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:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Swedish Orphan Biovitrum (Sobi):**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. The Haemophilia Society
   b. UK Haemophilia Centre Doctors' Organisation (UKHCDO)

4. **External Assessment Report** prepared by Kleijnen Systematic Reviews

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts:**
   a. Charles Hay, Professor of Haemostasis and Thrombosis, Consultant Haematologist, Director of the UK National Haemophilia Database (NHD) – clinical expert, nominated by Sobi
   b. Alice Taylor, Consultant Paediatric Haematologist – clinical expert, nominated by UKHCDO
   c. Edward Rippingale-Combes – patient expert, nominated by the Haemophilia Society
   d. Clive Smith – patient expert, nominated by the Haemophilia Society

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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Single technology appraisal

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

Document B

Company evidence submission

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ID6170_Efanesoctocog alfa_Haemophilia A_Document B [REDACTED]	4.0	Redacted	7th May 2024

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ABR	Annualised bleeding rate
AJBR	Annualised joint bleeding rate
AsBR	Annualised spontaneous bleeding rate
AtBR	Annualised traumatic bleeding rate
BMI	Body mass index
CHESS	Cost of Haemophilia across Europe – a Socioeconomic Survey
CI	Confidence interval
CRF	Case report form
DSU	Decision Support Unit
ED	Exposure days
EHL	Extended half-life
ePD	Electronic patient diary
ER	Emergency room
FAS	Full analysis set
Fc	Fragment crystallisable
FDA	Food and Drug Administration
FVIII	Clotting Factor VIII
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
Haemo-QoL	Haemophilia-specific Quality of Life questionnaire for children
HCRU	Health care resource utilisation
HJHS	Haemophilia Joint Health Score
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
IRR	Incidence rate ratio
ISTH	International Society on Thrombosis and Haemostasis
ITC	Indirect treatment comparison
ITI	Immune tolerance induction
IV	Intravenous
MAIC	Matching-adjusted indirect comparison
MD	Mean difference
MMRM	Mixed model repeated measures
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
OR	Odds ratio
PK	Pharmacokinetics
PPS	Per protocol set
PROMIS	Patient-Reported Outcomes Measurement Information System

Abbreviation	Definition
PSS	Personal social services
PTP	Previously treated patient
PUP	Previously untreated patient
QALY	Quality-adjusted life year
QW	Once weekly
Q2W	Every two weeks
Q4W	Every four weeks
RDI	Relative dose intensity
rFVIII	Recombinant clotting Factor VIII
SD	Standard deviation
SHL	Standard half-life
SLR	Systematic literature review
SOC	System order class
TEAE	Treatment-emergent adverse event
TSD	Technical support document
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centres Doctors Organisation
VWF	von Willebrand Factor

B.1 Decision problem, description of the technology and clinical care pathway

Haemophilia A is a rare, X-linked congenital bleeding disorder, resulting from the deficiency or complete absence of clotting Factor VIII (FVIII). In 2021–2022, there were almost 9,000 patients registered with haemophilia A within the United Kingdom (UK)

- Haemophilia is comprised of two subtypes; haemophilia A and haemophilia B, which result from the deficiency or complete absence of clotting FVIII or Factor IX (FIX), respectively (1, 2)
- Haemophilia A is the more common subtype, accounting for approximately 80% of cases (3)
- Registry data from the UK Haemophilia Centres Doctors' Organisation (UKHCDO) suggests that in 2021–2022, 8,959 patients were registered with haemophilia A in the UK (4)

Haemophilia A is associated with a notable clinical, humanistic, and economic burden

- Patients with haemophilia A experience prolonged bleeding, and depending on severity, can present with easy bruising, occasional spontaneous bleeding, and internal bleeding (including into the organs, joints and muscles) (5)
- Patients with moderate-to-severe haemophilia A are more likely to experience bleeding around their joints or muscles, as well as life-threatening bleeds (e.g. intracranial haemorrhage)
- Bleeding into the joint (haemarthrosis) leads to irreversible arthropathy; a debilitating condition associated with inflammation, pain, and joint damage that significantly impacts mobility and health-related quality of life (HRQoL) (6)
- An increasing number of target/problem joints are associated with poorer HRQoL in patients with severe haemophilia A (7)
- A cross-sectional, non-interventional survey was conducted to identify the prevalence and perception of pain among patients with haemophilia living in the UK. Out of 599 patients, 59% reported frequent pain, with 56% aware of pain constantly or most of the time (8)
- When asked to report on mobility, self-care, usual activities, pain, discomfort, anxiety and depression on a scale, where 1 represents the best imaginable health state, and 0 the worst, UK-based patients with haemophilia reported an

average health state of 0.59. This is notably lower than the UK national population average of 0.85 (9)

- An analysis of the economic burden of haemophilia in five European countries over 1 year (2014–2015) reported that an estimated mean per-patient annual direct cost of severe haemophilia within the UK of €116,963 (£100,623)[a] (10)
- After adjusting for age, patients with haemophilia are less likely to be engaged in employment than the general population (odds ratio [OR]: 0.48; 95% confidence interval [CI]: 0.33, 0.71) (11)
- Target joints (defined as three or more bleeds into a single joint within a 6-month period) are associated with a substantial economic burden for patients with severe haemophilia A across their lifespan. A retrospective analysis of the Cost of Haemophilia across Europe – a Socioeconomic Survey (CHESS) population reported that total costs increased with increasing target/problem joints within the CHESS-II population (€11,022 [£9,483] vs €27,098 [£23,315]) and CHESS-PAEDs population (€4,457 [£3,834] vs €14,039 [£12,078])[a] (12)

There remains a notable unmet need with current treatment options with regard to the adequate treatment and prevention of bleeds

- Despite advances in treatment, many patients living with haemophilia A continue to experience life-threatening bleeding, or joint bleeding resulting in pain, loss of function, and impaired work and societal participation (13-16). This can have a large impact on normal daily activities, including travel, working, hobbies, and physical activity
- Lower FVIII levels translate to poorer outcomes. In 2022, UK-based severe haemophilia A patients receiving recombinant Factor VIII (rFVIII) replacement therapy had a mean annualised bleeding rate (ABR) ranging from [redacted] to [redacted], with only [redacted] achieving zero bleeds (17)
- A recent cross-sectional survey across five European countries (including the UK) demonstrated that 60% of adult patients with moderate or severe haemophilia A treated with prophylaxis had one or more haemophilia-affected joints. Individuals with haemophilia-affected joints had higher rates of pain, pain medication use, and lower HRQoL compared with those without affected joints (18)

[a] Xe Currency Calculator. Accessed 29th August 2023. 1 EURO = 0.860382 GBP.

- Prophylaxis is the gold standard of care for children and adults with severe haemophilia A due to its proven ability to reduce joint and other bleeding episodes (19)
- Historically, the aim of prophylaxis has been to maintain FVIII trough levels above 1% (1 IU/dL). More recently, World Federation of Haemophilia guidelines acknowledge that most clinicians aim for FVIII trough levels of 3–5% (3–5 IU/dL), given that trough levels of 1–3% (1–3 IU/dL) are insufficient in preventing bleeds (20). However, there is an increasing body of evidence that suggests factor levels of around 30% (30 IU/dL) are necessary to substantially decrease bleeding risk (19, 21, 22). Furthermore, a recent review highlighted that factor levels of up to 50% (50 IU/dL) may be needed to achieve a near-zero joint bleed rate (23)
- The risk of arthropathy decreases by 7.7% for each 1% (1 IU/dL) increase in clotting factor, highlighting the need for higher factor levels to improve long-term joint and bleed outcomes (24)
- Raising FVIII levels to a higher threshold will therefore help prevent all bleeds; however, maintaining these levels is difficult with current treatments due to the considerable treatment burden, or not possible with some available treatments (e.g. non-factor therapy)
- Many patients with haemophilia A do not achieve their treatment goals and are continually faced with difficult decisions that lead them to adopt coping strategies. Factors such as bleeding risk, treatment efficacy, and injection schedule add to the mental burden of disease, even if patients are receiving prophylaxis (25)
- In a 2021 UK survey conducted by the Haemophilia Society, 75% of patients with bleeding disorders stated that they avoided certain activities because they were too risky (26)
- In a 2020 European study of patients with severe haemophilia A, 78% refrained from activities due to their joint health, and 49% reported regular bleeds and/or joint pain, despite adherence with treatment (27)

B.1.1 Decision problem

The submission focusses on part of the technology's marketing authorisation for efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A. The proposed population is narrower than the anticipated marketing authorisation because

the evidence base on efanesoctocog alfa is focussed on previously treated patients with severe haemophilia A. However, it should be noted that:

- Historically, factor products have been granted broad licenses despite lacking data in previously untreated patients (PUPs). There is a wealth of long-term evidence regarding the safety and efficacy of FVIII replacement products, reassuring regulatory bodies and healthcare practitioners (HCP)
- The non-factor therapy, emicizumab, was granted a licence that includes PUPs and previously treated paediatric patients despite lacking data. Regulatory bodies and clinical opinion agree that efficacy and safety data can be extrapolated to these patients (28), and emicizumab is now the market leader for the treatment of PUPs and previously treated patients (PTPs) in the UK.

This Company submission differs from the final National Institute for Health and Care Excellence (NICE) scope, with differences outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with haemophilia A	Patients with severe haemophilia A	The anticipated license for efanesoctocog alfa is [redacted] The evidence base for this submission comes from the Phase 3 XTEND-1 trial, which recruited previously treated patients (PTPs) with severe haemophilia A. No studies have assessed the use of efanesoctocog alfa in patients with mild/moderate haemophilia A or in previously untreated patients (PUPs).
Intervention	Efanesoctocog alfa	As per final scope	–
Comparator(s)	Established clinical management, including: • Prophylaxis and on-demand treatment with Factor VIII replacement therapy • Emicizumab	• PTPs: Emicizumab • PUPs: Emicizumab and efmoroctocog alfa	The aim of prophylaxis with replacement therapy for patients with severe haemophilia is to decrease the frequency of bleeding, thereby preventing subsequent joint damage (by preventing bleeding into the joints) and related sequalae (29). The majority of people with severe haemophilia A in the UK receive prophylaxis, and it is considered the treatment approach of choice by the UK Haemophilia Centre Directors Organisation (UKHCDO) and World Federation of Haemophilia. Any consideration of on-demand treatment should only be within the context of a prophylactic regimen, as an additional requirement following a bleed (e.g. following trauma or during surgery). In the UK, very few patients with severe haemophilia are treated with on-demand therapy, as it does not prevent bleeding and therefore results in significant joint damage (the rationale for prophylaxis). The minority of patients with severe haemophilia A who are currently treated with on-demand therapy are thought to be doing so for historical reasons/personal choice, or who have a milder clinical phenotype. Since launch in 2019, the proportion of patients receiving emicizumab has rapidly increased (4) and continues to do

			so, with it now being the standard of care in the UK for the treatment of PUPs and PTPs (17). The proportion of patients with severe haemophilia A receiving emicizumab has increased from [redacted]% in 2019, to [redacted]% at the end of 2022 (17). Furthermore, since Q2 2019, the use of SHLs has declined from [redacted]% to [redacted]% at the end of 2022 (17), and clinical opinion suggests that SHL use will be minimal in 5 years time (28). **PTPs** Sobi propose that the relevant comparator for PTPs is emicizumab, given it is now standard of care in patients with severe haemophilia A. Aligning to clinical opinion, it is anticipated that efanesoctocog alfa will be used in patients who would otherwise be offered emicizumab. Amongst PTPs, patients may switch away from rFVIII therapy for the following reasons: • Haemostasis is inadequately controlled and the patient experiences breakthrough bleeds with rFVIII prophylaxis • FVIII levels are not sufficient on rFVIII (i.e. poor pharmacokinetic coverage due to reduced AUC and shorter half-life) • Prophylaxis with multiple weekly IV injections with rFVIII is inconvenient or not possible (i.e. frequent injections results in poor compliance or adherence to rFVIII therapy) • The patient is seeking better QoL or to live a life that is as 'normal' as is possible. Aligned to UK guidelines, the HCP will utilise shared decision-making to tailor prophylaxis with the patient, basing therapy on PK data, patient activity, lifestyle, and patient preferences (29). **PUPs**

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Clinical advice provided to the Company stated that for PUPs, the choice of treatment results from parental decision. All patients with severe disease/bleeding phenotype will require prophylaxis, and the majority of parents select emicizumab (28). Some parents will select treatment with a FVIII therapy, often because their child has presented with a severe bleed that required emergency treatment with FVIII replacement therapy. In this instance, clinicians stated that an EHL would be the first choice of treatment for prophylaxis in newly diagnosed patients, among which, only efmoroctocog alfa is licensed for use in patients under the age of 12 years. As patients with severe haemophilia A will present early in life, any patients starting treatment with an EHL will be administered efmoroctocog alfa.
Outcomes	The outcome measures to be considered include: • ABR • Change in Factor VIII levels • Need for further treatment with Factor VIII injections • Durability of response to treatment • Complications of the disease (for example joint problems or joint surgeries) • Adverse effects of treatment • Mortality • HRQoL	As per final scope	–
Economic analysis	The reference case stipulates that the cost effectiveness of	As per final scope	–

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If evidence allows subgroups will be considered based on: • severity of haemophilia • presence or development of inhibitors • previous treatment status	No subgroups were considered in the Company submission.	In XTEND-1, all patients had severe haemophilia A and therefore subgroup analysis based on the severity of haemophilia was not possible. Furthermore, no inhibitors to efanesoctocog alfa were detected during XTEND-1 or XTEND-Kids. With regard to previous treatment status, patients who had prior prophylaxis were enrolled into Arm A, while those with prior on-demand therapy were enrolled into Arm B of XTEND-1.

Abbreviations: ABR, annualised bleeding rate; EHL, extended half-life; FVIII, clotting factor VIII; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IQR, interquartile range; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PRO, patient-reported outcome; PTP, previously treated patient; PUP, previously untreated patient; SHL, standard half-life; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

An overview of the technology being appraised in this submission (efanesoctocog alfa) in presented in Table 2. The draft summary of product characteristics (SmPC) is provided in Appendix C.

Table 2: Technology being appraised

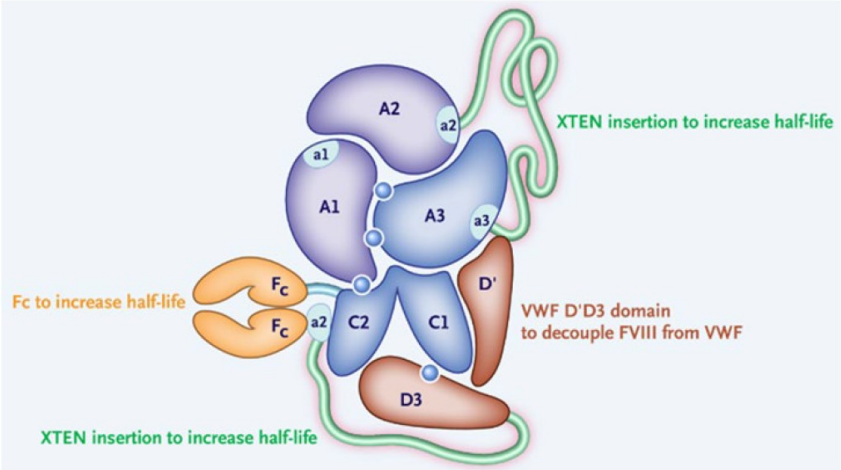
UK approved name and brand name	Efanesoctocog alfa ([redacted]®)
Mechanism of action	Efanesoctocog alfa is a novel fusion protein designed to decouple rFVIII from endogenous VWF in circulation (30). The protein is composed of a single rFVIII protein fused to dimeric Fc, the D′D3 domain of VWF (FVIII-binding domain), and two XTEN polypeptides (31, 32). Efanesoctocog alfa appends the D'D3 domain of VWF to FVIII, preventing binding to endogenous VWF and removing the limit on half-life extension imposed by VWF-FVIII interaction (31). XTEN polypeptides comprise repeats of six hydrophilic amino acids (glycine, alanine, proline, threonine, serine, and glutamic acid), which also provide half-life extension. The six amino acids are biodegradable and are considered non-immunogenic
Marketing authorisation/ CE mark status	Efanesoctocog alfa does not yet have UK marketing authorisation for the indication in this submission. FDA Breakthrough Therapy designation for haemophilia A was granted in February 2023 (33). A regulatory submission was made to the EMA in [redacted], with submission to the MHRA anticipated in [redacted]. CHMP positive opinion is anticipated in [redacted] and MHRA regulatory approval in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Efanesoctocog alfa is indicated for the [redacted] Patients are contraindicated if they experience hypersensitivity to the active substance or to any of the excipients listed in the SmPC
Method of administration and dosage	Prophylaxis: 50 IU/kg IV once weekly On-demand: 50 IU/kg IV as required
Additional tests or investigations	In general, all patients treated with FVIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected FVIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for FVIII inhibitors should be performed
List price and average cost of a course of treatment	List price (pending DHSC approval): £[redacted] per pack of 1,000 IU Price per unit (IU): £[redacted] Efanesoctocog alfa is available in the following pack sizes (priced per unit): 250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU, 4000 IU
Patient access scheme (if applicable)	Efanesoctocog alfa is available via a simple percentage discount • Proposed PAS price ([redacted] discount): [redacted] • 1,000 IU pack price: [redacted] • Cost per kg/year: [redacted] per kg/year

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; DHSC, Department of Health and Social Care; EMA, European Medicines Agency; Fc, fragment crystallisable; FDA, Food and Drug Administration; FVIII, clotting factor VIII; IV, intravenously; MHRA, Medicines & Healthcare Products Regulatory Agency; rFVIII, recombinant clotting factor VIII; VWF, von Willebrand factor.

B.1.2.1 Efanesoctocog alfa

Efanesoctocog alfa is a first-in-class, high-sustained Factor VIII (FVIII) replacement therapy anticipated to be indicated for [redacted]. The molecule comprises a single B-domain-deleted recombinant FVIII protein fused to dimeric fragment crystallisable (Fc), covalently coupled to the FVIII binding D'D3 domain of von Willebrand factor (VWF), and two XTEN polypeptides (B-domain and D'D3-domain moieties) (Figure 1) (34).

Figure 1: Structure of efanesoctocog alfa



Source: von Drygalski et al. 2023 (34).
Abbreviations: a1, a2, a3, acidic region 1, 2, 3; Fc, fragment crystallizable; FVIII, factor VIII; VWF, von Willebrand factor.

VWF acts as a chaperone for FVIII, meaning that the VWF clearance pathway imposes a half-life of up to 19 hours on FVIII replacement treatment (34). This is the main limitation of standard half-life (SHL) and extended half-life (EHL) FVIII replacement therapies. Efanesoctocog alfa extends half-life via three mechanisms:

1. An Fc domain that facilitates recycling through the neonatal Fc receptor pathway (34). Fc fusion is an established technology used to prolong the half-life of several drugs licensed for the treatment of several chronic diseases (35-37)

2. Covalent linkage to a VWF D′D3 factor VIII binding domain to decouple recombinant factor VIII from endogenous VWF (34)

3. Two XTEN polypeptides comprising repeats of six hydrophilic amino acids (glycine, alanine, proline, threonine, serine, and glutamic acid), to shield efanesoctocog alfa from proteolytic degradation and clearance (31, 38).

In adults and adolescents aged 12 years old and over, efanesoctocog alfa maintains plasma FVIII activity in the normal to near-normal range (>40 IU/dL; >40%) for 4 days post-administration. Plasma FVIII activity was maintained at 15 IU/dL (15%) 7 days post-

administration (Section B.2.6.1.5.5; Figure 7). In children <12 years old, efanesoctocog alfa maintained mean FVIII activity >40 IU/dL for 3 days, >15 IU/dL for ~5 days, and >10 IU/dL for ~7 days at steady state (Appendix O).

B.1.3 Description of the disease being evaluated

B.1.3.1 Disease overview

Haemophilia is a rare, X-linked congenital bleeding disorder comprised of two subtypes, haemophilia A and haemophilia B, which result from the deficiency or complete absence of clotting Factor VIII (FVIII) or Factor IX (FIX), respectively (1, 2). Haemophilia A is the more common subtype, accounting for approximately 80% of cases (3).

Factor VIII is a crucial protein in the intrinsic coagulation pathway, playing a key role in the generation of thrombin (39). A deficiency in FVIII results in failure to generate adequate thrombin for stable clot formation, and therefore, patients with haemophilia A present with excessive bleeding due to delayed/poor clot formation (40).

Severe haemophilia A often manifests in the first months of life, whereas mild or moderate disease usually presents later in childhood or adolescence, often incidentally or following trauma (20). In two-thirds of cases, haemophilia diagnosis occurs shortly after the delivery of an affected son to a mother who carries the affected gene. Diagnosis of haemophilia A caused by *de novo* mutations is usually made following spontaneous bleeding symptoms (3). Up to one third of patients with haemophilia have no family history (41).

Due to the X-linked pattern of inheritance, haemophilia A most commonly occurs in males (42). Females tend to be carriers of the disease; however, they may experience bleeding symptoms requiring treatment. Rarely, females may present with severe disease (e.g. homozygous haemophilia A gene mutations).

B.1.3.1.1 Classification

Haemophilia A is classified according to endogenous FVIII serum concentration or bleeding phenotype. FVIII concentration is expressed in international units (IU; where 1 IU is the concentration of FVIII in 1 mL of normal pooled plasma) or expressed as percentages of normal pooled plasma. Normal FVIII levels range between 50–150% (50–150 IU/dL) (3). The age of presentation and bleeding frequency are influenced by the severity of haemophilia A, based upon plasma levels of FVIII; mild (>5–<40 IU/dL) moderate (1–5 IU/dL), and severe (<1 IU/dL) (43, 44) (Table 3). More recently, FVIII levels of >40–<50 IU/dL have been defined as ‘near-normal,’ where levels do not fall within either the normal or mild haemophilia ranges (23).

Table 3: Classification of severity of haemophilia A

Clinical severity	Level of FVIII in the blood	Typical bleeding tendency
Mild	>5–<40% of normal level (>5 to <40 IU/dL)	• Easy bruising • Bleeding usually occurs following injury, surgical, or dental procedure • Might never have a bleeding problem requiring medical attention • Females may also have heavy or prolonged menstruation (menorrhagia) • Delayed diagnosis
Moderate	1–5% of normal level (1 to 5 IU/dL)	• Easy bruising • Bleeding due to minor injury • Occasional spontaneous bleeding • Likely to have problems after dental or surgical procedures, or a bad injury
Severe	<1% of normal level (<1 IU/dL)	• Easy bruising, including of mouth and nose • Bleeding into joints and muscles, potentially without obvious cause • Bleeding after dental or surgical procedures, or injuries, including minor bumps or knocks • Diagnosed in early infancy

Source: The Haemophilia Society (2023) (5), Peerlinck et al, 2010 (45), and Chambost et al, 2002 (46).

B.1.3.1.2 Epidemiology

The estimated prevalence of haemophilia A is 1:5,000 of the male population within the UK (5). Registry data from the UK Haemophilia Centres Doctors' Organisation (UKHCDO) suggests that in 2021–2022, there were 8,959 patients registered with haemophilia A in the UK (4). A total of 836 and 2,178 patients were registered with moderate or severe disease, respectively (4) (Table 4).

Table 4: Patients with congenital haemophilia A within the United Kingdom

	FVIII >5–<40% (mild)	FVIII 1–5% (moderate)	FVIII <1% (severe)
Total number of patients ≥18 years registered with haemophilia A	3,282	628	1,454
Total number of patients <18 years registered with haemophilia A	766	208	724
Total	4,048	836	2,178

Source: UKHCDO Registry data, 2021–2022 (4).
Abbreviations: FVIII, clotting Factor VIII.

B.1.3.2 Burden of disease

B.1.3.2.1 Clinical burden

Patients with haemophilia A experience prolonged bleeding, and depending on disease severity, can present with easy bruising, occasional spontaneous bleeding, and internal bleeding (including into the organs, joints and muscles) (5).

Patients with moderate-to-severe haemophilia A (<1 IU/dL) bruise easily and are more likely have symptoms of internal bleeding around their joints or muscles, experiencing pain. Frequent or inadequately treated bleeding into the joint (haemarthrosis) leads to irreversible arthropathy; a debilitating condition associated with inflammation, pain, and joint damage that significantly impacts mobility, physical activity, and HRQoL (6). Developments in treatments for bleeding disorders have improved life expectancy in patients with haemophilia A to near that of the general population. However, haemophilia A remains a life-threatening condition, representing a substantial health burden.

A systematic literature review (SLR) reported that severe haemophilia A is correlated with an increased risk of mortality, compared with mild and moderate disease (47). The majority (54.0–89.5%) of bleeding-related deaths reported were due to intracranial haemorrhage (47). The most recent UKHCDO report stated that five out of 52 patients with haemophilia A presenting with cerebral haemorrhage between 2021–2022 died as a result of the complication (4).

Patients with severe haemophilia A often experience notable pain and discomfort, particularly within target joints (defined as three or more bleeds into a single joint within a 6-month period), which are associated with a higher bleed frequency and lower HRQoL (EQ-5D) scores (48). A recent cross-sectional survey of five European countries (including the UK) demonstrated that 60% of adult patients with moderate or severe haemophilia A treated with prophylaxis had one or more haemophilia-affected joints (18). In a cross-sectional, non-interventional survey of 599 UK-based patients, 59% of patients reported frequent pain, with 56% aware of pain constantly or most of the time (8). Patients reporting pain every day, on three or more days, or at least once a week had significantly lower EQ-VAS scores compared with those reporting pain only with a bleed, or rarely/never experiencing pain ($p<0.001$) (8).

Another UK-wide survey in patients with bleeding disorders, of which 60% had haemophilia A, reported that 28% of respondents experienced pain as a result of their bleeding disorder all/most of the time (26). A further 34% of respondents reported that

they sometimes experience pain. For patients reporting joint pain every day, HRQoL scores are lower compared with those who experienced no joint pain (7).

Joint problems are associated with increased use of pain medication. A retrospective analysis of data from the Adelphi Real World Haemophilia Disease Specific Programme, included 120 physicians from France, Germany, Italy, Spain, and the UK, and 351 adults with moderate/severe haemophilia A (baseline factor level ≤5 IU/dL) currently receiving prophylaxis and without inhibitors. Any pain/discomfort at last assessment was reported more frequently by patients with a target joint compared with those without (85.7% vs 53.3%). A greater proportion of patients with problem joints were receiving pain medication compared with those without problem joints (73.2% vs 60.6%; p=0.0144), including higher rates of paracetamol and non-steroidal anti-inflammatory drug (NSAID) use (18).

B.1.3.2.1.1 Complications associated with haemophilia A

Haemophilic arthropathy

Haemarthrosis (bleeding into the joint) is a hallmark feature of severe and moderate haemophilia (49). A single episode of haemarthrosis can trigger a biological process that leads to joint synovitis and cartilage damage in the short term, and with significant or repeated minor episodes of haemarthrosis leading to the development of haemarthropathy in the longer term (50-52).

Synovitis is caused by blood in joints and can be asymptomatic (53). Pain onset and local discomfort are the most common signs that bleeding into the joints has occurred (acute joint bleeds), and symptoms usually resolve with FVIII replacement treatment and rehabilitation (20). Subacute joint bleeds occur after repeated bleeding episodes in the same joint, and at this stage, the joint and surrounding soft tissues do not fully recover. Clinical signs of joint damage persist and are detectable between bleeding episodes, with decreased mobility, joint swelling due to joint effusion or synovial hypertrophy, and muscle, ligament and capsular contractures. These manifestations are due to damage in the cartilage and bone, which may produce progressive deformity and disability, often requiring surgery (54).

Inhibitors

A major complication of treatment is the development of neutralising antibodies (inhibitors) against infused FVIII (42), occurring in approximately 20% of patients with haemophilia A (55). Patients with severe haemophilia A are more likely to develop inhibitors compared with patients with mild disease, however, there are a number of risk

factors for their development, including environmental factors (e.g. treatment intensity, infection, age, immunisations) (42), genetic mutation resulting in absence of the protein (56), family history of developing inhibitors, and patients of black African, Afro-Caribbean, or Hispanic descent (57, 58). Furthermore, inhibitor development most commonly occurs in patients who are naïve to FVIII exposure.

Intracranial haemorrhage

Intracranial haemorrhage (ICH) is a severe and life-threatening complication that is more common in patients with haemophilia relative to the general population. In a systematic review of studies describing 48,105 patients with haemophilia and 697,465 person-years from 1968 to 2016, the pooled ICH incidence rate was 2.3/1000 person-years in patients with haemophilia over a lifetime; this was much higher than the general population incidences of ICH (0.25/1,000 person-years) (59). In children and young adults aged ≤25 years with haemophilia, the pooled ICH incidence rate was 7.4 (95% CI: 4.9, 11.1) per 1000 person-years. The occurrence of ICH in haemophilia was estimated at 0.23% and 0.74% per year for lifetime populations in children and young adults, respectively.

B.1.3.2.2 Humanistic burden

Haemophilia A has a significant impact on HRQoL (2). Despite the availability of existing factor and non-factor treatments, patients living with haemophilia A experience breakthrough bleeding, resulting in pain, joint problems, functional impairment, and impaired work and societal participation. Studies have reported that patients experience anxiety and depression (60-62), and worry about being a burden to others (26).

