds during surgery or trauma, and late development of an inhibitor (in older childhood, adolescence or adulthood) will complicate any medical intervention, increase risk of bleeding, and will constitute a financial pressure on the NHS (12). There remains a strong argument for achieving tolerance to FVIII at a young age, as it allows access to all possible treatment options in adulthood. Patients who develop FVIII inhibitors and are treated with emicizumab may have issues in later life, as they cannot use rFVIII to treat bleeds. Rather they will require treatment with clotting Factor VIIa (FVIIa) products, which can be expensive and more burdensome with regard to administration. This is a notable issue when patients require surgery. Treatment with emicizumab requires additional rFVIII therapy to manage FVIII levels during surgery. Additional perioperative rFVIII therapy for a patient on emicizumab may be needed for 6–8 weeks.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix A: Alternative approaches to the indirect treatment comparisons

Efanesoctocog alfa versus emicizumab

Comparing Arm A of XTEND-1 to Arm D of HAVEN 3

Baseline characteristics

The baseline characteristics from Arm A of XTEND-1 and Arm D of HAVEN 3 are provided in Table 6. Across these trial arms, participants had comparable age, weight, and representation of Asian race. Compared with Arm D of HAVEN 3, Arm A of XTEND-1 had a lower proportion of White patients, patients with [redacted], a lower number of [redacted], and a higher proportion of patients with zero target joints.

Table 6: Baseline characteristics in XTEND-1 arm A and HAVEN 3 arm D

Characteristics	XTEND-1 Arm A	HAVEN 3 Arm D
	Total N=133	Total N=63
Age (years), mean (SD)	33.9 (15.3)	36.4 (14.4)
Weight (kg) mean (SD)	78.0 (19.3)	79.0 (15.42)
Race, n (%)		
White	71 (53.4)	47 (74.6)
Asian	29 (21.8)	12 (19.0)
Presence of targets joints, n (%)		
0 target joints	107 (80.5)	37 (58.7)
1 target joints	[redacted]	8 (12.7)
≥2 target joints	[redacted]	18 (28.6)
Number of any bleeds, mean (SD)	[redacted]	4.8†
% pts w/ <9 bleeds in prior 24 weeks (%)	[redacted]	84.1

†ABR in NIS participants, who were subsequently included in arm D of the HAVEN 3 trial.
Abbreviations: ABR, annualised bleeding rate; NIS, noninterventional study; pts, patients; SD, standard deviation.

The age of patients in HAVEN 3 ranged from 13 to 68 years and body weight from 52.8 to 139 kg. In total, [redacted] patients from the XTEND-1 population had characteristics outside of these ranges and were excluded before matching. A total of [redacted] XTEND-1 (Arm A) patients were included in the base-case scenario after harmonising the baseline characteristics ranges between XTEND-1 and HAVEN 3 (arm D) trials. [redacted] patients in the XTEND-1 trial had missing data for the number of any bleeds. Therefore, data from [redacted] patients in XTEND-1 were used in the updated MAIC with adjustment for pre-study ABR.

After matching for the base case, [redacted]% of XTEND-1 (Arm A) ESS was lost; the [redacted] (Table 7). Adding information on the number of any bleeds at baseline resulted in a loss of [redacted]% of the ESS.

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Table 7: Matching of baseline characteristics between XTEND-1 Arm A and HAVEN 3 Arm D

MAIC model	Variables	XTEND-1 arm A baseline			HAVEN 3 arm D (N=63)		XTEND-1 arm A after matching			
		Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS (%N)
Base case	Mean age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean weight	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	% White	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	% Asian	[redacted]			[redacted]		[redacted]			
	% pts w/ 0 TJ	[redacted]			[redacted]		[redacted]			
	% pts w/ 1 TJ	[redacted]			[redacted]		[redacted]			
	% pts w/ 2+ TJ	[redacted]			[redacted]		[redacted]			
Updated MAIC with adjustment for pre-study ABR	Mean age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean weight	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	% White	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	% Asian	[redacted]			[redacted]		[redacted]			
	% pts w/ 0 TJ	[redacted]			[redacted]		[redacted]			
	% pts w/ 1 TJ	[redacted]			[redacted]		[redacted]			
	% pts w/ 2+ TJ	[redacted]			[redacted]		[redacted]			
	Mean number of any bleeds	[redacted]	[redacted]		[redacted]†	[redacted]	[redacted]	[redacted]		

†ABR in NIS participants, who were subsequently included in ARM D of the HAVEN 3 trial.
Abbreviations: ABR, annualised bleeding rate; ESS, effective sample size; N/A, not applicable; NIS, noninterventional study; pts, patients; SD, standard deviation; TJ, target joint.

A histogram of weights for the base-case and updated MAIC with adjustment for pre-study ABR is provided in Figure 3 and Figure 4, respectively.

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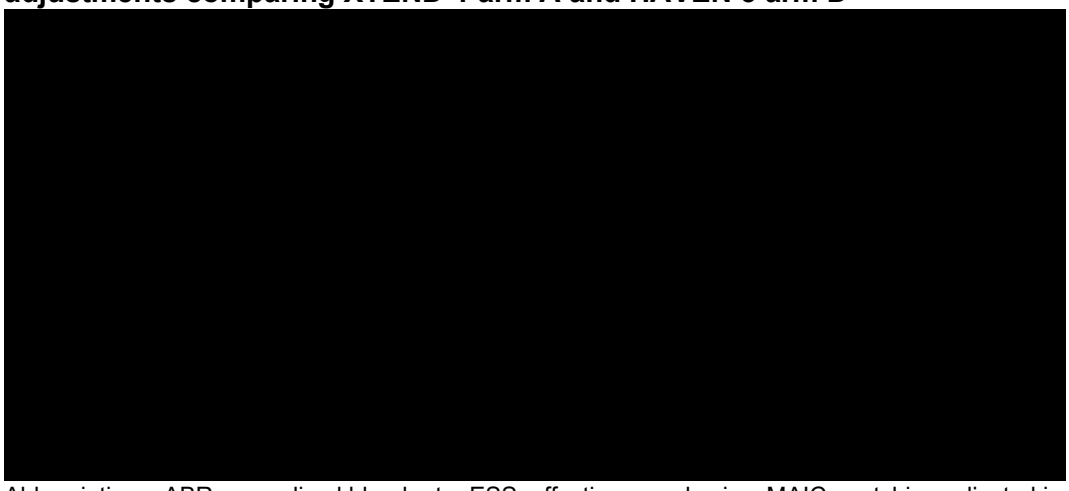
Figure 3: Base-case: histogram of weights from MAIC adjustments comparing XTEND-1 arm A and HAVEN 3 arm D

Abbreviations: ESS, effective sample size; MAIC, matching-adjusted indirect comparison.

Figure 4: Updated MAIC with adjustment for pre-study ABR: histogram of weights from MAIC adjustments comparing XTEND-1 arm A and HAVEN 3 arm D



Abbreviations: ABR, annualised bleed rate; ESS, effective sample size; MAIC, matching-adjusted indirect comparison.

Outcomes

The results for efficacy outcomes reported in both studies, used to compare efanesoctocog alfa with emicizumab are provided in Table 8.

Table 8: Efanesoctocog alfa vs emicizumab efficacy outcomes

Efficacy outcome	XTEND-1 arm A	HAVEN 3 arm D
	Total N=133	Total N=63
ABR any, mean (95% CI)	[redacted]	3.3 (2.2, 4.8)
ABR any treated, mean (95% CI)	[redacted]	1.6 (1.1, 2.4)
ABR spontaneous (treated), mean (95% CI)	[redacted]	0.5 (0.2, 0.9)
ABR joint (treated), mean (95% CI)	[redacted]	1.2 (0.7, 2.0)

Abbreviations: ABR, annualised bleeding rate; CI, confidence interval.

The ABR for emicizumab was estimated with negative binomial model. The outcomes for XTEND-1 were estimated similarly. Compared with emicizumab, efanesoctocog alfa was associated with a [redacted] rate of any bleeding, treated bleeding, and joint bleeding events in the naïve and base-case scenarios (Figure 5). It was also associated with [redacted] estimates for spontaneous and joint bleeding events in the case of the updated MAIC with adjustment for pre-study ABR.

Figure 5: Comparison of ABRs for efanesoctocog alfa compared with emicizumab

Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; IRR, incidence rate ratio; MAIC, matching-adjusted indirect comparison.

Efanesoctocog alfa versus efmoroctocog alfa in emicizumab population

MAIC adjusting both the A-LONG and XTEND-1 populations to the aggregate data from HAVEN 3

Baseline characteristics

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The baseline characteristics from the A-LONG individualised prophylaxis study and the HAVEN 3 trial arm D are provided in Table 9. Compared with HAVEN 3 Arm D, patients in the A-LONG individualised prophylaxis study had [redacted].

Table 9: Baseline characteristics in A-LONG individualised prophylaxis and HAVEN 3 Arm D

Characteristics	A-LONG individualised prophylaxis	HAVEN 3 Arm D
	Total N=117	Total N=63
Age (years), mean (SD)	[redacted]	36.4 (14.4)
Weight (kg) mean (SD)	[redacted]	79.0 (15.4)
Race, n (%)		
White	[redacted]	47 (74.6)
Asian	[redacted]	12 (19.0)
Presence of targets joints, n (%)		
0 target joints	[redacted]	37 (58.7)
1 target joints	[redacted]	8 (12.7)
≥2 target joints	[redacted]	18 (28.6)
Number of any bleeds, mean (SD)	[redacted]	4.8†
Prior prophylaxis, n (%)	[redacted]	63 (100)
Prior on-demand, n (%)	[redacted]	0 (0)

†ABR in NIS participants, who were subsequently included in ARM D of the HAVEN 3 trial.
Abbreviations: ABR, annualised bleed rate; NIS, noninterventional study; SD, standard deviation.

In total, [redacted] out of 117 patients received previous prophylactic therapy in the individualised prophylaxis arm ([redacted] patients received on-demand therapy and were excluded). The age of HAVEN 3 participants ranged from 13 to 68 years and body weight from 52.8 to 139 kg. [redacted] patients from the A-LONG population had characteristics outside of these ranges and were excluded before matching.

A total of [redacted] A-LONG (individualised prophylaxis) patients were included in the base-case scenario after harmonising the baseline characteristics ranges between A-LONG and HAVEN 3 (Arm D) trials. [redacted] patient in the XTEND-1 trial had missing data for the number of any bleeds. Therefore, data from [redacted] A-LONG patients were used in the updated MAIC with adjustment for pre-study ABR.

After matching for base case, [redacted]% of the A-LONG (individualised prophylaxis) ESS was lost; the [redacted] difference between studies was in the proportions of patients with [redacted]). Adding information on the number of any bleeds at baseline resulted in a loss of [redacted]% of the ESS; the [redacted] difference between studies was in the mean number of any bleeds ([redacted] among patients from A-LONG [individualised prophylaxis] versus 4.8 among patients from the HAVEN 3 study).

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Table 10: Matching of baseline characteristics between A-LONG individualised prophylaxis and HAVEN 3 Arm D

MAIC model	Variables	A-LONG individualised prophylaxis baseline			HAVEN 3 Arm D (N=63)		A-LONG after matching			
		Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS (%N)
Base case	Mean age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean weight	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	% White	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	% Asian	[redacted]			[redacted]		[redacted]			
	% pts w/ 0 TJ	[redacted]			[redacted]		[redacted]			
	% pts w/ 1 TJ	[redacted]			[redacted]		[redacted]			
	% pts w/ 2+ TJ	[redacted]			[redacted]		[redacted]			
Updated MAIC with adjustment for pre-study ABR	Mean age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean weight	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	% White	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
	% Asian	[redacted]			[redacted]		[redacted]			
	% pts w/ 0 TJ	[redacted]			[redacted]		[redacted]			
	% pts w/ 1 TJ	[redacted]			[redacted]		[redacted]			
	% pts w/ 2+ TJ	[redacted]			[redacted]		[redacted]			
	Mean number of any bleeds	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: ABR, annualised bleeding rate; ESS, effective sample size; ind, individualised; N/A, not applicable; MAIC, matching-adjusted indirect comparison; pts, patients; SD, standard deviation; TJ, target joint.

A histogram of weights for the base-case and updated MAIC adjusting for pre-study ABR is provided in Figure 6 and Figure 7, respectively.

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Figure 6: Base-case: histogram of weights from MAIC adjustments comparing A-LONG individualised prophylaxis and HAVEN 3 Arm D

Abbreviations: ESS, effective sample size; MAIC, matching-adjusted indirect comparison.

Figure 7: Extended MAIC 1: histogram of weights from MAIC adjustments comparing A-LONG individualised prophylaxis and HAVEN 3 Arm D

Abbreviations: ESS, effective sample size; MAIC, matching-adjusted indirect comparison.

Outcomes

ABR for efmoroctocog alfa was estimated with negative binomial model. The outcomes for XTEND-1 were estimated similarly.

Compared with efmoroctocog alfa, efanesoctocog alfa was associated with a [redacted] rate of treated bleeding, spontaneous bleeding and joint bleeding events (**Figure 8**).

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Figure 8: Comparison of ABRs for efanesoctocog alfa compared with efmoroctocog alfa

Abbreviations: ABR, annualised bleed rate; CI, confidence interval; IRR, incidence rate ratio; MAIC, matching-adjusted indirect comparison.

Summary of comparisons between all treatments

Base-case

A summary of comparisons for ABRs between all treatments is provided in Table 1. The comparisons were adjusted for age, weight, representations of White and Asian race, and representations of patients with 0, 1, ≥2 target joints. Baseline characteristics of XTEND-1 and ALONG participants were matched to the HAVEN 3 population.

Updated MAIC adjusting for pre-study ABRs

A summary of comparisons for ABRs between all treatments is provided in Table 2. The comparisons were adjusted for age, weight, representations of White and Asian race, representations of patients with 0, 1, ≥2 target joints, and number of any bleeds. Baseline characteristics of XTEND-1 and ALONG participants were matched to HAVEN 3 population.

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MAIC anchored by pre-study ABRs

Intra-patient comparisons in XTEND-1 and HAVEN 3 to anchor an ITC using prior SHL and EHL factor VIII therapy as the common comparator

Both XTEND-1 and HAVEN 3 provided the results of intra-patient comparisons. Both comparisons were conducted on the subset of patients who received prophylaxis in respective trials and the preceding prospective studies. The analysis was conducted on [redacted] out of [redacted] XTEND-1 Arm A patients (Table 11) and 48 out of 63 HAVEN 3 Arm D patients (Table 12).

The analyses were conducted using the pre-post approach comparing the ABR observed in respective trials with ABR values observed in the corresponding preceding studies in which participants were receiving standard FVIII prophylaxis. Data were correlated as the same patients were analysed in the interventional and non-interventional studies.

Both analyses reported incidence rate ratios (IRRs) allowing the assessment of the reduction of the incidence of bleeds in the respective trials compared with the corresponding non-interventional studies (pre-study versus on-study).

The estimated pre-study ABR was [redacted]% higher in HAVEN 3 patients compared with participants from the XTEND-1 study ([redacted]). The pre-study ABR may have an important impact on the IRR since the association between pre- and on-study ABRs is not linear. Moreover, a higher pre-study ABR in HAVEN 3 compared with XTEND-1 served a greater room for improvement and favoured emicizumab.

Table 11: XTEND-1 intrapatient comparisons

XTEND-1	Group A (N=133)	
	Pre-study prophylaxis	Efanesoctocog alfa prophylaxis
Primary endpoint		
ABR for efanesoctocog alfa prophylaxis		
Median ABR (IQR)	–	0 (0–1.04)
Mean ABR (95% CI), model based	–	0.71 (0.52–0.97)
Patients with zero bleeding episodes – no. (%)	–	86 (65)
Key secondary endpoint		
Intrapatient ABR comparison		
No. of pts evaluated	78	78
Median (IQR)	1.06 (0, 3.74)	0 (0, 1.04)
Mean ABR (95% CI), model based	2.96 (2.00, 4.37)	0.69 (0.43, 1.11)
Rate ratio vs. prestudy prophylaxis (95% CI)	–	0.23 (0.13, 0.42)
P value for superiority	–	P<0.001

Abbreviations: ABR annualised bleeding rate; CI, confidence interval; IQR, interquartile range.

Table 12: HAVEN 3 intrapatient comparisons

HAVEN 3	Group D in current trial: emicizumab prophylaxis (N=48)	Noninterventional study: Factor VIII prophylaxis (N=48)
Median duration of efficacy period (range), week	[redacted]	[redacted]

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HAVEN 3	Group D in current trial: emicizumab prophylaxis (N=48)	Noninterventional study: Factor VIII prophylaxis (N=48)
Annualised rate of bleeding events, model-based (95% CI)	[redacted]	[redacted]
Rate ratio vs control (95% CI)	[redacted]	[redacted]
Percent difference vs control	[redacted]	[redacted]
Median annualised rate of bleeding events (IQR)	[redacted]	[redacted]
Percent of participants with 0 bleeding events (95% CI)	[redacted]	[redacted]
Percent of participants with 0–3 bleeding events (95% CI)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IQR, interquartile range.

To account for differences in pre-study ABRs, a MAIC was conducted where [redacted] XTEND-1 patients were assigned weights to balance the pre-study ABR to value [redacted] reported in the noninterventional study preceding HAVEN 3 (Table 13). No other baseline characteristics were available for those [redacted] participants from HAVEN 3.

Table 13: Matching of pre-study ABRs for EXTEND-1 and HAVEN 3 Arm D

Variables	XTEND-1 (n=78)		HAVEN 3 arm D (N=48)	XTEND-1 after matching		
	Estimate	N	Estimate	Estimate	ESS	ESS (%N)
Pre-study ABR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, annualised bleeding rate; ESS, effective sample size; neg-bin, negative-binomial.

The ABRs of [redacted] XTEND-1 patients (both pre- and on-study) were re-estimated using weights generated during MAIC. The pre-study and on-study bleeding rates were estimated using separate negative binomial regression models, with and without weights generated using MAIC. After weighting, the estimated pre-study ABR for treated bleeds [redacted] from [redacted], which [redacted] with the bleeding rate reported for the non-interventional study preceding HAVEN 3. At the same time the estimated on-study ABRs remained [redacted] after weighting.

The IRRs versus pre-study ABRs were estimated using negative binomial regression models using unweighted and weighted data. Due to convergence issues, the effect of random intercept was omitted, however this had [redacted] on the estimate for unweighted comparison, [redacted].

The IRR estimated using weighted data was [redacted], which can be interpreted as follows: The replacement of the routine prophylaxis with efanesoctocog alfa in patients with ABR of [redacted] (population of HAVEN 3 pre-study) leads to [redacted]% reduction of the incidence of treated bleeds.

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Table 14: Comparison of ABRs in XTEND-1 using weights generated during the MAIC

	N	Unweighted ABR (95% CI)	Rate ratio versus pre-study (unweighted) (95% C()	Weighted ABR (95% CI)	Rate ratio versus pre-study (weighted) (95% CI)
			Negative binomial regression		Negative binomial regression
Pre-study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-study	[redacted]	[redacted]		[redacted]	

†Due to convergence issues, the effect of random intercept was omitted; however, this had [redacted] on the estimate for unweighted comparison, which were the [redacted] compared with those presented in the XTEND-1 manuscript (0.23 [0.13; 0.42]).
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; MAIC, matching-adjusted indirect comparison.

The re-estimated effect of efanesoctocog alfa in the population of HAVEN 3 was compared with the effect reported for emicizumab. The result of this comparison indicates that the replacement of standard FVIII prophylaxis with efanesoctocog alfa in patients with ABR = [redacted] allows for [redacted] greater reduction in the treated bleeds compared with the replacement using emicizumab (Table 15).

Table 15: Comparison of efanesoctocog alfa in the population of HAVEN 3 with emicizumab

	XTEND-1			HAVEN 3			Weighted rate ratio between XTEND-1 and HAVEN 3
	N	Re-weighted ABR (95%CI)	Rate ratio versus pre-study (weighted)	N	ABR (95%CI)	Rate ratio versus pre-study	
			Negative binomial regression			Negative binomial regression	
Pre-study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-study	[redacted]	[redacted]		[redacted]	[redacted]		

Abbreviations: ABR, annualised bleed rate; CI, confidence interval.

Appendix B: Utility analyses

Analysis based on combined XTEND-1, A-LONG and ASPIRE trials

FVIII activity at each bleeding event – XTEND-1, A-LONG, and ASPIRE

Out of all categories, the participants spent most of the time in the category with FVIII concentration >50%. Frequencies of bleeds were highest in categories with lower FVIII activity. The raw proportion of patients without any bleeds was not meaningful due to large differences in time spent across FVIII categories.