One study utilising data from the Cost of Haemophilia across Europe – a Socioeconomic Survey (CHESS) study, a cost-of-illness assessment in severe haemophilia across five European countries (including the UK) (63), reported that having one or more joint bleeds was associated with lower EQ-5D index scores compared with having no joint bleeds (64). A HRQoL regression model using the same CHESS data set, which controlled for haemophilia severity, age, body mass index (BMI), country, comorbidities, education level, and weight-adjusted clotting factor consumption, showed statistically significant improved mean EQ-5D-5L scores for patients with mild disease compared with moderate or severe disease (both $p<0.001$). Mean predicted HRQoL for patients with mild disease was 0.78 (95% CI: 0.73, 0.82), which was 13% lower for patients with severe disease (−0.105), and 11% lower (−0.089) for those with moderate disease (65).

A cross-sectional online survey of patients aged ≥13 years with haemophilia was conducted to assess health utilities (EQ-5D-3L, EQ-5D-5L, and SF-6D) (7), and included 122 patients from France and 62 in the UK, of which 98 (80.3%) and 53 (85.5%) had

haemophilia A, respectively. The majority of patients had severe haemophilia (77%) and were receiving a prophylactic regimen. The mean (standard error [SE]) utility values for haemophilia A of any severity were: 0.68 (0.32), 0.75 (0.26), and 0.70 (0.14) for the EQ-5D-3L, EQ-5D-5L, and SF-6D, respectively. Patients with haemophilia A who had ≥2 target joints had lower EQ-5D-3L utility values compared with patients with no target joints (0.43 vs 0.85; p<0.001).

Inadequately controlled bleeds pose an impact on the daily functioning of patients with severe haemophilia A. In the global HERO study, which assessed HRQoL of patients with haemophilia across ten countries (including patients from the UK), more than half (59%) of adult patients with haemophilia A reported limitations with physical activity, while 44% reported limitations in their usual activities. Median annual bleed frequency increased with worsening EQ-5D pain or discomfort (48). In a UK-based survey of patients with bleeding disorders, 75% of patients strongly agreed/agreed that they avoid certain activities they believe are too risky (26).

Higher FVIII activity levels are associated with improved HRQoL. In a CHESS-II regression analysis of patients with haemophilia A aged ≥18 years (37% severe) and without inhibitors, there was a significant relationship between FVIII activity and ABR, and FVIII activity and HRQoL; 25.6% increase in FVIII levels associated with reduction of one bleed per year, For every 1% increase in factor expression level, the average ABR decreased by 3.9% (66).

B.1.3.2.3 Economic and societal burden

Haemophilia A is associated with a notable economic impact. An analysis of the CHESS data set assessed the economic burden of haemophilia in five European countries over 1 year (2014–2015) (10). Clinical data were available for 996 patients with haemophilia A (78%), and 289 patients with haemophilia B. The total annual cost of severe haemophilia A and B for the five countries was estimated to be €1.55 (£1.3) billion, representing 0.05–0.16% of total annual healthcare expenditure. The estimated mean per-patient annual direct cost of severe haemophilia in the UK was €116,963 (£100,623)[b].

Target/problem joints are associated with a substantial economic burden in patients with severe haemophilia A. A retrospective analysis of the CHESS population studies (including UK-based patients) reported an increase in total costs was associated with increasing target/problem joints within the CHESS-II population (€11,022 [£9,483] vs €27,098 [£23,315]) and CHESS-PAEDs population (€4,457 [£3,834] vs €14,039

[b] Xe Currency Calculator. Accessed 29th August 2023. 1 EURO = 0.860382 GBP.

[£12,078])[b] (12). One European study (including UK-based patients), that analysed adults with haemophilia without inhibitors using the CHESS data set, reported that patients with one or more target joints had mean non-drug-related direct costs of €3,913 (£3,366) compared with €3,134 (£2,696) in those without target joints (average mean effect €799 [£687]; p<0.001)[b] (67).

Haemophilia A is associated with increased indirect costs (e.g. lost wages and undertaking part-time work instead of full-time work), which amount to an annual cost of $8,867 (£7,044)[c] per individual (68). A Danish study reported that after adjusting for age, compared with the general population, patients with haemophilia were less likely to be engaged in employment than the general population, with an odds ratio (OR) of 0.48 (95% CI: 0.33, 0.71). The employment rate was higher in the general population than people with haemophilia aged 45–64 years (83% vs 45%) yet was similar compared with people with haemophilia aged people 16–44 years (75% vs 78%) (11).

B.1.3.3 Clinical pathway of care

B.1.3.3.1 Prophylaxis

The primary goal of treatment is to prevent bleeding and to improve long-term outcomes (e.g. joint health), which can be achieved by prophylaxis (4). In haemophilia, prophylaxis is defined as the regular, continuous administration of haemostatic agents with an aim of reducing or preventing bleeding episodes (42). In clinical trials, this is investigated by measuring ABRs.

In the UK, prophylaxis is initiated at an increasingly early age, while adults who did not receive prophylaxis as a child commence treatment later in life to preserve musculoskeletal function (29). It is recommended that all children with severe haemophilia A, and patients of any severity who have sustained one or more spontaneous joint bleeds, should receive prophylaxis (29). According to the UKHCDO 2021/22 annual report (4), all three classes of currently available therapies (i.e. rFVIII therapies (SHLs and EHLs) and non-factor replacement therapy [emicizumab]) are used prophylactically in the UK, with the use of emicizumab increasing since launch.

Emicizumab is a humanised monoclonal antibody that mimics the function of activated FVIII without being affected by FVIII inhibitors. It is administered subcutaneously initially at 3 mg/kg once weekly for 4 weeks, then as maintenance at either 1.5 mg/kg once weekly (QW), 3 mg/kg every 2 weeks (Q2W), or 6 mg/kg every 4 weeks (Q4W) (69). Emicizumab is limited to prophylaxis, and therefore, adjunctive FVIII therapy is indicated

[c]Xe Currency Calculator. Accessed 29th August 2023. 1 USD = 0.794372 GBP.

for acute bleeds resulting from trauma or surgical procedures (70). Almost all patients with severe haemophilia A who are prescribed emicizumab will, in addition, be issued a small stock of FVIII for breakthrough bleeding, should it occur. Furthermore, given the limitation of emicizumab being limited to prophylaxis only, some clinicians seek to tolerise their patients to FVIII to ensure it can be used effectively on-demand and to avoid future development of inhibitors (28).

Since launch in 2019, the proportion of patients receiving emicizumab has rapidly increased (4) and continues to do so, with it now being the standard of care in the UK for the treatment of PUPs and PTPs (17). The proportion of patients with severe haemophilia A receiving emicizumab has increased from [redacted]% in 2019, to [redacted]% at the end of 2022 (17). Furthermore, since Q2 2019, the use of SHLs has declined from [redacted]% to [redacted]% at the end of 2022 (17), and clinical opinion suggests that SHL use will be minimal in 5 years time (28).

B.1.3.3.1.1 Previously treated patients (PTPs)

Previously treated factor patients requiring prophylaxis are predominantly treated with emicizumab, with the remainder generally treated with recombinant Factor VIII (rFVIII) therapy (4). Clinical opinion suggests there are several issues which lead clinicians to consider switching from currently available rFVIII prophylaxis to emicizumab (28):

- Haemostasis is inadequately controlled and the patient experiences breakthrough bleeds with rFVIII prophylaxis
- FVIII levels are not sufficiently controlled on rFVIII (i.e. poor pharmacokinetic coverage due to reduced area under curve [AUC] and shorter half-life)
- Prophylaxis with multiple weekly IV injections with rFVIII is inconvenient or not possible (i.e. frequent injections can lead to poor compliance or adherence to rFVIII therapy)
- The patient is seeking better quality of life or to live a life as ‘normal’ as is possible. Aligned to UK guidelines, HCPs will utilise shared decision-making to tailor prophylaxis with the patient, basing therapy on PK data, patient activity, lifestyle, and patient preferences (29).

There is a notable unmet need for further treatment options for people with severe previously treated haemophilia A, as there are limited treatment options other than emicizumab following treatment with existing FVIII replacement therapies.

B.1.3.3.1.2 Previously untreated patients (PUPs)

Previously untreated patients are usually offered rFVIII therapy (typically EHL therapy) or emicizumab prophylaxis upon diagnosis. Clinical experts consulted by the Company stated that, for PUPs, treatment received is usually based on parental choice since they are first treated at a very young age (28). All patients with severe disease and/or bleeding phenotype (e.g. moderate patients presenting as clinically severe) will require prophylaxis, and the majority of parents will select emicizumab, as it avoids the need for general anaesthetic and central venous access (28). Some parents will select treatment with a rFVIII therapy, often because their child has presented with a severe bleed that was originally treated with an emergency dose of rFVIII, and so they continued with this course of therapy. Clinicians stated that in this instance, an EHL would typically be the first choice of treatment for prophylaxis in PUPs, among which, only efmoroctocog alfa is licensed for use in patients under the age of 12 years (71), and is most commonly administered EHL within this patient population in UK clinical practice (28).

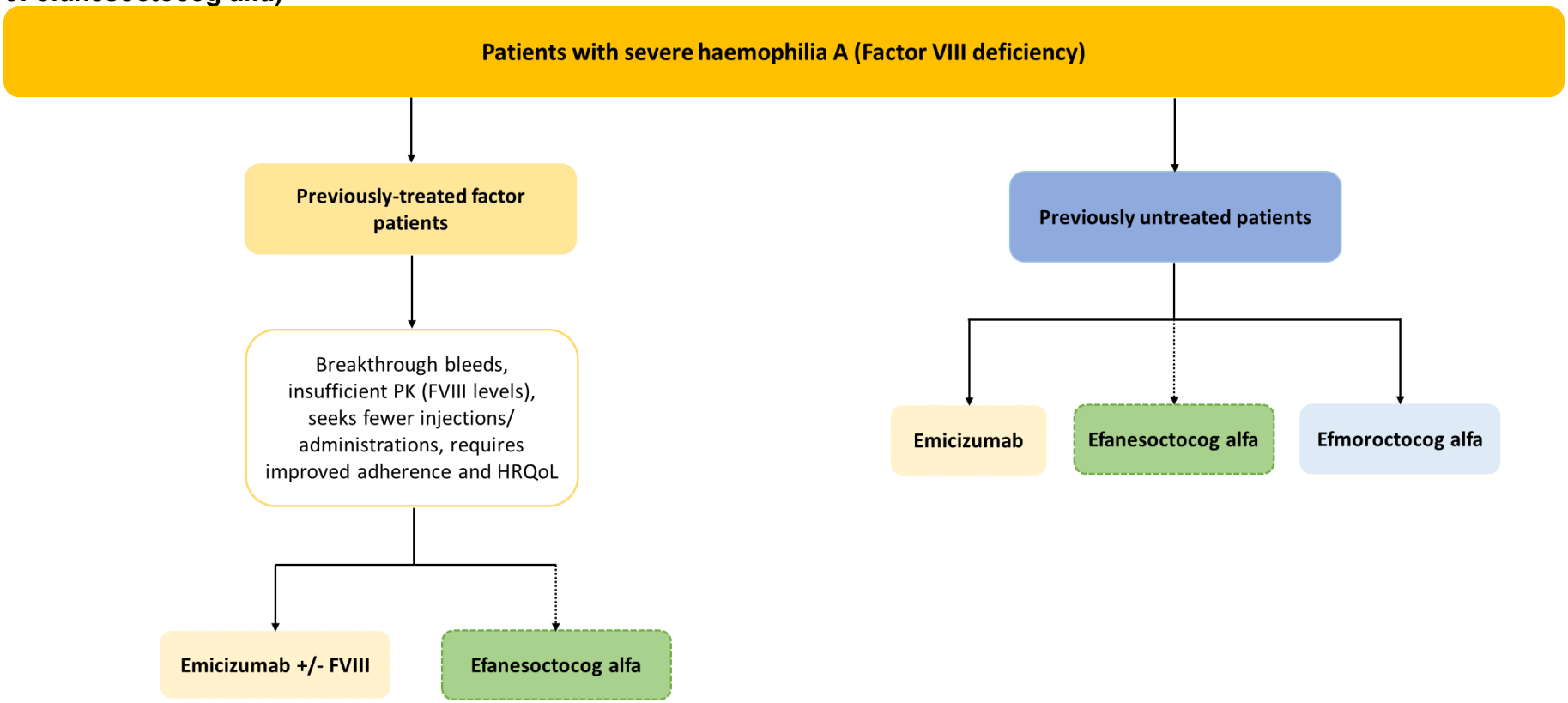
B.1.3.3.2 On-demand

Patients with haemophilia A may receive rFVIII 'on-demand' to treat breakthrough bleeding when it occurs, or to provide protection against bleeds during surgery. Therefore, it is not the standard-of-care for people with severe haemophilia in the UK and should only be viewed as an adjunct to prophylactic therapy (42).

B.1.3.3.3 Positioning of efanesoctocog alfa

The proposed positioning of efanesoctocog alfa for treating and preventing bleeding episodes in patients with severe haemophilia A is presented in Figure 2. In PTPs, it is anticipated that efanesoctocog alfa will be used in patients who would otherwise be offered emicizumab, as per clinical opinion (28). For PUPs, it is anticipated that efanesoctocog alfa will be offered as an alternative therapy to emicizumab or efmoroctocog alfa.

Figure 2: Treatment pathway for managing patients with severe haemophilia A (including proposed positioning of efanesoctocog alfa)



Abbreviations: FVIII, clotting factor VIII; HRQoL, health-related quality of life; PK, pharmacokinetics.

B.1.3.3.4 Unmet need

B.1.3.3.4.1 Recurrent bleeds and problem joints

Despite significant advances in the management of haemophilia A, a notable unmet need remains in the UK in terms of the prevention of bleeds, joint damage, and the associated long-term consequences. In 2022, patients with severe haemophilia A living in the UK receiving FVIII replacement therapy had a mean ABR ranging from [redacted], with only [redacted] achieving zero bleeds (17).

With current prophylactic treatment, patients still frequently develop target joints and haemophilic arthropathy (16), and therefore, there remains an unmet need to adequately reduce, or prevent, bleeding into the joints. Patients with target joints have higher rates of pain, increased pain medication use, and lower HRQoL compared with those without affected joints (30, 34). Associated pain and disability with target joints and arthropathy can lead to reduced productivity, impaired work and societal participation (e.g. hobbies, physical activity, and travel), and also have a negative impact on HRQoL (13-16, 20).

B.1.3.3.4.2 FVIII levels and limitations of current treatment

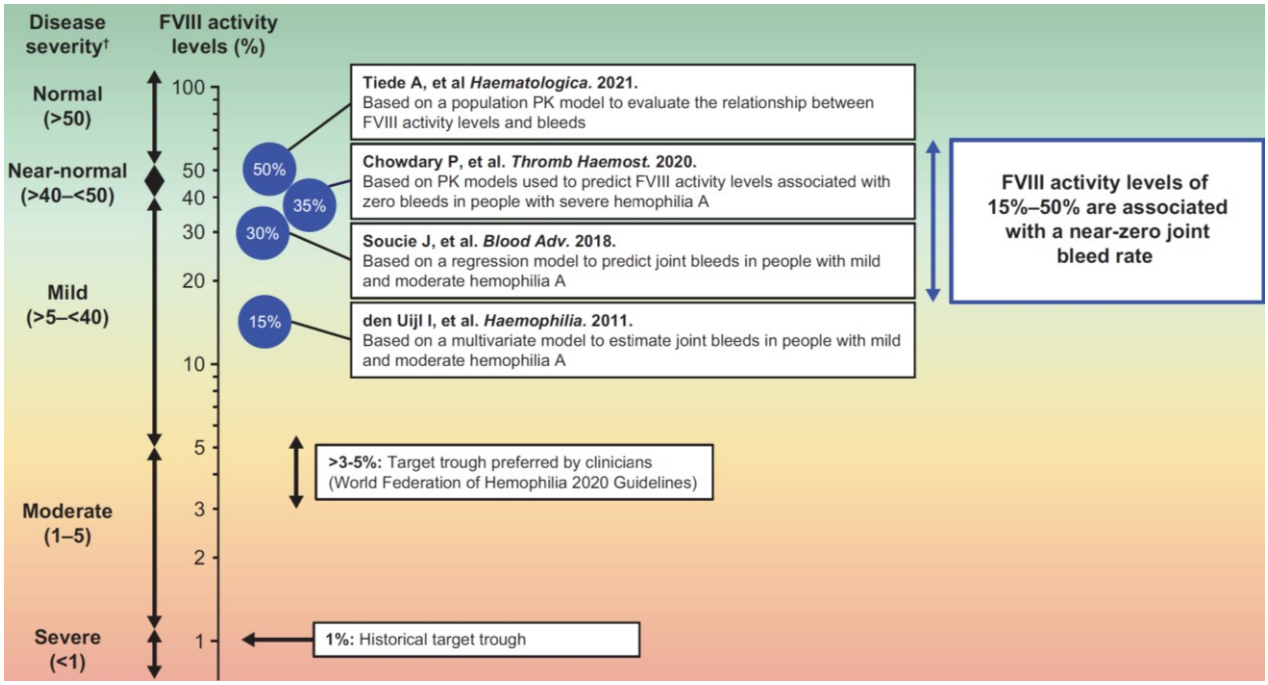
Studies suggest that high sustained FVIII levels (or increased weekly area under curve [AUC] in pharmacokinetic [PK] terms) may improve protection from bleeds and preserve joint health (20, 72). There is also consensus that target factor level is an important driver of treatment choice in patients living with haemophilia (73).

Factor replacement therapy

The UKHCDO recommends that a prophylaxis regimen should be determined jointly with the patient, and based on PK data, patient activity, and patient preferences (29). Historically, the goal of prophylaxis was to maintain FVIII activity trough levels of 1 IU/dL (1%) (20, 74). However, it is now well understood that trough levels of 1 IU/dL are inadequate to prevent all bleeding (75). There is an increasing body of evidence that suggests factor levels of at least 30 IU/dL (30%) are necessary to substantially decrease bleeding risk (19, 21, 22).

Higher FVIII levels correlate with a greater reduction in bleed rates (23, 76, 77). A narrative review conducted by Malec et al, 2023 reported that FVIII activity levels of up to 50 IU/dL (50%) may be needed to achieve a near-zero bleed rate (23).

Figure 3: FVIII activity levels associated with a near-zero bleed rate in haemophilia A



Source: Malec et al, 2023 (23).
†The World Federation of Hemophilia defines FVIII activity levels of <1% as severe haemophilia, 1–5% as moderate haemophilia, >5–<40% as mild haemophilia, and 50–100% as normal (20). FVIII activity levels of >40–<50% are defined in this Figure as near-normal.
Abbreviations: FVIII, clotting Factor VIII; PK, pharmacokinetics.

However, the achievement of higher FVIII levels is difficult with current rFVIII therapies, as the treatment burden can be prohibitive (71, 78, 79). Available rFVIII therapies have an average half-life of 12–19 hours in adults, and even less in children (80). Therefore, patients are required to regularly administer treatment to maintain sufficient FVIII levels, and in 2022, UK patients receiving rFVIII were still injecting up to [redacted] per week (17). In the Phase 3 PROPEL study, prophylaxis with rurioctocog alfa pegol required infusions every other day to achieve FVIII levels of 8–12 IU/dL (8–12%), with a mean of 3.6 (SD: 1.2) infusions per week (72). Frequent administration confers a substantial treatment burden on patients with haemophilia and their caregivers, with patients reporting an impact on their psychosocial well-being (30, 81). Patients who require frequent injections experience difficulty with venous access due to the formation of scar tissue (81).

Emicizumab

Factor VIII equivalence data with emicizumab prophylaxis are limited; current non-clinical and clinical data suggest that emicizumab provides FVIII-like levels of 10–15 IU/dL (10–15%), although these estimates are extrapolated from in vivo models and are difficult to establish unequivocally due to the differences in mechanism of action (82-86). Some of the risks associated with emicizumab treatment include thrombosis and

thrombotic microangiopathy in patients with inhibitors, and concomitant exposure to activated prothrombin complex concentrate (aPCC) (86).

For patients receiving emicizumab, rFVIII therapy must also be prescribed, as emicizumab cannot be used on-demand (e.g. to treat acute bleeds resulting from trauma or treatment for surgical procedures). This limits emicizumab to the prophylactic treatment of bleeds only (55). Because of this, all patients receiving emicizumab in the UK have an additional burden of requiring a contingency stock of rFVIII to take home. If they are bleed-free, this will eventually expire, be discarded, and replaced. Patients who continue to bleed intermittently, may have their stock of FVIII replenished more frequently. Generally, patients will retain a stock of [redacted] units; enough to treat two or three intercurrent bleeds and/or to start treatment for more serious bleeding, should it occur (17). Furthermore, while FVIII-like activity with emicizumab is believed to be maintained at 10–15 IU/dL (10–15%) (84, 85), adjunctive rFVIII therapy may be needed to increase levels to accommodate physical activity. As such, there is a need for a high sustained FVIII replacement that can be used as monotherapy to enable patients to live a life unburdened by their disease.

B.1.3.3.4.3 Efanesoctocog alfa in addressing unmet need

Efanesoctocog alfa is a new class of FVIII replacement therapy, known as a high sustained factor (HSF), designed to decouple recombinant FVIII from endogenous VWF, thus overcoming the VWF-imposed half-life ceiling. Single-dose efanesoctocog alfa 50 IU/kg has a mean terminal half-life of 43.3 hours, which is approximately three- to four-times longer than that of two EHLs; ruriocotocog alfa (15.4 hours) and octocog alfa (11.0 hours) (30). In the Phase 3 study XTEND-1, efanesoctocog alfa provided high-sustained FVIII levels in the normal to near-normal range (>40 IU/dL [>40%] for 4 days, and at 15 IU/dL [15%] on Day 7) (34).

The PK features of efanesoctocog alfa maintain normal to near-normal FVIII levels and allow for once-weekly dosing that addresses the current unmet need for less frequent administration of rFVIII for patients, providing FVIII levels that protect against bleeds and subsequent joint damage, and improving HRQoL by allowing them to live a more normal lifestyle less burdened by their disease and which is comparable with non-haemophilic individuals.

Once weekly administration with efanesoctocog alfa therefore has the potential to decrease the burden of disease through improved outcomes (e.g. reduction of bleeds, prevention of joint damage) due to maintained FVIII levels within the normal to near-normal range. Given that efanesoctocog alfa can be used both prophylactically and on-

demand, it can be used as monotherapy for the treatment of haemophilia A, removing the need for multiple treatments associated with non-factor therapy.

B.1.4 Equality considerations

There are no equality considerations for efanesoctocog alfa treatment in patients with severe haemophilia A.

B.2 Clinical effectiveness

The efficacy and safety of efanesoctocog alfa was investigated in two Phase 3, multicentre, open-label trials, XTEND-1 and XTEND-Kids

- XTEND-1 recruited previously treated patients ≥12 years old with severe haemophilia A (34, 87). The trial forms the clinical and economic evidence base of this submission
- XTEND-1 comprised two arms:
    - Arm A included patients receiving efanesoctocog alfa at a dose of 50 IU/kg IV once weekly (QW) on a prophylaxis treatment regimen for 52 weeks
    - Arm B included patients who were on an on-demand treatment regimen prior to the study. Arm B comprised two phases; an on-demand regimen, in which patients received efanesoctocog alfa at a dose of 50 IU/kg IV as on-demand treatment of bleeding episodes for the first 26 weeks, and a prophylaxis regimen, in which patients switched to receive efanesoctocog alfa at a dose of 50 IU/kg IV QW as prophylaxis for another 26 weeks
- A subgroup of patients participated in a prospective, observational pre-study prior to XTEND-1 (Study 242HA201/OBS16221) (34). The observational pre-study aimed to collect real-world prospective treatment and outcome data in previously treated patients with severe haemophilia A (Appendix P)
- XTEND-Kids recruited previously treated patients younger than 12 years of age with severe haemophilia A (88). A summary of the XTEND-Kids trial is presented in Appendix O

In XTEND-1, once weekly efanesoctocog alfa provided clinically meaningful bleed control, high protection from joint bleeds, and maintained FVIII levels in the normal to near-normal range for the majority of the week. In patients switching from other FVIII replacement therapies, efanesoctocog alfa demonstrated superiority over pre-study rFVIII prophylaxis

- XTEND-1 met its primary endpoint, with weekly prophylaxis with efanesoctocog alfa providing clinically meaningful projection against bleeds. The estimated mean annualised bleed rate (ABR) was 0.71 (95% CI: 0.52, 0.97), while the median ABR was 0.00 (95% CI: 0.00, 1.04)

- An intra-patient comparison with SoC FVIII prophylaxis in the pre-study demonstrated a mean number of bleeding episodes of 3.2 (standard deviation [SD]: 5.4). Switching to efanesoctocog alfa prophylaxis decreased the estimated mean ABR from 2.96 (95% CI: 2.00, 4.37) to 0.69 (95% CI: 0.43, 1.11), a reduction of 77%. The ABR rate ratio showed superiority over SoC FVIII prophylaxis, at 0.23 (95% CI, 0.13, 0.42; p<0.0001)
- Patients in Arm A had a mean annualised joint bleeding rate (AJBR) of 0.51 (95% CI: 0.36, 0.72). The estimated mean AJBR for spontaneous bleeds was 0.21 (95% CI: 0.14, 0.32). A total of 96 (72.2%) patients had no joint bleeds
- At baseline, 26 patients in Arm A reported a total of 80 target joints. Of these, 14 patients had at least 12 months of exposure to efanesoctocog alfa prophylaxis, having a total of 45 target joints at baseline. All 45 target joints for all 14 patients had resolved at Week 52
- At Week 23, mean FVIII activity levels were maintained in the normal to near-normal range (>40% [>40 IU/dL]) for up to 4 days post-administration, and remaining at 15% (15 IU/dL) by Day 7

Switching to prophylaxis from on-demand therapy resulted in high bleed control

- In Arm B, the estimated mean ABR of all bleeding episodes (treated and untreated) was 22.21 (95% CI: 19.41, 25.42) with on-demand treatment and 0.88 (95% CI: 0.42, 1.84) with prophylaxis
- Most patients with on-demand treatment (80.8%) had an ABR >5 for spontaneous bleeds, and seven (26.9%) patients had an ABR >20. After switching to prophylaxis, most patients (84.6%) had no spontaneous bleeds, and no patients had an ABR >5

Treatment with efanesoctocog alfa improved physical health and reduced pain compared with baseline values

- The least squares mean change from baseline to Week 52 in Haem-A-QoL Physical Health score (n=98) was –6.74 (95% CI: –10.13, –3.36; p=0.0001) demonstrating a statistically significant improvement in physical health, as perceived by patients aged 17 years or above. Patients in Arm B also experienced improvement, with a mean change from baseline of [redacted]
- In Arm A, patients aged 12 years or older had an estimated mean change from baseline to Week 52 in PROMIS Pain Intensity first item score of –0.21 (95%

CI: –0.41, –0.02; p=0.0276), thus demonstrating a statistically significant improvement in pain as perceived by patients. In Arm B, the mean (SD) change from baseline to Week 52 in PROMIS Pain Intensity first item score was [redacted]

In the absence of head-to-head trials comparing efanesoctocog alfa with each comparator, an unanchored matching-adjusted indirect comparison (MAIC) was conducted to compare the efficacy of prophylactic treatment with efanesoctocog alfa with emicizumab

- Compared with emicizumab, efanesoctocog alfa was associated with reduced incidence of any bleeds (treated and untreated) as well as with a lower rate of bleeds when compared specifically with an emicizumab QW regimen in patients with prior prophylaxis, and with a every 4 weeks (Q4W) regimen of emicizumab
- Efanesoctocog alfa demonstrated a trend for improving haemophilia joint health score (HJHS) compared with emicizumab

Efanesoctocog alfa was generally well tolerated, and reported treatment-emergent adverse events (TEAEs) were generally consistent with what is anticipated in an adult and adolescent population with severe haemophilia A

- The most frequently reported TEAEs by preferred term (>3% of patients overall) were headache (32 [20.1%] patients), arthralgia (26 [16.4%] patients), fall (ten [6.3%] patients), and back pain (nine [5.7%] patients)
- At least one treatment-emergent serious adverse event was reported in 15 (9.4%) patients overall
- Two (1.3%) patients from Arm A experienced TEAEs leading to treatment discontinuation
- One (0.6%) patient from Arm B experienced a TEAE leading to death (pancreatic carcinoma metastatic), which was assessed by the investigator as not being related to efanesoctocog alfa

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify relevant Phase 3 trials of FVIII replacement therapies and non-factor replacement therapies for the treatment of haemophilia A. The original searches were completed on the 10th February 2021, and updated on the 6th September 2023. Overall, 177 publications corresponding to 105 unique studies were identified, of which, a full data extraction was performed on 62 publications comprising 49 unique studies. Studies identified are listed in Table 5. Appendix D contains the full details of the process and methods used in the clinical SLR.

Table 5: Phase 3 identified by the clinical effectiveness SLR

Trial name(s)	Intervention(s)	Author, year
A-LONG (NCT01181128) and B-LONG (NCT01027364)	Eloctate	Wyrwich 2016
A-LONG (NCT01181128)	Eloctate	Mahlangu 2014
		Shapiro 2017
ATLAS-A/B (NCT03417245)	Fitusiran	Srivastava 2023
ATLAS-INH (NCT03417102)	Fitusiran	Young 2023
Explorer7 (NCT04083781)	Alhemo	Matsushita 2023
GENA-03	Nuwiq	Klukowska 2016
GENA-21b (NCT02256917)	Nuwiq	NCT02256917
GENEr8-1 (NCT03370913)	Roctavian	Dunn 2022
		Mahlangu 2023
		O'Mahony 2021
		Ozelo 2022
Guardian 1 (NCT00840086)	NovoEight	Lentz 2013
		Santagostino 2014
Guardian 3 (NCT01138501)	NovoEight	Kulkarni 2013
Guardian 4 (NCT01493778)	NovoEight	Yaish 2020
HAVEN 1 (NCT02622321)	Hemlibra	Oldenburg 2017
		Oldenburg 2019
HAVEN 2 (NCT02795767)	Hemlibra	Young 2019
		Young 2022
HAVEN 3 (NCT02847637)	Hemlibra	Kiialainen 2019
		Mahlangu 2018
HAVEN 5 (NCT03315455)	Hemlibra	Yang 2022
HAVEN 6 (NCT04158648)	Hemlibra	Negrier 2023
HAVEN 7 (NCT04431726)	Hemlibra	Escuriola-Ettingshausen 2023
Kids A-LONG (NCT01458106)	Eloctate	Young 2015
LEOPOLD I (NCT01029340)	Kovaltry	Saxena 2016
LEOPOLD II (NCT01233258)	Kovaltry	Kavakli 2015

Trial name(s)	Intervention(s)	Author, year
LEOPOLD Kids (NCT01311648)	Kovaltry	Ljung 2016
		Ljung 2023
NCT00543439	Xyntha/Refacto	NCT00543439
NCT01486927	Afstyla	Mahlangu 2016
NCT02093897	Afstyla	Stasyshyn 2017
NCT02210091	Adynovate	Mullins 2017
NCT02615691	Adynovate	Sidonio 2023
NCT03815318	SCT800	Xue 2021
NCT03947320	SCT800	Wu 2022
NCT04061109	TQG202	Xi 2022
NuPreviq (NCT01863758)	Nuwiq	Lissitchkov 2017
Pathfinder 2 (NCT01480180)	Esperoct	Giangrande 2017
Pathfinder 5 (NCT01731600)	Esperoct	Meunier 2017
Pathfinder 5 (NCT01731600) and Pathfinder 2 (NCT01480180)	Esperoct	Kearney 2019
Pathfinder 6 (NCT02137850)	Esperoct	Kenet 2023
Pathfinder 8 (NCT03528551)	Esperoct	Lentz 2022
PROLONG-ATE (NCT01736475)	Adynovate	Konkle 2015
PROPEL (NCT02585960)	Adynovate	Klamroth 2021
PROTECT VIII Kids (NCT01775618)	Jivi	Santagostino 2020
PROTECT VIII (NCT01580293)	Jivi	Reding 2017
PUPs A-LONG (NCT02234323)	Eloctate	Konigs 2022
Refacto Phase 3 study group	Refacto	Lusher 2003
		Courter 2001a
		Courter 2001b
SPINART (NCT00623480)	Kogenate FS	Manco-Johnson 2013
		Manco-Johnson 2017
STASEY (NCT03191799)	Hemlibra	Jimenez-Yuste 2022
XTEND-1 (NCT04161495)	Altuviiio	Von Drygalski 2023
		Von Drygalski 2023
		Weyand 2023
		Wilson 2023
–	Advate (rAHF-PFM) and RECOMBINATE rAHF (R-FVIII)	Tarantino 2004
–	Kogenate FS	Kreuz 2005
–	Nuwiq	Lissitchkov 2016
–	Recombinate	Bray 1994
–	Xyntha	Recht 2009
–	Xyntha	Rusen 2018

B.2.2 List of relevant clinical effectiveness evidence

The primary clinical efficacy and safety evidence for the use of efanesoctocog alfa for the treatment of severe haemophilia comes from the Phase 3 study XTEND-1. Data supporting the clinical evidence base were obtained from the clinical study report (CSR) (87) and the published study by von Drygalski et al, 2023 (34) (Table 6).

Supplementary data from the Phase 3 study, XTEND-Kids, which reported the efficacy and safety of efanesoctocog alfa in patients under 12 years of age with previously treated severe haemophilia A, supports the clinical evidence base for this submission (88). However, data from XTEND-Kids were not used to inform the economic evidence base of this submission.

A summary of the study design, methodology, and key results from XTEND-Kids is presented in Appendix O.

Table 6: Clinical effectiveness evidence

Study	XTEND-1 (NCT04161495)	XTEND-Kids (NCT04759131)
Study design	Phase 3, open-label, multinational, multicentre study	Phase 3, open-label, non-randomised study
Population	Previously treated patients ≥12 years old with severe haemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia)	Previously treated patients younger than 12 years of age with severe haemophilia (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia)
Intervention(s)	Efanesoctocog alfa	Efanesoctocog alfa
Comparator(s)	N/A	N/A
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	No
Reported outcomes specified in the decision problem	• **ABR** • Need for further treatment with FVIII injections • **Change in FVIII activity levels** • Complications of the disease e.g. joint problems or surgeries to treat joint problems) • Pharmacokinetics • **Adverse effects of treatment**	• ABR • Change in FVIII activity levels • Complications of the disease e.g. joint problems • Adverse effects of treatment • Pharmacokinetics • HRQoL

Study	XTEND-1 (NCT04161495)	XTEND-Kids (NCT04759131)
	• **Mortality** • **HRQoL**	
All other reported outcomes	N/A	N/A

Abbreviations: ABR, annualised bleeding rate; FVIII, clotting factor VIII; HJHS, Haemophilia Joint Health Score; HRQoL, health-related quality of life; N/A, not applicable.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 XTEND-1 trial design

XTEND-1 was an open-label, multicentre, Phase 3 study, involving previously treated patients aged 12 years or older, with severe haemophilia A (defined as endogenous FVIII activity <1 IU/dL [<1%]). XTEND-1 consisted of an up to 8-week screening period, an open-label treatment period of a maximum of 52 weeks, and a 2- to 3-week safety follow-up period, that was only applicable for patients who did not continue into an open-label extension study (Figure 4).

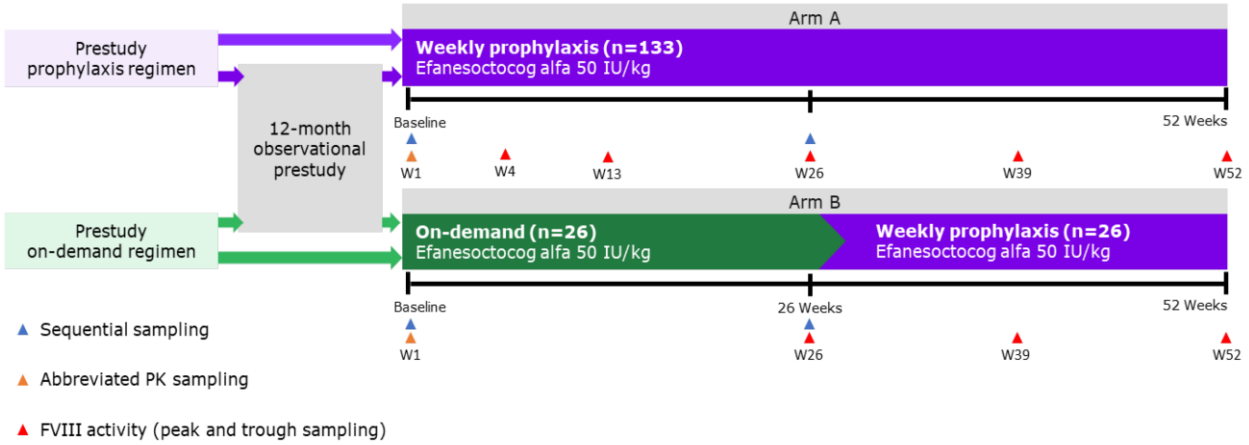
The study was comprised of two arms:

- **Arm A** included patients who were assigned to receive efanesoctocog alfa at a dose of 50 IU/kg IV once weekly (QW) on a prophylaxis treatment regimen for 52 weeks. To be included in Arm A, patients were required to have been receiving a prophylactic regimen prior to study enrolment.
- **Arm B** included patients who were on an on-demand treatment regimen prior to the study. To be included in Arm B, patients were required to have been receiving on-demand treatment with a marketed FVIII therapy, and to have had ≥6 bleeding episodes in the last 6 months or ≥12 bleeding episodes in the last 12 months. Arm B comprised two phases:
    - **On-demand regimen:** patients received efanesoctocog alfa at a dose of 50 IU/kg IV as on-demand treatment of bleeding episodes for the first 26 weeks
    - **Prophylaxis regimen:** patients switched to receive efanesoctocog alfa at a dose of 50 IU/kg IV QW as a prophylaxis treatment regimen for another 26 weeks.

A subgroup of patients participated in a prospective, observational pre-study prior to XTEND-1 (Study 242HA201/OBS16221) (34). The observational pre-study aimed to collect real-world prospective treatment and outcome data in patients with severe

haemophilia A previously treated with prophylaxis. Data were collected on bleeding episodes and treatment with standard-of-care FVIII prophylaxis.

Figure 4: Schematic of XTEND-1 trial design



Source: Supplementary material, von Drygalski et al, 2023 (34).
Abbreviations: FVIII, clotting factor VIII; PK, pharmacokinetic; W, week.

B.2.3.2 Eligibility criteria

Key inclusion and exclusion criteria are listed in Table 7.

Table 7: Key inclusion and exclusion criteria of XTEND-1

Key inclusion criteria	Key exclusion criteria
• Previously treated[†] patients with severe haemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia A) • Aged 12 years or older • Platelet count ≥100,000 cells/μL at screening • Patients who are HIV-positive must have a CD4 lymphocyte count >200 cells/mm^3 and a viral load of <400 copies/mL • Willingness and ability of patient or caregiver to complete training in the use of the study electronic patient diary	• Patients with a history of a positive inhibitor test or with a positive inhibitor test result (defined as ≥0.6 BU/mL) at screening • Clinical signs or symptoms of a decreased response to FVIII • Any concurrent, clinically significant liver disease (e.g. cirrhosis, portal hypertension, and acute hepatitis) • Serious active bacterial or viral infection present within 30 days of screening (other than chronic hepatitis or HIV) • Other known coagulation disorders in addition to haemophilia A • History of anaphylaxis or hypersensitivity associated with any FVIII product • Abnormal renal function, defined as serum creatinine >2.0 mg/dL at screening • Serum ALT or AST >5x ULN at screening • Serum total bilirubin >3x ULN at screening • Prohibited concomitant therapies (Table 8)

Key inclusion criteria	Key exclusion criteria
	• Treatment with an investigational product within 30 days or 5.5 half-lives prior to screening • Major surgery within 8 weeks prior to screening • Pregnant or breastfeeding females
Arm A only	
Prophylactic treatment regimen with a marketed FVIII product or prophylactic emicizumab for ≥6 months during the previous 12 months, with appropriate washout time	–
Arm B only	
At least 12 bleeding episodes in the previous 12 months or ≥6 bleeding episodes in the previous 6 months prior to study enrolment	–

†Previous treatment for haemophilia A was defined as any treatment with any recombinant and/or plasma-derived FVIII product, or cryoprecipitate for at least 150 EDs.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EDs, exposure days; FVIII, clotting Factor VIII; HIV, human immunodeficiency virus; ULN, upper limit of normal.

B.2.3.3 Settings and location where data were collected

XTEND-1 was conducted worldwide across 19 countries/regions, including Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Spain, South Korea, Taiwan, United Kingdom (UK), and the United States of America (USA), at 51 active centres. Due to screen failure, patients were enrolled in 48 of the 51 active centres.

In total, [redacted] study patients were enrolled across three UK sites.

B.2.3.4 Trial drugs and concomitant medications

B.2.3.4.1 Efanesoctocog alfa

Patients were treated with efanesoctocog alfa 50 IU/kg QW to provide high-sustained FVIII activity levels throughout the dosing interval and to decrease treatment burden with injection. During the scheduled study visits, efanesoctocog alfa was administered via slow push IV injection of 8±2 minutes, with the rate of administration being determined by the patient's comfort level.

B.2.3.4.2 Prior and concomitant medications

Permitted and prohibited concomitant medications are detailed in Table 8.

Table 8: Permitted and prohibited concomitant medications in XTEND-1

Permitted
• Local, topical, and/or inhaled steroids
Prohibited
• Vaccination within 30 days of screening • Acetylsalicylic acid or non-NSAID anti-platelet therapies within 2 weeks prior to screening • NSAIDs above the maximum dose specified in the regional prescribing information within 2 weeks of screening • Systemic treatment within 12 weeks prior to screening with chemotherapy and/or other immunosuppressive drugs (except for treatment of HCV or HIV) • Systemic corticosteroid treatment given daily or on alternate days for >14 days • Emicizumab use within 20 weeks prior to screening

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAID, non-steroidal anti-inflammatory drug.

B.2.3.5 Outcomes

Efficacy endpoints from XTEND-1 are presented in Table 9.

Table 9: Efficacy endpoints in XTEND-1

Primary endpoint
• ABR in Arm A
Key secondary endpoint
• Intra-patient comparison of ABR during the efanesoctocog alfa weekly prophylaxis treatment period vs the historical prophylaxis ABR was performed using non-inferiority testing for patients in Arm A
Other secondary endpoints
• ABR by type and location • ABR for all bleeding episodes • Intra-patient comparison of ABR in Arm B • Percentage of patients who maintain FVIII activity levels • Prophylactic dose and dosing interval • Number of injections and dose of efanesoctocog alfa to treat a bleeding episode • Assessment of response to efanesoctocog alfa treatment of bleeding episodes • Annualised joint bleeding rate • Target joint resolution • Haemophilia Joint Health Score • Haem-A-QoL and Haemo-QoL • PROMIS Pain Intensity and Physical Function
Surgery endpoints
• Investigator or surgeon’s assessment of patient haemostatic response to efanesoctocog alfa • Number of injections and dose to maintain haemostasis for major surgery • Total efanesoctocog alfa consumption for major surgery • Estimated blood loss for major surgery • Number and type of blood component transfusions for major surgery

Exploratory endpoints (Appendix N)
• HAL (in patients ≥18 years of age) and paediatric HAL (pedHAL; in patients <18 years of age) questionnaires • Treatment Satisfaction Questionnaire for Medications • EQ-5D-5L • PGIS • PGIC • Treatment preference survey • Physical Activity Monitor • Ultrasound measures, if applicable • Healthcare resource utilisation

Abbreviations: ABR, annualised bleeding rate; FVIII, clotting factor VIII; HAL, Haemophilia Activities List; PGIS, Patient Global Impression of Severity; PGIC, Patient Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Hypothesis objective

B.2.4.1.1 Primary and key secondary endpoints

The primary endpoint of mean ABR in the weekly prophylaxis treatment arm (Arm A) was analysed using an estimation approach.

In addition, as a key secondary endpoint, an intra-patient comparison of ABR between efanesoctocog alfa weekly prophylaxis treatment and historical prophylaxis treatment for patients in Arm A who had at least 6 months of historical data on prophylaxis treatment from observational study 242HA201/OBS16221 (34) was performed using a Wilcoxon Signed Rank test under the following statistical hypotheses:

$$H_0 \text{ (null): Median difference} \geq M \text{ versus } H_1 \text{ (alternative): Median difference} < M$$

where M is the non-inferiority margin. The null hypothesis was rejected if $p<0.025$, establishing non-inferiority of efanesoctocog alfa weekly prophylaxis treatment to historical prophylaxis. If non-inferiority was achieved, superiority was evaluated sequentially. The key secondary endpoint was analysed as part of a step-wise hierarchical testing procedure.

B.2.4.2 Sample size and power calculation

The sample size was estimated to rule out a greater-than-acceptable risk of immunogenicity. Assuming a drop-out rate of approximately 15%, a sample size of 124 patients in the prophylaxis arm was expected to provide 104 evaluable patients with at

least 50 exposure days (ED). An ED is defined as a 24-hour period in which one or more efanesoctocog alfa injections are administered. If ≤2 patients out of 104 evaluable patients developed an inhibitor, then the upper bound of an exact 95% CI would exclude 6.8%, a threshold determined at the Food and Drug Administration (FDA) Factor VIII Inhibitor Workshop held in 2003 (89). Approximately 124 patients who were previously on a prophylaxis treatment regimen were estimated to enrol in Arm A, a 52-week prophylaxis arm, of which approximately 16 patients were enrolled in the sequential pharmacokinetics (PK) subgroup. In addition, approximately 26 patients who were previously on an on-demand treatment regimen were estimated to enrol in Arm B, received efanesoctocog alfa on-demand for 26 weeks, followed by weekly prophylaxis for 26 weeks. Thus, the overall sample size was estimated at 150 patients (i.e. 124 in Arm A and 26 in Arm B).

B.2.4.3 Statistical analysis of the primary efficacy endpoint

The primary endpoint of mean ABR in the weekly prophylaxis treatment arm (Arm A) was analysed using an estimation approach. The mean ABR and one-sided 97.5% confidence interval was estimated using a negative-binomial regression model for the weekly prophylaxis treatment arm (Arm A). Based on currently marketed FVIII products, mean ABR during clinical trials typically ranges from two to five bleeds per year, but can be as high as six bleeding episodes per year (32, 90-92).

To demonstrate adequate control of bleeding consistent with currently marketed FVIII products, and to account for this variability, a clinically meaningful treatment effect may be claimed if the upper bound of the confidence interval of the estimated ABR is ≤6. In a Phase 3 study of recombinant factor VIII Fc fusion protein (rFVIIIFc), the mean ABR for an individualised prophylaxis arm was 2.9 and the dispersion factor was estimated at 2.3 (91). Based on 2,000 simulations of a negative binomial regression model with mean ABR of 2.9 and dispersion factor of 2.3, a sample size of 124 patients was estimated to provide at least 90% power for the upper bound of the one-sided 97.5% confidence interval to exclude an ABR >6, assuming a 15% drop out rate.

B.2.4.4 Statistical analysis of the key secondary endpoint

For the key secondary efficacy endpoint, an intra-patient comparison of ABR during the efanesoctocog alfa weekly prophylaxis treatment period vs the historical prophylaxis ABR was performed using non-inferiority testing for patients in Arm A who had at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221 (93). The non-inferiority margin was estimated based on the known treatment effect between on-demand and prophylaxis treatment. A meta-analysis of Phase 3 registrational studies for recombinant FVIII products that include both on-

demand and prophylaxis treatment arms estimated an average reduction of 31 bleeds per year between on-demand and prophylaxis treatment regimens (Appendix M). The lower bound of this treatment effect was 27 bleeds per year. Using a fixed margin approach to maintain a substantial amount (85%) of the treatment effect results in a non-inferiority margin of four bleeds. For a non-inferiority test of the null hypothesis (median difference in ABR exceeds or is equal to non-inferiority margin) vs the alternative hypothesis (median difference in ABR is less than non-inferiority margin), a sample size of 63 achieves 90% power to detect non-inferiority using a one-sided paired Wilcoxon Signed Rank test at a 0.025 significance level when the actual mean of paired differences is 0 and the non-inferiority margin is four. Without prior knowledge of the standard deviation of the paired differences, a conservative estimate of 10 was assumed. In order to account for drop-out and the use of the Per Protocol Set, at least 75 patients who have completed at least 6 months of participation in observational Study 242HA201/OBS166221 will be enrolled in Arm A.

If non-inferiority was achieved, then superiority was evaluated sequentially using a negative-binomial regression model. The paired ABR ratio and 95% CI was estimated using the full analysis set, and the treatment was considered superior if the upper limit of the 1-sided 97.5% CI of the intra-patient ABR difference is <1.

B.2.4.5 Statistical analysis of other secondary endpoints

A summary of the statistical analysis of other secondary endpoints is presented in Appendix M.

B.2.4.6 Multiplicity issues

Type I error for secondary endpoints was controlled through a hierarchical testing framework. The α-level was 0.05. Following the estimation approach described in Section B.2.4.3 for the primary endpoint (ABR in Arm A), the key and selected secondary endpoints were included in the hierarchy in the following order:

1. Arm A intra-patient comparison non-inferiority: ABR of efanesoctocog alfa weekly prophylaxis treatment vs historical prophylaxis treatment

2. Arm A intra-patient comparison superiority: ABR of efanesoctocog alfa weekly prophylaxis treatment vs historical prophylaxis treatment

3. Arm A change from baseline to Week 52: Haem-A-QoL physical health score

4. Arm A change from baseline to Week 52: PROMIS Pain intensity 3a past 7 days intensity of pain at its worst score (PAINQU6)

5. Arm A change from baseline to Week 52: Haemophilia Joint Health Score (HJHS) total score

No multiplicity adjustment was made on other secondary efficacy variables than mentioned in points 1–5.

B.2.4.7 Analysis sets

The populations for analysis reported in this submission are:

- **All-enrolled analysis set:** all patients who were enrolled in the study, regardless of whether they were dosed with efanesoctocog alfa or not. Patients were considered enrolled when the investigator had verified that they were eligible according to the eligibility criteria. Patient disposition and enrolment summaries were based on the all-enrolled analysis set
- **Full analysis set (FAS):** all patients who received ≥1 dose of efanesoctocog alfa. All analyses of demographics, baseline characteristics, and efficacy were based on the FAS, unless otherwise specified
- **Per protocol set (PPS):** a subset of the FAS, including patients who did not have important protocol deviations potentially impacting efficacy. The PPS was used for analysis of the key secondary efficacy endpoint, as well as sensitivity analysis of the primary endpoint
- **Safety analysis set (SAS):** the SAS was the same as the FAS. All analyses of safety were based on the SAS, unless otherwise specified
- **PK analysis set (PKAS):** all patients who had completed adequate blood sample collection to assess key PK parameters, as determined by the PK scientist. All analyses of PK were based on the PKAS, unless otherwise specified
- **Sequential PK subgroup:** all patients who had evaluable PK profiles for both baseline and repeat PK profiles, as determined by the PK scientist
- **Surgery subgroup:** all patients who underwent major surgery after the first dose of study drug.

B.2.4.8 Data management and patient withdrawals

Case report form (CRF) data were captured via data entry by study centre personnel in a database system owned by an external vendor. In addition, all data captured in the electronic patient diary (ePD) were available to the investigator via the vendor web-based portal; the investigator was to document in the electronic CRF new classification of bleeding episodes when the patient's classification reported in the ePD was judged as incorrect. Data quality checks were applied using manual and/or electronic verification

methods. An audit trail to support data query resolution and any modification to the data was maintained.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Appendix D presents the quality assessment of each of the trials identified in the SLR.

B.2.6 Clinical effectiveness results of the relevant trials

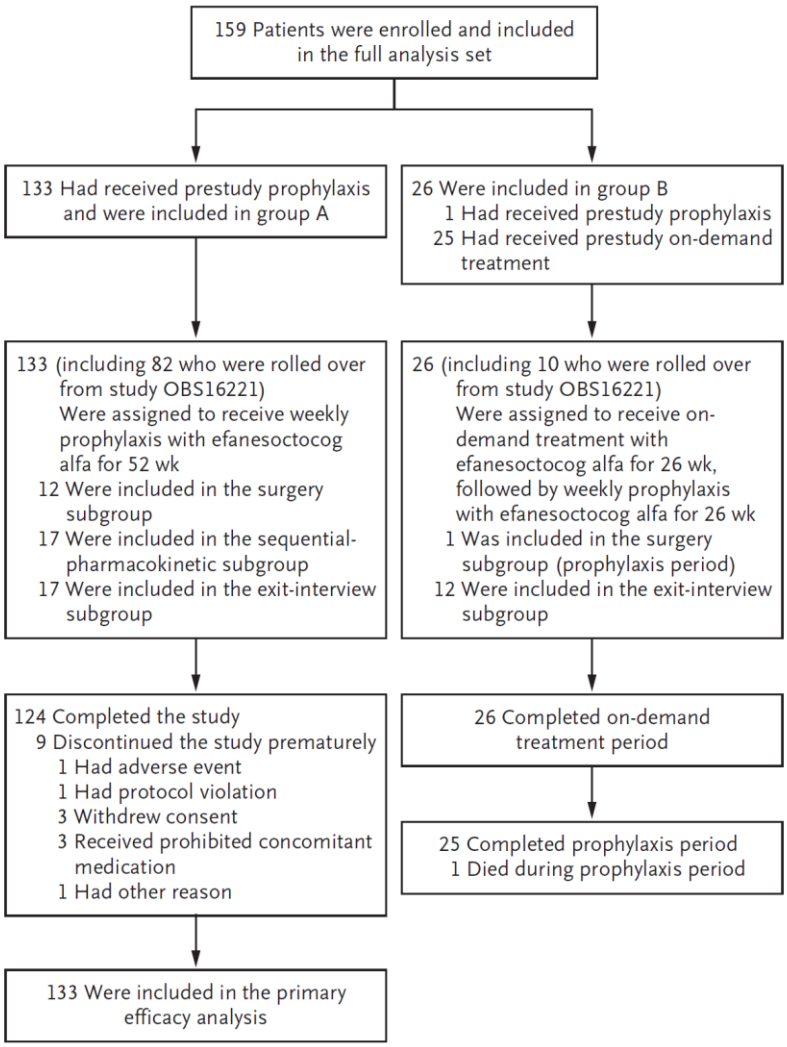
B.2.6.1.1 Patient disposition

In total, 170 patients were screened for the study; 11 (6.5%) of whom were excluded during the screening process. The most frequently reported reason for screening failure was related to the inclusion criteria for severe haemophilia A (three [1.8%] patients).

A total of 159 patients were enrolled; 133 in Arm A, and 26 in Arm B. All patients received ≥1 dose of efanesoctocog alfa. In total, 149 (93.7%) patients completed the study and 10 (6.3%) prematurely discontinued. In Arm A, the most frequently reported reasons for study discontinuation were the use of prohibited concomitant medication (three [1.9%] patients) and consent withdrawn (three [1.9%] patients). One patient in Arm B had been receiving pre-study prophylaxis but was incorrectly assigned to receive on-demand treatment. This was reported as a major deviation from the protocol. A single death in the Arm B prophylaxis period was secondary to metastatic pancreatic carcinoma and was assessed by the investigators as not being related to the study drug.

The flow of patients in XTEND-1 is presented in Figure 5, and a summary of analysis populations (defined in Section B.2.4.6) is provided in Table 10.

Figure 5: Flow of patients in XTEND-1



Source: von Drygalski et al, 2023 (34).

Table 10: Analysis populations in XTEND-1

Analysis population	Arm A N=133	Arm B		Overall N=159
		On-demand N=26	Prophylaxis N=26	
FAS	133 (100.0)	26 (100.0)	26 (100.0)	159 (100.0)
PPS	129 (97.0)	25 (96.2)	25 (96.2)	154 (96.9)
PKAS	133 (100.0)	26 (100.0)	26 (100.0)	159 (100.0)
Sequential PK subgroup	17 (12.8)	0	0	17 (10.7)
Surgery subgroup[†]	10 (7.5)	0	1 (3.8)	13 (8.2)
Safety	133 (100.0)	26 (100.0)	26 (100.0)	159 (100.0)

Source: Table 6, clinical study report (87).
Note: Percentages are based on the number of patients in the All-Enrolled Analysis Set; Patients are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each patient is counted only once in the overall column.
[†]Patients who have undergone major surgery after the first dose of study drug. Surgery reported after the last injection of efanesoctocog alfa is not counted in the specific treatment arm and regimen but counted in the overall column.
Abbreviations: FAS, full analysis set; PK, pharmacokinetics; PKAS, pharmacokinetics analysis set; PPS, per protocol set.

B.2.6.1.2 Demographics and baseline characteristics

Demographic data and baseline characteristics are presented in Table 11. The mean (standard deviation [SD]) age of patients was 35.4 (15.1) years (range: 12–72 years). All adolescents aged 12–17 years old were in treatment Arm A. One female patient was enrolled; all other patients were male.

Baseline disease characteristics were representative of an adult and adolescent population with severe haemophilia A. At study entry, all patients had a documented FVIII activity level <1%, or a documented genotype known to produce severe haemophilia A. The median age at start of first prophylaxis was 1.0 years (range: 0–35) for patients in Arm A. For [redacted] patients in Arm B receiving on-demand treatment for at least [redacted] EDs before study entry, an age at start of first prophylaxis was reported (median of 3.0 years [range: 0–62] and mean of [redacted] years). The majority of patients (125 [78.6%]) had no family history of a FVIII inhibitor.

Mean number of bleeding episodes reported during the 12 months prior to the study was 3.2 (SD: 5.4) in Arm A and 35.7 (SD: 22.2) in Arm B. Mean number of joint bleeds reported in the 12 months prior to the study was 2.3 (SD: 4.5) in Arm A and 27.4 (SD: 18.6) in Arm B. Of these joint bleeds, the mean number of spontaneous joint bleeds was [redacted] in Arm A and [redacted] in Arm B and the mean number of traumatic joint bleeds was [redacted] in Arm A and [redacted] in Arm B.

Additional baseline characteristics are presented in Appendix N.