Table 16: FVIII activity at each bleeding event

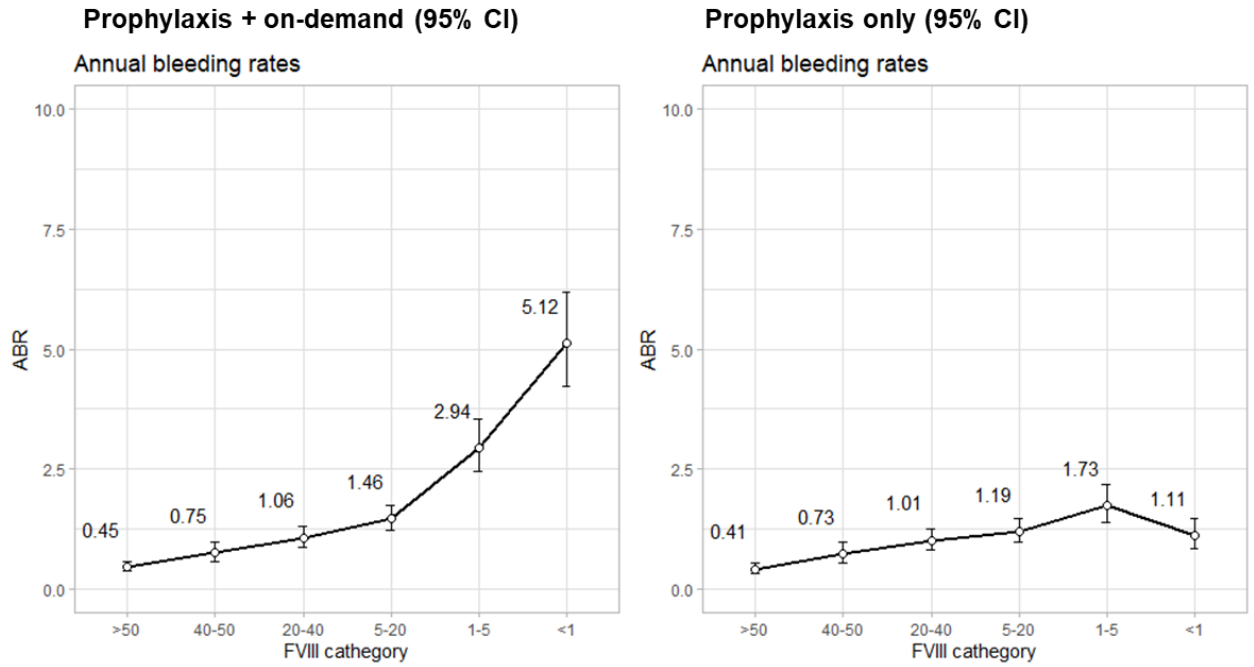
FVIII category		Pts analysed N	Total PYs spent in the category	% of time spent	Total number of any bleeds	ABR		Raw % of pts without any bleeds
ID	Definition					Crude	Estimated	
Prior prophylaxis + on-demand								
1	>50%	504	188.54	23%	198	1.05	0.45	81%
2	40%-50%	504	47.74	6%	79	1.65	0.75	89%
3	20%-40%	504	147.41	18%	345	2.34	1.06	75%

4	5%-20%	504	233.05	29%	703	3.01	1.46	60%
5	1%-5%	416	120.27	15%	678	5.63	2.94	58%
6	<1%	355	73.87	9%	1,056	14.28	5.12	67%
Prior prophylaxis only								
1	>50%	379	163.99	25%	174	1.06	0.41	78%
2	40%-50%	379	40.65	6%	73	1.79	0.73	87%
3	20%-40%	379	125.03	19%	304	2.43	1.01	72%
4	5%-20%	379	193.96	30%	547	2.82	1.19	60%
5	1%-5%	291	93.14	14%	371	3.98	1.73	65%
6	<1%	236	39.04	6%	111	2.84	1.11	82%

Abbreviations: ABR, annualised bleeding rate; FVIII, clotting factor FVIII; pts, patients; PY, patient years.

The negative-binomial model with random-effect intercept for Subject ID could not converge, therefore a Poisson regression was run. The estimated frequency of bleeding was relatively low for FVIII activity >20%, but increased in the categories with lower FVIII activity (Figure 9). In the subset of patients who were receiving prophylaxis before trial entry, the association between bleeding frequency and FVIII concentration was not very clear.

Figure 9: ABRs by FVIII concentration



Abbreviations: ABR, annualised bleed rate; CI, confidence interval; FVIII, clotting factor VIII.

TOBIT and linear models

The mean baseline utility values for previous prophylaxis or on demand treatment are provided in Table 17. The results of the regression coefficients are described in Abbreviations: SD, standard deviation.

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Table 18 using the TOBIT model, and Table 19 using the linear model.

Table 17: Mean baseline utility values

Previous treatment	Number of patients	Mean baseline utility (±SD)
Prophylaxis	335	0.7784 (0.2162)
On-demand	125	0.7695 (0.1900)
Any	460	0.7760 (0.2092)

Abbreviations: SD, standard deviation.

Table 18: TOBIT model regression co-efficients

Variable		Results of the regression coefficients							
		Prophylaxis only							
		Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**
Intercept		**0.4119**	**0.4868**	**0.4851**	**0.4864**	**0.3849**	**0.4675**	**0.4613**	**0.4491**
Baseline utility		**0.8092**	**0.7692**	**0.7690**	**0.7642**	**0.8151**	**0.7747**	**0.7747**	**0.7762**
7d_bleed_disutility		**–0.0676**	**–0.0663**	**–0.0661**	**–0.0649**	**–0.0789**	**–0.0760**	**–0.0757**	**–0.0738**
6m_bleed_disutility		**–0.0396**	**–0.0435**	**–0.0434**	**–0.0432**	**–0.0479**	**–0.0447**	**–0.0446**	**–0.0441**
Days since study initiation		**–0.00005**	**–0.00007**	**–0.00007**	**–0.00007**	Not used	Not used	Not used	Not used
Age		**–0.0047**	**–0.0053**	**–0.0053**	**–0.0052**	**–0.0047**	**–0.0053**	**–0.0053**	**–0.0052**
Proportion of time in <5%		Not used	Not used	Not used	–0.0782	Not used	Not used	Not used	**–0.1231**
Proportion of time in <15%		Not used	Not used	–0.0299	Not used	Not used	Not used	–0.0728	Not used
Proportion of time in <20%		Not used	–0.0277	Not used	Not used	Not used	–0.0728	Not used	Not used
Model fit	BIC	137.641	169.365	169.250	167.688	151.738	187.544	187.167	184.840
	AIC	95.750	123.101	122.986	121.424	115.083	146.420	146.043	143.717

Statistically significant results are in **bold**.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 19: Linear model regression co-efficients

Variable	Results of the regression coefficients								
	Prophylaxis only								
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**	**Model 9**
Intercept	**0.4248**	**0.4866**	**0.4813**	**0.4707**	**0.4132**	**0.4787**	**0.4713**	**0.4554**	**0.4588**
Baseline utility	**0.6152**	**0.5841**	**0.5841**	**0.5860**	**0.6153**	**0.5843**	**0.5844**	**0.5871**	**0.5868**
7d_bleed_disutility	**–0.0498**	**–0.0494**	**–0.0493**	**–0.0490**	**–0.0569**	**–0.0555**	**–0.0553**	**–0.0548**	**–0.0548**
6m_bleed_disutility	**–0.0298**	**–0.0321**	**–0.0320**	**–0.0320**	**–0.0361**	**–0.0332**	**–0.0330**	**–0.0330**	**–0.0329**

Variable		Results of the regression coefficients								
		Prophylaxis only								
Days since study initiation		**0.00004**	**–0.00005**	**0.00005**	**–0.00004**	Not used	Not used	Not used	Not used	Not used
Age		**–0.0028**	**–0.0031**	**–0.0031**	**–0.0030**	**–0.0029**	**–0.0032**	**–0.0032**	**–0.0031**	**–0.0031**
Proportion of time in <5%		Not used	Not used	Not used	–0.0601	Not used	Not used	Not used	**–0.0875**	**–0.0880**
Proportion of time in <15%		Not used	Not used	–0.0469	Not used	Not used	Not used	**–0.0697**	Not used	Not used
Proportion of time in 5–20%		Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	–0.0096
Proportion of time in <20%		Not used	–0.0492	Not used	Not used	Not used	**–0.0726**	Not used	Not used	Not used
Model fit	BIC	–1277.0	–1089.5	–1089.4	–1090.2	–1287.6	–1096.6	–1096.9	–1097.9	–1087.2
	AIC	–1318.9	–1135.7	–1135.7	–1136.4	–1324.3	–1137.7	–1138.0	–1139.0	–1133.5

Statistically significant results are in **bold**.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Analyses using only treated bleeds from XTEND-1 (all bleeds were treated in A-LONG and ASPIRE) were also considered, however as the majority of bleeds were treated results across the 3 trials, results are comparable between the two analyses. Models using only untreated bleeds were not possible due to the low number of events.

Table 20: TOBIT model regression coefficients, treated bleeds only

Variable	Results of the regression coefficients							
	Prophylaxis only							
Intercept	**0.4144**	**0.4867**	**0.4859**	**0.4882**	**0.3887**	**0.4669**	**0.4612**	**0.4511**
Baseline utility	**0.8058**	**0.7647**	**0.7646**	**0.7609**	**0.8108**	**0.7706**	**0.7709**	**0.7726**
7d_bleed_disutility	**–0.0692**	**–0.0679**	**–0.0678**	**–0.0664**	**–0.0808**	**–0.0778**	**–0.0774**	**–0.0754**
6m_bleed_disutility	**–0.0409**	**–0.0447**	**–0.0446**	**–0.0442**	**–0.0497**	**–0.0463**	**–0.0462**	**–0.0457**
Days since study initiation	**–0.00005**	**–0.00007**	**–0.00007**	**–0.00006**	Not used	Not used	Not used	Not used
Age	**–0.0047**	**–0.0053**	**–0.0053**	**–0.0052**	**–0.0047**	**–0.0053**	**–0.0053**	**–0.0052**

Variable		Results of the regression coefficients							
		Prophylaxis only							
Proportion of time in <5%		Not used	Not used	Not used	–0.0722	Not used	Not used	Not used	**–0.1152**
Proportion of time in <15%		Not used	Not used	–0.0225	Not used	Not used	Not used	–0.0644	Not used
Proportion of time in <20%		Not used	–0.0197	Not used	Not used	Not used	–0.0638	Not used	Not used
Model fit	BIC	137.084	168.959	168.876	167.417	150.548	186.836	186.513	184.223
	AIC	95.193	122.695	122.612	121.153	113.894	145.712	145.389	143.099

Statistically significant results are in **bold**.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 21: Linear model regression coefficients, treated bleeds only

Variable	Results of the regression coefficients								
	Prophylaxis only								
Intercept	**0.4269**	**0.4856**	**0.4811**	**0.4721**	**0.4160**	**0.4779**	**0.4712**	**0.4572**	**0.4572**
Baseline utility	**0.6123**	**0.5811**	**0.5812**	**0.5828**	**0.6118**	**0.5811**	**0.5812**	**0.5837**	**0.5837**
7d_bleed_ disutility	**–0.0519**	**–0.0512**	**–0.0511**	**–0.0508**	**–0.0592**	**–0.0574**	**–0.0571**	**–0.0567**	**–0.0567**
6m_bleed_ disutility	**–0.0304**	**–0.0322**	**–0.0321**	**–0.0322**	**–0.0372**	**–0.0337**	**–0.0335**	**–0.0336**	**–0.0336**
Days since study initiation	**0.00004**	**–0.00005**	**0.00005**	**–0.00004**	Not used	Not used	Not used	Not used	Not used
Age	**–0.0029**	**–0.0031**	**–0.0031**	**–0.0031**	**–0.0029**	**–0.0032**	**–0.0032**	**–0.0031**	**–0.0031**
Proportion of time in <5%	Not used	Not used	Not used	–0.0552	Not used	Not used	Not used	**–0.0820**	**–0.0820**
Proportion of time in <15%	Not used	Not used	–0.0412	Not used	Not used	Not used	**–0.0635**	Not used	Not used
Proportion of time in 5–20%	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	–0.0002

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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Variable		Results of the regression coefficients								
		Prophylaxis only								
Proportion of time in <20%		Not used	–0.0432	Not used	Not used	Not used	**–0.0660**	Not used	Not used	Not used
Model fit	BIC	–1277.5	–1089.4	–1089.4	–1090.2	–1288.7	–1096.9	–1097.1	–1098.2	–1087.6
	AIC	–1319.4	–1135.7	–1135.7	–1136.5	–1325.3	–1138.0	–1138.2	–1139.4	–1133.8

Statistically significant results are in **bold**.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

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Appendix C: Updated economic analyses

This appendix details the changes that have been made to the economic analysis to address concerns raised in the ACD. The rationale for the changes and for the scenario analyses performed is presented in the Company response to draft guidance. In addition to these changes, an updated PAS has also been included in the model, reducing the cost of efanesoctocog alfa to £[redacted]

Comparators

Following the draft guidance, the list of comparators included in the economic analysis has been updated. The committee requested that both SHLs and EHLs be included in the analysis for PUPs and for PTPs. As outlined in the response to the draft guidance, the company do not believe that SHLs are a relevant comparator in either population, and estimates of cost effectiveness vs SHLs have not been presented in the base case analysis. However, scenario analyses comparing to SHLs have been included. The assumptions on comparators used for the updated analyses are presented below.

Previously untreated patients

In PUPs, the committee preference was for the model to include SHL FVIII replacements therapies, including octocog alfa, simoctocog alfa and moroctocog alfa. As per the response to draft guidance, it has been assumed that only simoctocog alfa (NuwiQ) would be used, based on clinical feedback received.

According the SmPC, the usual dose for prophylaxis is 20–40 IU/kg, however shorter dose intervals or higher doses may be necessary for children or adolescents (42). This aligned with clinical feedback that the typical dose in PUPs was 30-50 IU/kg every 2–3 days. The mid-point of these figures has been selected for the dosing in the economic analysis, with a dose of 40 IU/kg every 2.5 days assumed.

As efmoroctocog alfa is the only EHL licensed for use in under 12s, no changes to the assumptions on EHL use in PUPs is required.

Previously treated patients

In PTPs, the committee requested both SHLs (octocog alfa, simoctocog alfa and moroctocog alfa) and EHLs (efmoroctocog alfa and, in PTPs only, turoctocog alfa pegol and rurioctocog alfa pegol) be included in the analysis. These have been incorporated into the model, under the assumption that there is no difference in efficacy between different treatments within each class, and only the costs will differ between therapies. As such, SHLs have each been incorporated as a single comparator, consisting of a weighted bucket of treatments at different prices, with weights taken from UKHCDO data. EHLs have been considered both separately and as a weighted bucket. Weights are shown in Table 22, rurioctocog alfa pegol has been excluded as it is no longer in the tender framework.

The dose of SHLs in PTPs is assumed to be 30 IU/kg every 2-3 days, in line with the SmPCs (42-45). For EHLs, the recommended dose of turoctocog alfa pegol is 50 IU/kg every 4 days (46), which is aligned with the dosing for efmoroctocog alfa.

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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Table 22: Weights used for drug costs

	Drug	% of patients	Cost per unit
EHLs	Efmoroctocog alfa	50%	[redacted]
	Turoctocog alfa pegol	50%	£0.85
SHLs	Simoctocog alfa	5%	£0.76
	Moroctocog alfa	30%	£0.50
	Turoctocog alfa	12%	£0.55
	Octocog alfa	53%	£0.71

Abbreviations: EHL, extended half-life; SHL, standard half-life.

Treatment efficacy

ABRs in the model have been updated in line with the analyses outlined in the response to draft guidance and presented in Appendix A. In the base-case analysis, the baseline rate of bleeds is taken from HAVEN-3, with rate ratios from the MAIC analyses including ABR at baseline as a matching factor used to determine the ABRs for efanesoctocog alfa and EHLs. The following scenarios have also been considered:

- Using the base-case MAIC to calculate ABRs for efanesoctocog alfa and EHLs
- Using the ABRs from XTEND-1 as the baseline
- Excluding untreated bleeds
- Using the intra-patient comparison ITC to calculate ABRs for efanesoctocog alfa and emicizumab, and using the intra-patient comparison from XTEND-1 for EHLs.

Where data from the MAIC is only available for treated bleeds, it has been assumed that the same treatment effect will hold for all bleeds. In scenarios using ABRs from the subgroups of patients using either SHLs or EHLs as their prior prophylaxis in XTEND-1, no ABRs for all bleeds have been calculated, and it is assumed that the ratio of all bleeds to treated bleeds is the same as in the total population.

For comparisons with SHLs, the intra-patient comparison from XTEND-1 has been used as the base-case. The proportion of patients experiencing a bleed with SHLs and EHLs has been taken from the pre-trial period in XTEND-1 (58%).

For patients treated with emicizumab, it is assumed that 30% of patients will have FVIII equivalence in the range 5-20% at any given time.

Utility values

Utility values have been re-estimated using data from XTEND-1, A-LONG and ASPIRE, with a variety of model specifications explored, as described in Appendix B. In the base-case analysis, the tobit model has been retained, as it accounts for floor and ceiling effects in utility data, and the analysis applies a disutility for FVIII <20%, as per the company submission. The analysis has been updated to use the baseline utility values observed in the trial data for FVIII above 20% and baseline utility values are adjusted with age proportional to the general population norms. Values used in the model base case are presented in Table 23.

Table 23: Utility values used in the base-case analysis

Health state	Utility value
FVIII>20% and no bleed in the last 6 months	0.7784
FVIII<20% and no bleed in the last 6 months	0.7349
FVIII>20% and a bleed in the last 6 months	0.7507
FVIII<20% and a bleed in the last 6 months	0.7072
Short-term disutility for a bleed	–0.0663

Abbreviations: FVIII, clotting factor VIII.

The following scenario analyses have been included:

- Disutility for FVIII<15%
- Disutility for FVIII<5%
- Separate disutilities for FVIII<5% and FVIII between 5% and 20%
- Age adjustments applied using the age coefficient in the utility models
- Linear models for utility
- No disutility associated with FVIII
- No disutility associated with FVIII for emicizumab
- Disutilities associated with infusion more than once a week.

Disutilities for more frequent infusions were taken from the CHESS II study (18), with the different values applied presented in Table 24. While more values are presented in the analysis, the selected value below include the largest and smallest estimated disutility.

Table 24: Disutilities for more frequent infusions

Model	Disutility
No effect	0
OLS B	-0.0745
Model 1	-0.027
Model 4	-0.107

Abbreviations: OLS, ordinary less squares.

Costs and resource use

The following changes have been made for costs and resource use in the model:

- Updated PAS for efanesoctocog alfa
- The cost of prophylactic treatments includes vial wastage based on weight, calculated using the method of moments
- The wastage of FVIII associated with emicizumab is calculated based on patients requiring 2 25 IU/kg doses available for treating bleeds. This cost is applied to the proportion of patients that will

not experience a treated bleed in a 2-year period, which is calculated as the probability of not having a treated bleed in 6 months, to the power of 4.

  - Scenario analyses without this cost have been included

- The cost of outpatient contacts for treating a bleed has been updated to the average cost of a haemophilia contact, including consultant led and non-consultant led and face-to-face and non-face-to-face contacts (£512.74)

  - Scenarios using a lower cost (non-consultant led, non-face-to-face, £345) for a single visit and without any resource use associated with a bleed have also been explored

- A single 50 IU/kg dose is assumed for treating bleeds with efanesoctocog alfa.

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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Updated model base case

Previously untreated patients

Table 25 presents the base-case results for PUPs. Efanesoctocog alfa is more effective and less costly than EHLs and emicizumab and is the dominant treatment option. Table 26 presents the outputs of the probabilistic analysis, which are well aligned with the deterministic results.

Table 25: Deterministic base-case results, PUPs (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	-	-	-	-	-
EHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: EHL, extended half-life; ICER, incremental cost-effectiveness ratio; LYF, life years gained; PAS, Patient Access Scheme; PUP, preciously untreated patients; QALY, quality-adjusted life years.

Table 26: Probabilistic results, PUPs (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: EHL, extended half-life; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; PUP, preciously untreated patients; QALY, quality-adjusted life years.

Previously treated patients

Table 27 and Table 28 presents the base-case results for PTPs with EHLs as separate comparators and with EHLs as a weighted bucket respectively. Efanesoctocog alfa is more effective and less costly than EHLs and emicizumab and is the dominant treatment option. Table 29 presents the outputs of the probabilistic analysis, which are well aligned with the deterministic results.

Table 27: Deterministic base-case results, PTPs (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Efmoroctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Turoctocog alfa pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: EHL, extended half-life; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; PTP, preciously treated patients; QALY, quality-adjusted life years.

Table 28: Deterministic base-case results, PTPs with EHLs combined (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	-	-	-	-	-
EHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: EHL, extended half-life; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; PTP, preciously treated patients; QALY, quality-adjusted life years.

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Table 29: Probabilistic results, PTPs (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: EHL, extended half-life; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; PTP, preciously treated patients; QALY, quality-adjusted life years.

Scenario analyses

Table 30 summarises the scenario analyses that have been carried out. In the PTP population, scenarios have been considered comparing the available EHLs individually, though retaining the assumption of equivalent efficacy. In both populations, scenarios considering different combinations of efficacy inputs have been considered, as have scenarios using different resource use assumptions, and excluding the cost of wasted FVIII for emicizumab. A number of scenarios have been considered using different utility values, and combinations of different assumptions.

Table 30: Scenario analyses considered

Scenario	Details
EHLs = 100% efmoroctocog alfa (PTPs only)	All EHL use is assumed to be efmoroctocog alfa
EHLs = 100% turoctocog alfa pegol (PTPs only)	All EHL use is assumed to be turoctocog alfa pegol
Baseline ABRs from XTEND-1	Baseline ABR from XTEND-1, with treatment effects for EHLs and emicizumab from the extended MAIC
Base-case MAIC without prior bleeds adjustment	Baseline ABR from HAVEN-3, with treatment effect from the MAIC without adjustment for prior bleeds
Intra-patient comparison	Baseline ABR from XTEND-1, with treatment effects for EHLs from the XTEND-1 intra-patient comparison and emicizumab from the intra-patient ITC
Intra-patient comparison in prior EHL patients only	Baseline ABR from XTEND-1 using the subgroup previously treated with EHLs, with treatment effects for EHLs from the XTEND-1 intra-patient comparison and emicizumab from the intra-patient ITC
Excluding untreated bleeds	Uses the rate of treated bleeds from HAVEN-3 as the baseline ABR
Lower resource use for treating bleeds	A single outpatient contact is required, with a cost £345.90
No resource use for treating bleeds	No resource use for treating bleeds
Utility model 6	The utility model excluding the coefficient for time in study is used
Linear model for utility	A linear model is used to assess utility scores, using the same coefficients as in the base-case
FVIII <15% for utility decrement	A FVIII cut-off of 15% is used for disutilities (Model 3)
FVIII <5% for utility decrement	A FVIII cut-off of 5% is used for disutilities (Model 4)
No FVIII decrement	No disutility associated with FVIII (Model 1)
No FVIII decrement for emicizumab	No utility decrement linked to FVIII is applied for emicizumab
No FVIII decrement for emicizumab, FVIII threshold <15%	A FVIII cut-off of 15% is used for disutilities, with no utility decrement for emicizumab
No FVIII decrement for emicizumab, linear model	No utility decrement linked to FVIII is applied for emicizumab and a linear model is used
No FVIII decrement for emicizumab, FVIII threshold <15%, linear model	No utility decrement linked to FVIII is applied for emicizumab and a linear model with a decrement for FVIII <15% is used
Utility decline with age from model	Utility declines with age as per the regression model, rather than proportionally to general population norms.
Frequent infusion disutility -0.027	Disutilities associated with more frequent infusions are included for the EHL arm

Scenario	Details
Frequent infusion disutility -0.0745	
Frequent infusion disutility -0.107	

Abbreviations: ABR, annualised bleed rate; EHL, extended half-life; FVIII, clotting factor VIII; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; PAS, Patient Access Scheme; PTP, patient treated population.

Previously untreated patients

Table 31 summarises the outputs of the scenario analyses for PUPs. The scenario analysis demonstrates that the results are not sensitive to the choices of clinical data used to estimate ABRs for each comparator. In each scenario varying the ABRs, efanesoctocog alfa remains the most effective treatment and the variation in incremental QALYs is small.
Changing assumptions around resource use have only a minor impact in the comparison with emicizumab, as incremental costs are driven by the list price for emicizumab. In scenarios reducing the resource use associated with a bleed and removing the cost of wasted FVIII with emicizumab, efanesoctocog alfa remains the dominant treatment. These scenarios are considered conservative, as the model is not accounting for the potential for increased resource use associated with bleeds for patients treated with emicizumab. Compared to EHLs, which for PUPs is only efmoroctocog alfa, efanesoctocog alfa remains dominant when a lower cost is applied for resource associated with a bleed, though when this cost is excluded entirely, efanesoctocog alfa becomes more expensive, and has an ICER of £17,533 vs EHLs.

Scenarios varying the assumptions around utility values are more influential. When a different model specification without time since treatment initiation is selected, the incremental QALYs for efanesoctocog alfa increase, and when a linear model is chosen, they increase in the comparison with EHLs, but decrease in the comparison with emicizumab. The assumptions around decrements associated with FVIII levels have a large impact on incremental QALYs. When this decrement is excluded for emicizumab the incremental QALYs are reduced to 0.13, and if a linear model is selected then emicizumab has a QALY [redacted], leading to a south-west quadrant ICER of £76,000,000 with the list price for emicizumab. However, the same scenario but using a threshold of 15% is used to assigning the disutility associated with FVIII, leads to a QALY [redacted] for efanesoctocog alfa, [redacted] with a threshold of 5%. These scenarios do not factor in that for the disutility associated with a bleed may be higher for patients treated with emicizumab, as they are not used to the IV infusions required for treating bleeds and are more likely to require a face-to-face visit to deal with bleeds. This is especially true for PUPs, who will have no prior experience of FVIII prophylaxis. Additionally, these scenarios do not account for the lack of 'peak protection' with emicizumab, which may also restrict people's activities.

Scenarios applying a disutility associated with more frequent infusion for EHLs lead to large QALY gains for efanesoctocog alfa, as this disutility is applied across a patient's lifetime.

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 10 June 2024. Please submit via NICE Docs.

Table 31: Scenario analysis, PUPs (PAS price)

Scenario	Vs EHLs			Vs emicizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Base case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Baseline ABRs from XTEND-1	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Base-case MAIC without prior bleeds adjustment	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Intra-patient comparison	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Intra-patient comparison in prior EHL patients only	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Excluding untreated bleeds	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Lower resource use for treating bleeds	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII wastage with emicizumab	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No resource use for treating bleeds	[redacted]	[redacted]	£17,533	[redacted]	[redacted]	Dominant
Utility model 6	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Linear model for utility	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
FVIII <15% for utility decrement	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
FVIII <5% for utility decrement	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab, FVIII threshold <15%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab, FVIII threshold <5%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab, linear model	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£76,092,627 (SW quadrant)

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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Scenario	Vs EHLs			Vs emicizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
No FVIII decrement for emicizumab, FVIII threshold <15%, linear model	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab, FVIII threshold <5%, linear model	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Utility decline with age from model	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Frequent infusion disutility - 0.027	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Frequent infusion disutility - 0.0745	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Frequent infusion disutility - 0.107	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

Abbreviations: ABR, annualised bleed rate; EHL, extended half-life; FVIII, clotting factor VIII; ICER, incremental cost-effectiveness ratio; Inc, incremental; MAIC, matching adjusted indirect comparison; PAS, Patient Access Scheme; PUP, patient untreated population, QALY, quality-adjusted life years; SW, Southwest; Vs, versus.

Previously treated patients

Table 32 presents the outputs of the scenario analysis for PTPs. The results of scenario analyses varying the source of ABRs for each treatment show minimal impact on results, with only small variations in the incremental QALYs. It is difficult to assess the impact of scenarios varying the incremental costs, both comparator arms contain treatments that are available at a confidential discount. In the scenarios comparing to efmoroctocog alfa, efanesoctocog alfa remains dominant in most scenarios, with only 3 scenarios showing an incremental cost. The first uses the baseline ABRs from XTEND-1, and efanesoctocog alfa has an ICER of £11,776. The second two are scenarios with lower resource use associated with bleeds. In the first, with a lower cost and single visit, the ICER vs efmoroctocog alfa is £15,488, rising to £44,843 with no resource use included.

As with PUPs, scenarios varying the assumptions around utility values are more influential and the scenario with no FVIII decrement for emicizumab and using a linear model once again leads to a QALY gain for emicizumab, though in PTPs the magnitude of the gain is smaller. In the remaining scenarios, efanesoctocog alfa remains the most effective treatment. Again, scenarios removing the disutility associated with lower FVIII for emicizumab do not account for the lack of peak protection offered with emicizumab, which means patients usual activities may continue to be restricted when treated with emicizumab, especially for those with an active lifestyle.

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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Table 32: Scenario analysis, PTPs (PAS price)

Scenario	Vs efmoroctocog alfa			Vs turoctocog alfa pegol			Vs emicizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Base case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Baseline ABRs from XTEND-1	[redacted]	[redacted]	£11,776	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Base-case MAIC without prior bleeds adjustment	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Intra-patient comparison	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Intra-patient comparison in prior EHL patients only	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Excluding untreated bleeds	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Lower resource use for treating bleeds	[redacted]	[redacted]	£15,488	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII wastage with emicizumab	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No resource use for treating bleeds	[redacted]	[redacted]	£44,843	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Utility model 6	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Linear model for utility	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

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Scenario	Vs efmoroctocog alfa			Vs turoctocog alfa pegol			Vs emicizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
FVIII <15% for utility decrement	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
FVIII <5% for utility decrement	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab, FVIII threshold <15%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab, FVIII threshold <5%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No FVIII decrement for emicizumab, linear model	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£517,596,845 (SW quadrant)
No FVIII decrement for emicizumab, FVIII threshold <15%, linear model	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

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Scenario	Vs efmoroctocog alfa			Vs turoctocog alfa pegol			Vs emicizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
No FVIII decrement for emicizumab, FVIII threshold <5%, linear model	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Utility decline with age from model	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Frequent infusion disutility -0.027	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Frequent infusion disutility -0.0745	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Frequent infusion disutility -0.107	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

Abbreviations: ABR, annualised bleed rate; EHL, extended half-life; FVIII, clotting factor VIII; ICER, incremental cost-effectiveness ratio; Inc, incremental; MAIC, matching adjusted indirect comparison; PAS, Patient Access Scheme; PTP, patient treated population, QALY, quality-adjusted life years; SW, Southwest; Vs, versus.

SHL comparison

Results of the comparison with SHLs are provided in Table 33 for PUPs and Table 34 for PTPs. In both cases, efanesoctocog alfa is both more effective and less costly, thus dominates SHLs.

Table 33: Results of the comparison with SHLs in PUPs (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER

Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	-	-	-	-
SHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; LYS, life years gained; PAS, Patient Access Scheme; PUP, preciously untreated patients; QALY, quality-adjusted life years; SHL, standard half-life.

Table 34: Results of the comparison with SHLs in PTPs (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	-	-	-	-
SHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; LYS, life years gained; PAS, Patient Access Scheme; PTP, preciously treated patients; QALY, quality-adjusted life years; SHL, standard half-life.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Haemophilia Society

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	The Haemophilia Society (THS) receives funding from a range of organisations, as well as from members of our community. Like many charities working in the healthcare sector, including haemophilia societies across the UK and Europe, some of that funding comes from pharmaceutical companies. You can read more about how we are funded here: https://haemophilia.org.uk/our-funding/how-we-are-funded/ Listed below are the corporate partners who have contributed to the costs of our work in 2023/24. **Events** Talking Red – LFB, SOBI Newly Diagnosed Family Weekend – Roche/Chugai, SOBI Youth Ambassadors and Youth Activities – Pfizer, LFB Haemfest – LFB The Big Get Together – Pfizer, Takeda **Advocacy** SACRed Project – LFB, Octapharma, Roche/Chugai, Takeda Haemophilia Journal subscription – Roche/Chugai Dental Survey – Nordic Pharma **Digital activities** 3 Peaks Challenge video -CSL, SOBI **Publications** Ageing Booklet – Octapharma Paediatric Dental Booklet – Nordic Pharma **Conference Attendance** EAHAD – LFB WFH – Roche/Chugai, SOBI **Core Activities** CSL
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Page 3 includes the line “The results of an indirect comparison of efanesoctocog alfa with emicizumab are unreliable, so whether one works better than the other is unknown.” This fails to take into account the higher peak and sustained increased factor levels provided by this treatment compared to emicizumab. These will be important considerations, particularly for people who take part in sport or exercise. Factor levels are known to be linked to decreased bleeding tendency and better protection from joint damage.
2	No reference is made to the mode of delivery of the treatment as an intravenous product compared to emicizumab which is delivered sub-cutaneously. Some people with haemophilia prefer intravenous injections, as this as been the case for all previous haemophilia treatments. Some people experience discomfort with subcutaneous injections as Emicizumab is a very viscous substance that can be uncomfortable to inject.
3	Section 3.2 says “[the committee] considered that differences in the treatment pathway meant that it was likely that the clinical- and cost-effectiveness outcomes would differ between people with severe and mild to moderate haemophilia A” the committee appeared to have misunderstood the treatment pathways for mild and moderate haemophilia A. Some people with moderate haemophilia A and, more rarely, people with mild haemophilia A will have a more severe bleeding phenotype and require prophylaxis to prevent bleeding and joint damage. These people will have the exact same treatment pathway as severe haemophilia A and their burden of treatment and bleed protection would be improved by this new technology compared to current factor replacement products in the same way. Additionally, all people with haemophilia A are registered with a haemophilia centre, and should be able to access regular review and full comprehensive care including physiotherapy, orthopaedic care, surgery, dental care, hepatology and infectious diseases, obstetrics and gynaecology, genetic counselling and psycho-social support regardless of whether they are on prophylactic or on-demand treatment so the pathway of referral, diagnosis and management should be same for all severities of haemophilia.
4	Section 3.4 discusses the complex set of advantages and disadvantages of different treatment products and treatment regimes for haemophilia A. The analysis does not consider two major points, firstly Altuvoct is a longer half-life product but works in the same way as existing factor replacement products. Altuvoct will be always be an improved treatment option for people who choose to receive factor prophylaxis as it will either provide better protection from bleeds due to higher trough levels or allow less frequent administration or both when compared IU for IU with current commissioned factor VIII products. Also, the committee does not seem aware that, unlike for emicizumab, there is no fixed dosing regimen for factor VIII prophylaxis with factor. This means that bleed protection and other outcomes can always be improved by increasing the dose or dosing frequency of the factor product used.
5	In section 3.7 the draft guidance discusses relevant comparators for PTPs and concludes that the company was not justified in excluding factor prophylaxis as a relevant comparator. We agree with this conclusion and note that the company is conflicted on this issue as the most commonly

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	preferred factor product, the only non-pegylated EHL available in the UK, is another product marketed by the company, efmoroctocog alfa (Elocta).
6	In section 3.8 the committee notes "There was no randomisation between on-demand and prophylactic efanesoctocog alfa for people having on-demand therapy when they entered the study." as a limitation of the XTEND-1 trial design. This criticism is wrong as it would have been unethical to require people to be on on-demand factor treatment as part of a trial when this is below the widely excepted standard of care and is known to lead to more frequent bleeds and increased joint degradation.
7	In section 3.10 the committee notes that the company positioned the treatment only for people with severe haemophilia A and therefore the committee could only make recommendations for this sub group of people with haemophilia A. This is misconceived by the committee, the product would also be an improved standard of care for people with mild or moderate haemophilia who receive prophylaxis due to their bleeding phenotype. It could also be expected to be better at bleed management for people who have on demand treatment due to its longer half-life but this is more uncertain and there are no published head to head comparisons that we are aware of.
8	In section 3.11 "The committee noted that people in HAVEN-3 had a higher bleeding rate at study entry than people in XTEND-1. This suggested that the population in HAVEN-3 had more severe disease or the measurement of bleeds differed across trials." While it is possible that bleeding phenotype differed between the two groups, it is more likely that bleeding rate at study entry would be a reflection the choice of dosing level and frequency. For people with haemophilia A on factor prophylaxis, an ABR of more than 1 usually reflects a failure to optimise treatment rather than pre-existing differences in patient bleeding tendency.
9	With reference to the comparative analysis referred to in section 3.14 and elsewhere, the model used appears to be only based on bleeds. To show the additional value of this new technology the model needs to incorporate at the very least, chronic joint damage, which has greater impact on relative costs and quality of life. In general this draft guidance does not take into account that this is a rare condition which is very close to falling into the highly specialised technology category. It is unreasonable to expect a high level of evidence of additional benefit from the three trials considered. NICE need to be explicit about what is required to improve on the evidence provided and which could demonstrate the clear additional benefit of higher factor levels for bleed prevention and prevention of joint damage.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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	Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	United kingdom Haemophilia Centre Doctors Organisation
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	UKHCDO and UKHCDO limited have received a grant from Roche for conducting a post marketing study of Emicizumab and also provided both Roche and Sobi with bespoke reports on fee for work basis.
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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Thank you for the opportunity to provide input on the committee's evaluation. UKHCDO would like to comment on the below areas. 1. Expressed uncertainties around the clinical effectiveness in relation to the trial design. 2. Comparators for clinical effectiveness. 3. Differences between the two classes of molecules (emicizumab and replacement therapy). 4. Use in mild and moderate haemophilia.
2	Section 3.8 (Pages 13 and 14 of 36) "The committee noted several limitations with the XTEND-1 trial design", and this is also reflected in comments in section 1.0. The limitations as described are listed below, and the committee concluded "that the clinical trial results suggested efanesoctocog alfa may be clinically effective at preventing bleeds for PTPs with severe haemophilia A". This uncertainty around the demonstration of clinical effectiveness appears to be responsible for the decision not to recommend treatment. We have addressed each item as a separate comment.
3	Section 1.0: Page 3 of 36 “clinical trial show fewer bleeding episodes for people having ongoing efanesoctocog alfa compared with on-demand efanesoctocog alfa" Section 3.8 (Pages 13 and 14 of 36) "There was no control arm comparing efanesoctocog alfa with the standard care" • The trial design is consistent with other molecules approved in the last 5 to 8 years and currently used in the NHS. As the committee knows, haemophilia is a rare disorder, making a typical randomised controlled trial used for small molecules in multifactorial diseases impractical and inappropriate.

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	• The study design for demonstrating effectiveness has been agreed upon by regulators globally. • Considering the changes in the standard of care, studies in the past 7 to 8 years have included an observational phase with the prevailing standard of care followed by an interventional phase. For haemophilia A, the current standard of care for patients without inhibitors is prophylaxis with either factor VIII or emicizumab. • The primary endpoint for clinical effectiveness was pre-specified in the prophylactic arm and was not a comparison with on-demand treatment. The cut-off was derived from data from natural history studies and previous trials. • Patients acting as their control in genetic disorders where the clinical effect of no treatment is known is appropriate. More importantly, the bleeds are a patient-reported outcome measure, and the subjective nature of such measures has been accepted. Indeed, patients tend to report similarly across the observational and interventional phases. • Although all patients have severe HA, the bleeding in this group is multifactorial, and randomisation would still not account for the inter-individual variability in bleeding tendency because of variations of coagulation system, joint damage, activity, adherence and other issues.
4	Section 3.8 (Pages 13 and 14 of 36) "no randomisation between on-demand and prophylactic efanesoctocog alfa" • Prophylactic treatment is the current standard of care, making randomisation to an on-demand arm unethical. In the UK and other developed countries, the on-demand treatment group is less than 2 to 3% of patients, which is a matter of patient choice, and this group is generally not inclined to participate in clinical trials. • Including on-demand patients in trials has become deeply controversial, with most participants now coming from developing countries, where participation offers access to treatment and the duration of on-demand treatment is limited. This has been a source of disquiet within the community.
5	Section 3.8 (Pages 13 and 14 of 36) "There is a high risk of bias when using intrapatient comparisons instead of comparing with a control arm, including placebo effect and effect of being in a clinical trial " "But it noted that the prior therapies used in the trial were not reflective of NHS practice". • The purpose of the intrapatient comparison was to demonstrate superiority over the current factor VIII prophylaxis.

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	• An intrapatient comparison was conducted with current factor VIII treatment, and the bleed rates at entry in the study are comparable to those reported with FVIII use in patients in the UK. • Patients in the observational phase are consented to and part of the clinical trial. • A control arm cannot address the issue of bias as explained previously and importantly outliers can significantly influence comparisons, mainly due to the subjective nature of the outcome measures. • Since these are open-label studies, it is unclear how the placebo effect might mask a bleed. Previous studies have shown that delayed and missed doses are associated with bleeds. The underlying disease mechanism will come into play if there is inadequate treatment. • Patients on emicizumab could not be enrolled in the clinical trial, as the long half-life results in a carry-over effect that potentially overestimates the treatment effect of the new molecules.
6	What should the comparator be, and what criteria should be used to select one? • Choosing the right comparator is essential for clinical trials in haemophilia. The primary goals of treatment are to prevent all spontaneous bleeds (controlling the bleeding tendency of haemophilia) and to prevent all bleeds (managing the disease in the context of the patient's everyday life). • Estimated Mean Annualized Bleeding Rate (ABR), as reported in trials, covers both the above scenarios, and considers significant baseline covariates in the analysis. • Estimated mean ABR in small cohorts is susceptible to outliers, and increasingly, studies are providing data on median ABR and the proportion of patients with no bleeds over 12 months. • Emicizumab has demonstrated the highest clinical efficacy to date, as measured by the estimated mean ABR and the proportion of patients with Zero ABR (annualised bleed rate) among the licensed products. • It holds the highest market share and is the appropriate comparator, as any new drug must be equally efficacious. • Clinical trials of emicizumab (and efanesoctocog alfa) have shown that around 60 to 70% of patients on these treatment regimens have Zero ABR, indicating excellent control of both spontaneous and minor traumatic bleeds.

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<table>
<tr><td></td><td>

SHL (standard half-life) and EHL (extended half-life) products are not suitable comparators, as outcomes in both clinical trials and real-world settings are consistently inferior to those of emicizumab and efanesoctocog alfa (see below)
Some patients prefer SHL and EHL and this is seen across the age spectrum as evidenced by the number of patients by age and product in the below table.
Importantly there has been reluctance to switch to pegylated factor VIII with use of the non-pegylated factor VIII being restricted.

<table>
<tr><th>Patient age group</th><th>Total</th><th>SHL</th><th>EHL</th><th>Emicizumab</th></tr>
<tr><td>< 6 years</td><td>197</td><td>26</td><td>35</td><td>136</td></tr>
<tr><td>6 – 11 years</td><td>227</td><td>30</td><td>46</td><td>151</td></tr>
<tr><td>11 – 17 years</td><td>214</td><td>45</td><td>45</td><td>124</td></tr>
<tr><td>18 years and older</td><td>1341</td><td>286</td><td>340</td><td>715</td></tr>
</table>
</td></tr>
<tr><td>7</td><td>Section 3.8 (Pages 14 of 36) "The committee noted that people in XTEND-1 had high bleeding rates" The bleeds on SHL and EHL factor VIII are in line with real-world data.

UK mean and median ABR, not adjusted for baseline covariates extracted for this analysis.

SHL: n=242, mean median (IQR) ABR: 2.81, 1.02 (0 – 3.22)
EHL: n=355, mean median (IQR) ABR: 2.28, 0 (0 – 2.89)
Emicizumab: n=904, mean median (IQR) ABR: 0.81, 0 (0 – 1.01)
On-demand: Not available
There has been less uptake of EHL in children, as only one product was licensed and when approved for use in routine care, there were certain caveats around the annual consumption.

</td></tr>
<tr><td>8</td><td>Section 3.3 (Page 7 of 36) “The committee concluded that the treatment for severe haemophilia A includes prophylaxis with factor VIII replacement therapy or emicizumab”.