Table 11: Summary of demographic and baseline characteristics, FAS

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Demographics					
Age (years)[†]					
Mean (SD)	33.9 (15.3)	42.8 (11.7)	42.8 (11.7)	44.3 (12.8)	35.4 (15.1)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12–17 years	25 (18.8)	0	0	1 (7.7)	25 (15.7)
18–64 years	104 (78.2)	25 (96.2)	25 (96.2)	12 (92.3)	129 (81.1)
≥65 years	4 (3.0)	1 (3.8)	1 (3.8)	0	5 (3.1)
Sex, n (%)					
Male	132 (99.2)	26 (100.0)	26 (100.0)	13 (100)	158 (99.4)
Female	1 (0.8)	0	0	0	1 (0.6)
Race, n (%)					
Asian	29 (21.8)	0	0	3 (23.1)	29 (18.2)
Black or African American	3 (2.3)	0	0	3 (23.1)	3 (1.9)
White	71 (53.4)	26 (100.0)	26 (100.0)	7 (53.8)	97 (61.0)
NR due to confidentiality regulations	26 (19.5)	0	0	3 (23.1)	26 (16.4)
Other	4 (3.0)	0	0	0	4 (2.5)
Region, n (%)[‡]					
Asia Pacific	33 (24.8)	0	0	4 (30.8)	33 (20.8)
Europe	67 (50.4)	14 (53.8)	14 (53.8)	5 (38.5)	81 (50.9)
North America	26 (19.5)	0	0	3 (23.1)	26 (16.4)
South America	7 (5.3)	12 (46.2)	12 (46.2)	1 (7.7)	19 (11.9)
Weight (kg)					
Mean (SD)	78.00 (19.29)	80.80 (18.04)	80.80 (18.04)	77.31 (9.66)	78.46 (19.06)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Baseline characteristics					
Age at diagnosis of severe haemophilia (years)					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Family inhibitor history, n (%)					
Yes	5 (3.8)	0	0	0	5 (3.1)
No	100 (75.2)	25 (96.2)	25 (96.2)	12 (92.3)	125 (78.6)
Unknown	28 (21.1)	1 (3.8)	1 (3.8)	1 (7.7)	29 (18.2)
Lowest documented historical FVIII level (%), n (%)					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of haemophilia treatment products administered throughout life[a], n (%)					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII Plasma-derived	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII Recombinant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII Cryoprecipitate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non FVIII product	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antifibrinolytic agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Desmopressin/DDAVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fitusiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEIBA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
rFVIIa (Novoseven)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Age at start of first prophylaxis regimen (years)					
Number	126	25	25	11	151
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	1.0	3.0	3.0	1.0	1.0
Min, Max	0 ; 35	0 ; 62	0 ; 62	0 ; 12	0 ; 62
<6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6–<10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10–<18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior exposure days to FVIII, n (%)					
<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50–<100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100–<150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of bleeds in the past 12 months					
Number	122	23	23	12	145
Mean (SD)	3.2 (5.4)	35.7 (22.2)	35.7 (22.2)	9.1 (21.8)	8.3 (15.5)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of joint bleeds in the past 12 months					
Number	121	21	21	12	142
Mean (SD)	2.3 (4.5)	27.4 (18.6)	27.4 (18.6)	7.9 (19.7)	6.0 (12.1)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Number of spontaneous joint bleeds in the past 12 months					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of traumatic joint bleeds in the past 12 months					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-study regimen					
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on pre-study regimen					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6–12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 16.2.4.1 and Table 16.2.4.3, Table 16.2.4.4 and Table 16.2.4.5, Data on file_CSR_01-EFC16293-16.2.4_demo_data (94).
Note: Percentages are based on the number of patients with non-missing data in the FAS; patients are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each patient is counted only once in the overall column.
†Age = year of informed consent – year of birth; ‡Asia Pacific includes Australia, Japan, Korea, and Taiwan. Europe includes Belgium, Bulgaria, Germany, Greece, Hungary, Italy, The Netherlands, Spain, and the United Kingdom. North America includes Canada, Mexico, and the United States. South America includes Argentina and Brazil.
Abbreviations: BMI, body mass index; FAS, full analysis set; FVIII, clotting Factor VIII, NR, not reported; rFVIII, recombinant factor VIII; SD, standard deviation.

B.2.6.1.3 Primary endpoint – mean annualised bleeding rates in Arm A

In the FAS, a total of 86 bleeding episodes were treated with efanesoctocog alfa in 133 patients who had an efficacy period in Arm A. The mean (SD) duration of the efficacy period was [redacted] weeks. The mean ABR estimated from the negative binomial model was 0.71 (95% CI: 0.52, 0.97) in Arm A (Table 12). The upper limit of the one-sided 97.5% CI was substantially less than the pre-specified value of six, demonstrating that the weekly prophylaxis treatment regimen with efanesoctocog alfa provided protection against bleeds, and a clinically meaningful treatment effect.

In Arm A, [redacted] patients had ≤5 bleeding episodes per year, with 86 (64.7%) patients having no bleeding episodes during the study.

Table 12: Primary efficacy endpoint, ABR, FAS

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Total number of treated bleeding episodes	[redacted]	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]	[redacted]
Duration of efficacy period (weeks)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
ABR			
Mean (SD)	0.71 [redacted]	21.42 (7.41)	0.69 (1.35)
Median	0.00	21.13	0.00
Number of bleeds			
0	86 (64.7)	0	20 (76.9)
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Mean ABR, model based[†] (95% CI)	0.71 (0.52, 0.97)	–	–

Source: Table 13, clinical study report (87).
Note: The efficacy period reflects the sum of all intervals of time during which patients were treated with efanesoctocog alfa according to the study arms and treatment regimens, excluding periods of pharmacokinetic evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
[†]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; SD, standard deviation.

B.2.6.1.3.1 Sensitivity analyses

Sensitivity analysis of the mean ABR, PPS

Results of the sensitivity analysis were consistent with the results of the primary analysis (Table 12). The mean ABR estimated from the negative binomial model was [redacted] in Arm A (Table 13).

Table 13: Summary of ABRs, sensitivity analysis, PPS

	Arm A N=129
Number of patients with an efficacy period	[redacted]
Total number of treated bleeding episodes	[redacted]
Total participant-years followed	[redacted]
Duration of efficacy period (weeks)	
Mean (SD)	[redacted]
Median	[redacted]
ABR	
Mean (SD)	[redacted]
Median	[redacted]
Number of bleeds	
0	[redacted]
>0–5	[redacted]
>5–10	[redacted]
>10–20	[redacted]
>20	[redacted]
Mean ABR, model based[†] (95% CI)	[redacted]

Source: Table 16.2.6.1.3, Data on file CSR_01-EFC16293_16_2_6_efficacy data (95).
Note: Five patients (four in Arm A and one in Arm B) with important protocol deviations were not included in the PPS.
[†]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; PPS, per protocol set; SD, standard deviation.

Sensitivity analysis of the mean ABR including patients with an efficacy period of at least 26 Weeks, FAS

Results of the sensitivity analysis including patients with an efficacy period of at least 26 weeks ([redacted]) were also consistent with the results of the primary analysis (Table 12). The mean ABR estimated from the negative binomial model was [redacted] in Arm A (Table 14).

Table 14: Summary of ABRs, patients with an efficacy period ≥26 weeks, sensitivity analysis, FAS

	Arm A N=128
Number of patients with an efficacy period	[redacted]
Total number of treated bleeding episodes	[redacted]
Total participant-years followed	[redacted]
Duration of efficacy period (weeks)	
Mean (SD)	[redacted]
Median	[redacted]
ABR	
Mean (SD)	[redacted]
Median	[redacted]
Number of bleeds	
0	[redacted]
>0–5	[redacted]
>5–10	[redacted]
>10–20	[redacted]
>20	[redacted]
Mean ABR, model based[†] (95% CI)	[redacted]

Source: Table 16.2.6.1.4, Data on file CSR_01-EFC16293_16_2_6_efficacy data (95).
[†]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; SD, standard deviation.

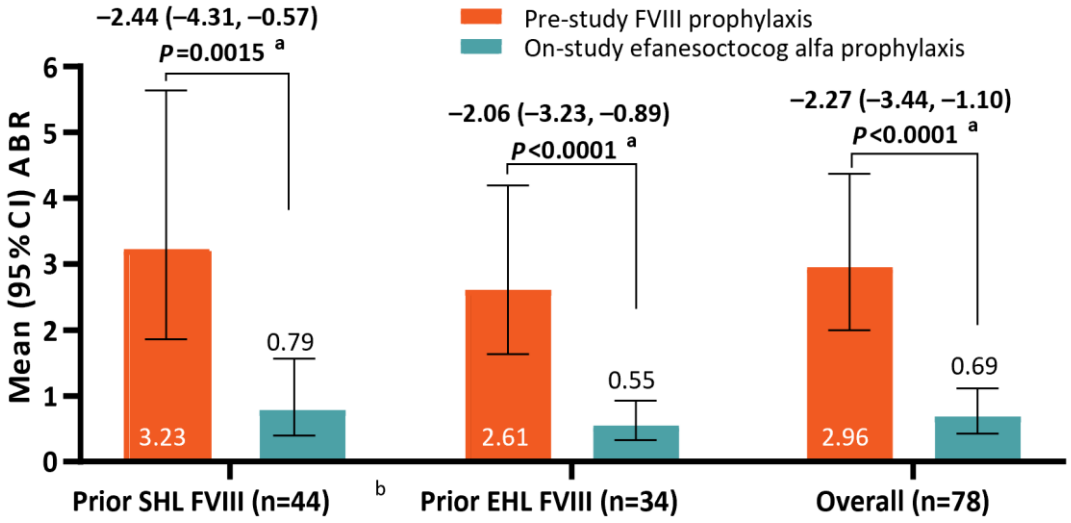
B.2.6.1.4 Key secondary endpoint – intra-patient comparison of ABR between efanesoctocog alfa prophylaxis and pre-study prophylaxis, Arm A

The non-inferiority of prophylaxis treatment with efanesoctocog alfa over historical prophylaxis on the key efficacy endpoint was evaluated as part of the prespecified hierarchical step-down testing procedure. The non-inferiority margin (i.e. four bleeds) was established via a fixed margin approach to maintain a substantial amount (85%) of the treatment effect between on-demand and prophylaxis, and the effect between the two regimens were estimated based on the meta-analysis of Phase 3 registrational studies for recombinant FVIII products (Appendix M).

Non-inferiority of prophylaxis treatment with efanesoctocog alfa over historical prophylaxis for mean ABR was demonstrated in the PPS (n=77), as the upper bound of the one-sided 97.5% CI of the difference between efanesoctocog alfa prophylaxis and historical prophylaxis (estimated mean difference: [redacted] was below the prespecified non-inferiority margin of four bleeds per year.

In the superiority testing of efanesoctocog alfa prophylaxis treatment over historical prophylaxis on the key efficacy endpoint in the prespecified hierarchical step-down testing procedure, efanesoctocog alfa resulted in a statistically significant decrease (–2.27 [–3.44, –1.10]; p<0.0001) in mean ABR (Figure 6; Table 15). The upper bound of the one-sided 97.5% CI of the ABR ratio between efanesoctocog alfa prophylaxis and historical prophylaxis was less than 1 (rate ratio: 0.23 [95% CI: 0.13, 0.42], or a rate reduction of 77% [95% CI: 58%, 87%]).

Figure 6: Intra-patient comparison of ABR between efanesoctocog alfa prophylaxis and pre-study prophylaxis, Arm A, FAS



Median (IQR) ABR	Pre-study FVIII prophylaxis	On-study efanesoctocog alfa prophylaxis
Prior SHL FVIII (n=44)[b]	1.05 (0.00–3.42)	0.00 (0.00–1.04)
Prior EHL FVIII (n=34)	1.10 (0.00–4.50)	0.00 (0.00–1.02)
Overall (n=78)	1.06 (0.00–3.74)	0.00 (0.00–1.04)

Source: Susen S, et al. OC 69.5. Presented at ISTH June 2023 (96).
[a]Mean difference (95% CI), P-values and mean (95% CI) were calculated using negative binomial regression model with treatment (on-study prophylaxis vs pre-study prophylaxis) as a covariate; [b]Pre-study SHL includes SHL rFVIII and plasma-derived FVIII.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; EHL, extended half-life; FAS, full analysis set; FVIII, clotting Factor VIII; IQR, interquartile range; SHL, standard half-life.

Table 15: Intra-patient comparison of ABR between efanesoctocog alfa prophylaxis and pre-study prophylaxis, Arm A, FAS

	Arm A N=133	
	Historical prophylaxis (OBS16221) N=78	Efanesoctocog alfa N=78
Number of patients with an observation or efficacy period	78	78

	Arm A N=133	
	Historical prophylaxis (OBS16221) N=78	Efanesoctocog alfa N=78
Total number of treated bleeding episodes	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]
Duration of observation or efficacy period (weeks)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
ABR		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
>0–5	[redacted]	[redacted]
>5–10	[redacted]	[redacted]
>10–20	[redacted]	[redacted]
>20	[redacted]	[redacted]
Negative binomial regression model†		
Mean ABR (95% CI)	2.96 (2.00, 4.37)	0.69 (0.43, 1.11)
Mean difference (95% CI)	–2.27 (–3.44, –1.10)	
Rate ratio (95% CI)	0.23 (0.13, 0.42)	
p-value (superiority)‡	p<0.0001	
Wilcoxon Signed Rank test		
Median ABR (Q1, Q3)	1.06 (0.00, 3.74)	0.00 (0.00, 1.04)
Median of paired difference (95% CI)¶	[redacted]	
p-value (non-inferiority)§	[redacted]	

Source: Table 15, clinical study report (87)
Note: The analysis is based on the Full Analysis Set and including patients in Arm A who have at least 6 months of efficacy period in the XTEND-1 study and at least 6 months of observation period on prophylaxis collected in Study OBS16221.
†Estimated using a negative binomial regression model with treatment (efanesoctocog alfa prophylaxis vs historical prophylaxis) as covariate; ‡P-value relates to the null hypothesis: rate ratio (efanesoctocog alfa prophylaxis/historical prophylaxis) = 1; ¶ Estimated using the Hodges-Lehmann method; §P-value relates to the null hypothesis: median of paired difference (efanesoctocog alfa prophylaxis - historical prophylaxis) = 4 based on Wilcoxon Signed Rank test.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; SD, standard deviation.

B.2.6.1.5 Other secondary endpoints

B.2.6.1.5.1 ABR by type of bleed

The rates of spontaneous and traumatic bleeds were low in Arm A (Table 16), with a mean annualised spontaneous bleeding rate (AsBR) of 0.29 (SD: 0.73). The majority of patients (n=107; 80.5%) had no spontaneous bleeds, and no patients had an AsBR >5.

In Arm B, the mean AsBR decreased after patients switched to prophylaxis treatment (0.45 [SD: 1.13]) compared with on-demand treatment (15.87 [SD: 9.28]). With on-demand treatment, [redacted] had an AsBR >5 for spontaneous bleeds, and [redacted] patients had an AsBR >20. After switching to prophylaxis treatment, most patients (n=22; 84.6%) had no spontaneous bleeds and no patients had an AsBR >5. For traumatic bleeds, the mean annualised traumatic bleeding rate (AtBR) was also lower with prophylaxis treatment than with on-demand treatment. Of note, mean ABR for spontaneous and traumatic bleeds during efanesoctocog alfa treatment in Arm B were similar to those observed in Arm A.

Table 16: Summary of ABR by type of bleed, FAS

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Total number of spontaneous bleeding episodes	[redacted]	[redacted]	[redacted]
Total number of traumatic bleeding episodes	[redacted]	[redacted]	[redacted]
Total number of unknown bleeding episodes	[redacted]	[redacted]	[redacted]
Spontaneous bleeding rate, patient-level			
Mean (SD)	0.29 (0.73)	15.87 (9.28)	0.45 (1.13)
Median	0.00	16.69	0.00
Number of bleeds			
0	107 (80.5)	1 (3.8)	22 (84.6)
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Spontaneous bleeding rate, population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Traumatic bleeding rate, patient-level			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Traumatic bleeding rate, population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Unknown type of bleeding rate, patient-level			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Unknown type of bleeding rate, population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]

Source: Table 16, clinical study report (87)

[†]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; SD, standard deviation.

B.2.6.1.5.2 ABR by location of bleed

In both Arm A and Arm B, joints were the most common location for bleeds. In Arm A, the mean annualised joint bleeding rate (AJBR) was 0.52 (SD: 1.09) (Table 17). In Arm B, the mean AJBR was lower after switching to prophylaxis treatment (0.61 [SD:1.33]) compared with on-demand treatment (17.45 [SD: 7.31]). The mean AJBR estimated from the negative binomial model was [redacted]. Of the 133 patients who had an efficacy period in Arm A, [redacted] had an AJBR of 5 or fewer episodes per year, with 96 (72.2%) patients having no joint bleeds during the study. In the on-demand group of Arm B, all patients had ≥1 bleed over the 12-month period; in contrast, 21 (80.8%) patients had no bleeds in the prophylaxis group of Arm B.

Table 17: Summary of ABR by location of bleed, FAS

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Total number of treated bleeding episodes at joint	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	0.52 (1.09)	17.45 (7.31)	0.61 (1.33)
Median	0.00	18.42	0.00
Number of bleeds			
0	96 (72.2)	0	21 (80.8)
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Total number of treated bleeding episodes at muscle	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Mean (SD), patient-level	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Total number of treated bleeding episodes, internal	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Total number of treated bleeding episodes at skin/mucosa	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Total number of treated bleeding episodes at an unknown location	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]

Source: Table 17, clinical study report (87)

[†]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; NC, not calculable; SD, standard deviation.

B.2.6.1.5.3 ABR for all bleeding episodes

In Arm A, the estimated mean ABR based on all bleeding episodes, i.e. treated and untreated, was low (1.11 [95% CI: 0.83, 1.48]) (Table 18), consistent with results for the primary endpoint using only treated bleeds (Section B.2.6.1.3).

In Arm B, the estimated mean ABR based on all bleeding episodes was 22.21 (95% CI: 19.41, 25.42) with on-demand treatment and 0.88 (95% CI: 0.42, 1.84) when patients switched to prophylaxis treatment (Table 18). These results are also consistent with the estimated ABR based on treated bleeds.

Table 18: Summary of ABR for all bleeding episodes, FAS

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Number of patients with an efficacy period	[redacted]	[redacted]	[redacted]
Total number of all bleeding episodes	[redacted]	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]	[redacted]
Duration of efficacy period (weeks)			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
ABR			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
ABR, model based[†]			
Mean (95% CI)	1.11 (0.83, 1.48)	22.21 (19.41, 25.42)	0.88 (0.42, 1.84)

Source: Table 16.2.6.4.6, data on file_ CSR_01-EFC16293_16_2_6_efficacy_data (95).
Note: Summaries are based on all bleeds (treated and untreated).
[†]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; SD, standard deviation.

B.2.6.1.5.4 Intra-patient comparison of ABR in Arm B

For 26 patients in Arm B, the efficacy of efanesoctocog alfa prophylaxis was compared with on-demand efanesoctocog alfa treatment (measured by ABR). The total number of participant-years followed was [redacted] with on-demand treatment and [redacted] with prophylaxis treatment (Table 19). The bleeding rate ratio for prophylaxis vs on-demand treatment was [redacted], corresponding to a clinically important reduction of [redacted] in ABR with prophylaxis treatment.

The distribution of the ABR showed that, with on-demand treatment, the majority of patients ([redacted]) had an ABR >10, whereas after switching to prophylactic treatment, the majority of patients ([redacted]) had no bleeds. Of note, mean ABR during prophylaxis treatment in Arm B approached the ABR observed in Arm A, and patients assigned to the prophylaxis group of Arm B had a median ABR of [redacted], with [redacted] of patients having ≤5 bleed episodes per year. In total, [redacted] patients had an ABR >20 with on-demand treatment, with ABR ranging up to [redacted]. Bleeds in these patients were predominantly spontaneous, except in [redacted] patients, who had mostly traumatic bleeds located in the joints.

Table 19: Intra-patient comparison of ABR between efanesoctocog alfa prophylaxis and pre-study prophylaxis, Arm B, FAS

	Arm B	
	On-demand N=26	Prophylaxis N=26
Number of patients with an observation or efficacy period	[redacted]	[redacted]
Total number of treated bleeding episodes	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]
Duration of observation or efficacy period (weeks)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
ABR		
Mean (SD)	[redacted]	[redacted]

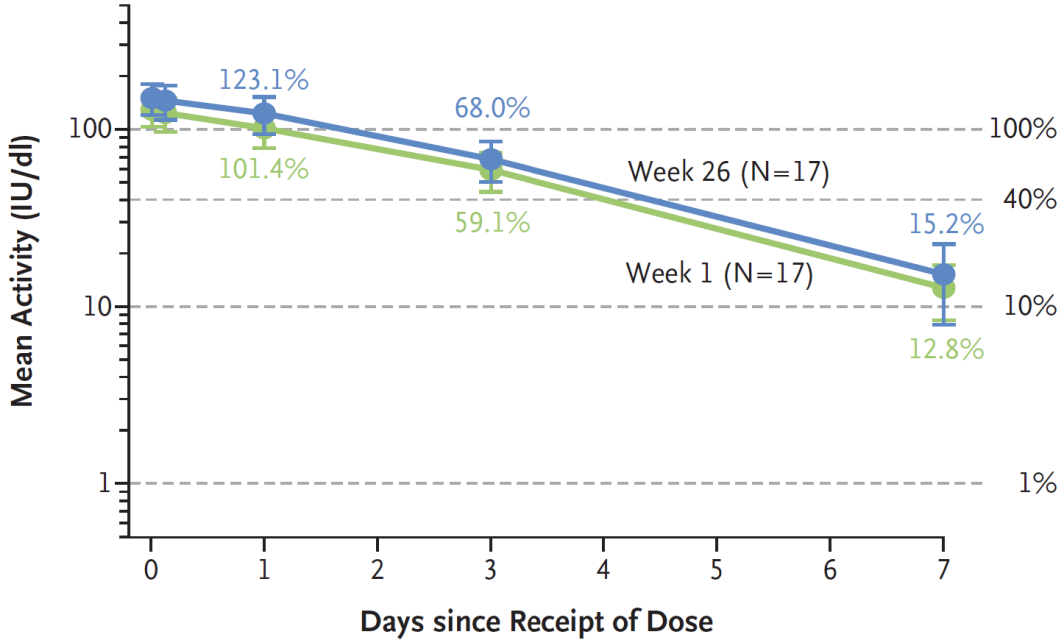
	Arm B	
	On-demand N=26	Prophylaxis N=26
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Number of bleeds		
0	[redacted]	[redacted]
>0–5	[redacted]	[redacted]
>5–10	[redacted]	[redacted]
>10–20	[redacted]	[redacted]
>20	[redacted]	[redacted]
Negative binomial regression model[†]		
Mean ABR (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
p-value (superiority)[‡]	[redacted]	

Source: Table 18, clinical study report (87)
Note: The analysis is based on the Full Analysis Set and including patients in Arm A who have at least 6 months of efficacy period in the XTEND-1 study and at least 6 months of observation period on prophylaxis collected in Study OBS16221.
[†]Estimated using a negative binomial regression model with treatment (efanesoctocog alfa prophylaxis vs historical prophylaxis) as covariate; ‡P-value relates to the null hypothesis: rate ratio (efanesoctocog alfa prophylaxis/historical prophylaxis) = 1.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; SD, standard deviation.

B.2.6.1.5.5 Maintenance of FVIII activity levels and pharmacokinetic variables

Factor VIII activity was well maintained over time, with levels remaining comparable at Day 7 measurements during Week 1 and Week 26 (Figure 7). The geometric mean half-life of efanesoctocog alfa was 47.0 hours (95% CI: 42.3, 52.2), the steady state clearance 0.439 mL per hour/kg (95% CI: 0.390, 0.493), the maximum FVIII activity 151 IU/dL (95% CI: 137, 167), and the area under the activity–time curve from hour 0 to infinity 11,500 hours × IU/dL (95% CI: 10,200, 13,000). There was minimal accumulation of once-weekly efanesoctocog alfa.

Figure 7: Factor VIII activity over time and pharmacokinetic variables, PKAS



Pharmacokinetic Variables	Sequential-Pharmacokinetic Subgroup (N=17)
	geometric mean (95% CI)
Half-life — hr	47.0 (42.3–52.2)
Maximum activity concentration — IU/dl	151 (137–167)
AUC_{0-tau} — hr×IU/dl	11,500 (10,200–13,000)
Clearance at steady state — ml/hr/kg	0.439 (0.390–0.493)
Incremental recovery — IU/dl per IU/kg	3.00 (2.71–3.31)

Source: Figure 2, von Drygalski et al, 2023 (34).
Note: The upper part of the figure shows plasma factor VIII activity levels measured by means of the activated partial-thromboplastin time–based one-stage clotting assay among 17 patients who underwent sequential blood sampling for pharmacokinetic assessment (sequential-pharmacokinetic subgroup). Error bars indicate the standard deviation of each value. The lower part of the figure shows calculated pharmacokinetic variables for baseline-corrected factor VIII activity at approximately Week 26 (including pharmacokinetic assessments starting at Days 183, 218, and 246). Values are for the full 14-day sampling period. AUC_0–tau denotes area under the activity–time curve over the administration interval.
Abbreviations: AUC, area under curve; CI, confidence interval; PKAS, pharmacokinetics analysis set.

In patients with evaluable FVIII activity levels 7 days after dosing, maintained FVIII activity levels of >5%, >10%, >15%, and >20% were observed in [redacted], respectively, with efanesoctocog alfa prophylaxis in Arm A (Table 20).

Table 20: Summary of percentage of patients who achieve trough FVIII activity levels >1%, >5%, >10%, >15%, and >20% 7 days after dosing, PKAS

	Arm A N=133 Pre-dose (trough)
Number of patients with ≥1 non-missing post-baseline result	[redacted]
Number of patients with all trough samples that are within 168±5 hours from the previous dose	[redacted]
Achieving trough FVIII activity levels[†]:	
>1%	[redacted]
>5%	[redacted]
>10%	[redacted]
>15%	[redacted]
>20%	[redacted]

Source: Table 19, clinical study report (87)

[†]Achieving trough FVIII activity levels above x% are based on the average trough samples (i.e. nominal 168-hour time point) from each scheduled visit (Week 4, Week 13, Week 26, Week 39, Week 52/EOS/ET) using the aPTT-based one-stage clotting assay. Patients with trough samples that are outside 168±5 hours from the previous dose will be excluded from this analysis.

Abbreviations: aPTT, activated partial thromboplastin time; EOS, end of study; ET, early termination; FVIII, clotting factor VIII; PKAS, pharmacokinetics analysis set.

B.2.6.1.5.6 Prophylactic dose and dosing interval

The mean (SD) average dosing interval (i.e. interval averaged over all dosing intervals administered during the efficacy period) was 7.01 (0.26) days for the patients who received efanesoctocog alfa prophylaxis. The mean dosing interval was similar between Arm A and the prophylaxis part of Arm B.

The mean (SD) average weekly dose of efanesoctocog alfa was 51.28 (2.13) IU/Kg for the patients who received prophylaxis. The mean dose was also similar between Arm A and the prophylaxis part of Arm B (Table 21).

Table 21: Summary of prophylactic dose and prophylactic dosing interval, FAS

	Arm A	Arm B	
	Prophylaxis (N=133)	On-Demand (N=26)	Overall (N=159)
Number of patients with an efficacy period	[redacted]	[redacted]	[redacted]
Average weekly dose (IU/kg)†			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
Average dosing interval (days)[‡]			
Number	[redacted]	[redacted]	[redacted]

	Arm A	Arm B	
	Prophylaxis (N=133)	On-Demand (N=26)	Overall (N=159)
Mean (SD)	7.01 (0.28)	7.01 (0.09)	7.01 (0.26)
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	6.96; 7.01	6.98; 7.00	6.97; 7.01
Min; Max	6.0; 9.4	6.9; 7.3	6.0; 9.4

Source: Table 10, clinical study report (87)

†The average weekly dose is the total IU/kg of all prophylactic doses extrapolated to a weekly amount; ‡Average dosing interval is the sum of days in all eligible dosing intervals divided by the number of eligible intervals. Eligible intervals are prophylactic dosing intervals that are not separated by a bleeding episode or surgical/rehabilitation period.

Abbreviations: FAS, full analysis set; SD, standard deviation.

B.2.6.1.5.7 Number of injections and dose to treat bleeding episodes

In total, across the two treatment arms, 362 bleeds were treated with efanesoctocog alfa. Analysis per bleeding episode showed that overall, all but one of the bleeding episodes (99.7%) were controlled with less than two injections of efanesoctocog alfa, with 96.7% controlled by only one injection (Table 22). No bleeding episode required more than three injections.

The mean (SD) number of injections (i.e. including initial and follow-up injections) required for resolution of a bleeding episode was 1.0 (0.2). Per bleeding episode, the mean (SD) total dose was [redacted] IU/kg (Table 23). Results were generally similar between Arm A and Arm B on-demand with regard to the number of injections and the mean dose to treat a bleeding episode.