Section 3.4 (Page 8 of 36) “NHS practice, most people with haemophilia A have emicizumab, which is given subcutaneously, rather than intravenous factor VIII replacement therapies”.

Section 3.4 (Page 9 of 36) “But some healthcare professionals consider that emicizumab may be associated with a lower rate of bleeds than factor VIII replacement therapies," also discussed on pages 8 and 36.</td></tr>
</table>

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	Section 3.4 (Page 9 of 36) “The committee concluded that a new treatment option with effective bleeding control and a less frequent dosing schedule would be welcomed by people with haemophilia A" 3.16 (page 23 of 36) The committee agreed with the EAG's logic that the sources used for efficacy outcomes should be consistent *UKHCDO agrees with all the above statements.*
9	Section 3.4 (Page 8 of 36) "there is uncertainty about the level of bleed coverage with emicizumab compared with factor VIII replacement therapies”. • Emicizumab is an FVIIIa mimetic, providing a constant level of protection equivalent to approximately 20% factor VIII levels, but interindividual variability is expected. Unlike factor VIII, emicizumab does not allow for treatment intensification in anticipation of sports or surgery, which can cause bleeds. As such, physically active patients may choose to continue with replacement therapy or reduce physical activity if they experience excessive bleeds. • At 20% factor levels, some mild bleeds may be missed until they cause larger hematomas or joint inflammation due to the absence of peaks that can arrest bleeding. • With factor VIII, there is extensive experience, and apart from the disadvantage of intravenous infusion, there is flexibility to adjust treatment based on the patient's activity and to intensify treatment if the response is inadequate after a full evaluation. • While emicizumab is less burdensome for patients and clinicians, it may not offer the same level of protection as efanesoctocog alfa for active patients. Similarly, the patients who prefer not to use a mimetic now have suboptimal protection. • We also draw attention to the fact that the half-life extension provides protection from bleeding similar to emicizumab for up to 7 days (equivalent to mild haemophilia), with superior protection for 3-4 days out of 7. This advantage is offset by the need for intravenous infusion, which remains a choice for patients. The superior protection is achieved with fewer injections, and for children and their families, this comes with quality-of-life improvement that cannot be exaggerated. Patients have expressed that it 'feels like I don't have haemophilia anymore'.
	Section 3.7 (Page 11 of 36) “So, it agreed that the company's choice to exclude factor VIII replacement therapy as a comparator in PTPs was not justified" We agree this should include both clinical and cost-effectiveness.

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	Section 3.1 (Page 5 of 36) "The committee recognised that severe haemophilia A is a chronic condition that significantly affects the lives of people affected by it" This should be updated to say it is a chronic and life-threatening condition. The significant effect is related to both disease burden (complications of disease) and treatment burden (measures for disease control and management of complications)
	Section 3.11 (Page 16 of 36) “The committee noted that people in HAVEN-3 had a higher bleeding rate at study entry than people in XTEND-1. This suggested that the population in HAVEN-3 had more severe disease or the measurement of bleeds differed across trials”. The bleeding rates in HAVEN -3 was comparable for real world data and but also had a substantial number of patients from developing countries where factor VIII prophylaxis was not as optimised. There has been steady decrease in the ABR over time, with increasing number of patients with Zero ABR and no joint damage.
	3.10 (page 15 of 36) "The EAG highlighted that the population in XTEND-1 was narrower than the scope and anticipated licence for efanesoctocog alfa because it excluded: ▪ people with mild and moderate haemophilia A ▪ people under 12 years ▪ PUPs ▪ people with inhibitors to factor VIII" UKHCDO comments • There is no requirement for PUP studies, and data collection is now recommended as part of phase 4 studies. • The kids' study has now been published and shows similar effectiveness. • Efa is contraindicated in patients with factor VIII inhibitors like any other replacement therapy. • Mild and moderate HA – see below.
	Section 3.2 (Page 6 of 36) : "The committee considered this but concluded that it had not been presented with clinical- and cost-effectiveness evidence for people with mild to moderate haemophilia A" There is an acknowledgement of the different pathways. • While the license is broad, the cost and clinical effectiveness analysis has been restricted to severe haemophilia.

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	• Prevention of bleeding to avoid long-term complications, including premature death, is restricted to severe haemophilia A and some patients with moderate haemophilia who clinically behave like severe haemophilia A. Prophylaxis is indicated in this group and included in the trial. Both cost and clinical effectiveness have been presented for this group. • *In patients with any severity of haemophilia, treatment is indicated for management of bleeds and surgery.* • Management of Bleeds: This is included in the current trial. These are random events, but clinical effectiveness has been demonstrated. • Management of Surgery: This is also included in the current trial, and clinical effectiveness was demonstrated for the management of minor and major surgery. • As the management of these relevant clinical scenarios is covered, the license for replacement therapies—where the missing factor is replaced by recombinant protein—has always included their use in mild and moderate patients. • Most mild and moderate patients are unable to self-treat. Any long-acting product will decrease the need to travel to a centre daily for infusions, reduce the need to centralise all procedures at the treatment centre and facilitate remote management of surgery. This has been the case with long-acting factor IX products, which have a similar half-life to Efa. • Any decision to exclude this group will be in line with the license and would become evident in an equality impact analysis.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novo Nordisk Ltd

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1	Our understanding is that after a positive NICE recommendation, haemophilia products will still fall in-line with routine commissioning, facilitated by The Medicines Procurement and Supply Chain (MPSC) team within NHS England. Bearing this in mind, we would consider Efanesoctocog alfa to be classed as an Enhanced Half-Life (EHL) FVIII product. As per the most recent tender exercise conducted in 2024 by MPSC,

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	Efanesoctocog alfa would be competitively ranked and appraised versus other EHL FVIII products (lot 2). The relevant marketed comparators in the UK in this segment are currently; turoctocog alfa pegol, rurioctocog alfa pegol and efmoroctocog alfa – which Novo Nordisk would therefore consider to be the most relevant comparators. Novo Nordisk propose NICE to consider only these treatments as relevant comparators to ensure current and future consistency of appraisal within the considered class of products.
2	The economic analyses performed for this appraisal **do not include the following key elements**. - **A distinction between joint and non-joint bleeds:** Joint bleeds are commonly included in haemophilia models as they have historically been a key endpoint in clinical trials of haemophilia treatments. Evidence suggests that they are linked to lower quality of life and higher costs compared to non-joint bleeds. - **Adverse events:** Adverse events for each comparator used are often included in economic evaluations as they are typically associated with lower quality of life and increased costs. However, this model does not seem to consider them making it unclear whether they have any effect on the ICERs. Novo Nordisk **proposes including joint bleeds and adverse events in the economic analyses** of this appraisal to ensure that all the evidence have been considered. These suggestions align with the model design of etranacogene dezaparvovec [ID3812], which was deemed appropriate for decision making by the committee and represents the only other NICE appraisal of a haemophilia treatment product.
3	Novo Nordisk agrees with the EAG and NICE that **it is irrelevant to consider disutility by FVIII activity level** for non-factor replacement therapies. This is due to the fact that, non-factor replacement therapies, as highlighted by the committee, do not function by replacing factor VIII, making factor VIII activity levels unsuitable for assessing bleeding protection.
4	The economics analyses do not consider the following important utilities related to the treatment with haemophilia therapies. - **Disutilities related to dosing frequency (e.g. weekly and monthly) and administration method (e.g. subcutaneous and IV)** are not included in the economic analyses even though there is evidence suggesting that treatment features in HA affect QoL (Johnston, 2021). - **Caregiver disutilities** are not considered however the scope of this appraisal included patients of all ages including children. It is expected that haemophilia will have a negative effect on the quality of life of both patients and their caregivers. The carers' disutility could be different depending on the different treatments' characteristics, but the Company did not provide any evidence to assess that. Novo Nordisk proposes the inclusion of the above disutilities to ensure that all the evidence have been considered.
5	Novo Nordisk agrees with NICE on the inappropriateness of the wastage assumptions incorporated in the model. While it was assumed that patients could round up their dose for prophylaxis treatment, the model does not incorporate any calculations to estimate the impact this may have on the cost of treatment. Additionally, the wastage assumption for the on-demand treatment of patients on emicizumab potentially overestimates the amount of octocog alfa wasted. It is unclear why 6000 IU were chosen as the amount of octocog alfa offered to patients prescribed with emicizumab. It also seems unlikely that within a two-year period, all patients with no bleeds will not use any octocog alfa, considering it can also be utilized for minor surgeries such as dental extractions.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roche Products Ltd

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1	Roche notes the clinical evidence included within the company submission is for previously treated people (PTPs), which has been accepted for previously untreated people (PUPs) based on the assumption that similar treatment effects would be expected in these groups. Roche does not disagree with this, however would like to highlight the importance of considering factor VIII inhibitor development in patients treated with FVIII therapies. Approximately 30% of patients with severe haemophilia A who are treated with existing FVIII therapies will develop an inhibitor. Inhibitors typically develop within the first 50 - 75 exposure days of FVIII, which means a higher

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	risk of inhibitor development in those patients with no or minimal previous exposure to FVIII e.g. PUPs. Roche would request for this to be considered for potential treatment effect differences between PTPs and PUPs due to inhibitor development.
2	The guidance states that healthcare professionals are unlikely to use efanesoctocog alfa in patients with factor VIII inhibitors, which Roche agrees with for patients with long term inhibitors, however existing factor VIII therapies are used for immune tolerance induction (ITI) in previously untreated people (PUPs) who develop inhibitors whilst on factor VIII treatment. ITI involves high doses of factor VIII regularly over a prolonged period of time and there are existing guidelines from the UKHCDO for ITI in the UK. Roche therefore requests that this aspect is considered.
3	Roche agrees that treatment with emicizumab (prophylaxis) with a short half life (SHL) factor VIII replacement therapy (on demand) is a relevant comparator for both previously treated people (PTPs) and previously untreated people (PUPs), and would like to highlight that there is published evidence for patients treated long-term with emicizumab (prophylaxis) to show relatively high zero treated bleed rates for patients which were maintained overall at intervals of 24-weeks up to 144 weeks duration across HAVEN 1-4 studies (Callaghan et al, *Blood* 2021). Patients with zero treated bleeds would subsequently not be frequently using on-demand SHL factor VIII replacement therapy. As per the EAG and committee conclusions in relation to wastage, Roche proposes that appropriate direct and indirect costs are associated with this comparator arm, specifically in relation to the frequency of on demand SHL factor VIII likely used by patients treated with emicizumab.
4	Roche considers that it is not clear throughout the guidance that some differentiators for efanesoctocog alfa with existing factor VIII replacement therapies are not relevant for comparison with emicizumab. It is stated that efanesoctocog alfa brings a reduced dosing schedule for patients compared with existing treatments but this is only in relation to existing factor VIII therapies and not in comparison to emicizumab. This is also applicable where the different modes of action between emicizumab and factor VIII therapies need to be considered, including where factor VIII levels are considered important and may be less relevant for emicizumab. Roche would request that this is reviewed to ensure consistency and clarity throughout.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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NICE National Institute for Health and Care Excellence

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 10 June 2024. Please submit via NICE Docs.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Non applicable

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NICE National Institute for Health and Care Excellence

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Non applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Non applicable
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**(Has all available evidence been taken into account?)**

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NICE National Institute for Health and Care Excellence

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	The updated paediatric evidence (XTEND-KIDS) should be included in appraisal of effectiveness of efanesoctogog- i.e. a single dose of efanesoctogog 50IU/kg resolving 95% of bleeds in children under 12 years of age, regardless of type of location. Similarly, no bleed required more than 2 doses for resolution. This has enormous costing significance, since will reduce the cost of daily factor being required for several days.
2	**(Has all available evidence been taken into account?)** We therefore do not think that the models submitted adequately represent clinical and cost effectiveness interpretations. There was no comparison with standard half-life products. Clinicians who have had experience of this product recognise that it is more effective at bleed prevention than a standard half-life FVIII to an unprecedented degree. The half-life extension provides protection from bleeding to a similar degree as emicizumab at 7 days from treatment (that is equivalent to mild haemophilia) whilst at the same time providing superior protection to emicizumab for 3-4 days out of 7.
3	**(Has all available evidence been taken into account?)** The committee report reflects that there is no comparison with emicizumab. An important extension of this applies to the use of efanesoctogog in young children who have started prophylaxis with emicizumab. This may facilitate immune tolerance to FVIII at a young age (and smaller weight), avoiding a cohort of older children/young adults developing FVIII inhibitors later in life with the attendant low probability of achieving immune tolerance. There is national data from outside the UK demonstrating approximately 50% FVIII inhibitor development in haemophilia A babies and young children on emicizumab who have needed FVIII exposure for bleed and surgical treatment. The long term health economic burden of an adult haemophilia A population 50% of whom require rFVIIa therapy for bleeds and surgical cover should be taken into consideration. This product offers parents with babies on emicizumab a realistic way of exposing their son to FVIII to ensure tolerance. It is extremely unlikely that any of them would chose another FVIII product going forwards.
4	**(Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?)** The summary of the limitations of the current approach to prophylaxis of severe haemophilia A with factor VIII somewhat diminishes the extraordinary impact that requirement for venepuncture can have on a young child's life. As reflected by the patient experts, there can be very real trauma for the child who has to be forcibly restrained every other day to receive treatment. This is not measured in any manner by costing models. This superior bleed prevention, is achieved with fewer injections rather than more and for children and their families this comes with quality of life improvement that cannot be exaggerated. Patients have expressed that it 'feels like I don't have haemophilia any more'.
5	**(Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?)** To suggest that emicizumab is a viable alternative for all patients with severe haemophilia A has not been fully embraced by all haemophilia treaters. There remain ongoing concerns about whether emicizumab offers 'good enough' bleed prevention for very active young children.

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	Prophylaxis should prevent breakthrough bleeding, but this has not been the real-world experience. If bleeds require additional factor VIII treatment, this should also be accounted for- in terms of product cost, and cost of delivery (eg- if a child is on emicizumab, it is unlikely his parents will be adept in peripheral factor VIII treatment- therefore breakthrough bleeds will require medical review and treatment in A&E and urgent care centres, with all that entails for inconvenience for the family and burden on healthcare resources).
6	**(Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?)** Again, the cost-effectiveness models do not in anyway adequately represent the potential reduction in both healthcare resource, financial and emotional costs that once-weekly factor VIII administration could offer to families of small boys who would otherwise require Port-A-Cath insertion if they choose factor VIII prophylaxis as opposed to emicizumab (which is true for many). The cost of a hospital bed, inpatient admission, general anaesthetic, oversight of anaesthetist/ interventional radiologist/ surgeon, ongoing post-operative care and specialist nurse training in Port-A-Cath use reflects the cost to the hospital/ NHS. The surgery, pain, risk of infection and bleeding (to list but a few potential complications) reflects the cost to the child.
7	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No- for the same reasons mentioned above regarding the real-world experience, but also the Markov economic model definitely missing out on the nuance of what is meant by a 'bleed'. One significant joint bleed can result in life-altering disability in haemophilia; versus a 'cutaneous bleed' or simple bruise, not having any longer-term sequelae.
8	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** I would counter that the current recommendations may discriminate against age, on the basis that children are typically the most active haemophilia patients- and thereby most at risk of trauma-induced bleeding. Again, the prospect of an intravenously administered medication being admininstered every 7 days as opposed to every 2 or 3 days- has enormous consequences for their emotional, mental and physical health; particualrly as they are growing into the label of a chronic disease.

Insert extra rows as needed

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Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

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Single Technology Appraisal

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Comment on the draft guidance consultation, section 1 (Recommendations) I am a 61 year old man with severe haemophilia A. I would like to make NICE aware of the huge beneficial impact the product has made to my life. I joined the mother (main) study, EFC16293, in August 2019 on the recommendation of my doctor. I remained on this part of the study until October 2021. I was having such a good experience of the product that I joined the extension study, LTS16294, from October 2021 to the present. The first thing to say is that since August 2019 I have had no bleeding episodes at all. Prior to this I was, on average, getting a bleed a month. In the time I have been on the product I have had to have a tooth extracted, numerous fillings and a tooth implant done. All this was done by a local dentist without any problems with bleeding. I also underwent a procedure to have an injection into my lower back due to a stenosis and encountered no bleeding problems. As well as the efficacy of the product, it is a once a week prophylactic injection which is quick and easy to administer. Previously I was having two or three prophylaxis injections per week, with the associated wear and tear on my veins. My trough level of FVIII after a week remains at a very good level for preventing bleeds. This has knock on psychological benefits for me. I am far more confident doing physical activity towards the end of the weekly cycle than I have been in the past, knowing that the FVIII levels remain high. This has meant that I am able to lead a fuller life than I had on the previous prophylactic cycle. I am very disappointed that NICE is not recommending this product at this time, and hope that this consultation period will help them to reconsider.	

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]: EAG critique of consultation response

Produced by Kleijnen Systematic Reviews (KSR) Ltd., in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 19/06/2024

Introduction

This document provides the External Assessment Group's (EAG's) critique of the materials submitted to the National Institute for Health and Care Excellence (NICE) in response to the Draft Guidance Document (DGD) issued following the first technology appraisal committee meeting for efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A. Materials were submitted by the company plus several other stakeholders.[1-6] The EAG critique focuses on the company's DGD response.[1]

The following sections are structured according to the source of comments, and the comment number where applicable. Since a number of comments are opinion-based without substantiation, the EAG has focused on those where potentially new sources of information are mentioned or specified changes to the input, method and estimates from the economic model.

EAG critique of company's response

Comment 1: Comparator treatments

The company acknowledged that the committee requested comparisons with:[1]

Previously untreated patients (PUP)

- Emicizumab
- Standard half-life (SHL) FVIII (octocog alfa, simoctocog alfa, or morcotocog alfa)
- Efmoroctocog alfa

Previously treated patients (PTP)

- Emicizumab
- SHL FVIII (octocog alfa, simoctocog alfa, or morcotocog alfa)
- Extended half-life (EHL) FVIII (efmoroctocog alfa, turoctocog alfa pegol, or rurioctocog alfa pegol)

In response they stated that they have provided comparisons with other FVIIIs for PUPs and PTPs, but maintain the original position that emicizumab for PTPs and emicizumab and efmoroctocog alfa for PUPs are the most appropriate comparators based on current treatment patterns and clinical advice.

They also stated that: [redacted][1]

To make their point that the comparators should only be emicizumab and efmoroctocog, the company presented the latest data from the National Haemophilia Database (NHD) (see Figure 1).[1]

Figure 1: Proportion of replacement therapies used prophylactically in severe haemophilia A (baseline factor VIII <1%) and no current inhibitor, in the UK, 2023

Source: Figure 1, company response to DGD.[1]
Abbreviations: EHL, extended half-life; SHL, standard half-life; UK, United Kingdom.

They also cited clinical opinion that there will continue to be a significant and ongoing decline in the usage of SHLs so that their usage will be *"…negligible in 5-years' time."* (p. 17) [1]They also stated that older patients who remain on SHLs are unlikely to switch *"…due to indifference or reluctance…"* (p. 18)

EAG comment: The EAG continue to argue, as stated in the EAG report, that any current treatment (standard of care) is a comparator even if only a small percentage of patients currently receive it. The evidence cited by the company therefore confirms that SHL factor VIII is a comparator, at least for those patients who currently receive it and for which efanesoctocog alfa would be a substitute. This percentage does seem likely to decrease, but, according to the company expert opinion, is likely to remain non-zero for some years.

Comment 2: Indirect treatment comparison

The indirect treatment comparisons (ITCs) have been updated by the company.[1] A summary of the results is shown in Table 1 and description of the various types of ITC discussed below.

Table 1: Outputs of the ITC using a MAIC or based on intra-patient comparison

	MAIC base case		MAIC with adjustment for pre-study ABR		Based on intra-patient comparison
Efficacy outcome	EFA vs efmo	EFA vs emi	EFA vs efmo	EFA vs emi	EFA vs emi
	IRR (95%CI)	IRR (95%CI)	IRR (95%CI)	IRR (95%CI)	IRR (95%CI)
ABR any	–	[redacted]	–	[redacted]	–
ABR any treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	MAIC base case		MAIC with adjustment for pre-study ABR		Based on intra-patient comparison
ABR spontaneous (treated)	[redacted]	[redacted]	[redacted]	[redacted]	–
ABR joint (treated)	[redacted]	[redacted]	[redacted]	[redacted]	–
Source: Tables 1, 2 and 5 of company response to DGD. ABR = annualised bleed rate[1]					

Matching adjusted indirect comparison (MAIC) adjusting both the A-LONG and XTEND-1 populations to the aggregate data from HAVEN 3

In accordance with the DGD, the company have provided an updated MAIC with adjustment for pre-study adjusted bleeding rate (ABR) for the comparison of XTEND-1 Arm A with HAVEN 3 arm D.[1] To this has been added a MAIC to adjust A-LONG. This is despite the company arguing that pre-study bleed rate is not a suitable indicator of severity. The company argue that this is because the bleed rate will be driven by the standard of care patients were receiving at the time and that the efanesoctocog alfa study (XTEND-1) has a lower baseline ABR than the emicizumab study (HAVEN-3) because it is more recent, and it is likely that standard of care treatments have improved over time.

A comparison between Table 1 (base-case MAIC outputs) and Table 2 (updated MAIC with adjustment for pre-study ABR) shows that adding pre-study ABR causes the rates of various types of bleed to [redacted] for efanesoctocog alfa and [redacted] for efmoroctocog alfa. This leads to [redacted] incidence rate ratios (IRRs) of efanesoctocog alfa vs. both emicizumab and efmoroctocog alfa.

In the company's updated cost effectiveness analyses, the updated MAIC with adjustment for pre-study ABR has been used to estimate the ABRs for the various treatments.

EAG comment: The problem with the company's disputing the validity of including baseline ABR as an adjustment factor is that it is irrelevant whether it indicates severity or not: what is relevant is whether it is prognostic, and the fact that it affects outcome, indicates that it might be. Therefore, it does seem relevant to have included it in the MAIC. This is notwithstanding any potential lack of generalisability to UK clinical practice, given that the adjustment for baseline ABR might also reduce this if it is true that standard of care has improved and ABR reduced as a result. However, the main purpose of population adjustment such as MAIC is to reduce any bias on the treatment effect on (difference between intervention and comparator in) the outcome regardless of the baseline outcome, in this case ABR.[7] Of course, it might be that the treatment effect, as well as prognosis varies with baseline ABR, but it is a drawback of an unanchored ITC that it relies on the assumption that this is not the case.

Analyses using outcomes from the pre-study period and intra-patient comparisons directly

In response to the DGD, the company have also presented the following, for treated ABR only:[1]

- intra-patient comparisons of pre-study vs. on-study efanesoctocog alfa in XTEND-1:
  - versus pre-study SHL FVIII prophylaxis
  - versus pre-study EHL FVIII prophylaxis
  - versus any pre-study prophylaxis (mixed SHL and EHL) - already presented in the CS (see Section 3.2.7.1.3 of EAG report)
- an ITC on treated bleeds only using the pre-study treatment (mixed SHL and EHL) of each of the XTEND-1 and HAVEN 3 trials as a common comparator.

This ITC, which is based on the intra-patient comparison provides an estimate of IRR between efanesoctocog alfa and emicizumab, which is [redacted] than that according to the MAIC (see Table 5 of the company response to the DGD).

EAG comment: The advantage of the intra-patient comparison is that there is no confounding by patient characteristics pre-observation i.e. before the pre-study measurement period. The disadvantage is that the potential effect of any underlying trend between pre-study and study outcome, e.g. the effect of pre-study treatment on study treatment outcome, which might affect both the intervention (efanesoctocog alfa) or the comparator (not observed because only a single arm study). The effect of pre-treatment has to some extent been examined in terms of on-demand vs. prophylaxis in the comparison with emicizumab (see Section 3.4.2.1, EAG report) and the EAG concluded that it seemed to make little difference to outcome. This is [redacted] by the intra-patient comparison between efanesoctocog alfa and either SHL or EHL, i.e. [redacted]. However, there might also be a trend due to patients being recruited when their condition is already improving independent of the intervention, often referred to as regression towards the mean. However, it does seem that this is unlikely given the length of the pre-study period i.e. 12 months.

Anchoring the ITC by using the on-demand arms of each trial

The company declined to perform this analysis on the basis of lack of adequate comparability of patients between the intervention and the common comparator by which the ITC would be anchored, that being the on-demand arm of each of the XTEND-1 and HAVEN 3 trials.[1] Specifically, the company argued that the patients in Arm A and B of XTEND-1 were from *"non-overlapping sub-populations"* (p. 18) i.e. on-demand and prophylaxis respectively and therefore not amenable to adjustment by propensity score matching (PSM) to make them more comparable in terms of prior bleed rate and risk of joint involvement. They also stated that the ITC would be further undermined by the lack of randomisation to the prior prophylaxis intervention arm of HAVEN-3 (Arm D). Finally, they argued that the treatments that might have been used as common comparator i.e. some form of on-demand therapy could not be regarded as being the same in the two trials, citing the difference in ABR between pre-study on-demand and on-demand use of efanesoctocog alfa in XTEND-1.

EAG comment: The EAG consider agree with the arguments presented by the company as to flaws in an ITC anchored by on-demand treatment as common comparator. However, it is unclear to the EAG that these flaws are any worse than those already identified in other approaches, such as unanchored ITC adjusted using a MAIC and intra-patient comparisons. Also, it is unclear that prior therapy has that much of an effect on prognosis, as mentioned above and first mentioned by the EAG in the EAG report, e.g. the IRR for ABR (any bleeding) for efanesoctocog alfa vs. emicizumab QW was [redacted] when Arm A of XTEND-1 compared to Arm D of HAVEN 3 (prior prophylaxis population) and 0.34 [0.12; 0.95] when compared to Arm A of HAVEN 3 (prior on-demand population). Also, HAVEN 3 did have a randomised part whereby patients were randomised to either emicizumab prophylaxis or on-demand treatment, albeit patient who previously had been on on-demand treatment. To support the company's argument of lack of overlap, it might have been useful to have provided empirical evidence of this.

Comment 3: Utilities

In the DGD, it is stated that the utilities used by the company are uncertain, and several concerns were raised.

Extending efanesoctocog alfa data to other FVIII or emicizumab

The committee raised concerns that it may not be possible to extend efanesoctocog alfa data to other FVIII therapies or emicizumab, due to the differences in dose frequency and the mode of administration.

The company addresses this issue as follows:

- Little is known about the impact on HRQoL in patients when receiving intravenous (IV) versus subcutaneous (SC) injections, assuming the same treatment schedule. The company identified one study which explored patient preferences for haemophilia A treatment with combinations of frequency and mode of injections included as attributes indicated that IV versus SC had only a small influence on patient preference.
- The same study showed that treatment frequency did have an influence, with injections once a week clearly being preferred over three times a week. This was confirmed in another study, based on cross-sectional real-world data, which showed a higher EQ-5D for patients with only one injection per week then patients with two or more per week.
- The updated company base case does not include a disutility for two or more injections per week, though this would be relevant for the assessment of efanesoctocog alfa versus EHL and SHL. However, the model now uses utilities based on data analysis of both the XTEND-1 study (efanesoctocog alfa) as the A-LONG and ASPIRE studies (with efmoroctocog alfa) and according to the company injection frequency could not be included as a covariate. However, the company does include disutilities for higher injection frequencies in a scenario analysis. The company did not incorporate a potential utility gain for a once per 2-week schedule in patients receiving emicizumab, as they anticipated a very limited impact.

The assumption that the type, severity, and location of bleeds were identical for the different treatments under evaluation

The committee expressed concerns that the utility analysis that was done by the company did not differentiate between the type, severity, or location of bleeds, and that these had been assumed to be identical between treatments. The company argues that the utility analysis was conducted based on studies assessing very effective therapies and thus, the number of events observed was very low. Additionally, there was a limited number of EQ-5D measurements. Given the limited number of observations corresponding to dependent and independent variables the data does not allow for a higher granularity of the investigation, e.g. by bleed location.

In addition, the company argues that as the ITC shows that efanesoctocog alfa is approximately equally effective in preventing treated bleeds and treated joint bleeds, it is likely that the proportion of joint bleeds among treated bleeds is similar across treatments. This would suggest that applying different utilities for treated bleeds and treated joint bleeds would have little effect on the ICERs.

The disutilities did not capture the impact of chronic pain from subclinical bleeds

The company acknowledges that the impact of chronic pain due to subclinical bleeds is not explicitly modelled, though it is captured implicitly in the utility analysis as utility and chronic pain both correlate with FVIII. In the XTEND-1 study, pain intensity was included as a secondary outcome, at it was found that patients receiving prophylaxis with efanesoctocog alfa had less pain than patients treated with FVIII treatments. However, the HAVEN 3 study did not include outcomes measuring pain, so no comparison on that endpoint was possible between efanesoctocog alfa and emicizumab, and thus it is not possible to model the direct link between pain, treatment and utility.

Insufficient justification of the Company's preferred model or parameter set, and use of the Tobit model

In the DGD the committee expressed that the company did not provide sufficient justification for its choice of preferred Tobit model from those tested. The company explains that the model selection was based first on the AIC, which left Model 1 and 2, and from these the model with a coefficient for FVIII<20% was preferred as this aligned with input from clinicians that people would modify their behaviour once the no longer have peak protection.[1]

The company has now updated the utility analysis to include data from A-LONG and ASPIRE and to test additional parameters in the modelling. Also, both Tobit and linear models were explored. The results from Tobit and the linear regressions are quite consistent, thus the Tobit models have been retained in the base case analysis, however scenarios using linear models have also been explored and provide similar results. For patients with FVIII above 50%, the original model assumed a utility equal to that of the general population, however, in the updated model the company applies the baseline utility value from the clinical trial data. To this baseline utility, like in the original model, decrements for bleeds and low FVIII levels are applied. In addition, the utility decreases proportionally with the general population decline in utility in the base case, whilst a scenario analysis is run using the coefficient for age to reflect age-related decline in QoL.

EAG comments: Regarding the response to the first three issues raised in the draft guidance, the EAG considers the argumentations set out by the company reasonable. Furthermore, the EAG welcomes the revised utility analysis that is now presumably based on more data, and on data in both efanesoctocog alfa and efmoroctocog alfa. However, the EAG also has several misgivings about the utility analysis, some of which have not been resolved since the original utility analysis:

- Besides the coefficients of the models, no information is provided about the utility analysis: how many patients were included, how many observations, was there missing data, does the model take the correlated observations per patient into account? Also, what are the standard errors and confidence intervals for the coefficients? In the Excel model, a standard error was simple based on a percentage of the value of the coefficient, rather than the standard error that follows from the analysis. Thus, there is no way to assess the uncertainty around the estimated coefficients. In addition, in the PSA all coefficients are varied independently, instead of correlated according to the variance-covariance matrix.
- To the EAGs surprise, the coefficients of utility regression models presented by the company in their response to the DGD are exactly the same as those presented in the original company submission. Comparing Table 18 in the company's response to the DGD with Table 4.10 in the EAG report, all coefficients as well as the AIC and BIC of model 2, 4, 6 and 8 match the values of the original models 1, 2, 3, and 4. This makes it extremely unlikely that the data set(s) on which the utility models for the company's response were fitted are different from those used in the original submission, and it appears that the only change compared to the original submission is that now four alternative models were fitted as well.
- The company has chosen the same Tobit model, model 2 in the new set of models (see Table 18 of the company's comments on the DGD), as was used in the original model. However, this is not the model with lowest AIC/BIC; instead model 1, which does not include time in a certain FVIII range as covariate, has the lowest AIC/BIC.
- In the EAG report it was already explained that the covariate for days since treatment initiation was disregarded in the calculation of utilities in the Excel model, and that the exclusion of any covariate can lead to a change in the coefficients of other covariates. Thus, the EAG considers that the choice of model should be restricted to models 5-8, which do not include a coefficient

for days since start of the study. Out of these four models, model 5 has the lowest AIC/BIC (115.1/151.7), much lower than models 6-8 which all include a disutility for FVIII below a certain level. Of these three, the model with FVIII<5% as covariate has the lowest AIC/BIC (143.7/184.8, next best 146.0/187.17).

Comment 4: The link between FVIII and QoL

In the guidance document the committee indicated a need for justification that factor VIII levels affect quality of life in people with haemophilia A and how they do this, including people who receive emicizumab. The company explained in the comments the following:

- Clinical advice received by the company stated patients with higher FVIII levels are more able to undertake their usual activities.
- The company presented a study report of a cross-sectional real-world study in which the association between FVIII level and QoL was assessed.[8] This study confirmed that an increase in FVIII level is associated with an increase in QoL. In the discussion of their findings, the authors of the study report explain that their findings were similar to those found in a similar study in patients with haemophilia B.
- The company also presented a study report describing the results of so-called exit-interviews with 29 patients at the end-of-study or end-of-treatment of the XTEND-1 trial. Of the 17 patients who were enrolled in Arm A, 13 reported "wearing off" with the treatment they received prior to XTEND-1; this "wearing off" could include more pain, stiffness, feeling unprotected, breakthrough bleeds, and limited physical activities.[9]
- Patients treated with emicizumab tend to have a more stable protection over time, as emicizumab concentrations are well maintained between doses. But as there is still a decline concentration between two dosages, it is reasonable to assume that some patients receiving emicizumab also have periods in which they feel less protected. In the original submission, the company assumed that 100% of patients receiving emicizumab could be classified in the FVIII range 5-20%, and that a disutility should be applied when the FVIII level drops below 20%. After further literature review, the company has adjusted the distribution of patients receiving emicizumab over the different FVIII ranges to 30% in the range 5-20%, 40% in the range 20-40% and 30% in the range 40-50%.
- In the updated model, the company still uses 20% as the threshold below which a disutility should be applied. Additionally, the company has explored a range of scenarios where the threshold is varied to 15% and 5%, as well as scenarios where no disutility was applied to patients treated with emicizumab.

EAG comment: The EAG considers the argumentation that at low levels of FVIII the quality of life of patients decreases compelling. The important question though is which level is considered low in this regard, to which the EAG has no clear answer. From that perspective it is useful to have a range of options explored in the scenario analyses. In the scenario where the FVIII threshold for declined QoL is set at 15%, the EAG noticed a small error in the model. For all treatments except emicizumab it was possible to estimate the percentage of time in the range 40-15% and 15-5%, however, for the emicizumab no adjustments were made. This means that in this scenario it is assumed that 30% of patients fall in the 15-5% range (was 20-5%) and 40% in the 40-15% range (was 40-20%). The EAG has corrected this by assuming a linear decline in the range 20-5% from 30% to 0%, which leads to an estimate of 20% of emicizumab patients falling in the 15-5% range.

Comment 5: Wastage costs

The draft guidance states that the wastage costs for efanesoctocog alfa and efmoroctocog alfa are uncertain and that the committee would like to see an updated economic model to account for vial wastage associated with prophylactic treatment. The company has incorporated this for all prophylactic treatments for adult patients. However, in people under 18 the drug acquisition costs are included without wastage as weight is more variable in children, especially in very young children, and as they grow it is likely that the dose they receive will at different times be varied up or down. This was confirmed by a clinical expert consulted by the company. The company explained that incorporating vial wastage in a population whose weight changes from cycle to cycle would be complicated to implement in the model and is not expected to have a large impact on cost-effectiveness estimates, as all comparators use weight-based dosing schedules.

With regards to the small supply of SHL that patients treated with emicizumab keep on hand to treat a bleeding, the company has corrected the way in which wastage is calculated due to some patients not having a bleeding in the two years before the SHL expires. In this correction, the company also considers that no SHL is used for bleeds that are not treated. Thus, where for emicizumab the probability of not having a bleed is 44% per cycle, the probability of not having to treat a bleeding per cycle is 73%. Thus, the proportion of patients that don't experience a bleed in 2 years is equal to the probability of not experiencing a bleed in a 6-month cycle to the power of 4 which is 28%. The company explored the uncertainty around these wastage costs in 2 scenarios, one without any SHL wastage, and one where the wastage is halved.

EAG comment: The EAG concurs with the approach used by the company to account for wastage associated with the prophylactic treatment as well as wastage due to an unused SHL reserve in patients treated with emicizumab.

Comment 6: Resource cost and use for managing bleeds

The DGD states that the resource use and costs for managing bleeds are uncertain. The Company submission assumes that patients who experience a bleed would have 1.11 contact with a haematologist on average, with 6% of bleeds requiring an Accident and Emergency (A&E) visit and this was confirmed to be a reasonable assumption during discussions with clinical experts. The External Assessment Group (EAG) noted that bleeds were likely to be mild to moderate and could be managed on the phone and often by specialist nurses, also highlighting that there were more up-to-date costs that could be applied.

The company has sought further clinical input on how bleeds are managed. The clinical experts consulted stated that for a typical bleed, patients would phone a nurse, then administer treatment at home. There would be a follow-up with the centre which would include a multi-disciplinary team (MDT) review for joint bleeds. For bleeds outside of work hours, patients would get to A&E for treatment and then follow-up with the specialist centre the following day. They also highlighted that patients using emicizumab are 'deskilled' with IV and are more likely to require assistance with treating their bleeds.

To reflect the critique from the EAG and committee and additional input from the clinical experts consulted, the cost of bleed management in the model base-case has been updated and additional sensitivity analyses performed. The cost per visit used in the base case is the weighted cost across Service Code 309 using the 2021/22 NHS reference costs (£512.74), which includes face-to-face and non-face-to-face outpatient contacts, both consultant-led and non-consultant led. This will reflect bleeds

that can be resolved over the phone and those that do not require a consultant contact but will also reflect requirement for MDT meeting associated with joint bleeds. This retains the assumption of 1.11 contacts per bleed, plus 6% requiring an A&E visit. A scenario has also been included that uses the average cost of a single non-consultant-led, non-face-to-face contacts (£345.90), assuming all bleeds can be resolved over the phone with a single contact. A scenario without resource use for bleeds has also been included.

The clinical experts also highlighted that patients using emicizumab are 'deskilled' with IV and are more likely to require assistance with treating their bleed, indicating that the assumption of equal costs for each arm may be conservative.

ERG comment: The EAG concurs with the cost estimate that is now based on a mixture of face-to-face and non-face-to-face outpatient contacts, as well as consultant-led and non-consultant-led. This is likely the reflect the variation observed in practice.

Comment 7: The indirect comparison of efanesoctocog alfa with emicizumab

The company respond to the critique of in the draft guidance regarding the ITC by mentioning that the ESS did not drop below 50% of the initial sample size and reiterating the advantage of efanesoctocog alfa versus emicizumab in reduced bleed rate and HJHS.

EAG comment: Given the general unreliability of comparative analyses that do not used randomised control trial (RCT) data, the EAG continue to recommend caution in inferences regarding the size of treatment effect. However, multiple sensitivity analyses using various methods, as summarised in Table 1, do give some indication of the range of possible estimates, which might be plausible.

Comment 8: The impact of a new treatment option with a less frequent dosing schedule

The EAG has no further comments.

Comment 9: Switching treatments

The EAG has no further comments.

Comment 10: Textual clarifications, factual inaccuracies, and typographical errors

Randomisation in XTEND-1

The company claim that there was a misunderstanding of the XTEND-1 trial design.[1] This is because the draft guidance refers to a lack of randomisation between on-demand and prophylactic treatment when the trial was not designed to compare two arms for the same population.

EAG comment: It is unclear to the EAG how the draft guidance indicates any misunderstanding by stating something that is true about the trial even if that was the case because of deliberate design.

Missing dosing regimen and emicizumab wash-out period

The company provide two points of clarification that: dosing in XTEND-Kids was once-weekly, and that the wash-out period for emicizumab was 20 weeks.[1]

Comment 11: Long-term benefits not captured by the quality-adjusted life years (QALY)

The EAG has no further comments.

Company's results of updated cost effectiveness model

In light of the various comments and requests from the committee, the company has updated the model substantively.

The following changes were made:

- **Comparators:** Following the request from the committee, the company has updated the model to allow comparison of efanesoctocog alfa to SHLs and other EHLs beside efmoroctocog alfa. The company did not include the SHLs as a comparator in their updated base case as they do not consider these treatments a relevant comparator in either population (see Comment 1).
    - ***Previously untreated patients*:** Based on clinical feedback, the company incorporated only the SHL simoctocog alfa (NuwiQ) in the model, at a dose of 40 IU/kg every 2.5 days. No other EHLs were included as efmoroctocog alfa is the only EHL licensed for use in children younger than 12 years.
    - ***Previously treated patients***: The SHLs octocog alfa, simoctocog alfa, and moroctocog alfa, and EHLs efmoroctocog alfa, turoctocog alfa pegol, and rurioctocog alfa pegol are now included in the analysis. In the model it is assumed that there is no difference in efficacy between different treatments within each class, and only the costs will differ between therapies. As such, SHLs have each been incorporated as a single comparator, consisting of a weighted bucket of treatments at different prices, with weights taken from UKHCDO data (see Table 22 in the company's response to the DGD). EHLs have been considered both separately and as a weighted bucket.
- **Treatment efficacy:** The company made the following changes to model input based on various comments from the committee in the DGD
    - **Using results adjusted MAIC:** In their response to the DGD, the company presented an MAIC where ABR at baseline was included as covariate. In addition, rather than using the propensity score matched ITC to estimate relative treatment effectiveness between efanesoctocog alfa and efmoroctocog alfa, now a MAIC was used to compare emicizumab and efmoroctocog alfa. The results of this revised MAIC are used in the updated model (see Table 1 in this document and Appendix A in the company's response to the DGD).
    - **Baseline ABR:** In the revised model, all ABRs are estimated using the ABR from emicizumab in the HAVEN-3, arm D study as a baseline. This was done as now both efanesoctocog alfa and efmoroctocog alfa are compared to emicizumab through MAICs.
- **Distribution emicizumab patients over FVIII levels:** As treatment with emicizumab does not entail replacement of FVIII, but rather circumvents the need for FVIII to preventing bleeding and bleeding-related complications, patients cannot be classified as being in a certain FVIII range the same way it is done for efanesoctocog alfa, the EHL, and SHL treatments included in the model. In the original submission, the company assumed that 100% of patients receiving emicizumab could be classified in the FVIII range 5-20%. After further literature review, the company has adjusted the distribution of patients receiving emicizumab over the different FVIII ranges to 30% in the range 5-20%, 40% in the range 20-40% and 30% in the range 40-50%.
- **Utility values based on new analysis**: According to the company's response to the DGD, the revised model now uses utilities based on the new utility analysis with was updated to include data from A-LONG and ASPIRE. However, as explained in the EAG comments under Comment 3 from the company, the new model coefficients are the same as those in the original model. However, more models have now been explored, also including a model with no

disutility for low FVIII levels and one with a disutility for FVIII below 15%. In addition, the model now includes the option to include a disutility for treatments requiring more than 1 injection per week.