Table 22: Number of injections required for resolution of a bleeding episode, FAS

	Arm A N=133	Arm B		Overall N=159
		On-demand N=26	Prophylaxis N=26	
Per bleeding episode				
Number†	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	1.0 (0.2)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Number of injections				
1	[redacted]	[redacted]	[redacted]	350 (96.7)
2	[redacted]	[redacted]	[redacted]	11 (3.0)
3	[redacted]	[redacted]	[redacted]	0
4	[redacted]	[redacted]	[redacted]	[redacted]
Per patient‡				
Number¶	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B		Overall N=159
		On-demand N=26	Prophylaxis N=26	
Number of injections				
1–2	[redacted]	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 20, clinical study report (87).
†Number = total number of treated bleeding episodes. Percentages are based on this number; ‡The number of injections required to resolve each bleeding episode is averaged across all bleeding episodes per patient; ¶Number = number of patients with ≥1 treated bleeding episode. Percentages are based on this number.
Abbreviations: FAS, full analysis set; SD, standard deviation.

Table 23: Summary of dose (IU/kg) of efanesoctocog alfa required for resolution of a bleeding episode, FAS

	Arm A	Arm B		Overall (N=159)
	Prophylaxis (N=133)	On-Demand (N=26)	Prophylaxis (N=26)	
Number of patients with an efficacy period	[redacted]	[redacted]	[redacted]	[redacted]
Per bleeding episode				
Average dose per injection (IU/kg)				
Number†	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Total dose (IU/kg)				
Number†	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Per participant per bleeding episode				
Average dose per injection (IU/kg)‡				
Number¶	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min ; Max	[redacted]	[redacted]	[redacted]	[redacted]
Total dose (IU/kg)§				
Number¶	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A	Arm B		Overall (N=159)
	Prophylaxis (N=133)	On-Demand (N=26)	Prophylaxis (N=26)	
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 16.2.6.4.11, data on file_ CSR_01-EFC16293_16_2_6_efficacy_data (95).
[†]Number = total number of treated bleeding episodes; [‡]The average dose per injection (IU/kg) used to resolve each bleeding episode is averaged across all bleeding episodes per patient; [¶]Number = number of patients with ≥1 treated bleeding episode; [§]The total dose (IU/kg) used to resolve each bleeding episode is averaged across all bleeding episodes per patient.
Abbreviations: FAS, full analysis set; SD, standard deviation.

B.2.6.1.5.8 Response to treatment of bleeding episodes

Patient's assessment of response

Patients assessed the response to each injection of efanesoctocog alfa for treating a bleed using a 4-point scale of excellent, good, moderate, and none, based on International Society on Thrombosis and Haemostasis (ISTH) standardised definitions in haemophilia (43).

Overall, across the two treatment arms, [redacted] injections were administered to treat [redacted] bleeding episodes. Of these injections, [redacted] were evaluated for response, with the majority (n=[redacted]; [redacted] %) rated as producing an excellent or good response (Table 24). For [redacted] patients who reported no response to therapy, [redacted] required no follow-up injections and one required one follow-up injection. Among the [redacted] patients who reported a moderate response, [redacted] in Arm A had a follow-up injection within 72 hours of the first injection. Analysis based on first injections for treating a bleeding episode showed similar results. Results were generally similar between Arm A and Arm B.

Table 24: Patient's assessment of response to efanesoctocog alfa treatment of bleeding episodes, FAS

	Arm A N=133	Arm B		Overall N=159
		On-demand N=26	Prophylaxis N=26	
Each injection				
Based on injections with an evaluation				
Number[†]	[redacted]	[redacted]	[redacted]	[redacted]
Excellent or Good	[redacted]	[redacted]	[redacted]	[redacted]
Excellent	[redacted]	[redacted]	[redacted]	[redacted]
Good	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]
Based on all injections				
Number[‡]	[redacted]	[redacted]	[redacted]	[redacted]
Excellent or Good	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B		Overall N=159
		On-demand N=26	Prophylaxis N=26	
Excellent	[redacted]	[redacted]	[redacted]	[redacted]
Good	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]
Response not provided	[redacted]	[redacted]	[redacted]	[redacted]
First injection for each bleeding episode				
Based on injections with an evaluation				
Number†	[redacted]	[redacted]	[redacted]	[redacted]
Excellent or Good	[redacted]	[redacted]	[redacted]	[redacted]
Excellent	[redacted]	[redacted]	[redacted]	[redacted]
Good	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]
Based on all injections				
Number‡	[redacted]	[redacted]	[redacted]	[redacted]
Excellent or Good	[redacted]	[redacted]	[redacted]	[redacted]
Excellent	[redacted]	[redacted]	[redacted]	[redacted]
Good	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]
Response not provided	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 21, clinical study report (87)
Note: 'None' means that there was no improvement.
†Number = number of injections (or bleeding episodes as appropriate) with a response. Percentages are based on the number during the efficacy period; ‡Number = number of injections (or bleeding episodes as appropriate) reported. Percentages are based on this number during the efficacy period.
Abbreviations: FAS, full analysis set; SD, standard deviation.

Physician's assessment of response

At each visit, physicians provided an assessment of the patient's response to efanesoctocog alfa using a 4-point scale of excellent, effective, partially effective, or ineffective. In Arm A, the physician's global assessment of patient response to efanesoctocog alfa treatment was excellent for [redacted]% (n=[redacted]) of all visits and effective for [redacted]% (n=[redacted]) of the visits. [redacted]patients had a response to efanesoctocog alfa treatment assessed as partially effective or ineffective by the physician at any visit (Table 25).

The assessments were generally consistent over the course of the study: [redacted]% (n=[redacted]) to [redacted]% (n=[redacted]) of patients had a global response to treatment assessed by the physician as excellent during the study. In Arm B, the physician's global assessment of patient response to on-demand treatment was excellent for [redacted]% and effective for [redacted]%

for all visits and the response to prophylaxis treatment was excellent for [redacted]% and effective for [redacted]% for all visits.

Table 25: Summary of physician's global assessment of the participant's response to the efanesoctocog alfa

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Week 4			
Number[+]	[redacted]	[redacted]	–
Excellent	[redacted]	[redacted]	–
Effective	[redacted]	[redacted]	–
Partially effective	[redacted]	[redacted]	–
Ineffective	[redacted]	[redacted]	–
Week 13			
Number[+]	[redacted]	[redacted]	–
Excellent	[redacted]	[redacted]	–
Effective	[redacted]	[redacted]	–
Partially effective	[redacted]	[redacted]	–
Ineffective	[redacted]	[redacted]	–
Week 26			
Number[+]	[redacted]	[redacted]	–
Excellent	[redacted]	[redacted]	–
Effective	[redacted]	[redacted]	–
Partially effective	[redacted]	[redacted]	–
Ineffective	[redacted]	[redacted]	–
Week 39			
Number[+]	[redacted]	–	[redacted]
Excellent	[redacted]	–	[redacted]
Effective	[redacted]	–	[redacted]
Partially effective	[redacted]	–	[redacted]
Ineffective	[redacted]	–	[redacted]
Week 52/EOS/ET			
Number[+]	[redacted]	–	[redacted]
Excellent	[redacted]	–	[redacted]
Effective	[redacted]	–	[redacted]
Partially effective	[redacted]	–	[redacted]
Ineffective	[redacted]	–	[redacted]
Total responses			
Number[+]	[redacted]	[redacted]	[redacted]
Excellent	[redacted]	[redacted]	[redacted]
Effective	[redacted]	[redacted]	[redacted]

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Partially effective	[redacted]	[redacted]	[redacted]
Ineffective	[redacted]	[redacted]	[redacted]

Source: Table 16.2.6.4.13, data on file_ CSR_01-EFC16293_16_2_6_efficacy_data (95).
Note: Assessments during major surgical/rehabilitation periods are excluded.
[†]Percentages are based on the number of patients with non-missing observations at the respective visit.
Abbreviations: EOS, end of study; ET, early termination;.

B.2.6.1.5.9 Intra-patient comparison of AJBR in Arm B

In Arm B, the AJBR for treated episodes was analysed in the FAS using negative-binomial regression. The joint bleeding rate ratio for prophylaxis versus on-demand treatment was [redacted] (95% CI: [redacted]), corresponding to a clinically important reduction of [redacted] (95% CI: [redacted]) in AJBR with prophylaxis treatment (Table 26). The distribution of the AJBR indicated that in general, AJBR was higher with on-demand treatment than with prophylaxis treatment. [redacted] patients ([redacted]%) had an AJBR >20 with on-demand treatment, while [redacted] patients had an AJBR greater than 5 with prophylaxis treatment.

Table 26: Intra-patient comparison of AJBR in Arm B, FAS

	Arm B	
	On-demand (N=26)	Prophylaxis (N=26)
Number of patients with an efficacy period	[redacted]	[redacted]
Total number of treated joint bleeding episodes	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]
Duration of efficacy period (weeks)		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
AJBR		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
0	[redacted]	[redacted]
>0-5	[redacted]	[redacted]
>5-10	[redacted]	[redacted]
>10-20	[redacted]	[redacted]
>20	[redacted]	[redacted]

	Arm B	
	On-demand (N=26)	Prophylaxis (N=26)
Negative Binomial regression model†		
Mean AJBR (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)		[redacted]
p-value (superiority)‡		[redacted]

Source: Table 16.2.6.4.14, data on file_ CSR_01-EFC16293_16_2_6_efficacy_data (95).
Note: summaries are based on treated joint bleeds.
†Estimated using a repeated negative binomial model with treatment (prophylaxis vs on-demand) as covariate; ‡p-value relates to paired rate ratio (prophylaxis/on-demand) ≥0.5.
Abbreviations: AJBR, annualised joint bleeding rate; FAS, full analysis set; SD, standard deviation.

B.2.6.1.5.10 Target joint resolution

A target joint was defined as a major joint into which ≥3 spontaneous bleeding episodes occurred in a consecutive 6-month period. Resolution was achieved when ≤2 bleeds occurred into that joint during 12 months of continuous exposure (43). At baseline, 26 patients in Arm A reported a total of [redacted] target joints. Of these, 14 patients had ≥12 months of exposure to efanesoctocog alfa prophylaxis, having a total of 45 target joints at baseline. Analysis based on spontaneous bleeds showed that all 45 target joints for all 14 patients with ≥12 months of exposure to prophylaxis had resolved at Week 52 (Table 27).

Table 27: Target joint resolution based on spontaneous bleeds, FAS

	Arm A N=133
Patients with target joints at baseline†	26
Patients with ≥12 months continuous exposure	14
Patients with ≥1 target joints resolved	14 (100.0)
Total number of target joints at baseline†	[redacted]
Total number of target joints from patients with ≥12 months continuous exposure	45
Total number target joints resolved‡	45 (100.0)
Number of spontaneous bleeds in target joints resolved*	
0	[redacted]
1	[redacted]
2	[redacted]

Source: Table 22, clinical study report (87).
†A target joint at baseline is defined as a major joint with ≥3 spontaneous bleeding episodes in a consecutive 6-month period prior to entry to the study, captured at baseline; ‡A target joint resolved is defined as ≤2 spontaneous bleeds into that joint during 12 months of continuous exposure. Percentage is calculated out of patients with at least 12 months continuous exposure; *Percentage is calculated out of total number of joints from patients with at least 12 months continuous exposure.
Abbreviations: FAS, full analysis set.

B.2.6.1.5.11 Haemophilia Joint Health Score

Six joints (left ankle, right ankle, left elbow, right elbow, left knee, right knee) were scored according to the following criteria: swelling, duration of swelling, muscle atrophy,

crepitus, flexion loss, extension loss, instability, joint pain, and strength. Gait was scored based on walking and climbing stairs. The total score was the sum of scores from all six joints plus the gait score (range 0–124, highest score being the most severe disease). In Arm A, the change from baseline in HJHS was analysed as part of the hierarchical testing procedure using mixed-effect model with repeated measures (MMRM).

In Arm A, patients who were on a stable pre-study prophylaxis treatment presented with a baseline mean (SD) HJHS total score of 18.1 (18.4). The estimated mean change in HJHS Total score from baseline to Week 52 was –1.54 (95% CI: –2.70, –0.37; p=0.0101) demonstrating a statistically significant improvement in functional measure of joint health. In Arm B, the mean (SD) HJHS Total score at baseline was 26.3 (13.2). The mean (SD) change from baseline to Week 52 in HJHS total score was [redacted], indicating an improvement in joint health (Table 28).

Table 28: Mean change in HJHS total score from baseline to Week 52, MMRM, FAS

	Arm A		Arm B	
	Prophylaxis (N=133)		On-demand->Prophylaxis (N=26)	
	Actual result	CFB	Actual result	CFB
Total Score				
Baseline				
Number	116	–	25	–
Mean (SD)	18.1 (18.4)	–	26.3 (13.2)	–
Median	[redacted]	–	[redacted]	–
Week 26				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)[†]		–1.54 (0.59)		
95% CI[†]	–	(–2.70, –0.37)	–	–
p-value	–	0.0101	–	–

Source: Table 23, clinical study report (87).
Note: higher HJHS scores denote poorer joint health.
[†]The LS mean (SE) and 95% CI were estimated by mixed-effect model with repeated measures, with visit as fixed effect, and baseline HJHS total score as a covariate.
Abbreviations: CFB, change from baseline; CI, confidence interval; FAS, full analysis set; HJHS, haemophilia joint health score; LS, least squares; MMRM, mixed-effect model of repeated measures; SD, standard deviation; SE, standard error.

B.2.6.1.5.12 Haem-A-QoL Physical Health score

Quality of life data were collected in adult patients aged 17 years or older via the Haem-A-QoL questionnaire (Table 29) and in adolescent patients aged 12 to 16 years via the

Haemo-QoL questionnaires (Appendix M). Lower scores represent better HRQoL; therefore, a negative change from baseline represents improvement during the course of the study.

In Arm A, for patients aged 17 years and older, the mean (SD) Physical Health score was 37.02 (23.83) at baseline. The least squares mean change from baseline to Week 52 in Haem-A-QoL Physical Health score (n=98) was –6.74 (95% CI: –10.13, –3.36; p=0.0001) demonstrating a statistically significant improvement in physical health, as perceived by patients aged 17 years or above. Patients in Arm B also experienced improvement, with a mean change from baseline of [redacted]

Table 29: Mean change in Haem-A-QoL physical health subscale scores from baseline to Week 52 in patients ≥17 years old, MMRM, FAS

Domain	Arm A		Arm B			
	Prophylaxis (N=110)		On-demand->Prophylaxis (N=26)		Overall (N=136)	
Visit	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Baseline						
Number	104	–	[redacted]	–	[redacted]	–
Mean (SD)	37.02 (23.83)	–	[redacted]	–	[redacted]	–
Median	[redacted]	–	[redacted]	–	[redacted]	–
Week 26						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52						
Number	104	98	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	29.66 (23.40)	–6.79 (18.59)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)[†]		–6.74 (1.71)				
95% CI[†]	–	(–10.13, –3.36)	–	–	–	–
p-value	–	0.0001	–	–	–	–

Source: Table 16.2.6.3.1, data on file_CSR_01-EFC16293-16.2.6_efficacy data (95)
Note: The physical health scores are presented as the Transformed Scale Score ranging from 0–100, with lower scores indicating a better quality of life. A score can be calculated when at least 50% of questions are answered (non-missing and not N/A); Assessments during major surgical/rehabilitation periods are excluded.
[†]The LS mean (SE) and 95% CI are estimated by MMRM, with visit as fixed effect, and baseline Haem-A-QoL physical health score as a covariate.
Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model of repeated measures; SD, standard deviation; SE, standard error.

B.2.6.1.5.13 Haemo-QoL Physical Health score

Table 30: Summary of Haemo-QoL total score and subscale scores and changes from baseline by visit (13–16 years old), FAS

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Total Score		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Physical Health		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Feeling		
Baseline		

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
View of Yourself		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Family		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–

Domain	Arm A Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Friends		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1 ; Q3	[redacted]	[redacted]
Min ; Max	[redacted]	[redacted]
Support You Felt You Were Receiving		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

Domain	Arm A Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Other People		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Sports and School		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Dealing with Haemophilia		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Treatment		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Future		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Romantic Relationships		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

Source: Table 16.2.6.3.4, Data on file_CSR_01-EFC16293-16.2.4_demo_data (94).
Note: the total and subscale scores are presented as the Transformed Scale Score ranging from 0–100, with lower scores indicating a better quality of life. A score can be calculated when at least 50% of questions are answered (non-missing and not N/A); Assessments during major surgical/rehabilitation periods are excluded; There are no participants from Arm B whose age meets the requirement for the Haemo-QoL, thus Arm B and overall columns are not presented.
Abbreviations: SD, standard deviation.

B.2.6.1.5.14 PROMIS pain intensity and physical function

Patient-Reported Outcomes Measurement Information System (PROMIS) data were collected for all participants for pain intensity, and separately in patients aged 18 years or above and those younger than 18 years for pain interference and physical health. For each PROMIS instrument, the total raw score was converted into a T-score for each

patient. The T-score rescales the raw score into a standardised score with a mean of 50 and a SD of 10. For negatively worded concepts like Pain Intensity 3a and Pain Interference, a T-score of 60 is one SD worse than average. For positively worded concepts like Physical Function and Physical Activity, a T-score of 60 is one SD better than average.

Pain intensity

In Arm A, the change from baseline to Week 52 in PROMIS Pain Intensity 3a past 7 days intensity of pain at its worst score (PAINQU6, referred to as PROMIS Pain Intensity first item) was analysed as part of the hierarchical testing procedure using an MMRM model.

In Arm A, patients aged 12 years or older had an estimated mean change from baseline to Week 52 in PROMIS Pain Intensity first item score of –0.21 (95% CI:–0.41, –0.02; p=0.0276). This improvement was also clinically meaningful, since it was within the range of the meaningful within-group change (–0.5 to –0.2) determined using a post-hoc psychometric analyses of these data from XTEND-1 (97).

In Arm B, the mean (SD) change from baseline to Week 52 in PROMIS Pain Intensity first item score was [redacted] (Table 31).

Table 31: Mean change in PROMIS Pain Intensity (PAINQU6), FAS

Visit	Arm A		Arm B			
	Prophylaxis (N=133)		On-demand->Prophylaxis (N=26)		Overall (N=159)	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Baseline						
Number	125	–	[redacted]	–	[redacted]	–
Mean (SD)	2.47 (1.15)	–	[redacted]	–	[redacted]	–
Median	[redacted]	–	[redacted]	–	[redacted]	–
Week 26						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52						
Number	127	119	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	2.21 (1.21)	–0.21 (1.20)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)[†]		–0.21 (0.10)				
95% CI[†]		(–0.41, –0.02)				
p-value		0.0276				

Source: Source: Table 16.2.6.3.6, data on file_ CSR_01-EFC16293-16.2.6_efficacy data (95)
Note: The past 7 days intensity of pain at its worst score (PAINQU6) is the first item from PROMIS Pain Intensity 3a. The analysis is based on the raw score, ranging from 1 to 5. Lower score means a better outcome; Assessments during major surgical/rehabilitation periods are excluded.
[†]The LS mean (SE) and 95% C.I. are estimated by MMRM with visit as fixed effect, and baseline PROMIS Pain Intensity 3a first item (i.e. past 7 days intensity of pain at its worst score) as covariate.
Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed-effect model with repeated measures; PAINQU6, PROMIS Pain Intensity 3a past 7 days intensity of pain at its worst score; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; SE, standard error.

Physical Function

The PROMIS-SF Physical Function score reflects the ability to perform activities of daily living. In Arm A, of 108 patients aged 18 years or older, 103 completed the PROMIS-SF Physical Function questionnaire at baseline and 102 at Week 52. The mean Physical Health score was [redacted] at baseline, which increased slightly at Week 52 ([redacted]), suggesting a trend for an improvement in Physical Function 6b T-score (mean [SD] change from baseline to Week 52 of [redacted] (Table 32).

Table 32: Summary of PROMIS-SF Physical Function 6b T-score

Visit	Arm A		Arm B			
	Prophylaxis (N=108)		On-demand->Prophylaxis (N=26)		Overall (N=134)	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Baseline						
Number	[redacted]	–	[redacted]	–	[redacted]	–
Mean (SD)	[redacted]	–	[redacted]	–	[redacted]	–
Median	[redacted]	–	[redacted]	–	[redacted]	–
Week 26						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 16.2.6.3.12, data on file_ CSR_01-EFC16293-16.2.6_efficacy data (95)
Note: The T-score rescales the raw scale score (sum of scores from all questions answered) into a standardized score with a mean of 50 and standard deviation of 10, based on scoring tables provided in PROMIS Scoring Manuals. Higher score means a better outcome; Assessments during major surgical/rehabilitation periods are excluded.
Abbreviations: Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

B.2.6.1.6 Exploratory secondary endpoints

All exploratory secondary endpoints are presented in Appendix N.

B.2.7 Subgroup analyses

B.2.7.1 Subgroup analyses of ABR

Subgroup analyses of the mean ABR were performed on the FAS. The treatment effects were consistent across subgroups defined by age categories, bleeding phenotype at baseline, number of target joints at screening or dosing and dosing interval compliance, confirming the primary endpoints (Figure 8).

Figure 8: Forest plot of ABR and 95% CI by subgroup, FAS

Source: Figure 3, clinical study report (87).
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; NC, not calculable.

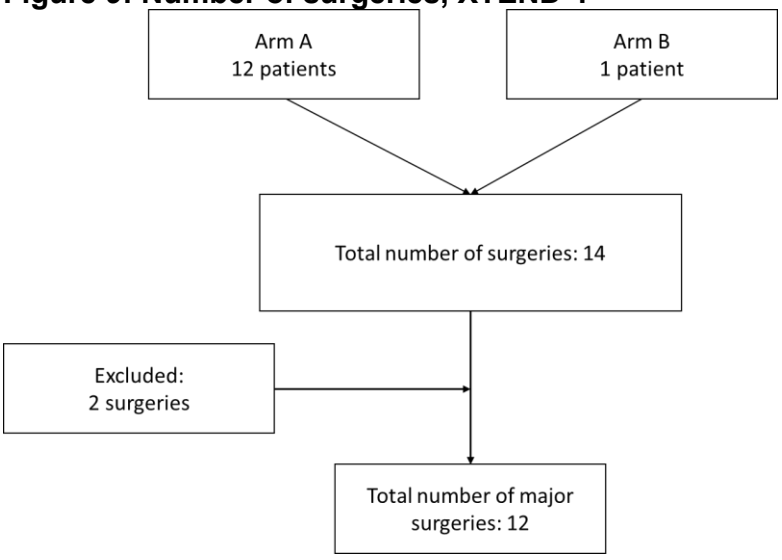
B.2.7.2 Surgery subgroup analyses

Patients who underwent major surgery during the study were included in the surgery subgroup to assess the efficacy of efanesoctocog alfa in the control and prevention of bleeding in the surgical setting.

A total of 14 major surgeries were performed in 13 patients. Of the 13 patients, one was in Arm B; all other patients were assigned to Arm A.

[redacted] In two of the 13 patients, both in Arm A, major surgeries (osteosynthesis of right tibia and coronary artery bypass) took place after the last efanesoctocog alfa dosing and thus, two surgeries were not considered in the assessments of major surgeries (Figure 9).

Figure 9: Number of surgeries, XTEND-1



The investigators'/surgeons' assessment of the participant's haemostatic response to efanesoctocog alfa treatment was collected 24 hours post-surgery based on the ISTH 4-point response scale of excellent, good, fair, and poor. A lower average score indicates a better investigators'/surgeons' assessment of response to surgery with efanesoctocog alfa treatment. Investigators'/surgeons' assessment of the participant's haemostatic response was available in all 12 major surgeries that occurred while the patient was receiving efanesoctocog alfa.

Haemostatic response was rated as excellent by the investigators/surgeons for all 12 major surgeries (Table 33), indicating that intraoperative and postoperative blood loss was deemed comparable with what would be expected for a patient without haemophilia.

Table 33: Summary of investigators'/surgeons' assessment of patient's haemostatic response to efanesoctocog alfa treatment, surgery subgroup

	Surgery subgroup (N=13)
Number of major surgeries	12
Assessment of response, n (%)	
Excellent or Good	12 (100)
Excellent (=1)	12 (100)
Good (=2)	0
Fair (=3)	0
Poor/none (=4)	0
Number	12
Mean (SD)	1.0 (0.0)
Median	1.0

Source: Table 26, clinical study report (87)
Note: Percentages are based on the number of major surgeries with assessments; The analysis is based on the major surgeries conducted during the treatment regimen, excluding the surgeries conducted after the last efanesoctocog alfa dose. Those excluded major surgeries are counted in the capital N in the header.
Abbreviations: SD, standard deviation.

B.2.8 Meta-analysis

Not applicable.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 ITC methodology

In the absence of head-to-head trials comparing efanesoctocog alfa with each comparator, an indirect treatment comparison (ITC) was conducted to compare the efficacy of prophylactic treatment with comparators (98). For the interest of this submission, the comparisons of efanesoctocog alfa with emicizumab or efmoroctocog alfa are presented here, as both therapies are considered comparators of interest. The analysis primarily focussed on previously treated patients, consistent with the inclusion criteria of XTEND-1.

An SLR (Section B.2.1) was conducted to identify relevant Phase 3 clinical trials in patients with haemophilia A. Two Phase 3 trials were utilised as the evidence base for the ITC; HAVEN 3 to compare with emicizumab (99, 100), and A-LONG, to compare with efmoroctocog alfa (91, 101). However, the inclusion criteria differed between arms of XTEND-1 and HAVEN 3; in XTEND-1, only those receiving episodic treatment could be allocated to on-demand arms, while in HAVEN 3, prophylaxis was assessed in patients receiving either prophylaxis or on-demand treatments before entry. Moreover, the

treatments administered as episodic regimens differed across studies, therefore on-demand arms could not be considered as common comparators for anchored between-treatment comparisons. Thus, XTEND-1 did not form a connected network with the emicizumab trial, therefore the anchored comparison using either Bucher's indirect comparison or network meta-analysis were not feasible for the comparison between efanesoctocog alfa and comparators. The effects of efanesoctocog alfa versus emicizumab were assessed in disconnected studies and were compared using unanchored matching-adjusted indirect comparison (MAIC), while the comparison of efanesoctocog alfa versus efmoroctocog alfa used propensity score matching (PSM) methods, as proposed in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 guidelines (102).

B.2.9.1.1 Comparison with emicizumab

The NICE DSU TSD 18 guidelines specify the scope of variables that shall be used for matching in the unanchored indirect treatment comparison using MAIC and simulated treatment comparison (STC) methods. Relying on the conditional constancy of absolute effects assumption, the differences between absolute outcomes that would be observed in each trial are entirely explained by imbalances in prognostic variables and effect modifiers, thus both shall be included as covariates in the model (102). Therefore, in all analyses using the MAIC method XTEND-1 patient-level data was adjusted for every baseline characteristic provided that adequate data is reported in the comparator studies.

Following the matching of baseline characteristics, the effects of efanesoctocog alfa were re-estimated using the weights obtained during the matching procedure, so that the new estimates could be interpreted as the effects of efanesoctocog alfa when administered in the population of the comparator trial. For consistency, the new effects were estimated using the same statistical methods as adopted the comparator trial.

The rates for comparators estimated using negative binomial model are directly reported from the model as the log of the rates. The between-treatment comparison expressed on the log scale and exponentiated results in the estimate of incidence rate ratio (IRR). On the other hand, the absolute difference in rates calculated from two mean (SD) values results in the comparison following normally distributed mean difference (MD) in the incidence rate.

All ABRs in HAVEN 3 were calculated using a negative binomial model with stratification for the history of previous bleeds (<9 or ≥9 bleeding events in the previous 24 weeks). ABRs for XTEND-1 were estimated using the same regression model, but without stratification factor due to lack of data regarding history of bleeds within 24 weeks prior to enrolment.

B.2.9.1.2 Comparison with efmoroctocog alfa

The comparison between efanesoctocog alfa and efmoroctocog alfa was made using PSM methods, as individual patient data (IPD) was available from both XTEND-1 and A-LONG trials. The PSM method allowed for estimation of both IRR and MD for incidence rate comparison between efanesoctocog alfa and efmoroctocog alfa, due to availability of IPD from both studies.

The following information was traced during the PSM and reported:

- The comparison of baseline characteristics between XTEND-1 and A-LONG trial
- Effective sample size
- Bar charts for distribution of weights
- Estimates of efficacy before and after adjustment as well as the results of population-adjusted indirect comparison.

Optimal full matching was performed using the MatchIt package (Ho et al, 2011) (103) in R Studio, which called functions from the optmatch package (Hansen & Klopfer, 2006) (104, 105).

B.2.9.2 Feasibility of the NMA

B.2.9.2.1 Comparisons with emicizumab

Appendix D presents an overview of the outcomes assessed across XTEND-1 and HAVEN 3. The comparison between efanesoctocog alfa and the emicizumab trial was feasible, due to reporting from XTEND-1 trial for patients with prior prophylaxis (Arm A) and for patients with prior on-demand regimen (Arm B), and the effects of efanesoctocog alfa could be estimated using the same statistical methods as adopted the comparator trial due to availability of individual patient data from XTEND-1 trial. The following comparisons were made:

- Arm D of HAVEN 3, emicizumab QW (prior prophylaxis) vs Arm A of XTEND-1 (prior prophylaxis)
- Arm A of HAVEN 3, emicizumab QW (prior O-D) vs Arm B of XTEND-1 (prior O-D)
- Arm B of HAVEN 3, emicizumab Q2W (prior O-D) vs Arm B of XTEND-1 (prior O-D)

- Pooled Arms A, B and D of HAVEN 3, emicizumab QW and Q2W vs pooled Arms A and B of XTEND-1.