- **Baseline utility**: In the new model, the baseline utility, used for patients with FVIII levels >20% and no bleedings in the past six months, is now based on utility at baseline in patients who had previous prophylactic treatment in X-TEND1, A-LONG, and ASPIRE (0.78, n=335), instead of the age-matched general population (0.92).
- **Updated PAS for efanesoctocog alfa:** In this revised submission, the cost per unit efanesoctocog alfa [redacted].
- **Wastage included:** For all treatments, but only for adults, the model now takes wastage into account. Additionally, the cost of wastage in patients treated with emicizumab, due to not using the 'rescue' supply of FVIII before the expiration date has been corrected by the company.
- **Resource use for treated bleed:** The cost of outpatient contacts for treating a bleed has been updated to the average cost of a haemophilia contact, including consultant led and non-consultant led and face-to-face and non-face-to-face contacts (£512.74)
- **Dosage for treating bleeds**: It is now assumed that bleeds in patients receiving efanesoctocog alfa are treated with a single 50 IU/kg dose instead of 25 IU/kg as assumed in the original submission.

Based on the revised model, the company has presented updated base case results, plus a large number of scenario analyses, many in response to requests from the committee. Tables 2, 3 and 4 present the base case results for both populations.

Table 2: Deterministic base-case results, previously untreated patients (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL (efmoroctocog alfa)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Source: Table 25 company response to DGD
EHL, extended half-life; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life years; SHL, standard half-life

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Table 3: Deterministic base-case results, preciously treated patients (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-

Efmoroctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Turoctocog alfa pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Source: Table 27 company response to DGD Abbreviations: EHL, extended half-life; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life years; SHL, standard half-life						

Table 4: Deterministic base-case results, preciously treated patients, with EHLs combined (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Source: Table 28 company response to DGD Abbreviations: EHL, extended half-life; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life years; SHL, standard half-life						

In their response to the DGD, the company presents a large set of scenario analyses, which are described in in Table 5. The results of these analyses can be found in Tables 31 and 32 of the company's response to the DGD. Furthermore, Table 33 and 34 in the same document present the results of a comparison of costs and effectiveness with efanesoctocog alfa versus SHLs.

Table 5: Scenario analyses considered

Scenario	Details
EHLs = 100% efmoroctocog alfa (PTPs only)	All EHL use is assumed to be efmoroctocog alfa
EHLs = 100% turoctocog alfa pegol (PTPs only)	All EHL use is assumed to be turoctocog alfa pegol
Baseline ABRs from XTEND-1	Baseline ABR from XTEND-1, with treatment effects for EHLs and emicizumab from the extended MAIC
Base-case MAIC without prior bleeds adjustment	Baseline ABR from HAVEN-3, with treatment effect from the MAIC without adjustment for prior bleeds
Intra-patient comparison	Baseline ABR from XTEND-1, with treatment effects for EHLs from the XTEND-1 intra-patient comparison and emicizumab from the intra-patient ITC
Intra-patient comparison in prior EHL patients only	Baseline ABR from XTEND-1 using the subgroup previously treated with EHLs, with treatment effects for EHLs from the

Scenario	Details
	XTEND-1 intra-patient comparison and emicizumab from the intra-patient ITC
Excluding untreated bleeds	Uses the rate of treated bleeds from HAVEN-3 as the baseline ABR
Lower resource use for treating bleeds	A single outpatient contact is required, with a cost £345.90
No FVIII wastage with emicizumab	The cost of wastage in patients treated with emicizumab, due to not using the 'rescue' supply of FVIII before the expiration date is excluded.
No resource use for treating bleeds	No resource use for treating bleeds
Utility model 6	The utility model excluding the coefficient for time in study is used
Linear model for utility	A linear model is used to assess utility scores, using the same coefficients as in the base-case
FVIII <15% for utility decrement	A FVIII cut-off of 15% is used for disutilities (Model 3)
FVIII <5% for utility decrement	A FVIII cut-off of 5% is used for disutilities (Model 4)
No FVIII decrement	No disutility associated with FVIII (Model 1)
No FVIII decrement for emicizumab	No utility decrement linked to FVIII is applied for emicizumab
No FVIII decrement for emicizumab, FVIII threshold <15%	A FVIII cut-off of 15% is used for disutilities, with no utility decrement for emicizumab
No FVIII decrement for emicizumab, FVIII threshold <5%	A FVIII cut-off of 5% is used for disutilities, with no utility decrement for emicizumab
No FVIII decrement for emicizumab, linear model	No utility decrement linked to FVIII is applied for emicizumab and a linear model is used
No FVIII decrement for emicizumab, FVIII threshold <15%, linear model	No utility decrement linked to FVIII is applied for emicizumab and a linear model with a decrement for FVIII <15% is used
No FVIII decrement for emicizumab, FVIII threshold <5%, linear model	No utility decrement linked to FVIII is applied for emicizumab and a linear model with a decrement for FVIII <5% is used
Utility decline with age from model	Utility declines with age as per the regression model, rather than proportionally to general population norms.
Frequent infusion disutility - 0.027	Disutilities associated with more frequent infusions are included for the EHL arm
Frequent infusion disutility - 0.0745	
Frequent infusion disutility - 0.107	
Source: Table 30 company response to DGD ABR, annualised bleed rate; EHL, extended half-life; FVIII, clotting factor VIII; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; PAS, Patient Access Scheme; PTP, patient treated population.	

EAG additional scenarios

In the EAG comments on the company's response 'Comment 3', it was discussed that the utility model selected by the company (model 2) for their updated model was not the one with the lowest AIC (model 1). Further, models 1 to 4 include time from study initiation as covariate, but this covariate was subsequently not used in estimating the utility. In that situation, the model should be selected from those not including this variable as covariate, i.e. model 5 to 8. Of these, model 5, which does not include a variable for time spent below a FVIII threshold level, had the lowest AIC. As such, it would be a suitable choice. However, based on patient reports, it appears that below a certain FVIII threshold level quality of life is affected regardless of the occurrence of bleedings. Based on this information, the EAG considers model 8 to be the best choice. This model defines the threshold FVIII at 5%; it has the lowest AIC among model 6, 7, and 8, and is the only of the 3 models where the coefficient for the threshold variable is statistically significant different from 0.

Thus, below we present the results based on the updated company base case, once using model 8 for the estimation of utilities, to reflect the EAG preferred choice, and once with model 5 as it has the lowest AIC. In addition, a scenario is presented where a threshold of 15% is used (model 7), but with a correction of the percentage of emicizumab patients having an FVIII level below 15% (i.e. 20% of patients, pro-rated based on 30% of patients having an FVIII level between 5% and 20%), as in this scenario presented by the company the percentage assumed to be below 15% was the same as the percentage below 20% (i.e. 30% of patients). Table 6 presents the results for the PUP population, and table 7 for the PTP population.

Table 6: EAG scenarios, previously untreated patients (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs versus baseline (£)	Incremental QALYs versus baseline	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Updated company base case						
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL (efmoroctocog alfa)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
EAG preferred scenario: Model 8 for utilities						
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL (efmoroctocog alfa)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Alternative scenario: Model 5 for utilities						

Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL (efmoroctocog alfa)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Alternative scenario: Model 7 for utilities, including correction % emicizumab below 15% FVIII						
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL (efmoroctocog alfa)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
EHL, extended half-life; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life years; SHL, standard half-life						

.

Table 7: EAG scenarios, previously treated patients (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs versus baseline (£)	Incremental QALYs versus baseline	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Updated company base case						
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Model 8 for utilities						
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Model 5 for utilities						
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-
EHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Model 7 for utilities, including correction % emicizumab below 15% FVIII						
Efanesoctocog alfa	[redacted]	[redacted]	-	-	-	-

EHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SHL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
EHL, extended half-life; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life years; SHL, standard half-life						

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[1] National Institute for Health and Care Excellence. *Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]: Draft guidance comments form. Swedish Orphan Biovitrum Ltd ('Sobi') [Document provided by NICE]*. London: NICE, 2024. 55p.

[2] National Institute for Health and Care Excellence. *Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]: Comments on the draft guidance received through the NICE website. Paul Spicer [Document provided by NICE]*. London: NICE, 2024. 1p.

[3] National Institute for Health and Care Excellence. *Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]: Draft guidance comments form. Roche Products Ltd [Document provided by NICE]*. London: NICE, 2024. 4p.

[4] National Institute for Health and Care Excellence. *Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]: Draft guidance comments form. Novo Nordisk Ltd [Document provided by NICE]*. London: NICE, 2024. 4p.

[5] National Institute for Health and Care Excellence. *Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]: Draft guidance comments form. Alice Taylor [Document provided by NICE]*. London: NICE, 2024. 5p.

[6] National Institute for Health and Care Excellence. *Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]: Draft guidance comments form. United Kingdom Haemophilia Centre Doctors Organisation [Document provided by NICE]*. London: NICE, 2024. 10p.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

Company response to questions after postponed ACM2

July 2024

File name	Version	Contains confidential information	Date
ID6170_Efanesoctocog alfa_Haemophilia A_Company response after postponed ACM2_[CON]	1.0	Yes	23rd July 2024

Based on the evidence provided in response to the draft guidance consultation, the committee has identified some areas in which they would like further information. NICE would like to provide the company with an opportunity to address these areas, to support the upcoming committee discussion. We would be grateful if you could provide responses, including supporting evidence, on the following priority areas:

1. Comparators

1.1. PRIORITY: Please explain the rationale behind the company's use of the UKHCDO data to inform SHL distributions in model instead of the UKNHD data provided by NHS England at ACM1. Please provide supporting evidence if relevant.

(The company would like to draw to your attention to the fact that we have obtained the most accurate proportion of patients treated with SHLs, EHLs and emicizumab that reflects the company decision problem population – further details are towards the end of this answer.)

To avoid any misunderstanding, the company would first like to clarify that the UK Haemophilia Centre Doctors Organisation (UKHCDO) and the National Haemophilia Database (NHD) are part of the same group – the NHD operates within the UKHCDO. The two acronyms are often used interchangeably to refer to the same database from which real-world data (RWD) on haemophilia patients is extracted. This is the sole registry database for UK RWD on haemophilia patients and is sometimes referred to as UKHCDO data and other times as the NHD data. This means that the data collected from NHS England and the Company is derived from the same dataset.

The data used by the Company to inform the distribution of standard half-life (SHL) products in previously treated patients (PTP) was taken from the latest UKHCDO annual report (2023),[1] which represents the latest published data on treatment use in patients in the UK. The key limitation of this data is that it contains both prophylactic and on-demand (OD) use, but these data cannot be separated out. It is therefore assumed that the distribution of SHL use does not differ between prophylaxis and OD use. This limitation is also

present in the NHD data presented at ACM1, but the details of the analysis were not presented. For example, it is not clear which year this data is from, and if it represents current use in clinical practice or if it has been derived from older analyses. As such, the Company give preference to published data. However, in PTPs the distribution is similar between the data sources, except for no turoctocog alfa use in the NHD data presented at ACM1, and the choice of data source is not expected to be a driver of results.

In previously untreated patients (PUP), clinical input to the Company indicated that SHLs were only used prophylactically where there was a particular concern that a person may develop inhibitors. Where this is the case, simoctocog alfa is used as this is perceived to have a low risk of inhibitor development. As such, the Company selected to use clinical opinion in preference over published data that cannot distinguish between prophylactic and OD use.

The UKHCDO data cannot be used to inform the total proportion of patients being treated prophylactically with SHLs, as it includes both prophylactic and on-demand use. This contrasts with the Company decision problem population which is distinguished by the PUPs and PTPs population being appraised in severe prophylactic patients only. Therefore, interpreting the data provided by NHS England comes with some caveats in that the under 12 year old contain both PUPs and PTPs, and the on-demand usage will cover a multitude of uses (i.e. surgery, acute breakthrough bleed management, traumatic breakthrough bleed management, the use of rFVIII by emicizumab patients – contingency stock (plus additional repeated prescriptions for contingency stock that has gone out of date) and top-ups when a patient wishes to have higher factor level protection – e.g. for sport. Finally, as people may be issued with more than one product type in any given year, there is some double counting of people between product groups within years which adds to the difficulty in interpreting the data. Because of these caveats it can be assumed that the SHL figures are heavily overrepresented in the data provided by NHS England.

The Company still maintains, as do clinical experts, that emicizumab is the most relevant comparator. The market trend corroborates this opinion, and in

a world with or without efanesoctocog alfa, this trend would continue to rise Indeed, clinicians inform us, that if efanesoctocog alfa would be made available in the UK it would be offered to patients who would otherwise be offered emicizumab.

Please note, to ensure that the most up-to-date depiction of market shares was presented in the draft guidance consultation response and ACM2, Sobi submitted a specific request to the NHD to obtain market shares in the population considered in the decision problem – severe haemophilia A patients without inhibitors receiving prophylactic therapy. Due to the specificity of the Company request, Sobi believe this represents the most accurate source of data to reflect clinical practice. It is hoped that this may help to resolve some of the uncertainties regarding the comparators in this appraisal.[2] Specifically, the Company requested market share data in the specific population under appraisal (i.e. severe, without inhibitors, prophylaxis, and double counting corrected). Therefore, Sobi believe this to be the most accurate representation of market shares available to help inform decision making. On this point, the Company would like to seek clarification of the patient cohort detailed in slide 19 of the ACM2 slide set since it is not clear whether this represents the population under appraisal, has been corrected for double counting, or the year it was collected.

1.1.1. EAG comment

The company have provided some clarification regarding their data source and highlighted that there is a lack of transparency in the source of the data provided by NHSE, (referred to as the UKNHD). They have also updated their data to 2024. These data suggest that a substantial percentage of patients still receive SHL prophylaxis (8% for those aged up to 11 years and 14% for 12 years and older), with the corresponding values for those receiving EHL prophylaxis being 16% and 23% (Figure 1 of the report requested by SOBI of the NHD[2]). Note that there is no breakdown of EHL by specific product.

2. ITC

2.1. PRIORITY: Please provide further detail on the alternative ITC approaches presented in the company response to the draft guidance (comment 2), including uncertainties in the ITCs:

2.1.1. Specifically, please provide an explanation of why the relative effectiveness estimates differ depending on approach chosen

The incidence rate ratios (IRRs) for respective bleeding events are very consistent. The point estimates for IRRs for respective comparisons and outcomes are [redacted] The relative effects from three different approaches for each bleeding type are shown in Table 1.

Table 1: Comparison of MAIC outcomes

	Base-case MAIC	Updated MAIC adjusted for pre-study ABR	Anchored MAIC through pre-study regimen
Efanesoctocog alfa vs efmoroctocog alfa			
ABR any treated	[redacted]	[redacted]	[redacted]
ABR spontaneous (treated)	[redacted]	[redacted]	[redacted]
ABR joint (treated)	[redacted]	[redacted]	[redacted]
Efanesoctocog alfa vs emicizumab			
ABR any	[redacted]	[redacted]	[redacted]
ABR any treated	[redacted]	[redacted]	[redacted]
ABR spontaneous (treated)	[redacted]	[redacted]	[redacted]
ABR joint (treated)	[redacted]	[redacted]	[redacted]

Note, statistically significant results are bolded.
Abbreviations: ABR, annualised bleed rate; MAIC, matching adjusted indirect comparison.

Some slight differences can be explained with the underlying methodological differences between respective matching-adjusted indirect comparison (MAIC) approaches.

The **base-case analysis** was an unanchored MAIC in which patient level data from ARM-A of the XTEND-1 trial were matched to aggregated characteristics from either individual prophylaxis arm of the A-LONG trial (for comparison vs efmoroctocog alfa) or arm D of the HAVEN 3 trial (for comparison vs emicizumab).

The **updated MAIC** used an unanchored MAIC, although patient level data from both XTEND-1 and A-LONG were matched to aggregated data from arm D of HAVEN 3. Therefore, all estimates represent efficacy in the population of HAVEN 3 trial. Additionally, one additional variable (pre-study annualised bleed rate [ABR]) was included in the updated MAIC.

The **anchored MAIC** was used to compare efanesoctocog alfa vs emicizumab through standard prophylaxis regimens as common arms. For this reason, a pre-post approach comparing the ABR observed in respective trials with ABR values observed in the corresponding preceding studies in which participants were receiving standard FVIII prophylaxis. This analysis had the properties of an anchored comparison, therefore it was not required to account for the differences in prognostic factors, only effect modifiers. Matching was conducted only for pre-study ABR, which could interact with the relative effects.

Despite these differences the relative estimates were consistent, which indicates the robustness of the results.

Table 2: Comparison of MAIC approaches

	Base-case MAIC	Updated MAIC adjusted for pre-study ABR	Anchored MAIC through pre-study regimen
Method	Unanchored MAIC	Unanchored MAIC	Anchored MAIC (through pre-study prophylaxis as common reference)
Reference population	A-LONG for comparison *vs* efmoroctocog alfa HAVEN 3 for comparison *vs* emicizumab	HAVEN 3 for all comparisons	HAVEN 3 (adjusted only for pre-study ABR)
Patient data	• ARM A XTEND-1 (PLD) • Indiv. prophylaxis A-LONG (aggregated) • Arm D HAVEN 3 (aggregated)	• ARM A XTEND-1 (PLD) • Indiv. prophylaxis A-LONG (aggregated) Arm D HAVEN 3 (aggregated)	Only patients who took part in non-interventional studies preceding XTEND-1 and HAVEN 3 were included. Thus, the analysis included: • 78 participants from group A of XTEND

	Base-case MAIC	Updated MAIC adjusted for pre-study ABR	Anchored MAIC through pre-study regimen
			• 48 participants from HAVEN 3 group D
Characteristics for adjustment	• Age • Body weight • Race • TJ at baseline	• Age • Body weight • Race • TJ at baseline • Pre-study ABR	• Pre-study ABR
Interpretation of the relative effect	Incidence rate ratio between efanesoctocog alfa and comparator administered in the population of comparator study • **Vs efmoroctocog alfa** The relative effect between efanesoctocog alfa and efmoroctocog alfa in the population of A-LONG • **Vs emicizumab** The relative effect between efanesoctocog alfa and emicizumab in the population of HAVEN 3	Incidence rate ratio between efanesoctocog alfa and comparator administered in the population of HAVEN 3	Incidence rate ratio between efanesoctocog alfa and comparator administered in the population of HAVEN 3 (adjustment only for pre-study ABR)

Abbreviations: ABR, annualised bleed rate; MAIC, matching adjusted indirect comparison; PLD, patient level data; TJ, target joint.

2.1.2. EAG comment

The company appear to have complied with the request for clarification, noting both the similarity in outcome between the different approaches, but also providing an explanation of any differences. These differences seem to largely be due to either matching to different populations in the unanchored MAICs or the use of an anchored instead of unanchored comparison where the pre-study regimen data were used.

2.2. PRIORITY: Please provide data presenting the *spread of outcomes for ABR for efanesoctocog alfa and comparators, ideally in a histogram*

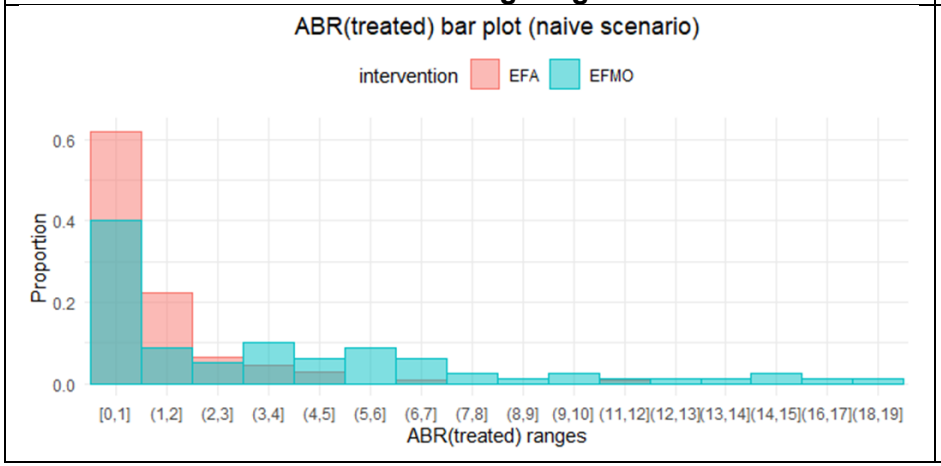
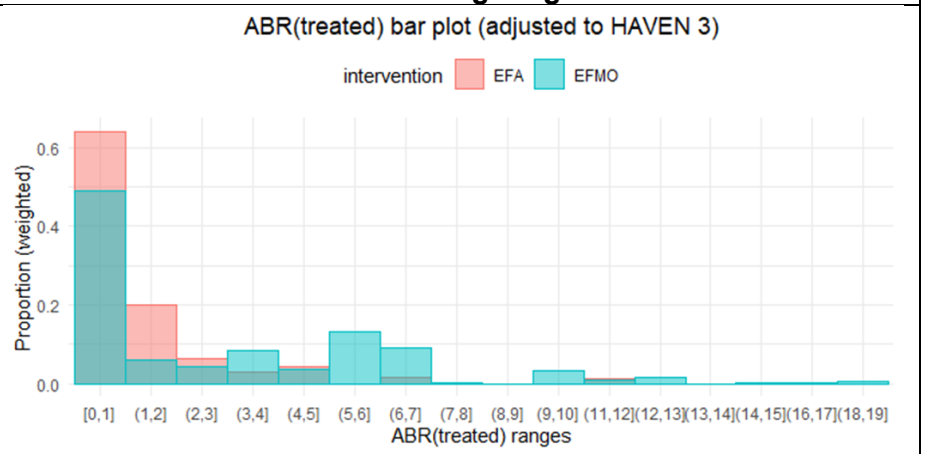
Histograms for efanesoctocog alfa and efmoroctocog alfa are presented for any treated bleeds (Figure 1), joint bleeds (Figure 2), and spontaneous bleeds (Figure 3). These can only be developed based on patient level data, which are only available from the XTEND and A-LONG studies. For HAVEN 3 and other studies, ABRs were reported as the output of negative binomial regression models – this information doesn't allow to draw histograms on the distribution of ABRs.

The histograms show that before and after adjustment, the proportion of patients with no bleeds and very low bleeding incidence (0 to 2) is higher with efanesoctocog alfa compared to efmoroctocog alfa. Additionally, there were no patients with significantly higher ABRs for efanesoctocog alfa in contrast with efmoroctocog alfa. This pattern was observed before and after weighting.

2.2.1. EAG comment

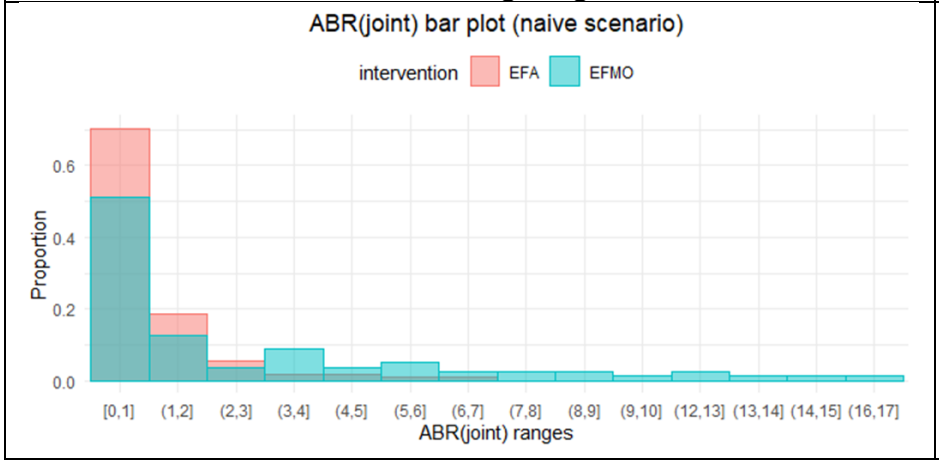
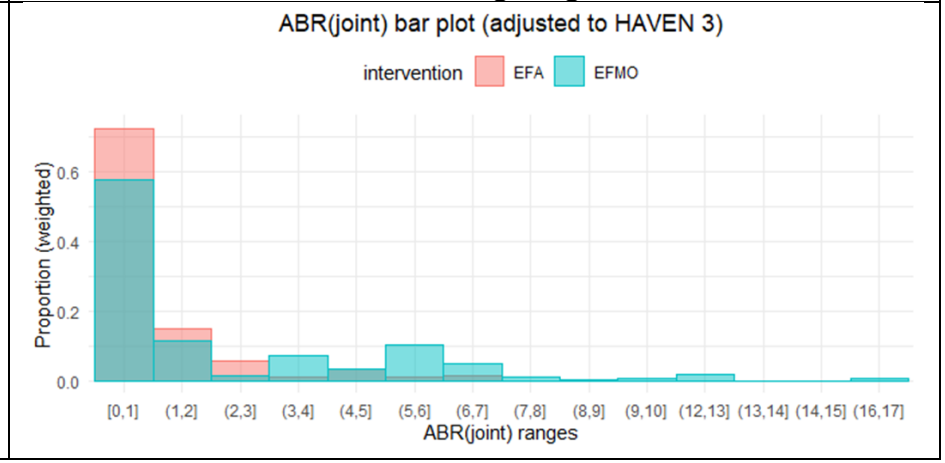
The clarification question was not entirely clear to the EAG i.e. data presenting the spread of outcomes for ABR for efanesoctocog alfa and comparators, ideally in a histogram. However, the company's interpretation seems reasonable, and histograms have been provided where data were available.

Figure 1: Histogram for any treated bleeds

Before weighting	After weighting
	

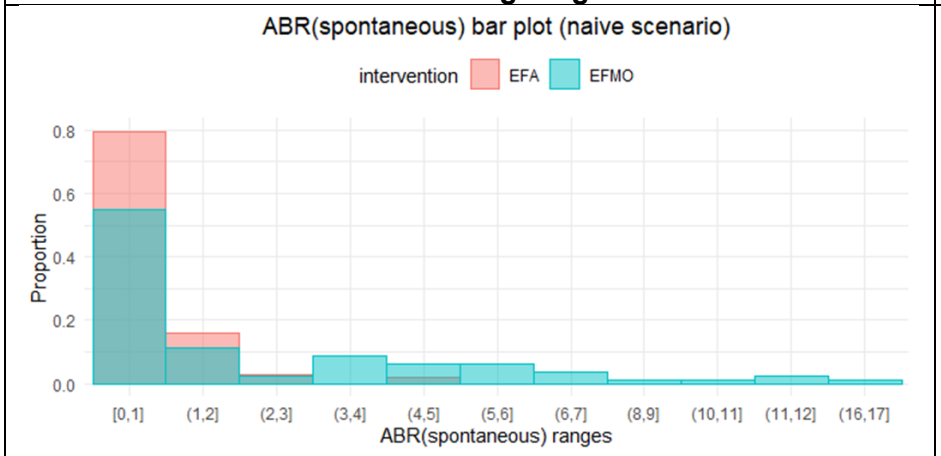
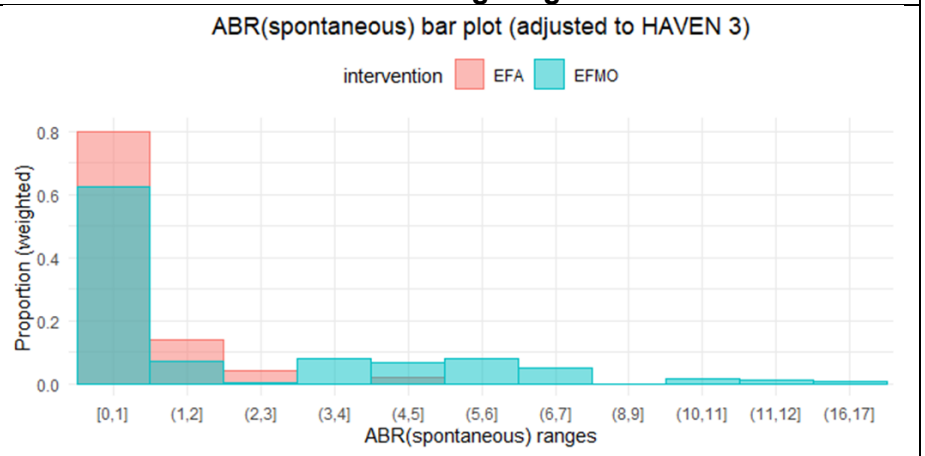
Abbreviations: ABR, annualised bleed rate; EFA, efanesoctocog alfa; EFMO, efmoroctocog alfa.

Figure 2: Histogram for any bleeds

Before weighting	After weighting
	

Abbreviations: ABR, annualised bleed rate; EFA, efanesoctocog alfa; EFMO, efmoroctocog alfa.

Figure 3: Histogram for spontaneous bleeds

Before weighting	After weighting
	

Abbreviations: ABR, annualised bleed rate; EFA, efanesoctocog alfa; EFMO, efmoroctocog alfa.

3. Utilities

3.1. PRIORITY: Please provide further detail regarding the methodology and results of the updated TOBIT model

3.1.1. Methodology: Please confirm:

- **Top priority: That the data sets for the regression models have been updated since the original company submission. If not, please provide updated TOBIT models with the updated data sets.**

The data set used for all regression models, in both the Company submission and the response to the draft guidance, was based on the XTEND-1, A-LONG and ASPIRE trials, as described in the response to the draft guidance. The Company apologises for any confusion that may have been caused here.

3.1.1.1. How many patients were included in the analysis

335 patients were included in the analysis, which include:

- 127 patients from X-TEND1
- 81 patients from A-LONG
- 127 patients from ASPIRE.

3.1.1.2. How many observations were available

A total of 1,262 observations were included in the regression analysis.

3.1.1.3. Was there missing data and how was this accounted for

Only visits with full set of data required for the analysis were included in the regression analysis. If, for any reason, required data was missing (e.g. No observation utility) it was not included in the analysis.

3.1.1.4. Does the model take correlated observations per patient into account

Yes, random intercept LINEAR and TOBIT models with patient ID as factor were used to account for the fact that several observations were derived from the same patients (correlated data).

3.1.2. Results

3.1.2.1. Please provide the standard errors and confidence intervals for coefficients

Table 3 and Table 4 present standard errors (SE) and confidence intervals (CI) for the TOBIT and LINEAR models, respectively.

Table 3: TOBIT models

Variable		Results of the regression coefficients (SE) [95% CI]							
		Prophylaxis only							
		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Intercept	Mean (SE)	**0.4119** (0.0397)	**0.4868** (0.0511)	**0.4851** (0.0475)	**0.4864** (0.0427)	**0.3849** (0.0389)	**0.4675** (0.0509)	**0.4613** (0.0473)	**0.4491** (0.0424)
	Upper 95% CI	0.4897	0.5870	0.5783	0.5700	0.4612	0.5672	0.5540	0.5322
	Lower 95% CI	0.3341	0.3866	0.3920	0.4027	0.3086	0.3677	0.3686	0.3660
Baseline utility	Mean (SE)	**0.8092** (0.0314)	**0.7692** (0.0335)	**0.7690** (0.0335)	**0.7642** (0.0338)	**0.8151** (0.0316)	**0.7747** (0.0332)	**0.7747** (0.0332)	**0.7762** (0.0340)
	Upper 95% CI	0.8707	0.8348	0.8347	0.8304	0.8769	0.8397	0.8399	0.8429
	Lower 95% CI	0.7478	0.7035	0.7033	0.6980	0.7532	0.7096	0.7096	0.7094
7d_bleed_ disutility	Mean (SE)	**-0.0676** (0.0202)	**-0.0663** (0.0206)	**-0.0661** (0.0206)	**-0.0649** (0.0205)	**-0.0789** (0.0198)	**-0.0760** (0.0201)	**-0.0757** (0.0201)	**-0.0738** (0.0201)
	Upper 95% CI	-0.0280	-0.1066	-0.0258	-0.0247	-0.0402	-0.0365	-0.0362	-0.0343
	Lower 95% CI	-0.1071	-0.0260	-0.1064	-0.1052	-0.1177	-0.1155	-0.1152	-0.1132
6m_bleed_ disutility	Mean (SE)	**-0.0396** (0.0138)	**-0.0435** (0.0152)	**-0.0434** (0.0152)	**-0.0432** (0.0151)	**-0.0479** (0.0134)	**-0.0447** (0.0149)	**-0.0446** (0.0149)	**-0.0441** (0.0147)
	Upper 95% CI	-0.0126	-0.0138	-0.0137	-0.0135	-0.0215	-0.0155	-0.0154	-0.0152
	Lower 95% CI	-0.0667	-0.0732	-0.0731	-0.0729	-0.0742	-0.0740	-0.0738	-0.0729
Days since study initiation	Mean (SE)	**-0.000053** (0.000009)	**-0.000067** (0.000011)	**-0.000066** (0.000011)	**-0.000065** (0.000011)	Not used	Not used	Not used	Not used
	Upper 95% CI	-0.000034	-0.000044	-0.000044	0.000043				
	Lower 95% CI	-0.000071	-0.000089	-0.000089	-0.000088				
Age	Mean (SE)	**-0.0047** (0.0007)	**-0.0053** (0.0008)	**-0.0053** (0.0008)	**-0.0052** (0.0008)	**-0.0047** (0.0007)	**-0.0053** (0.0008)	**-0.0053** (0.0008)	**-0.0052** **(0.0008)**

Variable		Results of the regression coefficients (SE) [95% CI]							
		Prophylaxis only							
		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
	Upper 95% CI	-0.0033	-0.0038	-0.0038	-0.0037	-0.0032	-0.0037	-0.0037	-0.0036
	Lower 95% CI	-0.0062	-0.0068	-0.0068	-0.0067	-0.0062	-0.0068	-0.0068	-0.0067
Proportion of time in <5%	Mean (SE)	Not used	Not used	Not used	-0.0782 (0.0571)	Not used	Not used	Not used	**-0.1231** (0.0581)
	Upper 95% CI				0.0338				-0.0092
	Lower 95% CI				-0.1901				-0.2370
Proportion of time in <15%	Mean (SE)	Not used	Not used	-0.0299 (0.0502)	Not used	Not used	Not used	-0.0728 (0.0494)	Not used
	Upper 95% CI			0.0685				0.0239	
	Lower 95% CI			-0.1282				-0.1696	
Proportion of time in <20%	Mean (SE)	Not used	-0.0277 (0.0546)	Not used	Not used	Not used	-0.0728 (0.0537)	Not used	Not used
	Upper 95% CI		0.0794				0.0324		
	Lower 95% CI		-0.1347				-0.1780		
Model fit	BIC	**137.641**	169.365	169.250	167.688	**151.738**	187.544	187.167	184.840
	AIC	**95.750**	123.101	122.986	121.424	**115.083**	146.420	146.043	143.717

Note: Statistically significant results are presented in **bold**.
Abbreviations: AIC, Aikike information criterion; BIC, Bayesian information criterion; CI, confidence interval; SE, standard error.

Table 4 LINEAR models

Variable		Results of the regression coefficients								
		Prophylaxis only								
		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
Intercept	Mean (SE)	**0.4248** (0.0354)	**0.4866** (0.0410)	**0.4813** (0.0396)	**0.4707** (0.0381)	**0.4132** (0.0354)	**0.4787** (0.0411)	**0.4713** (0.0397)	**0.4554** (0.0380)	**0.4588** (0.0452)
	Upper 95% CI	0.4939	0.5666	0.5587	0.5450	0.4824	0.5588	0.5487	0.5297	0.5472
	Lower 95% CI	0.3557	0.4066	0.4040	0.3964	0.3440	0.3985	0.3938	0.3811	0.3705
Baseline utility	Mean (SE)	**0.6152** (0.0310)	**0.5841** (0.0330)	**0.5841** (0.0330)	**0.5860** (0.0330)	**0.6153** (0.0311)	**0.5843** (0.0331)	**0.5844** (0.0331)	**0.5871** (0.0331)	**0.5868** (0.0332)
	Upper 95% CI	0.5546	0.6485	0.6486	0.6504	0.6762	0.6489	0.6490	0.6518	0.6516
	Lower 95% CI	0.6758	0.5196	0.5197	0.5216	0.5544	0.5197	0.5198	0.5225	0.5219
7d_bleed_ disutility	Mean (SE)	**-0.0498** (0.0179)	**-0.0494** (0.0182)	**-0.0493** (0.0182)	**-0.0490** (0.0182)	**-0.0569** (0.0180)	**-0.0555** (0.0184)	**-0.0553** (0.0184)	**-0.0548** (0.0184)	**-0.0548** (0.0184)
	Upper 95% CI	-0.0147	-0.0137	-0.0136	-0.0133	-0.0217	-0.0195	0.0193	-0.0189	-0.0189
	Lower 95% CI	-0.0850	-0.0851	-0.0850	-0.0847	-0.0921	-0.0914	-0.0912	-0.0908	-0.0908
6m_bleed_ disutility	Mean (SE)	**-0.0298** (0.0091)	**-0.0321** (0.0098)	**-0.0320** (0.0098)	**-0.0320** (0.0098)	**-0.0361** (0.0091)	**-0.0332** (0.0099)	**-0.0330** (0.0099)	**-0.0330** (0.0099)	**-0.0329** (0.0099)
	Upper 95% CI	-0.0119	-0.0129	-0.0128	-0.0128	-0.0184	0.0138	-0.0136	-0.0136	-0.0136
	Lower 95% CI	-0.0479	-0.0516	-0.0515	-0.0515	-0.0540	-0.0528	-0.0526	-0.0526	-0.0526
Days since study initiation	Mean (SE)	**-0.000036** (0.000008)	**-0.000045** (0.000010)	**-0.000045** (0.000010)	**-0.000045** (0.000010)	Not used	Not used	Not used	Not used	Not used
	Upper 95% CI	-0.000020	-0.000026	-0.000026	-0.000026					
	Lower 95% CI	-0.000053	-0.000065	-0.000065	-0.000064					
Age	Mean (SE)	**-0.0028** (0.0005)	**-0.0031** (0.0005)	**-0.0031** (0.0005)	**-0.0030** (0.0005)	**-0.0029** (0.0005)	**-0.0032** (0.0005)	**-0.0032** (0.0005)	**-0.0031** (0.0005)	**-0.0031** (0.0005)
	Upper 95% CI	-0.0019	0.0020	-0.0020	-0.0020	-0.0019	-0.0021	-0.0021	-0.0021	-0.0021
	Lower 95% CI	-0.0038	-0.0041	-0.0041	-0.0041	-0.0039	-0.0042	-0.0042	-0.0042	-0.0042
Proportion of time in <5%	Mean (SE)	Not used	Not used	Not used	-0.0601 (0.0364)	Not used	Not used	Not used	**-0.0875** (0.0361)	**-0.0880** (0.0363)
	Upper 95% CI				0.0111				-0.0170	-0.0171
	Lower 95% CI				-0.1312				-0.1580	-0.1587
Proportion of time in <15%	Mean (SE)	Not used	Not used	-0.0469 (0.0308)	Not used	Not used	Not used	**-0.0697** (0.0305)	Not used	Not used

Variable		Results of the regression coefficients								
		Prophylaxis only								
		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
	Upper 95% CI			0.0133				-0.0101		
	Lower 95% CI			-0.1070				-0.1293		
Proportion of time in 5-20%	Mean (SE)	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	-0.0096 (0.0685)
	Upper 95% CI									0.1241
	Lower 95% CI									-0.1436
Proportion of time in <20%	Mean (SE)	Not used	-0.0492 (0.0334)	Not used	Not used	Not used	**-0.0726** (0.0332)	Not used	Not used	Not used
	Upper 95% CI		0.0160				-0.0079			
	Lower 95% CI		-0.1145				-0.1374			
Model fit	BIC	-1277.0	**-1089.5**	**-1089.4**	**-1090.2**	-1287.6	**-1096.6**	**-1096.9**	**-1097.9**	**-1087.2**
	AIC	-1318.9	**-1135.7**	**-1135.7**	**-1136.4**	-1324.3	**-1137.7**	**-1138.0**	**-1139.0**	**-1133.5**

Note: Statistically significant results are presented in **bold**.
Abbreviations: AIC, Aikike information criterion; BIC, Bayesian information criterion; CI, confidence interval; SE, standard error.

3.1.3. EAG comment

The company clarified that the utility models used both in the original company submission and the response to the draft guidance were identical because they were based on the same data from the XTEND-1 study (efanesoctocog alfa; 127 patients), the A-LONG (efmoroctocog alfa; 81 patients) and ASPIRE studies (efmoroctocog alfa; 127 patients). Considering the additional responses provided by the company, the EAG has no further comments on the data used to estimate the linear and TOBIT models. However, the EAG maintains that the choice of the utility model should be restricted to models 5-8, which do not include a coefficient for days since start of the study as this covariate was subsequently not used in the utility estimations. Out of models 5-8, model 5 has the lowest AIC/BIC (115.1/151.7) but does not account for a disutility due to lower levels of FVIII. The EAG acknowledges that based on patient reports, lower levels of FVIII may impact the patients' quality of life regardless of the occurrence of bleedings. Based on this, the EAG considers model 8 to be the best choice. This model defines the threshold of FVIII at 5%; it has the lowest AIC (143.7/184.8) among models 6, 7, and 8, and is the only of the 3 TOBIT models where the coefficient for the threshold variable is statistically significant different from 0.

4. Additional queries

The following are further issues that are **provided for information only**. These are issues that have been identified as **potential concerns** that may warrant further discussion during the committee meeting. **The company should be ready to respond** during the meeting, but a written response is not expected.

These include:

4.1. Clarification of how patients were advised to report bleeds in clinical trials – were any criteria used?

Details on how patients were advised to record bleeds in the clinical trials can be found listed below. Where possible, this information has been derived from study protocols, or from the clinical papers and/or their supplementary materials. Please note that we have been unable to identify how bleeds were defined and reported for all trials (where this information was not included in the relevant paper and the study protocol could not be sourced).

For those studies in which reporting methods were outlined, all were collected via patient diaries/patient records. Bleeds were subsequently reviewed via telephone and/or clinic visit, depending on the study. Bleeding episodes were defined in the XTEND-1, HAVEN 3 and A-LONG study protocols as per the standardised definitions of the International Society of Thrombosis and Hemostasis (ISTH) Subcommittee on Standards and Criteria, FVIII/FIX.[3]

In summary, the manner in which treated bleeds were reported can be considered broadly comparable in those trials where this information was accessible. This is especially true for the XTEND-1, HAVEN 3 and A-LONG trials. The Company is unable to comment on the studies where this information could not be sourced.

XTEND-1 (efanesoctocog alfa)

Participants will be supplied with an electronic patient diary (ePD) at the Baseline visit to record all bleeding episodes and doses of BIVV001 administered after the Baseline visit. Entries are to be made in a timely manner and it is preferred that details of doses are entered immediately upon administration or within 7 days. Participants will be prompted to enter bleeding

location, type (spontaneous or traumatic), and reasons for dosing (prophylaxis or treatment of a bleeding episode).

During the clinic visits and telephone calls with the participant, the Investigator will review the bleeding episode data in the ePD. If the Investigator judges that the classification by the participant/caregiver was incorrect, the Investigator will document it in the participant's medical records with the rationale for the new classification, and in the eCRF, documenting the new classification of the bleeding episode according to the Investigator and whether or not the participant/caregiver agreed with this new classification

Definition of a bleed: In this study, a standardized definition of a bleeding episode based on International Society on Thrombosis and Haemostasis (ISTH) criteria will be used [3]. A bleeding episode is defined as an episode that starts from the first sign of bleeding and ends no more than 72 hours after the last injection to treat the bleeding episode. Any subsequent bleeding at the same location and injections administered ≤72 hours from the previous injection will be considered as the same bleeding episode. Multiple bleeding locations treated with a single injection will also be considered a single bleeding episode.