In comparisons of individual arms, ABRs for any bleed (treated and untreated), treated bleeds, spontaneous treated bleeds and joint treated bleeds were assessed. In the comparison of pooled arms, change from baseline in HJHS joint score and total score were assessed.

B.2.9.2.2 Comparisons with efmoroctocog alfa

Appendix D presents an overview of the outcomes assessed between XTEND-1 and A-LONG. The comparison between efanesoctocog alfa and the efmoroctocog alfa was feasible, due to the availability of IPD from both Phase 3 studies.

B.2.9.3 NMA results

B.2.9.3.1 Baseline characteristics

Prior to estimating weights, the population of XTEND-1 was trimmed to remove patients with baseline characteristics outside of the reported range for HAVEN 3. For comparisons with individual arms, this was based on age and body weight. For the comparison with the pooled arms, this was based on age and body mass index (BMI).

The baseline characteristics of patients in HAVEN 3 compared with XTEND-1 are presented in Table 34.

Table 34: Baseline characteristics

	HAVEN 3 Range of baseline variables			XTEND-1 IPD				
Arm	**Age (years)**	**Body weight (kg)**	**BMI (kg/m^2)**	**Arm (N)**	**Age (years)**	**Body weight (kg)**	**BMI (kg/m^2)**	**Patients remaining after restrictions (N)**
Arm D (prior PHX)	13–68	52.8–139	N/A	**Arm A** (n=133)	12–72	33.9–132.8	N/A	119
Arm A (prior O-D)	19–77	53.1–107.3	N/A	**Arm B** (n=26)	23.5–68.5	50–119.5	N/A	22
Arm B (prior PHX)	20–65	56.3–121.4	N/A	**Arm B** (n=26)	23.5–68.5	50–119.5	N/A	24
Arms A, B & D with evaluable HJHS	13–77	N/A	19.2–40.6	**Pooled arms** (131, HJHS assessed)	12–68.5	N/A	15.0–40.8	114

Abbreviations: BMI, body mass index; HJHS, Haemophilia Joint Health Score; IPD, individual patient data; N/A, not applicable; O-D, on-demand; PHX, prophylaxis.

B.2.9.3.1.1 Emicizumab QW (prior prophylaxis)

The comparison between interventions was adjusted for the following baseline variables:

- Age (mean and standard deviation),
- Body weight (mean and standard deviation),
- Presence of target joints, including:
    - Proportion of patients without target joints
    - Proportion of patients with one target joint, and
    - Proportion of patients with two or more target joints
- Most abundant racial groups, including:
    - Proportion of white patients, and
    - Proportion of Asian patients.

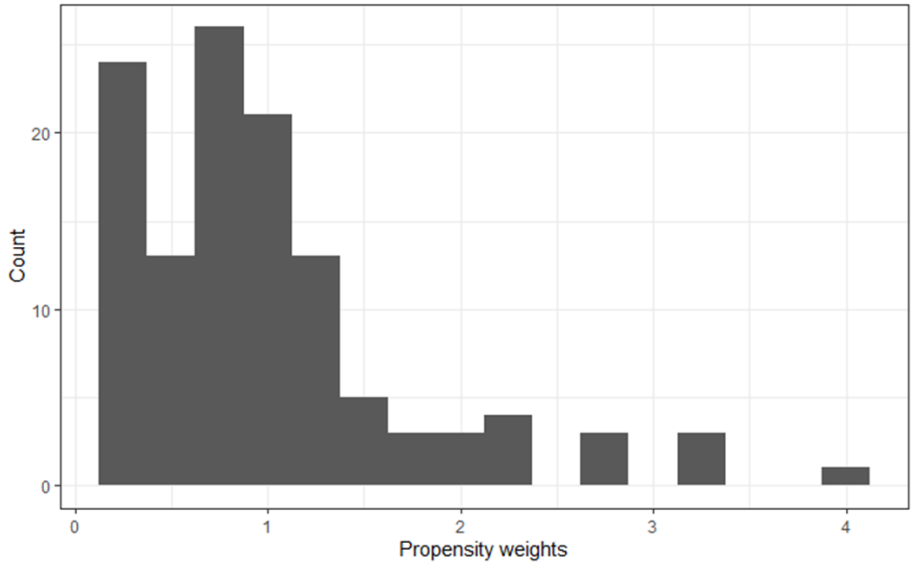
All baseline characteristics of the XTEND-1 arm A were adequately matched to aggregated data from HAVEN III arm D, so that there were no differences between both populations. The estimated effective sample size (ESS) was reduced from 119 to 76 patients following matching, which corresponds to 64% of the initial sample (Table 35).

Table 35: Matching of baseline characteristics between XTEND-1 Arm A and HAVEN 3 Arm D

Variables	XTEND-1 Arm A, baseline			HAVEN 3 Arm D, baseline		XTEND-1 Arm A, after matching			
	Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS %
Mean age	34.91	14.23	119	36.4	14.4	36.4	14.4	76	64%
Mean weight	81.26	16.74		79.0	15.4	79.0	15.4		
% pts with 0 TJ	78.2%	N/A		58.7%	N/A	58.7%	N/A		
% pts with 1 TJ	5.9%			12.7%	N/A	12.7%			
% pts with 2+ TJ	16.0%			28.6%	N/A	28.6%			
% White	54.6%			74.6%	N/A	74.6%			
% Asian	21.0%			19.0%	N/A	19.0%			

Abbreviations: ESS, effective sample size; N/A, not applicable; pts, patients; SD, standard deviation; TJ, target joint.

Figure 10: Histogram of weights from MAIC adjustments comparing with HAVEN 3 Arm D



Abbreviations: MAIC, matching-adjusted indirect comparison.

B.2.9.3.1.2 Emicizumab QW (prior O-D)

The comparison between interventions was adjusted for the following baseline variables:

- Age (mean and standard deviation),
- Body weight (mean and standard deviation) and
- Proportion of patients with one or more target joints.

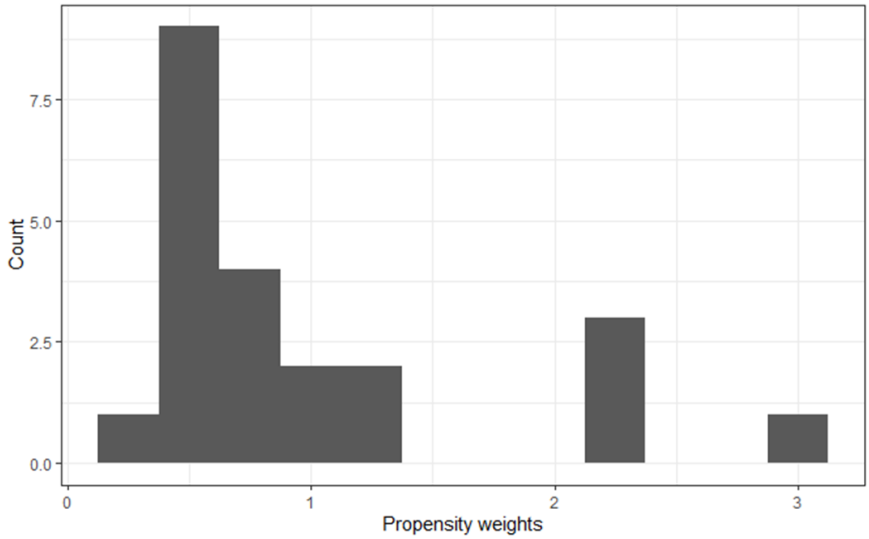
All baseline characteristics of the XTEND-1 Arm B were adequately matched to aggregated data from HAVEN 3 Arm A, so that there were no differences between both populations. The estimated ESS was reduced from 22 patients to 14 patients following matching, which corresponds to 65% of the initial sample (Table 36).

Table 36: Matching of baseline characteristics between XTEND-1 Arm B and HAVEN 3 Arm A

Variables	XTEND-1 Arm B, baseline			HAVEN 3 Arm A, baseline		XTEND-1 Arm B, after matching			
	Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS %
Mean age	42.86	12.42	22	39.8	14.0	39.8	14.0	14	65%
Mean weight	77.46	12.44		80.9	13.6	80.9	13.6		
% patients with 1+ TJ	86.4%	N/A		94.4%	N/A	94.4%	N/A		

Abbreviations: ESS, effective sample size, N/A, not applicable; SD, standard deviation, TJ, target joint.

Figure 11: Histogram of weights from MAIC adjustments comparing to HAVEN 3 Arm A



Abbreviations: MAIC, matching-adjusted indirect comparison.

B.2.9.3.1.3 Emicizumab Q2W (prior on-demand therapy)

The comparison between interventions was adjusted for the following baseline variables:

- Age (mean and standard deviation),
- Body weight (mean and standard deviation) and
- Proportion of patients with one or more target joints.

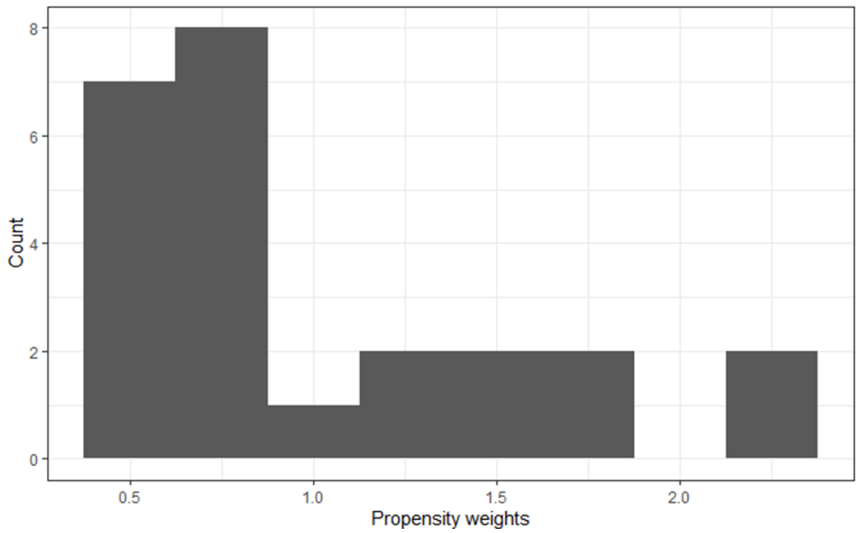
All baseline characteristics of the XTEND-1 arm B were adequately matched to aggregated data from HAVEN 3 arm B, so that there were no differences between both populations. The estimated ESS was reduced from 24 patients to 19 patients following matching, which corresponds to 78% of the initial sample (Table 37).

Table 37: Matching of baseline characteristics between XTEND-1 arm B and HAVEN 3, Arm B

Variables	XTEND-1 Arm B, baseline			HAVEN 3, Arm B, baseline		XTEND-1 Arm B, after matching			
	Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS %
Mean age	42.00	10.87	24	40.4	11.4	40.4	11.4	19	78%
Mean weight	82.45	17.50		81.8	18.9	81.8	18.9		
% patients with 1+ TJ	87.5%	N/A		77.1%	N/A	77.1%	N/A		

Abbreviations: ESS, effective sample size, N/A, not applicable; SD, standard deviation, TJ, target joint.

Figure 12: Histogram of weights from MAIC adjustments comparing to HAVEN 3 Arm B



Abbreviations: MAIC, matching-adjusted indirect comparison.

B.2.9.3.1.4 Emicizumab QW and Q2W

The comparison between interventions was adjusted for the following baseline variables:

- Age (mean and standard deviation)
- BMI (mean and standard deviation)
- Proportion of patients with one or more target joints
- Most abundant racial groups, including:
    - Proportion of white patients, and
    - Proportion of Asian patients
- Proportion of patients treated prophylactically prior to enrolment
- Proportion of human immunodeficiency virus (HIV)-positive patients
- Baseline HJHS scores (mean and standard deviation), including:
    - Total score for change from baseline in HJHS Total score, and
    - Joint score for change from baseline in HJHS Joint score.

All baseline characteristics of Arms A and B from XTEND-1 were adequately matched to aggregated data from HAVEN 3, so that there were no differences between both populations. However, the estimated ESS was reduced from 114 patients to 36 patients following matching, which corresponds to 32% of the initial sample (Table 38).

Table 38: Matching of baseline characteristics between XTEND-1 and HAVEN 3 QW & Q2W

MAIC model	Variables	XTEND-1 pooled arms, baseline			HAVEN 3, baseline (N=107)		XTEND-1 pooled arms, after matching			
		Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS %
Model for HJHS Total Score	Mean age	36.04[†]	14.23[†]	113	35.7	N/A	35.7	14.3	37	32%
	Mean BMI	26.25	4.19		26.0	N/A	26.0	3.8		
	% pts w/ 1+ TJ	32.7%	N/A		66.4%	N/A	66.4%	N/A		
	% White	61.1%	N/A		59.8%	N/A	59.8%			
	% Asian	20.4%	N/A		26.2%	N/A	26.2%			
	Prior prophylaxis	82.3%	N/A		43.9%	N/A	43.9%			
	Baseline HJHS Total Score	21.30	18.38		22.2	19.5	22.2	19.5		
	% HIV	12.4%	N/A		15.9%	N/A	15.9%	N/A		
Model for HJHS Joint Score	Mean age	36.02[†]	14.17[†]	114	35.7	N/A	35.7	12.5	36	32%
	Mean BMI	26.22	4.19		26.0	N/A	26.0	3.8		
	% pts w/ 1+ TJ	32.5%	N/A		66.4%	N/A	66.4%	N/A		
	% White	61.4%	N/A		59.8%	N/A	59.8%			
	% Asian	20.2%	N/A		26.2%	N/A	26.2%			
	Prior prophylaxis	82.5%	N/A		43.9%	N/A	43.9%			
	Baseline HJHS Joint Score	19.51	17.23		20.7	18.6	20.7	18.6		
	% HIV	12.3%	N/A		15.9%	N/A	15.9%	N/A		

All covariate values for adjustment are from baseline, except:

[†]XTEND-1 arm B baseline age was increased by 26 weeks to compensate for duration of O-D phase

Abbreviations: ESS, effective sample size; HJHS, Hemophilia Joint Health Score; N/A, not applicable; O-D, on-demand; pts, patients; SD, standard deviation; TJ, target joint.

Figure 13: Histogram of weights for the MAIC comparison with pooled HAVEN 3 arms, HJHS joint score

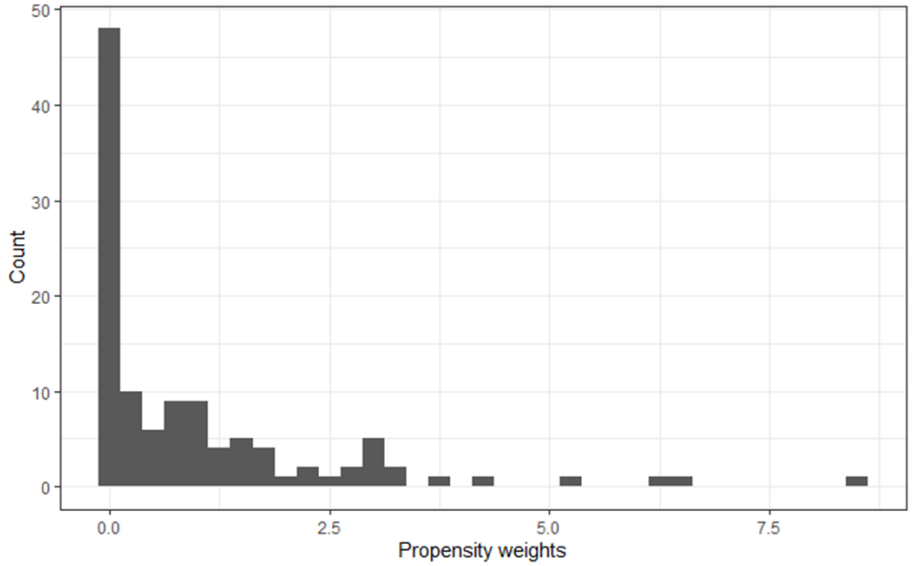
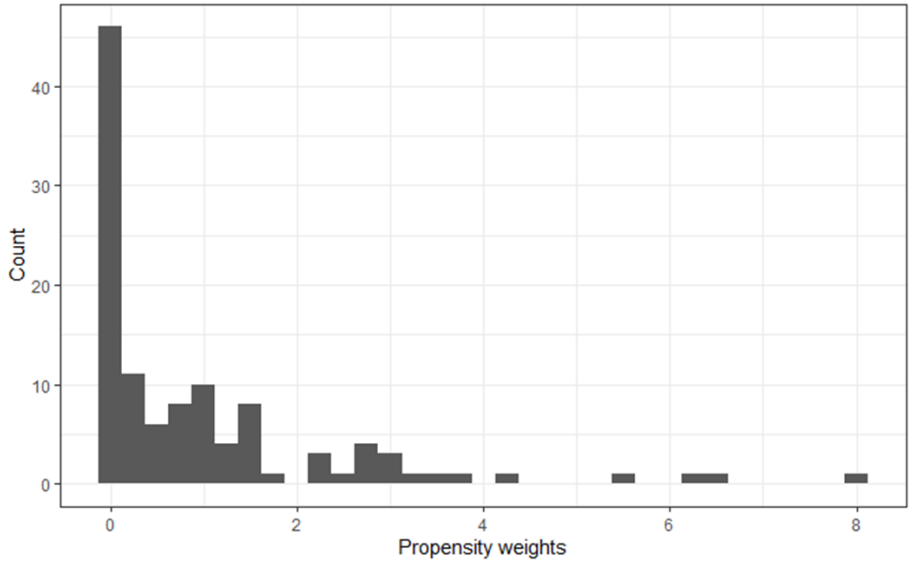


Figure 14: Histogram of weights for the MAIC comparison with pooled HAVEN 3 arms, HJHS total score



B.2.9.3.1.5 Efmoroctocog alfa

Pooled arms of the XTEND-1 trial were compared with A-LONG, since both cohorts recruited patients receiving prophylactic and on-demand treatment prior to enrolment. The age of A-LONG study patients ranged from 12–65 years and the body weight ranged from 42–127 kg, thus population from XTEND-1 had slightly wider range of age and body weight values comparing with A-LONG (Table 39). In the analysis, all patients from XTEND-1 and A-LONG individualised prophylaxis arm were included, assessing treatment-effect comparison after matching patients for baseline characteristics using PSM full matching method.

Table 39: Pre-selection of XTEND-1 patients with comparable baseline characteristics

Study	Range of baseline variables		XTEND-1 IPD		
	Age (years)	Body weight (kg)	Arm (N)	Age (years)	Body weight (kg)
A-LONG individualised prophylaxis	12–65	42–127	Pooled arms (159)	12–72	33.9–132.8

Abbreviations: IPD, individual patient data.

The comparison between interventions was adjusted for the following baseline variables:

- Age (mean and standard deviation),
- Body weight (mean and standard deviation),
- Proportion of patients treated prophylactically prior to enrolment,
- Presence of target joints, including:
    - Proportion of patients with 0 target joint, and
    - Number of target joint per patient (mean and standard deviation),
- Prior bleeds (mean and standard deviation),
- Proportion of HIV-positive patients,
- Proportion of hepatitis C virus (HCV)-positive patients,
- Baseline Haem-A-QoL scores (mean and standard deviation), including:
    - Total score for change from baseline in Haem-A-QoL Total score, and
    - Physical score for change from baseline in Haem-A-QoL Physical score.

A summary of the baseline characteristics before and after matching is presented in Appendix D.

B.2.9.3.2 Outcomes

B.2.9.3.2.1 Efanesoctocog alfa vs emicizumab

Efanesoctocog alfa was associated with significantly lower incidence of any bleeds (treated and untreated) compared with emicizumab QW prior prophylaxis, emicizumab QW prior on-demand therapy, and emicizumab Q2W. The results for ABR (any treated bleeding) and ABR (joint treated bleeding) versus emicizumab QW with prior prophylaxis were also statistically significant (Table 40; Figure 15). There were no significant between-treatment differences regarding the incidence of any treated bleeds,

spontaneous treated bleeds, and joint treated bleeds in comparison with emicizumab QW prior on-demand therapy, and emicizumab Q2W (Table 40), which was likely due to insufficient statistical power for the comparison of these less frequent outcomes.

The difference in HJHS Total score and HJHS Joint score (after adjustment for all covariates, including the baseline HJHS scores) was statistically significant (Table 40), however, the MAIC-adjustment was associated with 68% information loss. The exclusion of prior regimen from the list of covariates for the MAIC adjustment allowed to preserve most (55%) of information, however the difference in HJHS Total score and HJHS Joint score became statistically non-significant (Figure 15).

The comparison regarding the proportion of patients without bleeds during follow-up was not attempted, due to different observation periods between XTEND-1 (Arm A: 52 weeks, Arm B: 26 weeks) and HAVEN 3 (Group A on prior on-demand therapy: median 29.6 weeks, Group B on prior on-demand therapy: median 31.3 weeks, and Group D on prior prophylaxis: 33.7 weeks) studies.

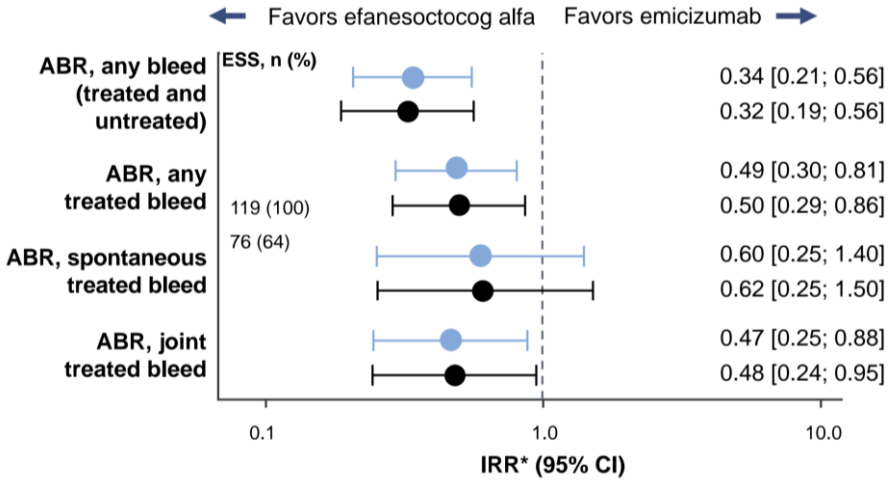
Table 40: Summary of the results for the comparison between efanesoctocog alfa vs emicizumab based on HAVEN 3

Endpoint	Results for comparison between efanesoctocog alfa *vs* emicizumab (HAVEN 3)			
	***vs* EMI QW (prior PHX)**	***vs* EMI QW (prior OD)**	***vs* EMI Q2W (prior OD)**	***vs* EMI QW & Q2W (prior OD & PHX)**
ABR (any bleeding) (IRR)	**0.32 [0.19; 0.56]**	**0.34 [0.12; 0.95]**	**0.28 [0.10; 0.81]**	N/A
ABR (any treated bleeding) (IRR)	**0.50 [0.29; 0.86]**	0.46 [0.16; 1.37]	0.47 [0.15; 1.44]	N/A
ABR (spontaneous treated bleeding) (IRR)	0.62 [0.25; 1.50]	0.45 [0.11; 1.89]	1.35 [0.30; 6.18]	N/A
ABR (joint treated bleeding) (IRR)	**0.48 [0.24; 0.95]**	0.59 [0.18; 1.49]	0.63 [0.17; 2.29]	N/A
HJHS Total score (MD)	N/A	N/A	N/A	**–2.37 [–4.36; –0.39]**
HJHS Joint score (MD)	N/A	N/A	N/A	**–2.06 [–3.97; –0.14]**

Notes:	
	Favours Efanesoctocog alfa, significant
	Favours Efanesoctocog alfa, not significant
	Favours comparator, not significant
n/a	*No data/analysis not feasible*
bold	***Statistically significant difference***

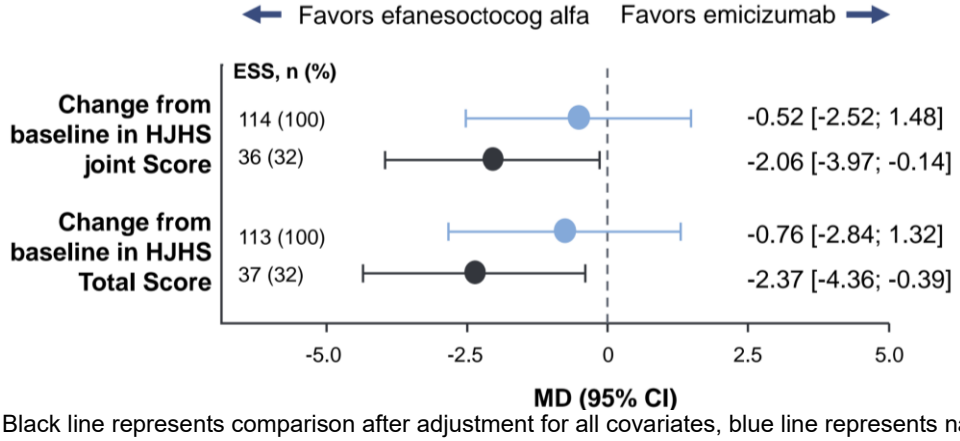
Abbreviations: ABR, annualised bleeding rate; EMI, emicizumab; HJHS, Haemophilia Joint Health Score; OD, on-demand; PHX, prophylaxis; QW, once weekly, Q2W, every 2 weeks; IRR, incidence rate ratio; MD, mean difference.

Figure 15: Comparison of ABRs for efanesoctocog alfa compared with emicizumab QW in patients with prior prophylaxis



*IRR gives clinically interpretable results on the relative scale (treatment results in % change in risk relative to comparator). Black line represents comparison after adjustment for all covariates, blue line represents naïve comparison. Following matching of baseline characteristics, the ESS of the XTEND-1 population was reduced from 119 to 76 patients (64%).
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; ESS, effective sample size; IRR, incidence rate ratio; QW, once weekly.

Figure 16: Comparison of HJHS scores between efanesoctocog alfa and emicizumab QW & Q2W (model with all covariates except prior regimen)



Black line represents comparison after adjustment for all covariates, blue line represents naïve comparison. HJHS data were only available for the pooled cohort (Arms A, B, and D) in HAVEN 3. Following matching of baseline characteristics, the ESS of the XTEND-1 population was reduced from 114 to 36 patients (32%) for HJHS joint score and from 113 to 37 (32%) for HJHS total score.
Abbreviations: CI, confidence interval; ESS, effective sample size; HJHS, Haemophilia Joint Health Score; MD, mean difference; PHX, prophylaxis.

B.2.9.3.2.2 Efanesoctocog alfa vs efmoroctocog alfa

Efanesoctocog alfa was associated with a statistically significant lower incidence of any treated bleeding, spontaneous treated bleeding, and joint treated bleeding compared with efmoroctocog alfa prophylaxis. The proportion of bleeding-free patients was statistically significantly higher for efanesoctocog alfa for all bleeding types. There were no significant between-treatment differences regarding the FVIII consumption and Haem-A-QoL Total and Physical scores (Table 41).

Table 41: Summary of the results for the comparison between efanesoctocog alfa vs efmoroctocog alfa based on A-LONG

Endpoint	Results for comparison between efanesoctocog alfa vs efmoroctocog alfa
ABR (any treated bleeding) (IRR)	**0.29 [0.17; 0.51]**
ABR (spontaneous treated bleeding) (IRR)	**0.21 [0.09; 0.49]**
ABR (joint treated bleeding) (IRR)	**0.37 [0.20; 0.71]**
Proportion of patients without any treated bleeding (OR)	**1.99 [1.20; 3.30]**
Proportion of patients without spontaneous treated bleeding (OR)	**2.06 [1.21; 3.52]**
Proportion of patients without joint treated bleeding (OR)	**1.73 [1.12; 2.67]**
Factor VIII consumption, IU/kg/y (MD)	–1,032 [–2,621; 557]
Haem-A-QoL Total score (MD)	–2.43 [–8.48; 3.62]
Haem-A-QoL Physical score (MD)	–7.01 [–14.69; 0.67]

Notes:	
	Favours Efanesoctocog alfa, significant
	Favours Efanesoctocog alfa, not significant
bold	***Statistically significant difference***

Abbreviations: ABR, annualised bleeding rate; EFMO, efmoroctocog alpha; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; IRR, incidence rate ratio; MD, mean difference; OR, Odds ratio.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

The objective of this analysis was to compare efficacy, patient-reported outcomes and FVIII usage between efanesoctocog alfa and comparators. The comparisons were based on the results of the pivotal XTEND-1 trial, which did not form network connections with the studies assessing emicizumab or efmoroctocog alfa. Therefore, to minimise the risk of bias associated with imbalanced effect modifiers and prognostic factors across studies, a population-adjusted comparison using MAIC or PSM were used, as recommended by the NICE DSU guidelines (102).

Unanchored comparisons are inherently associated with a number of limitations due to necessity of making several strong assumptions including conditional constancy of the absolute effects, under which all prognostic variables and effect modifiers shall be matched. Moreover, from the technical point of view, the conduction of the MAIC is limited by the quality and precision of the reporting of baseline characteristics in the comparator trials, since the matching can be carried out only against reported aggregated data. Another limitation of the analysis was the exclusion of zero bleed rates as an outcome. However, this comparison was not feasible due to the differences in trial lengths.

The credibility of MAIC depends also on the similarity of populations across trials, since insufficient overlapping of baseline characteristics may lead to a loss of information expressed with a large drop in effective sample size. As a consequence, the estimates

drawn are based on a small amount of data, and therefore, may not be reliable. However, this is a common issue in the rare disease setting, as inherently patient numbers will be low. In this analysis, the effective sample 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 (102).

B.2.9.5 Conclusions for the ITC

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 QW regimen in patients with prior prophylaxis and with Q4W regimen. Moreover, efanesoctocog alfa tends to improve HJHS assessment compared with emicizumab.

Compared with efmoroctocog alfa, efanesoctocog alfa was associated with significant reductions in all bleeding outcomes assessed. It was also associated with a reduction in FVIII consumption and improvements in quality of life.

B.2.10 Adverse reactions

B.2.10.1.1 Summary of treatment-emergent adverse events

Of the 159 patients in the safety analysis set, 123 (77.4%) experienced a total of [redacted] TEAEs (Table 42). In Arm A, Arm B on-demand, and Arm B prophylaxis, [redacted] TEAEs were reported in 108 (81.2%) patients, 22 TEAEs were reported in 12 (46.2%) patients, and 11 TEAEs were reported in eight (30.8%) patients, respectively. In the surgery subgroup (comprising 13 patients), three TEAEs were reported for [redacted]. Within the safety analysis set, at least one treatment-emergent serious adverse event (TESAE) was reported in 15 (9.4%) patients overall. One (0.6%) patient from Arm B experienced a TEAE leading to death (pancreatic carcinoma metastatic), and two (1.3%) patients from Arm A experienced TEAEs leading to treatment discontinuation.

Table 42: Overall summary of TEAEs, SAS

Category	Arm A N=133	Arm B		Surgery subgroup† N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Total number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 TEAE	108 (81.2)	12 (46.2)	8 (30.8)	[redacted]	123 (77.4)
Patients with ≥1 treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of TESAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 TESAE	13 (9.8)	2 (7.7)	0	[redacted]	15 (9.4)
Patients with ≥1 treatment-related TESAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of TEAESIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 TEAESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to treatment discontinuation	2 (1.5)	0	0	[redacted]	2 (1.3)
Deaths	0	1 (3.8)	0	[redacted]	1 (0.6)

Source: Table 28, clinical study report (87).

†Includes AEs occurring during a major surgical/rehabilitation period. But AEs which occur on the day of the major surgical/rehabilitation period starts will be included in the columns treatment arm and regimen, they will not be included in the column of surgery subgroup.

Abbreviations: SAS, safety analysis set; TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent adverse event of special interest; TESAE, treatment-emergent serious adverse event.

B.2.10.1.2 Adverse events by system organ class and preferred term

Within the safety analysis set (n=159), TEAEs were most commonly reported in the following system order classes (SOC) (≥10% of patients overall); musculoskeletal and connective tissue disorders ([redacted] patients), nervous system disorders ([redacted] patients), injury, poisoning and procedural complications ([redacted] patients), infections and infestations ([redacted] patients), general disorders and administration site conditions ([redacted] patients), gastrointestinal disorders ([redacted] patients) and investigations ([redacted] patients).

The most frequently reported TEAEs by preferred term (>3% of patients overall) were headache (32 [20.1%] patients), arthralgia (26 [16.4%] patients), fall (ten [6.3%] patients), back pain (nine [5.7%] patients), COVID-19 and fatigue ([redacted] patients, each), contusion, haemophilic arthropathy, and nasopharyngitis ([redacted] patients, each), and joint injury, pain in extremity and toothache ([redacted] patients, each).

Table 43 presents a summary of TEAEs by SOC and preferred term, occurring in >3% of patients.

Table 43: Summary of TEAEs by SOC and preferred term (in >3% of patients), SAS

System organ class Preferred Term, n (%)	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Total number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least one TEAE	108 (81.2)	12 (46.2)	8 (30.8)	123 (77.4)
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatic carcinoma metastatic	0	1 (3.8)	0	1 (0.6)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Lymphadenopathy	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	26 (19.5)	5 (19.2)	1 (3.8)	32 (20.1)
Syncope	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Excessive cerumen production	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]

System organ class Preferred Term, n (%)	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis allergic	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]	[redacted]	[redacted]
Large intestine polyp	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	25 (18.8)	1 (3.8)	0	26 (16.4)
Back pain	8 (6.0)	1 (3.8)	0	9 (5.7)
Haemophilic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Coagulation factor VIII level increased	[redacted]	[redacted]	[redacted]	[redacted]
SARS-CoV-2 test positive	[redacted]	[redacted]	[redacted]	[redacted]
Red blood cell count increased	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Fall	10 (7.5)	0	0	10 (6.3)
Contusion	[redacted]	[redacted]	[redacted]	[redacted]

System organ class Preferred Term, n (%)	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Joint injury	[redacted]	[redacted]	[redacted]	[redacted]
Limb injury	[redacted]	[redacted]	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]	[redacted]	[redacted]
Tooth fracture	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]
Social circumstances	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy of partner	[redacted]	[redacted]	[redacted]	[redacted]
Product issues[†]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 16.2.7.2, data on file_CSR_01-EFC16293-16.2.7_ae_data (106).

Note: Patients were included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each patient was counted only once in the overall column; Events were coded using MedDRA version 24.1; Patients were counted once if they reported multiple events in the same system organ class or preferred term; Table sorted by SOC internationally agreed order and decreasing frequency of PT in the overall group; AEs which occur during a major surgical/rehabilitation period were excluded, but AEs which occur on the day of the major surgical/rehabilitation period starts were included.

[†]Product issue was due to device (needle) breakage.

Abbreviations: AE, adverse event; PT, preferred term; SAS, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

B.2.10.1.3 Treatment-related adverse events

The majority of TEAEs were assessed by the investigator as unrelated to efanesoctocog alfa treatment (safety analysis set, n=159). In total, [redacted] TEAEs were considered related to treatment in [redacted] patients, all in Arm A (Appendix F). Treatment-related TEAEs included coagulation FVIII level increased ([redacted] patients), headache ([redacted] patients), and CD4 lymphocytes decreased, protein urine present, injection site dermatitis, malaise, and dysphoria ([redacted], each). Of the TEAEs assessed as related, [redacted] of CD4 lymphocytes decreased was assessed by the investigator as serious and resulted in discontinuation of efanesoctocog alfa.

B.2.10.1.4 Serious adverse events

The majority of TEAEs were assessed by the investigator as mild in severity. Of the 159 patients included in the safety analysis set, 15 patients experienced at least one TESAE, the most common of which was haemophilic arthropathy ([redacted] from Arm A) (Table 44).

Table 44: Summary of TESAEs by SOC and preferred term, SAS

System organ class Preferred Term, n (%)	Arm A	Arm B		Overall (N=159)
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	
Total number of TESAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least one TESAE	13 (9.8)	2 (7.7)	0	15 (9.4)
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatic carcinoma metastatic	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cubital tunnel syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Status epilepticus	[redacted]	[redacted]	[redacted]	[redacted]
Ulnar tunnel syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthropathy	[redacted]	[redacted]	[redacted]	[redacted]
Haemophilic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]
Mobility decreased	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]

System organ class Preferred Term, n (%)	Arm A	Arm B		Overall (N=159)
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	
CD4 lymphocytes decreased	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Combined tibia-fibula fracture	[redacted]	[redacted]	[redacted]	[redacted]
Traumatic haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]
Central venous catheter removal	[redacted]	[redacted]	[redacted]	[redacted]
Product issues	[redacted]	[redacted]	[redacted]	[redacted]
Device breakage	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 16.2.7.13, data on file_CSR_01-EFC16293-16.2.7_ae_data (106).
Note: Patients were included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each patient was counted only once in the overall column; Events were coded using MedDRA version 24.1; Patients were counted once if they reported multiple events in the same system organ class or preferred term; Table sorted by SOC internationally agreed order and decreasing frequency of PT in the overall group; AEs which occur during a major surgical/rehabilitation period were excluded, but AEs which occur on the day of the major surgical/rehabilitation period starts were included.
Abbreviations: AE, adverse event; PT, preferred term; SAS, safety analysis set; SOC, system organ class; TESAE, treatment-emergent serious adverse event.

B.2.10.1.5 Deaths

During the course of XTEND-1, one death was reported in one patient from Arm B. The patient had a medical history of hepatitis C virus (HCV) and died on Day 217 of metastatic pancreatic carcinoma, which was reported as a TESAE on Day 173. The TESAE was assessed by the investigator as not related to treatment.

B.2.10.1.6 Subgroup analysis

Subgroup analyses of TEAEs by predefined intrinsic and extrinsic factors (age, BMI, race, HIV status, HCV status, geographic region, and COVID-19 impact) were generally consistent with TEAEs in the overall study population. No unique patterns or trends were identified in any subgroup. A summary of the subgroup analyses is presented in Appendix F.

B.2.10.2 Overview of safety of efanesoctocog alfa

Efanesoctocog alfa was generally well tolerated and reported TEAEs were generally consistent with what is anticipated in an adult and adolescent population with severe haemophilia A. Inhibitor development to FVIII was not detected, and there were no reports of serious allergic reaction, anaphylaxis, or vascular thrombotic events. In addition, no clinically meaningful patterns or trends were identified in laboratory or vital sign parameters.

B.2.11 Ongoing studies

There is one ongoing, long-term study investigating the safety and efficacy of efanesoctocog alfa in previously treated patients with haemophilia A (XTEND-ed), the extension study of XTEND-1 (NCT04644575). The study has enrolled 261 patients and is estimated to complete in February 2027. XTEND-ed enrolled [redacted] patients from four UK-based sites.

B.2.12 Innovation

Efanesoctocog alfa, a high sustained factor, is a novel fusion protein designed to decouple rFVIII from endogenous VWF in circulation (30). It appends the D'D3 domain of VWF to FVIII, preventing binding to endogenous VWF. Efanesoctocog alfa harbours a pharmacokinetic profile independent of VWF, allowing patients with severe haemophilia to maintain high sustained FVIII activity levels within normal to near-normal (>40%) range for up to 4 days after injection, and within the mild haemophilia range (>5–<40%) for up to a week.

Despite treatment advances in haemophilia A, patients continue to experience bleeds, pain, and disability, which have a major impact on physical, mental, and emotional health. In a study of 63 patients with moderate/severe haemophilia A receiving PK-guided prophylaxis with rurioctocog alfa, at FVIII levels of 30–40 IU/dL, nearly 90% of patients were estimated to achieve zero bleeds (107).

Clinician opinion stated that prophylaxis is the mainstay for patients. While prophylaxis with current rFVIII products decreases the risk of bleeding episodes and improves clinical outcomes, existing FVIII therapies require frequent IV administration several times a week or every other day to maintain FVIII trough levels above a target threshold of at least 1%. Patients in England report a preference for less frequent administration of prophylactic treatment (108), which may affect compliance for therapies that require more frequent administration. Therefore, there is a notable unmet need for replacement therapies with an extended half-life that can control bleeds and provide optimal prevention of bleeding episodes by maintaining high-sustained factor levels for between dosing intervals, while reducing the treatment burden (19, 107).

Due to its high-sustained and further prolonged half-life compared with EHLs, efanesoctocog alfa addresses these unmet needs by providing high-sustained FVIII activity levels for the majority of the week, improving bleed prevention, and offering greater protection against joint damage. Clinicians have stated to Sobi that efanesoctocog alfa offers a 'paradigm shift' with regard to prophylaxis in haemophilia A, potentially offering patients the possibility of a life without bleeds, improved joint health,

and improved HRQoL; reducing anxiety associated with bleed anticipation, frequent administration of treatment, and increasing participation in physical activity (28). Furthermore, treatment with efanesoctocog alfa may reduce treatment burden associated with current FVIII therapies and emicizumab, and potentially improve treatment compliance; patients experience reduced damage from joint bleeds, there will be a reduced need for inpatient stays and surgery (108, 109).

B.2.13 Interpretation of clinical effectiveness and safety evidence

In XTEND-1, efanesoctocog alfa administered as weekly prophylaxis in adolescent and adult previously treated patients with severe haemophilia A demonstrated notable protection against bleeds and clinically meaningful treatment effect, as shown by an estimated mean ABR of 0.71 (95% CI: 0.52, 0.97) with median ABR (Q1; Q3) of 0.00 (0.00; 1.04). The ABRs were consistently low across type (spontaneous or traumatic) and location (joint, muscle, internal, or skin/mucosa) of bleeding, when including untreated and treated bleeding episodes, as well as in all subgroups studied including patients aged 12 through 17 years. Weekly prophylaxis with efanesoctocog alfa demonstrated superior protection against bleeds vs pre-study FVIII prophylaxis, with a reduction of 77% in estimated mean ABR in patients already on a pre-study SoC prophylactic treatment regimen.

Weekly prophylaxis demonstrated statistically significant improvements in physical functioning and pain. Furthermore, prophylaxis with efanesoctocog alfa demonstrated statistically significant improvement in the clinical symptoms and signs of joint damage, reflected by a meaningful reduction in HJHS score. Notably, taking into consideration that the majority of patients were already on prophylactic treatment prior to XTEND-1, changes from baseline observed in this study represent a clinically important benefit with efanesoctocog alfa over the existing SoC prophylactic treatment.

Efanesoctocog alfa was effective for the treatment of bleeds. Most bleeds (96.7%) were controlled by a single injection with a mean dose per injection of [redacted] IU/kg, and the haemostatic efficacy in treatment of bleeds was rated by the patients as excellent or good in 94.9% of first injections. Efanesoctocog alfa was effective for perioperative management with a haemostatic response, rated as excellent by the investigators/ surgeons in all of the major surgeries and the pre-operative loading dose was sufficient to maintain haemostasis in all patients during surgery.

Efanesoctocog alfa was generally well tolerated and reported TEAEs were generally consistent with what is anticipated in an adult and adolescent population with severe haemophilia A. Inhibitor development to rFVIII was not detected, and there were no reports of serious allergic reaction, anaphylaxis, or vascular thrombotic events. In

addition, there were no unique safety findings identified during the major surgery/rehabilitation period.

Once weekly 50 IU/kg of efanesoctocog alfa in previously treated patients with severe haemophilia A was well tolerated and was efficacious as a prophylactic therapy in terms of ABR, with superior protection against bleeds compared with pre-study standard-of-care FVIII prophylaxis. Efanesoctocog alfa also demonstrated clinically meaningful improvements in physical functioning, pain intensity, and joint health. In addition, efanesoctocog alfa was effective for the control of bleeding episodes and provided haemostatic efficacy for surgical procedures.

B.3 Cost effectiveness

The cost-effectiveness analysis demonstrated that efanesoctocog alfa is a cost-effective treatment option for both PUPs and PTPs with severe haemophilia A

- The economic analysis considered patients with severe haemophilia A
- The model structure comprised three mutually exclusive health states; No bleeds, Any bleeds, and Dead
- Base-case results showed that efanesoctocog alfa is associated with more quality-adjusted life years (QALYs) compared with emicizumab or efmoroctocog alfa. When using the patient access scheme (PAS) prices for efanesoctocog alfa and efmoroctocog alfa, efanesoctocog alfa was associated with an incremental cost-effectiveness ratio (ICER) of £18,211 versus efmoroctocog alfa and dominated emicizumab
- Probabilistic sensitivity analyses and scenario analyses supported the base-case analysis, suggesting that the cost-effectiveness of efanesoctocog alfa is stable to the uncertainty within the model
- The model was validated by clinical experts, and externally validated using the Assessment of the Validation Status of Health-Economic (AdViSHE) decision models checklist

B.3.1 Published cost-effectiveness studies

The economic SLR, conducted in September 2023, identified a total of 2,977 hits. After removing the duplicates, titles and abstracts of 2,968 records were screened and 45 of them were retained for full-text review. Finally, 24 economic models (reported in 24 articles) were included to the extraction process. Of the 24, two models were from a UK perspective.

A summary of the included studies from a UK perspective is provided in Table 45. Details of other included studies are provided in Appendix G.

Table 45: Summary list of published cost-effectiveness studies (UK studies)

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Benson et al, 2021 (110)	2020	• Markov Model • 70 year time horizon • 28-day cycle length • Discount: 3.5% • Perspective: NHS • Currency: GBP	Male patients ≥12 years with severe haemophilia A	Turoctocog alfa pegol had the highest QALY gain (0.35–1.05) compared with other treatments	Total cost†: Turoctocog alfa pegol: £8,001,516 Rurioctocog alfa pegol: £8,028,043 Efmoroctocog alfa: £8,022,383 Damoctocog alfa pegol: £8,071,614	NR
Kragh et al, 2023 (111)	2022	• Markov model • Lifetime time horizon • 6-month cycle length • Perspective: NR • Currency: GBP	Male patients ≥12 years with haemophilia A without inhibitors	0.014	Incremental costs: £–4,614,882	Dominant

†If incremental costs/QALYs are not presented in publication, the table provide total costs/QALY
Abbreviations: GBP, Great British Pound; ICER, incremental cost-effectiveness ratio; NR, not reported; QALY, quality-adjusted life year.

B.3.2 Economic analysis

B.3.2.1 Patient population

The population included in the cost-effectiveness analysis consisted of patients of with severe haemophilia A. While the marketing authorisation also allows for the treatment of people with mild or moderate disease, no studies have assessed the clinical efficacy of efanesoctocog alfa in these populations.

No studies have assessed the use of efanesoctocog alfa in PUPs and the cost-effectiveness analysis is based on data from PTPs. However, clinical opinion supports the extrapolation of safety and efficacy data to PUPs. Consequently, the same efficacy data is applied for both the PUP and PTP populations.

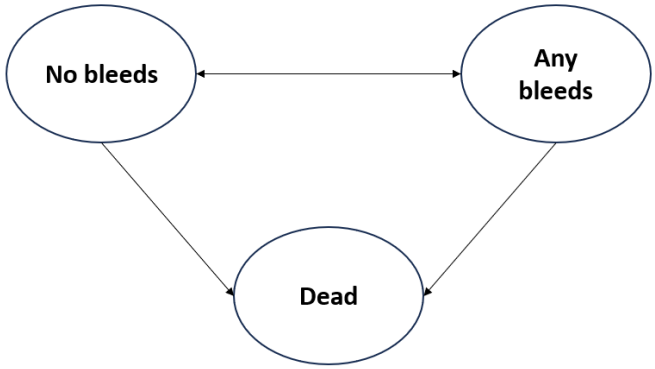
B.3.2.2 Model structure

The model was developed in Microsoft® Excel and structured as a Markov model, in line with other model structures used in previous economic evaluations in haemophilia A (111-114). The model structure is depicted in Figure 17, and comprises three mutually exclusive health states:

- No bleeds
- Any bleeds
- Dead.

All patients enter the model in the “No bleeds” state. Patients can transition to the “Any bleeds” state and receive efanesoctocog alfa or a comparator. From the “Any bleeds” state, patients can transition back to the “No bleeds” state. Patients can transition to the “Dead” state from any state in the model; this is an absorbing state.

Figure 17: Model schematic



The model can also differentiate patients across different FVIII levels, which is used to assess HRQoL. People with higher FVIII levels are less likely to experience bleeds and

are more able to undertake the usual activities. An individuals FVIII level is not constant, with a peak immediately after infusion and then reducing over time until the next infusion. In each cycle, the model estimates the proportion of time a patient will spend with FVIII in different ranges. The model can divide FVIII levels into six groups: ≤1%, 1–5%, 5–20%, 20–40%, 40–50%, and >50%, however in the base-case analysis, the model only differentiates between people with FVIII above or below 20%, with scenario analysis considering a 5% threshold. The model also includes an option to specify ABRs by FVIII level, however this has not been applied in this analysis.

B.3.2.2.1 Time horizon

The model considered a lifetime time horizon. As XTEND-1 reported a mean starting age of 35.4 years, a time horizon of 65 years was expected to adequately capture long-term clinical and economic consequences of haemophilia A.

B.3.2.2.2 Cycle length

The model used a 6-month cycle length which was considered sufficiently long to account for health events. A half-cycle correction was applied using the life table method to account for uncertainty in the timing of transitions within the cycle period, where the time in each cycle was estimated using the average of the number of people at the start and end of the cycle.

B.3.2.2.3 Discounting

In the base case, a discount rate of 3.5% per annum was applied in line with current NICE methods guide (2022) (115). Discount rates for costs and health outcomes of 0% and 6% were explored in scenario analyses.

B.3.2.2.4 Perspective

The analysis was conducted from the perspective of the National Health Service (NHS) and personal social services (PSS) in England and Wales, in line with current NICE guidelines (115).

B.3.2.3 Features of the economic analysis

Key features of the economic analysis are outlined in Table 46.

Table 46: Features of the economic analysis

Factor	Current appraisal	
	Chosen values	Justification
Patient population	Patients with severe haemophilia A	No studies have assessed the efficacy of efanesoctocog alfa in mild or moderate haemophilia A, and so no evidence has been

Factor	Current appraisal	
	Chosen values	Justification
		submitted for these patients (Table 1)
Model structure	Markov model	In line with NICE reference case (115) and published literature (111-113)
Health states	Three health states: • No bleeds • Any bleeds • Dead	In line with NICE reference case (115) and published literature (111)
Time horizon	Lifetime	In line with NICE reference case (115)
Cycle length	6 months (half cycle correction was applied)	In line with NICE reference case (115)
Perspective	NHS and PSS	In line with NICE reference case (115)
Discounting per year of costs and utilities	3.5% per annum	In line with NICE reference case (115)
Health effects	QALYs and life years	In line with NICE reference case (115)
Treatment waning effect?	None	Not considered appropriate in line with clinical opinion (28)
Source of clinical efficacy and safety	XTEND-1 and XTEND-Kids trials	In line with NICE reference case (115)
Source of utilities	XTEND-1 clinical trial	In line with NICE reference case (115)
Source of costs	NHS BSA National Schedule of NHS costs PSSRU	In line with NICE reference case (115)

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal social services; QALY, Quality-adjusted life-year; QoL, quality of life, UK, United Kingdom.

B.3.2.4 Intervention and comparators

B.3.2.4.1 Intervention

The intervention considered in this analysis is efanesoctocog alfa, administered intravenously at a dose of 50 IU/Kg QW.

Efanesoctocog alfa is a first-in-class, high-sustained FVIII replacement therapy indicated for [redacted]. The molecule comprises a single B-domain-deleted recombinant FVIII protein fused to Fc, covalently coupled to the FVIII binding D'D3 domain of VWF, and two XTEN polypeptides (B-domain and D'D3-domain moieties); the structure of which extends the compound's time in circulation. It is the first investigational FVIII therapy that breaks through the VWF ceiling, which imposes a half-life limitation on current FVIII therapies (34).

B.3.2.4.2 Comparators

The final scope states that the comparators for efanesoctocog alfa should be established clinical management without efanesoctocog alfa, including:

- Established clinical management (including prophylaxis, on-demand treatment with FVIII replacement therapy)
- Emicizumab.

Since launch in 2019, the proportion of patients receiving emicizumab has rapidly increased (4) and continues to do so, with it now being the standard of care in the UK for the treatment of PUPs and PTPs (17). The proportion of patients with severe haemophilia A receiving emicizumab has increased from [redacted]% in 2019, to [redacted]% at the end of 2022 (17). Furthermore, since Q2 2019, the use of SHLs has declined from [redacted] % to [redacted] % at the end of 2022 (17), and clinical opinion suggests that SHL use will be minimal in 5 years time (28).

B.3.2.4.2.1 Previously untreated patients

Clinical advice provided to the Company stated that for newly diagnosed patients, the choice of treatment results from parental decision. All patients with severe disease/bleeding phenotype will require prophylaxis, and the majority of parents select emicizumab, as it avoids the need for general anaesthetic and central venous access (28). Some parents will select treatment with a FVIII therapy, often because their child has presented with a severe bleed that required emergency treatment with FVIII replacement therapy. For the majority of newly diagnosed patients, an EHL would be the first choice of treatment for prophylaxis, among which, only efmoroctocog alfa is licenced for use in patients under the age of 12 years (71). As patients with severe haemophilia A will present early in life, any patients starting treatment with an EHL will be administered efmoroctocog alfa.

As such, the comparators in the PUP population are:

- Emicizumab
- Efmoroctocog alfa.

For long-term prophylaxis, the recommended dose of efmoroctocog alfa is 50 IU of factor VIII per kg body weight at intervals of 3–5 days (71). In the cost-effectiveness analysis, a dose of 50 IU/kg every 4 days was modelled.

Emicizumab, a humanised bispecific antibody, is administered at a dose of (69):

- 1.5 mg/kg QW

- 3 mg/kg once Q2W
- 6 mg/kg once Q4W.

Dosing information for both treatment and the comparators was summarised in Table 55 in Section B.3.5.1.1. Clinical opinion provided to Sobi stated that the Q2W was the most frequently used, and this is aligned with evidence from the National Haemophilia Database (NHD), which shows the mean treatment frequency per week to be [redacted] in patients under 12 years old, and [redacted] in patients aged 12 years and older (17). As such, the Q2W dose was modelled in the cost-effectiveness analysis.

B.3.2.4.2.2 Previously treated patients

Amongst PTPs, clinicians advised that patients may switch away from FVIII therapy to emicizumab for the following reasons (28):

- A patient's haemostasis is inadequately controlled (i.e. they are still bleeding)
- A patient's rFVIII levels are not sufficiently controlled (i.e. poor PK coverage due to low peaks/troughs/AUC/short half life)
- Frequent injections resulting in poor compliance/adherence to rFVIII.

In PTPs, it is anticipated that efanesoctocog alfa will be used in patients who would otherwise be offered emicizumab. Currently, following FVIII treatment there is currently no other choice of treatment apart from emicizumab. Therefore, it is appropriate to compare efanesoctocog alfa to emicizumab only in this analysis. The dosing for emicizumab does not vary between PUPs and PTPs.

B.3.3 Clinical parameters and variables

B.3.3.1.1 Patient characteristics

Patient characteristics at baseline for the PTP population were based on patient-level data from the XTEND-1 and are presented in Table 47. In PUPs, it was assumed that patients will start treatment at 1 year old. Weight for these patients were derived from growth charts for boys up to age 18 years (116, 117) (Table 48), and were then assumed to be equal to the PTP population.

Table 47: Patient characteristics in the XTEND-1 and XTEND-Kids trials

Patient characteristics	PUPs	PTPs (34)
Mean age (years)	1.0	35.4
Proportion male (%)	99.4%	99.4%
Mean body weight (Kg)	Derived from growth charts	78.46

Abbreviations: PTPs, previous treated patients; PUPs, previously untreated patients.

Table 48: Weight by age for PUPs

Age (years)	Weight (kg)
0.5	7.94
1	9.65
1.5	10.95
2	12.20
3	14.30
4	16.50
5	18.60
6	20.80
7	23.10
8	25.60
9	28.40
10	31.40
11	34.60
12	38.10
13	43.00
14	49.20
15	55.40
16	60.60
17	64.30
18+	78.46

Abbreviations: PUPs, previously untreated patients.

B.3.3.2 Annual bleeding rate and proportion of patients with bleedings

B.3.3.2.1 Annual bleeding rate

In the base-case analysis, the model considered any bleeds (treated and untreated) to assess the impact of bleeds on quality of life. However, as not all bleeds are treated, the model required ABRs for any bleeds and treated bleeds to calculate the proportion of bleeds that are treated, and therefore incur a cost.

The ABRs applied in the model were obtained from XTEND-1 for efanesoctocog alfa and from the MAIC (Section B.2.9) for emicizumab and efmoroctocog alfa. The mean ABR for any bleeds in Arm A of XTEND-1 was used in the base-case analysis (as per study protocol, all reported ABRs were treated in XTEND-1), as patients in Arm A had previously received prophylactic treatment and were deemed to be more representative of patients in UK clinical practice because guidelines recommended prophylactic treatment for all people with severe haemophilia A.

The ABR for any bleeds for emicizumab was calculated using the IRR for any bleeds (treated and untreated) from the HAVEN study within the MAIC comparing

efanesoctocog alfa with emicizumab Q2W. While this assesses outcomes in patients previously receiving OD therapy, this is not expected to be a treatment-effect modifier, and the rate ratio is expected be applicable in the prior-prophylaxis population. This is supported by clinical opinion (28), and by the alternative MAIC analyses performed comparing with QW emicizumab, which demonstrated a consistent rate ratio across populations. The HAVEN 3 study demonstrated that weekly and bi-weekly doses of emicizumab have similar efficacy (99, 100). Scenario analyses were performed to test the impact this assumption (Section B.3.10), including:

- Applying the ABR (for any bleeds) from HAVEN 3 Arm B for emicizumab and applying the MAIC IRR to obtain the ABR (for any bleeds) for efanesoctocog alfa
- Using the ABR (for any bleeds) from Arm B of XTEND-1 to inform the baseline ABR (for any bleeds) for efanesoctocog alfa
- Using the weighted average ABR from Arms A and Arm B of XTEND-1 to inform the baseline ABR (for any bleeds) for efanesoctocog alfa
- Applying the IRR from the MAIC comparing Arm A of XTEND-1 to Arm D of HAVEN 3 (emicizumab QW, prior-prophylaxis).