Any injection to treat the bleeding episode that is administered >72 hours after the preceding one will be considered the first injection to treat a new bleeding episode in the same location.

Any injection used to treat subsequent bleeding at a different location will be considered a separate bleeding episode, regardless of the time from the last injection to treat a bleeding episode

Source: Protocol for von Drygalski et al.[4]

HAVEN 3 (emicizumab)

Patients (or patient's legally authorized representative) will complete an electronic bleed and medication questionnaire whenever a bleed occurs, or at least weekly to confirm all bleeds have been recorded. For each bleeding episode, they will provide information on the above topics as well as on the medication used to treat the bleed. Haemophilia medications that were taken will also be collected through the bleed and medication questionnaire. In the

event that the electronic bleed and medication questionnaire is not available, a paper version of the bleed and medication questionnaire may be utilized.

The patient is able to edit and delete bleeds and medications for 24 hours after they are entered. Furthermore, the investigator and patient are instructed to review the data together at every clinic visit.

Definition of a bleed: An event is considered a bleed if coagulation factors are administered to treat signs or symptoms of bleeding (pain, swelling, etc.). A standardized definition of bleed, adapted from criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Hemostasis and similar to that used in a recent clinical study, will also be utilized in this study,[3, 5] which includes the following additional criteria:

- Bleeds starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections are ≤72 hours apart, are considered the same bleed
- Any injection to treat the bleed, taken >72 hours after the preceding injection, is considered the first injection to treat a new bleed at the same location
- Any bleed at a different location is considered a separate bleed regardless of time from last injection.

Source: Protocol for Mahlangu et al.[6]

A-LONG (efmoroctocog alfa)

[redacted]

[redacted]

Source: A-LONG protocol.[7]

Turoctocog alfa pegol (Pathfinder 2)

Method of reporting bleeds was not specified in the clinical paper.[8]

We have reviewed multiple sources but were unable to locate the study protocol.

Simoctocog alfa (GENA-08)

Method of reporting bleeds was not specified in the clinical paper.[9]

We have reviewed multiple sources but were unable to locate the study protocol.

Moroctocog alfa

Method of reporting bleeds was not specified in the clinical paper.[10]

We have reviewed multiple sources but were unable to locate the study protocol.

Turoctocog alfa (guardian™ 1)

Details about all treated bleeding episodes (including location, cause and severity) were recorded in either the medical records or in the patient's diary. Bleeding episodes were treated with turoctocog alfa as soon as they were identified.[11]

Further detail is not provided in the clinical paper and we were unable to locate the study protocol.

Octocog alfa

Method of reporting bleeds was not specified in the clinical paper.[12]

We have reviewed multiple sources but were unable to locate the study protocol.

4.2. Evidence underpinning the assumption that [redacted]% of people having emicizumab are expected to switch to efanesoctocog alfa if available in the NHS

[redacted]

There are a range of reasons as to why patients may switch from emicizumab to efanesoctocog alfa, these include - patient preference, inadequate control of breakthrough bleeds, insufficient factor levels to offer sufficient protection

for the patient's lifestyle, regular pain at injection site, or other continued issues, such as joint pain.

4.3. Availability of registry data on bleed rates for each treatment in UK population, and how those data compare to modelling

UK registry data on bleed rates to compare to the model outputs is only partially available. Even if it was fully available, such an analysis would be flawed.

As per the Company response to Question 1.1, the NHD is the sole registry for UK RWD on haemophilia patients. However, bleeding rates are not published within its annual reports.

Even if these data were fully available, the insights generated by comparing model outputs that utilise clinical trial results with RWD would be difficult to interpret. For example, it is reasonable to expect reported bleed rates in the NHD to be lower than those reported by a clinical trial, all else equal, as the incentives to report (bleeding) events outside of the clinical study setting are lower. It is also the case that the NHD does not record information on untreated bleeds. Similarly, it is known that patients are less likely to have switched to emicizumab in the UK if they were 'doing well' on FVIII, meaning that those receiving emicizumab are unlikely to represent an 'average' patient [1]. Thus, modelled results and RWD are unlikely to be similar as a result of differences in data recording and patient selection processes, and ultimately comparisons between them are fundamentally unsound.[13]

4.4. Results of the outstanding ITC approach requested in the draft guidance (using on-demand arms to anchor ITC) or further justification for not conducting this analysis

As stated in the response to the draft guidance, an analysis using OD arms to anchor the ITC is not feasible, as it makes the underlying assumption that all OD arms are equivalent. This is unlikely to be the case, as OD treatments for haemophilia have different pharmacokinetic profiles, affecting the duration and intensity of their action.

In HAVEN 3, patients randomised to the OD arm continued with their pre-trial treatment regimen, while in XTEND-1 patients in the OD phase were treated

with efanesoctocog alfa when they experienced a bleed. The pre-study ABR in Arm B was 35.7, but was 21.4 during the OD period of Arm B, suggesting that OD treatment with efanesoctocog alfa was more effective than the patients' prior OD regimen. Given that the OD arms cannot be considered equivalent, this analysis is not considered feasible as results will be biased.

Additionally, as there was no randomisation in XTEND-1, there is no arm in which to assess the treatment effect. Instead, the suggestion was that a comparison with Arm A be performed using propensity score matching, but as Arm A and Arm B are non-overlapping populations, this is not feasible.

Finally, the relevant comparator in HAVEN 3 for Arm A of XTEND-1 would be with Arm D. However, this arm was not included in the randomisation and similarly contains a non-overlapping population compared to the remainder of HAVEN 3. As no individual patient data is available, no matching exercise would be possible, and any comparison with Arm D would remain a naïve comparison.

4.5. Explanation and justification for how parameters from the TOBIT model have been applied to the economic model

In the economic model, it was assumed that the coefficients in the TOBIT models could be applied linearly to estimate utility values. Scenario analyses were conducted to test this assumption, and submitted in the response to draft guidance, demonstrating that use of linear models had minimal impact on the results.

4.6. Effect on the PSA of including correlation of coefficients according to the variance-covariance matrix

This analysis is currently being explored and the Company will be prepared to discuss the results during ACM2.

4.7. Evidence supporting the disutility for low FVIII and the suggested FVIII threshold

The Company maintain that a disutility can be considered for low factor levels. As detailed below, evidence suggests that factor levels of at least 15–20% are necessary to provide improved bleed protection and prevent bleeding when engaging in higher risk or more intensive activities.

A post-hoc analysis of the PROPEL study demonstrated that FVIII activity levels ≥20% were associated with lower total, spontaneous, spontaneous joint, and traumatic ABRs compared with FVIII activity levels below this threshold.[14] Additionally, a minimum level of ~20% has recently been suggested as a good therapeutic target to prevent joint bleeds[15]. A recent narrative review by Malec and Matino highlights that the minimum FVIII activity level associated with a near-zero joint bleed rate is 15%.[16] Similarly, a target FVIII level of 15–30% is what should be considered when engaging in sporting activities.[16]

It is also worth noting that, in addition to bleed protection, there are several outcomes in the XTEND-1 trial that demonstrated improvements that may be attributable to the sustained FVIII activity levels achieved whilst on treatment. For example, efanesoctocog alfa was associated with significant improvements in pain and joint health. PROMIS pain intensity demonstrated an improvement between baseline and Week 52 of -0.21 (95% CI: -0.41, -0.02; p=0.0276) [4]. Similarly, a modest but significant improvement in Haemophilia Joint Health Score (HJHS) was observed in patients treated with efanesoctocog alfa vs previous FVIII prophylaxis, with an estimated mean change in HJHS total score from baseline to Week 52 of -1.54 (95% CI: -2.70, -0.37; p=0.01).[4]

Exit interviews conducted with 29 participants in the XTEND-1 trial demonstrate improvements across a range of concepts in most patients.[17] For example, in those with difficulties before study participation, improvement in the ability to walk desired distance was observed in 80%, improvement in the ability to move without pain in 88.5%, and improvement in join paint in 89.3%. All participants stated that the improvements they experienced during the study were meaningful to them and all participants identified efanesoctocog alfa as their preferred treatment over pre-study therapy.

Whilst patients may not be aware of their precise factor level, they will have a good understanding of their level of protection. For example, patients will know they are able to engage in intensive activities the day of their factor injection and will know to avoid such activity nearer to their next dose. This will therefore influence the activities that they engage in. This is evidenced by

an analysis exploring treatment preferences of patients participating in the XTEND-1 trial, in which 92% (142/155) of patients preferred efanesoctocog alfa over their previous treatment, with one of the most common reasons given for this preference was that they 'felt better protected' (64%; 91/142).[18]

Furthermore, clinical opinion suggests that some patients treated with emicizumab may top-up on factor before engaging in higher-risk activities, due to emicizumab providing FVIII equivalency below that which is necessary to protect against more intensive activities.

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Products issued to people with severe haemophilia A resident in England by treatment group, 2023

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National Haemophilia Database 1/8/24

BACKGROUND

Sobi are currently managing an ongoing HTA with NICE for the pipeline therapy - efanesoctocog alfa. Post the first NICE appraisal committee meeting (ACM), further analysis has been requested in order to better to characterise the proportion of standard half-life recombinant factor VIII (SHL rFVIII) use by people with severe haemophilia A (PwSHA, baseline FVIII level < 1%). This will allow the committee and Sobi to better understand the relevant comparators for the appraisal.

It should be recognised, however that the standard of care in severe haemophilia A is prophylaxis. Prophylaxis is conducted principally with products designed for prophylaxis, - extended half-life factor VIII products and emicizumab. Standard half-life factor VIII products are used principally for treatment on demand, surgery and intercurrent bleeding. Such standard half-life products are falling out of use for prophylaxis. Many patients treated *principally with emicizumab or EHL-VIII,* will use small quantities of SHL-VIII for contingency stock or breakthough bleeding. For that reason, if one looks just at the number of patients who have used SHL-VIII one would gain the false impression that it is more frequently used than it is. The two parts of the report give a slightly different take on the same question.

Part 1: METHODOLOGY

This report describes people with severe haemophilia A (PwSHA, baseline FVIII level < 1%) resident in England and not reported to have a current inhibitor or to be receiving trial products, registered with the National Haemophilia Database (NHD) in the calendar year 2023. PwSHA were assigned to a unique treatment group according to their NHD-reported product issue data, as follows:

- Those issued emicizumab (emi) within the year were allocated to the emicizumab group, regardless of any other products they were issued.
- Then those issued enhanced half-life recombinant factor VIII (EHL rFVIII) were allocated to the EHL rFVIII group, regardless of any other products they were issued.
- Then those issued standard half-life recombinant factor VIII (SHL rFVIII), and were indicated on the NHD to be on prophylaxis, were allocated to the SHL rFVIII prophylaxis group, regardless of any other products they were issued.
- Then those issued standard half-life recombinant factor VIII (SHL rFVIII), and not indicated on the NHD to be on prophylaxis, were allocated to the SHL rFVIII on demand group, regardless of any other products they were issued.
- Those remaining were allocated to the 'No Emi or rFVIII issued this year' group.

Age was calculated as of 1st January 2023.

RESULTS

There were 1926 PwSHA resident in England and registered with the NHD in 2023. Excluding those reported to have an inhibitor or to be receiving trial products left n=1740. Table 1 itemises the numbers of PwSHA issued individual products (FVIII and emicizumab) for each treatment group as defined above. Please note that PwSHA may be issued multiple products, and product types, within the year. The total PwSHA by treatment group presented is the number of unique PwSHA in each group, and is therefore lower than the sum of PwSHA numbers by product.

DISCUSSION

Assuming PwSHA in the emicizumab and EHL rFVIII treatment groups are all treated prophylactically, these results show that 339/364 (93%) of those aged under 12 years, and 1186/1376 (86%) of those aged 12 years and over are on a prophylactic treatment regime. For those aged under 12 years, this includes 249/364 (68%) treated with emicizumab, 65/364 (17%) treated with EHL rFVIII, and 25/364 (7%) treated prophylactically with SHL rFVIII. For those aged 12 years and over, this includes 699/1376 (51%) treated with emicizumab, 328/1376 (24%) treated with EHL rFVIII, and 159/1376 (12%) treated prophylactically with SHL rFVIII.

The proportion of PwSHA issued SHL rFVIII products for prophylaxis is diminishing rapidly. These products are mainly used for treatment on-demand, surgery and intercurrent bleeding. Products such as emicizumab, and EHL rFVIII products are really designed for prophylaxis. Prophylaxis products are the appropriate comparator.

Table 1 - Products issued to people with severe (baseline factor VIII <1 IU/dl) haemophilia A (PwSHA) resident n England by treatment group, 2023

(Exclusions: PwSHA reported to have an inhibitor or to be receiving trial products in 2023)

Age	Product type	Product	Emicizumab (n)	rFVIII EHL (n)	rFVIII SHL prophylaxis (n)	rFVIII SHL on demand (n)	No Emi or rFVIII issued this year (n)	PwSHA (n)
<12 years	Non-factor	Emicizumab	249	0	0	0	0	249
	EHL rFVIII	Elocta	67	62	0	0	0	129
		Esperoct	0	3	0	0	0	3
	SHL rFVIII	Advate	72	5	11	5	0	93
		Nuwiq	33	6	10	11	0	60
		ReFacto AF	14	2	4	2	0	22
		NovoEight	10	0	0	0	0	10
	No products issued	No products issued	0	0	0	0	9	9
	Total	PwSHA (n)	249	65	25	16	9	364
>=12 years	Non-factor	Emicizumab	699	0	0	0	0	699
	EHL rFVIII	Esperoct	73	166	0	0	0	239
		Elocta	71	154	0	0	0	225
		ADYNOVI	1	13	0	0	0	14
	SHL rFVIII	Advate	182	21	72	52	0	327
		ReFacto AF	117	9	50	44	0	220
		NovoEight	65	13	34	12	0	124
		Nuwiq	4	0	4	3	0	11
	pdFVIII	pdFVIII	2	0	0	1	3	6
	No products issued	No products issued	0	0	0	0	77	77
	Total	PwSHA (n)	699	328	159	110	80	1376

BACKGROUND

Sobi are currently managing an ongoing HTA with NICE for the pipeline therapy - efanesoctocog alfa. Post the first NICE appraisal committee meeting (ACM), further analysis has been requested in order to better to characterise the proportion of SHL use in severe haemophilia A. This will allow the committee and Sobi to better understand the relevant comparators for the appraisal.

Part 2 METHODOLOGY

This report describes people with severe haemophilia A (PwSHA, baseline FVIII level < 1%) without a current inhibitor registered with the NHD throughout the calendar year 2023. PwSHA were assigned to a unique product category (“SHL rFVIII” , “EHL rFVIII” or “Emicizumab”) according to their treatment issue data, as reported to the NHD.

There were 2263 people with severe haemophilia A (PwSHA, baseline FVIII level < 1 registered with the NHD throughout the calendar year 2023. PwSHA with a reported current inhibitor (n=191), or who were issued bypassing agent, pdFVIII or trial products (n=26) were excluded.

People who weren’t issued treatments (n=95), and those categorized in the SHL group who didn’t report regimen type as prophylaxis, were excluded (n=232).

PwSHA’s age is calculated as of 1st January 2023.

RESULTS

The number of PwSHA with no inhibitor who were issued treatment and/or reported as using it prophylactically, categorized by age group and product category, is presented in Table 1.

Table 1. Number of UK people with severe haemophilia using prophylaxis with no current inhibitor by age group and treatment product category, 2023

Age Group	Product Category					
	SHL rFVIII		EHL rFVIII		Emicizumab	
	n	%	n	%	n	%
0-15	41	8.8%	105	22.4%	322	68.8%
16 and over	160	12.8%	359	28.7%	732	58.5%
0-17	54	10.2%	123	23.1%	355	66.7%
18 and over	147	12.4%	341	28.7%	699	58.9%
0-19	60	10.3%	137	23.6%	384	66.1%
20 and over	141	12.4%	327	28.7%	670	58.9%
0-21	67	10.6%	160	25.2%	407	64.2%
22 and over	134	12.4%	304	28.0%	647	59.6%
0-24	76	10.3%	196	26.5%	468	63.2%
25 and over	125	12.8%	268	27.4%	586	59.9%
0-29	102	11.2%	241	26.4%	570	62.4%
30 and over	99	12.3%	223	27.7%	484	60.0%
0-34	126	11.7%	295	27.3%	659	61.0%
35 and over	75	11.7%	169	26.4%	395	61.8%
Total (all age)	201	11.7%	464	27.0%	1054	61.3%

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A (ID6170): Post-ACM2 Analyses

Request from committee:

Conduct analyses comparing efanesoctocog alfa to a single basket of all current treatments, including standard half-life [SHL] factor VIII replacement therapy, extended half-life [EHL] factor VIII replacement therapy and emicizumab. The distribution of treatments within the basket should be based on market share from Professor Charles Hay of the National Haemophilia Database on 1 August 2024 (people with severe haemophilia A and no inhibitors, treated prophylactically during 2023, included in committee papers).

Exploratory analyses conducted by NICE technical team and verified by EAG:

Cost-effectiveness analyses:

- Compared efanesoctocog alfa to a basket of current treatments based on the cost-effectiveness model, using the committee's preferred base case assumptions at ACM2
    - **Methodology:** Total costs and total QALYs for comparators weighted by market share and summed. Then compared to the total costs and QALYs for efanesoctocog alfa to provide an ICER.

Price comparison

- Compared annual treatment costs per patient of efanesoctocog alfa to a basket of current treatments, based on annual drug acquisition cost only:
    - **Methodology:** Annual treatment acquisition costs for EHLs, SHLs and emicizumab per patient were weighted by market

share and summed. This was compared to the annual drug acquisition cost of efanesoctocog alfa per patient to provide a cost saving or cost incurrence.

    - Technical team's preferred approach is to use emicizumab costs that include a loading dose for 1st 4 weeks and weight-based dosing in children (total undiscounted treatment costs/undiscounted number of life years accumulated, EAG suggested approach)

- Results are also presented for 2 alternative approaches to emicizumab costs:

    a. Assuming equal split of emicizumab dosing (1.5mg/kg weekly, 3.0mg/kg once every 2 weeks and 6.0mg/kg once per month) without loading dose

    b. Using emicizumab dose in company and EAG model (1.5mg/kg QW, EAG suggested approach)

Budget impact model

- Compared world with efanesoctocog alfa to world without efanesoctocog alfa based on budget impact model developed by Resource Impact Assessment (RIA) team at NICE, in discussion with NHS England and the company

    - **Methodology**: Unit cost in the BIT were updated to reflect a weighted average of unit costs for SHLs and EHLs.

Detailed below is a summary of results provided to committee after the second meeting.

All results include PAS for efanesoctocog alfa and confidential comparator prices (current as of September 2024). As comparator discounts are confidential, results are not presented here.

Summary of results considered in decision making: PUPs

1. ***Cost effectiveness results using individual comparators (SHLs included as a basket, efmoroctocog only EHL considered):***

   Table 1 Error! No sequence specified.**: EAG base case deterministic cost effectiveness results (utilities model #8 with disutility for FVIII <5%, N.B incremental vs. cheapest treatment or next non-dominated comparator), market share data from Professor Charles Hay of National Haemophilia Database 01/08/2024**

2. ***Cost effectiveness analyses using basket of comparators:***

   Table 2: Cost-effectiveness results for previously untreated patients (PUPs) using a basket of comparators (EAG base case assumptions, market share data from Professor Charles Hay of National Haemophilia Database 01/08/2024)

3. ***Price comparison using annual treatment costs only PUPs (EAG base case assumptions, market share data from Professor Charles Hay of National Haemophilia Database 01/08/2024):***

a) using emicizumab loading dose for 1st 4 weeks followed by modelled emicizumab dose (1.5mg/kg QW) in adults and weight based dosing in children
b) using equal split of emicizumab dosing (1.5mg/kg weekly, 3.0mg/kg once every 2 weeks and 6.0mg/kg once per month) without loading dose
c) using modelled emicizumab dose (1.5mg/kg QW)

Summary of results considered in decision making: PTPs

1. ***Cost effectiveness results using individual comparators (with EHLs included as a basket and SHLs included as a basket):***

   Table 3 Error! No sequence specified.**: EAG base case deterministic cost effectiveness results (utilities model #8 with disutility for FVIII <5%, N.B incremental vs. cheapest treatment or next non-dominated comparator), market share data from Professor Charles Hay of National Haemophilia Database 01/08/2024**

2. ***Cost effectiveness analyses using basket of comparators***

   Table 4: Cost-effectiveness results for previously treated patients (PTPs) using basket of comparators (EAG base case assumptions, market share data from Professor Charles Hay of National Haemophilia Database 01/08/2024)

3. ***Price comparison using annual treatment costs only for PTPs (EAG base case assumptions, market share data from Professor Charles Hay of National Haemophilia Database 01/08/2024):***

a) using emicizumab loading dose for 1st 4 weeks followed by modelled emicizumab dose (1.5mg/kg QW) in adults and weight based dosing in children
b) using equal split of emicizumab dosing (1.5mg/kg weekly, 3.0mg/kg once every 2 weeks and 6.0mg/kg once per month) without loading dose
c) using modelled emicizumab dose (1.5mg/kg QW)

BIT results (PUPs and PTPs combined)

- Budget impact in people who are on emicizumab
- Budget impact in people who are on factor VIII replacement therapy
- Overall budget impact at year 3