For the comparison with efmoroctocog alfa, an analysis of any bleeds (treated and untreated) was not possible, as these data were not collected in the A-LONG study (as per study protocol, all reported ABRs were treated in A-LONG). Instead, the IRR from the MAIC for treated bleeds was applied.

The same approach was taken to calculate the ABR for treated bleeds for all treatments, and this was then used to calculate the proportion of bleeds which are treated. Table 49 summarised ABRs for any bleeds and treated bleeds used in the base-case analysis.

Table 49: Summary of ABRs applied in the base-case analysis

Treatment	ABR (any bleed)	IRR for any bleed	ABR (treated bleeds)	IRR for treated bleeds	% of bleeds treated	Source
Efanesoctocog alfa	1.11	–	0.71	–	64%	XTEND-1 (34)
Emicizumab	3.96	0.28	1.51	0.47	38%	MAIC (Section B.2.9.3.2.1)
Efmoroctocog alfa	3.83	0.29	2.45	0.29	64%	MAIC (Section B.2.9.3.2.2)

Abbreviations: ABR, annualised bleeding rate; MAIC, matching-adjusted indirect comparison.

B.3.3.2.2 Proportion of patients with bleedings

Due to differing assessment periods between trials, the proportion of patients experiencing a bleed was not assessed in the MAIC comparing efanesoctocog alfa with emicizumab. As such, the proportion of patients experiencing a bleed in each cycle was taken directly from the relevant clinical trials for efanesoctocog alfa and emicizumab.

As with ABRs, the baseline proportion of patients experiencing a bleed in one cycle was obtained from XTEND-1 for efanesoctocog alfa. In order to align with the model cycle length and the outcomes reported in HAVEN 3, the probability of experiencing a bleed was reassessed at 6 months for efanesoctocog alfa. At Month 6, 44 of 133 patients (33.1%) had experienced a bleed with efanesoctocog alfa.

The value for emicizumab was obtained directly from Arm D of HAVEN 3. The Arm D population was again selected as it comprised patients who previously received prophylaxis and were considered more generalisable to UK clinical practice. While prior therapy (on-demand or prophylaxis) is not considered a treatment effect modifier, it may be a prognostic factor and so the value from Arm D is preferred. Scenario analyses using values from Arm A and Arm B were also considered (Section B.3.10). The assumption that unadjusted values can be used in the model is also conservative. While no direct comparison of the proportion of patients experiencing a bleed was made in the MAIC analysis, after the application of MAIC weights comparing with HAVEN 3 Arm D, the proportion of patients in Arm A of XTEND-1 that experienced a bleed by Month 12 was reduced from 39.25% to 36.03% (118).

For the comparison with efmoroctocog alfa, the OR from the ITC for the proportion of patients with a treated bleed (1.99) was applied to the value for efanesoctocog alfa. Table 50 summarised proportion of patients with bleedings used in the base-case analysis.

Table 50: Proportion of patients with bleedings used in the base case

Treatment	Proportion of patients with bleeding events	Source
Efanesoctocog alfa	33.1%	XTEND-1 Arm A
Emicizumab	55.6%	HAVEN 3 Arm D
Efmoroctocog alfa	49.6%	ITC (Section B.2.9.3.2.2)

Abbreviations: ITC, indirect treatment comparison.

B.3.3.3 Estimating Factor VIII levels

A disutility associated with lower FVIII levels may be applied in the model, therefore, a method for estimating FVIII activity level for each treatment was necessary. The

pharmacokinetic plasma concentration equation from Benson et al, 2021 was used for this purpose:

$$C(t) = D * IR * \frac{e^{-\frac{t}{MRT}}}{1 - e^{-\frac{\tau}{MRT}}}$$

Where:

- D is the dose of a given treatment,
- IR is the incremental recovery,
- MRT is the mean residence time,
- t is the time since the dose,
- τ is the dosing interval.

Where *IR* and *MRT* are functions of volume of distribution at steady state (V_{SS}) and clearance, with *IR* set to the inverse of V_{SS} and *MRT* equal to V_{SS} divided by clearance.

For efanesoctocog alfa and efmoroctocog alfa, the required parameters were taken directly from the clinical trials (XTEND 1 and A-LONG), and pharmacokinetic data were available for both one-stage and chromogenic substrate assays, hence distributions of patients through states were estimated for both assays. The one-stage assay was the primary assay used in XTEND-1 and was applied in the base-case analysis.

Distribution of patients across states was estimated by calculating the time points at which FVIII activity level achieved health state defining breakpoints (1%, 5%, 20%, 40%, and 50%). If the time to achieve breakpoint was longer than the assumed time to the next dose the proportion of the time in health states below that factor activity level was considered to be 0%.

To calculate the time to achieve factor activity level breakpoint, a transformed equation from Benson et al, 2021 (110) was used:

$$t = Ln\left(\frac{D * IR}{Breakpoint * \left(1 - e^{-\frac{\tau}{MRT}}\right)}\right) * MRT$$

This approach is only applicable to FVIII treatments, thus for emicizumab data from Retout et al, 2020 (119) was used to inform the estimated FVIII level over time. An equation similar to the one for FVIII treatments was used; however, absorption rate was additionally included:

$$C(t) = \frac{D}{V_d} * \frac{K_a}{K_a - K_e} * \left(\frac{e^{-K_e * t}}{1 - e^{-K_e * \tau}} - \frac{e^{-K_a * t}}{1 - e^{-K_a * \tau}} \right)$$

Where:

- D is the dose,
- V_D is the volume of distribution,
- K_e is the elimination rate constant equal to 1/MRT,
- K_a is absorption rate constant,
- t is time,
- τ is interval between doses.

Based on analysis presented in Shima et al, 2016 (82), conversion factor between 1 µg of emicizumab and FVIII activity per dL was estimated to be 0.3. Therefore, to calculate FVIII activity level distribution for emicizumab, values achieved from above equations were additionally multiplied by 0.3. The study by Windyga et al, 2020 (120) states that the average minimal FVIII activity of emicizumab was around 15%. This was in accordance with performed calculations for emicizumab QW, where FVIII activity levels were estimated to be between 15.1% and 17.9%. For the less frequent dosing, FVIII activity levels have shown higher variability; 13.7–19.5% for emicizumab Q2W and 11.2–22.9% for emicizumab Q4W. Considering these ranges of FVIII activity, the FVIII level for emicizumab in the model was set to 5–20% across all time points.

Table 51 summarises the parameters used to calculate FVIII levels, and Table 52 summarises the distribution of FVIII by treatment.

Table 51: Parameters used to estimate FVIII levels over time

Treatment	Dose [IU/kg]	Dose frequency [h]	Clearance [mL/h/kg]	Vss [mL/kg]
Efanesoctocog alfa, chromogenic substrate assay	50	168	0.21	11.5
Efanesoctocog alfa, one-stage assay	50	168	0.51	31.6
Emicizumab	3.0 mg/kg	336	0.162	148.6
Efmoroctocog alfa, chromogenic substrate assay	50	96	2.21	54.0
Efmoroctocog alfa, one-stage assay	50	96	2.14	52.0

Abbreviations: V_{SS}, volume of distribution at steady state.

Table 52: Summary of FVIII distributions applied in the model

Treatment	<1%	1–5%	5–20%	20–40%	40–50%	≥50%
Efanesoctocog alfa (chromogenic substrate assay)	0.0%	0.0%	0.1%	22.2%	7.1%	70.5%
Efanesoctocog alfa (one-stage assay)	0.0%	0.0%	20.7%	25.7%	8.3%	45.3%
Emicizumab	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%
Efmoroctocog alfa, chromogenic substrate assay	0.0%	25.1%	35.3%	17.7%	5.7%	16.2%
Efmoroctocog alfa, one-stage assay	0.0%	24.6%	35.1%	17.6%	5.7%	17.1%

B.3.3.4 Mortality

Long-term survival data suggest that patients with haemophilia A receiving efanesoctocog alfa have comparable survival with the age-adjusted general population. Therefore, in the model, the probability of death was based on general population mortality. Mortality remained the same for all model health states, with the probability changing over time based on patient age. Mortality was also assumed equal for all treatments. General population mortality data were obtained from the most recent UK National life tables reported by the Office of National Statistics (ONS) (121). The annual probabilities of death by sex and age were converted to rates of death. The rates were weighted for the proportion of males in the model, and then converted to per cycle probabilities of death by age. The model used the sex-weighted per cycle probability of death based on the mean patient age at each cycle.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

The EQ-5D-5L was collected in XTEND-1 at baseline, Week 26 and Week 52 and responses were mapped to the EQ-5D-3L (Section B.3.4.2).

B.3.4.2 Mapping

In the XTEND-1 trial, EQ-5D-5L was used as a measure of HRQoL, and therefore, responses were mapped to EQ-5D-3L prior to the analysis. The mapping from EQ-5D-5L to EQ-5D-3L was conducted using the algorithm proposed by Decision Support Unit (Hernández Alava et al, 2017) (122), using the 'EEPRU dataset' (Hernández Alava et al, 2020) (123).

B.3.4.3 Health-related quality of life studies

B.3.4.3.1 Identification of studies

An SLR was completed on the 20th June 2022 to identify relevant HRQoL studies in patients with haemophilia. Overall, the SLR identified 22 publications reporting 20 studies on utilities. Of the 20 publications, 11 reported utilities data in primary costing studies, including six studies that were analyses of data from the CHESS and CHESS US trials. One study, Benson et al, 2021 (110) reported a value of 0.94 for general population utility, which was applied in this analysis. A summary of the search strategy is presented in Appendix H.

B.3.4.3.2 Description of identified studies

A complete description of the identified studies is presented in Appendix H.

B.3.4.4 Health-related quality of life data used in the cost-effectiveness analysis

Baseline utility values for people without a bleed were derived from age-adjusted general population utility values from the UK (124). Previous studies (110, 125) have reported that utility values for patients without a bleed and with FVIII above 50% are comparable to general population utilities, and clinical experts agreed that these patients would be comparable with the general population (28).

Utility decrements due to bleeding events and due to lower FVIII levels were obtained from XTEND-1 (34). Decrements due to bleeds were divided into two categories:

- Long-term utility loss caused by bleeding
- Short-term utility loss due to bleeding.

In the short-term, patients who experience a bleed present with a reduction in HRQoL due to associated pain and discomfort, and because additional doses of FVIII can be burdensome for patients. In the long-term, patients who have experienced bleeds often feel anxiety about repeated events, and this may limit the activities they are able to undertake. Clinical experts highlighted that the longer patients go without experiencing a bleed, the less anxious they feel (28). Utility decrements were therefore also applied for patients with lower FVIII levels. Troughs in FVIII are associated with a higher risk of bleeding events and can limit the activities patients are able to undertake (28).

Utility decrements were calculated based on patient-level data using the TOBIT model. The following independent variables were used for calculation:

- Occurrence of a bleed in the past 6 months; used to capture long-term utility loss caused by bleeding
- Occurrence of a bleed in the past 7 days; used to capture short-term utility lost due to bleeding
- Treatment arm
- Time since baseline in months
- Age
- Utility value measured via EQ-5D at baseline
- Proportion of time spent with <5% or <20% FVIII activity level.

In total, four regression models were performed using different independent variables. Two models applied the proportion of the time spent with FVIII activity level <20% (Model 1 and Model 3), while two used the proportion of the time spent with a FVIII activity level <5% (Model 2 and Model 4). For two models "days since study initiation" variable was used (Model 1 and Model 2), while for other two models, this variable was excluded.

Table 53: Utility regression models based on clinical trials data

Variable	Model 1	Model 2	Model 3	Model 4
Intercept	**0.4868**	**0.4864**	**0.4675**	**0.4491**
Baseline utility	**0.7692**	**0.7642**	**0.7747**	**0.7762**
7-day bleed disutility	**–0.0663**	**–0.0649**	**–0.0760**	**–0.0738**
6-month bleed disutility	**–0.0435**	**–0.0432**	**–0.0447**	**–0.0441**
Days since study initiation	**–0.00007**	**–0.00007**	Not used	Not used
Age	**–0.0053**	**–0.0052**	**–0.0053**	**–0.0052**
Proportion of time in <5%	Not used	–0.0782	Not used	**–0.1231**
Proportion of time in <20%	–0.0277	Not used	–0.0728	Not used
Model fit				
AIC	169.365	167.688	187.544	184.84
BIC	123.101	121.424	146.42	143.717

Note: Results in **bold** are statistically significant.
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Models that included time from study initiation had the best fit (Model 1 and Model 2), however the difference in fit between these models was minimal, as was the difference in the impact of bleeds. Model 1 was used in the base-case analysis, as patients treated with efanesoctocog alfa and emicizumab are not expected to spend time with FVIII below 5%. Disutility due to age was incorporated in the general population mortality

(Section B.3.3.3); therefore, the result of disutility due to age was not applied to avoid double counting. Scenario analyses using the disutility for <5% and excluding the impact of FVIII on HRQoL were included.

Table 54 summarised the utility values used in this cost-effectiveness analysis.

Table 54: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Baseline utility	Age-adjusted general population utility	N/A	Section B.3.4.3.1; p128	Patients with a higher FVIII level that have not experienced a bleed in the last 6 months are comparable with the general population
Disutility for FVIII <20%	–0.0277	–0.1901, –0.0337	Section B.3.4.1; p127	Patients with lower FVIII are less able to undertake their usual activities due to the higher probability of experiencing a bleed
Long-term disutility due to bleedings	–0.0435	–0.0729, –0.0135	Section B.3.4.1; p127	Patients with recent bleeding events may have ongoing anxiety about repeat events
Short-term disutility due to bleedings	–0.0663	–0.1051, –0.0247	Section B.3.4.1; p127	Bleeds can be painful for patients and limit their ability to conduct their usual activities
Bleeding duration (used for short-term disutility)	7 days		Section B.3.4.1; p127	–

Abbreviations: CI, confidence interval; FVIII, clotting Factor FVIII; N/A, not applicable; SE, standard error.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify relevant cost and health care resource use (HCRU) data to populate the economic model. Searches were completed on the 13th June 2022. Overall, the SLR identified 40 publications reporting on 31 studies. Of the 40 publications eligible for review, 17 reported costs data in primary costing studies, 14 reported costs data in cost-effectiveness studies, and eight reported costs data in cost modelling studies. An overview of the cost and HCRU SLR is presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Acquisition costs

The posology of considered treatments was based on the summary of product characteristics for each drug; average dosing was assumed (79, 86, 126). The unit cost for all drugs was based on NHS data (127), apart from cost data for efanesoctocog alfa and efmoroctocog alfa (list and PAS price), which were provided by the Company.

With regard to emicizumab treatment, patients are often administered FVIII in the event of an acute bleed. Any remaining FVIII may be wasted if no further bleeding occurs before its expiry date. Additional costs of such doses was included for the proportion of patients that do not experience a treated bleed (56%, HAVEN 3 Arm D). It was assumed that this would include the cost of 6000 IU of octocog alfa, every 4 cycles.

Dosing and drug costs for treatments included in the analysis are presented in Table 55.

Table 55: Dosing and drug cost

Treatment	Dose	Price per unit	Source
Baseline drug cost			
Efanesoctocog alfa (list price)	50 IU/kg QW	£2.40/IU	Sobi
Efanesoctocog alfa (PAS price)	50 IU/kg QW	[redacted]	Sobi
Emicizumab	3 mg/kg Q2W	£80.51/mg	BNF (128)
Efmoroctocog alfa (CMU contract price)	50 IU/kg Q4D	[redacted]	Sobi
Bleeding management drug cost			
Efanesoctocog alfa	25 IU/kg	£2.40/IU	Sobi
Efanesoctocog alfa (PAS price)	25 IU/kg	[redacted]	Sobi
Efmoroctocog alfa (CMU contract price)	25 IU/kg	[redacted]	Sobi
Octocog alfa	25 IU/kg	£0.71/IU	BNF (129)

Abbreviations: BIW, twice a week; BNF, British National Formulary; CMU, commercial medicines unit; PAS, patient access scheme; QW, once weekly; Q2W, every 2 weeks; Q4D, every 4 days; Q4W, every 4 weeks.

For prophylaxis, clinicians will round doses up or down to obtain the most efficient use of FVIII therapies and with emicizumab. As such, no drug wastage has been modelled. Relative dose intensity (RDI) was assumed to be 100% for each treatment.

B.3.5.2 Health-state unit costs and resource use

The model inputs are based all observed bleeds from the clinical trials, however not all bleeds are treated. The proportion of treated bleeds for each comparator was determined using trial data and MAIC outputs and is summarised in Table 56.

Table 56: Proportion of bleeds requiring treatment

Comparator	Proportion of treated bleeds
Efanesoctocog alfa	64%
Emicizumab	38%
Efmoroctocog alfa	64%

Clinical experts advised that in most cases, when a patient experiences a bleed on currently available FVIII therapy, treating to a FVIII level of 50% and aiming to bring the patient back to within normal FVIII levels is enough to resolve the most commonly occurring breakthrough bleeds (e.g. joint bleeds) (28). This tends to be resolved with 2x 2000 IU doses of rFVIII, equating to a dose of approximately 25 IU/kg. This is aligned with the required dose specified in the octocog alfa SmPC:

$$Required\ units\ =\ body\ weight\ (kg) \times\ desired\ factor\ VIII\ rise\ (\%) \left(\frac{IU}{dL}\right) \times\ 0.5$$

Clinicians also felt that the high sustained pharmacokinetic profile of efanesoctocog alfa would allow for 1x 25 IU/kg dose to resolve the same type of bleed (28).

For breakthrough bleeds while on emicizumab, factor levels need to be raised using a FVIII factor replacement therapy. Clinical experts advised that this is usually the same rFVIII treatment that they were being given prior to switching to emicizumab (28).

Table 57 summarises the dosage and the number of administrations for each bleeding event for efanesoctocog alfa, efmoroctocog alfa. Since the launch of emicizumab, a large number of patients have switched from a SHL to emicizumab, and so octocog alfa was chosen to treat bleeds for patients on emicizumab.

Table 57: Dosage and administration for bleeding management (Clinical opinion)

Treatment	Dose	Number of administrations per bleeding event	Source
Efanesoctocog alfa	25 IU/Kg	1	Clinician consultation report (28)
Octocog alfa	25 IU/Kg	2	Clinician consultation report (28)
Efmoroctocog alfa	25 IU/Kg	2	Clinician consultation report (28)

Abbreviations: IU, international unit; kg, kilogram.

No resource use was required for the “No bleeds” state. Therefore, no health-state costs were incurred in this health state. For the “Any bleeds” state, administration costs of bleeding management were included in the analysis. Bleed management procedure includes accident and emergency (A&E) visits, specialist visits, and nurse visits. The number of A&E and specialist visits required per event were estimated based on the study by Shrestha et al, 2017 (130). For each bleeding event, the study reported more

than one specialist visit, so it was assumed that an additional nurse visit would not be necessary. The same number of visits was used in the model for each considered treatment. The number of HCP contacts was obtained from US data, and clinicians confirmed that this data appeared reasonable, as typically patients would have a consultation with the haematologist, either face-to-face or via phone call, and avoid A&E, where possible (28).

Costs of ER, specialist, and nurse visits were based on the National Cost Collection for the year 2020–2021 (131). An A&E visit cost was based on the total average cost for Accident & Emergency from Healthcare Resource Groups (HRG) data. The cost of a specialist visit was based on the average *Outpatient Attendances Data for Clinical Haematology* (service code 303), while the nurse visit cost was based on *Specialist Nursing, Haemophilia Nursing Service, Adult, face to face* (currency code N17AF) cost. Cost data for bleeding management procedures are presented in Table 58.

Cost of blood tests was not included in the model, as it would not differ between intervention and comparators.

Table 58: Cost of bleeding management procedures

Procedure	Visits per bleed	Cost per procedure (£)	Source
ER visit	0.06	296.87	2021/22 National Cost Collection data (131)
Specialist visit	1.11	193.24	2021/22 National Cost Collection data (131)
Nurse visit	0	45.11	2021/22 National Cost Collection data (131)

Abbreviations: ER, emergency room.

B.3.5.3 Miscellaneous unit costs and resource use

No miscellaneous costs were considered in this analysis.

B.3.6 Severity

Severity weights are not expected to be applicable for this submission. Table 59 and Table 60 summarise the QALY shortfall in PUPs and PTPs, respectively. Expected QALYs were generated using England and Wales lifetables (121) and general population utility values for the UK derived from the HSE 2014 dataset reported by Hernandez-Alava et al, 2022 (124).

Table 59: QALY shortfall in PUPs

Treatment	Expected general population QALYs	Total QALYs in the model	Absolute shortfall	Proportional shortfall
Emicizumab	25.13	[redacted]	[redacted]	[redacted]
Efmoroctocog alfa		[redacted]	[redacted]	[redacted]

Abbreviations: PUPs, previously untreated patients; QALY, quality-adjusted life year.

Table 60: QALY shortfall PTPs

Treatment	Expected general population QALYs	Total QALYs in the model	Absolute shortfall	Proportional shortfall
Emicizumab	19.71	[redacted]	[redacted]	[redacted]

Abbreviations: PTPs, previously treated patients; QALY, quality-adjusted life year.

B.3.7 Uncertainty

Haemophilia A is a rare disease and generating comparative efficacy data can be challenging, as the number of patients included in clinical trials is typically small. While the methods applied to generate comparative efficacy data for this submission are in line with best practice, the nature of the disease leads to uncertainty in the estimates.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of base-case analysis inputs is provided in Table 61.

Table 61: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Efanesoctocog alfa ABR	1.11	Gamma (0.83 to 1.48)	Section B.3.3.2.1
Efmoroctocog alfa ABR IRR	0.29	Lognormal (0.17 to 0.51)	
Emicizumab Q2W ABR IRR	0.28	Lognormal (0.1 to 0.81)	
Efanesoctocog alfa treated bleeds ABR	0.71	Gamma (0.52 to 0.97)	
Efmoroctocog alfa treated bleeds ABR IRR	0.29	Lognormal (0.17 to 0.51)	
Emicizumab Q2W treated bleeds ABR IRR	0.47	Lognormal (0.15 to 1.44)	
Percentage of patients with bleeds, efanesoctocog alfa	0.23	Beta (0.16 to 5.31)	Section B.3.3.2.2
Percentage of patients with bleeds, efmoroctocog alfa OR	1.99	Lognormal (1.20 to 3.30)	
Percentage of patients with bleeds, emicizumab	0.56	Beta (0.43 to 3.68)	
A&E visits per bleed	0.06	Normal (0 to 2)	Section B.3.5.2
Haematologist visits per bleed	1.11	Normal (0 to 2)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
A&E cost per visit	296.87	Gamma (237.50 to 356.24)	
Haematologist cost per visit	538.88	Gamma (431.11 to 646.66)	
Efanesoctocog alfa, cost per unit	[redacted]	Fixed	Section B.3.5.1.1
Emicizumab, cost per unit	80.51	Fixed	
Efmoroctocog alfa, price per unit	[redacted]		
Octocog alfa, cost per unit	0.71	Fixed	
Disutility in the any bleed states	–0.0435	Beta (–0.0732 to –0.0137)	Section B.3.4.4
Occurrence of bleed	–0.0663	Beta (–0.1065 to –0.0260)	
Disutility for FVIII below 20%	–0.0277	Beta (–0.1347 to 0.0793)	

Abbreviations: ABR, annualised bleeding rate; A&E, accident and emergency; CI, confidence interval; FVIII, clotting Factor VIII; IRR, incidence rate ratio; OR, odds ratio; Q2W, every 2 weeks.

B.3.8.2 Assumptions

A summary of assumptions is provided in Table 62.

Table 62: Assumptions

Assumption	Justification
The ABR in Arm A of XTEND-1 is representative of the of the expected ABR for patients treated with efanesoctocog alfa in clinical practice. The IRR from the MAIC comparing efanesoctocog alfa with emicizumab Q2W can be applied to this baseline to obtain the ABR for patients treated with emicizumab	Arm A of XTEND-1 contained patients that had previously been treated with a prophylactic regimen, which is usual clinical practice in the treatment of patients with severe haemophilia A within the UK. While the IRR from the MAIC was assessed in the prior-OD populations from XTEND-1 and HAVEN 3, this was the only analysis possible comparing with emicizumab Q2W. However, the results of the ITC were consistent across the different analyses comparing with emicizumab and, prior-OD is not expected to be a treatment effect modifier. These assumptions were evaluated in scenario analyses
The proportion of patients without a bleed for emicizumab can be taken directly from HAVEN 3 without need for adjustment	It was not possible to generate an estimate of relative efficacy for emicizumab due to differences in the time frames reported. This assumption is considered conservative, as the proportion of patients experiencing a bleed in XTEND-1 after MAIC weights have been applied is lower than the unadjusted figure

Assumption	Justification
Patients with severe haemophilia A that have not experienced a bleed in the last 6 months and with FVIII above 20% have comparable QoL with those in the general population	In line with clinical expert opinion and previous studies (28, 110, 125)
There is no drug wastage associated with prophylaxis for severe haemophilia A	In clinical practice, the dose of rFVIII or emicizumab used can be tailored to the patient, and typically clinicians will round the dose up or down to achieve minimal wastage
Patients with a bleed will require additional doses of rFVIII and a proportion may require additional HCP contacts	In line with published literature (130) and clinical opinion (28). Clinicians confirmed that the modelled rate of HCPs contacts was reasonable for a UK population (28)
Patients who have a bleed while on prophylaxis with emicizumab will be treated with octocog alfa	This assumption does not impact efficacy and is in line with clinical opinion and market trends (28)

Abbreviations: ABR, annualised bleed rate; FVIII, clotting factor VIII; HCP, healthcare practitioner; IRR, incidence rate ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OD, on-demand; QoL, quality of life; Q2W, every 2 weeks; rFVIII, recombinant clotting Factor VIII; UK, United Kingdom.

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

B.3.9.1.1 PUPs

Table 63 presents the base-case results for PUPs, while Table 64 presents the net health benefit. Efanesoctocog alfa is associated with more QALYs than emicizumab or efmoroctocog alfa. At PAS price, efanesoctocog alfa had lower costs than emicizumab and thus dominated emicizumab. Efanesoctocog alfa had an incremental cost-effectiveness ratio (ICER) of £18,211 compared with efmoroctocog alfa when the net price was used for both drugs.

Table 63: Base-case results, PUPs (efanesoctocog alfa PAS price, efmoroctocog alfa PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	[redacted]	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	[redacted]	[redacted]	0.000	[redacted]	£18,211	£18,211
Emicizumab	[redacted]	27.054	[redacted]	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 64: Net health benefit, PUPs (efanesoctocog alfa PAS price, efmoroctocog alfa PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Efmoroctocog alfa	[redacted]	22.940	–	–	–	–
Efanesoctocog alfa	[redacted]	23.500	[redacted]	[redacted]	0.05	0.22
Emicizumab	[redacted]	22.806	[redacted]	[redacted]	–411.01	–274.05

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.9.1.2 PTPs

Table 65 presents the base-case results for PTPs and Table 66 presents the NHB. Efanesoctocog alfa produced more QALYs than emicizumab at a lower cost when applying the PAS price, and thus dominated emicizumab.

Table 65: Base-case results, PTPs (efanesoctocog alfa 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]	22.369	[redacted]	–	–	–	–	–
Emicizumab	[redacted]	22.369	[redacted]	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 66: Net health benefit, PTPs (efanesoctocog alfa PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Efanesoctocog alfa	[redacted]	[redacted]	–	–	–	–
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	–475.60	–317.26

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 5,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

Table 67 presents the outputs of the PSA for PUPs. Outcomes were congruent with outputs of the deterministic analysis. Figure 20 presents the CEAC. Efanesoctocog alfa dominated emicizumab in all simulations when using the PAS price. Compared with efmoroctocog alfa, efanesoctocog alfa was [redacted] of simulations, and cost-effective in [redacted] of simulations assuming a willingness-to-pay (WTP) threshold of £20,000 per QALY, and [redacted] of simulations using a threshold of £30,000 per QALY.

Table 67: Probabilistic results, PUPs (efanesoctocog alfa PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	[redacted]	–	–	–	–
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£19,633	£19,633
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PUP, previously untreated patients; QALYs, quality-adjusted life years.

Figure 18: Cost-effectiveness plane vs efmoroctocog alfa, PUPs

Abbreviations: PUP, previously untreated patients; QALYs, quality-adjusted life years.

Figure 19: Cost-effectiveness plane vs emicizumab, PUPs

Abbreviations: PUP, previously untreated patients; QALYs, quality-adjusted life years.

Figure 20: Cost-effectiveness acceptability curve, PUPs

Abbreviations: PUP, previously untreated patients; WTP, willingness-to-pay.

Table 68 presents the results of the PSA for the PTP population. Results are aligned with those from the deterministic analysis. Figure 21 and Figure 22 present the CEP and CEAC for the PTP population respectively, demonstrating that efanesoctocog alfa is dominant in all simulations.

Table 68: Probabilistic results, PTPs (efanesoctocog alfa PAS price)

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

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PTP, previously treated patients; QALYs, quality-adjusted life year.

Figure 21: Cost-effectiveness plane vs emicizumab, PTPs

Abbreviations: PTP, previously treated patients; QALYs, quality-adjusted life years.

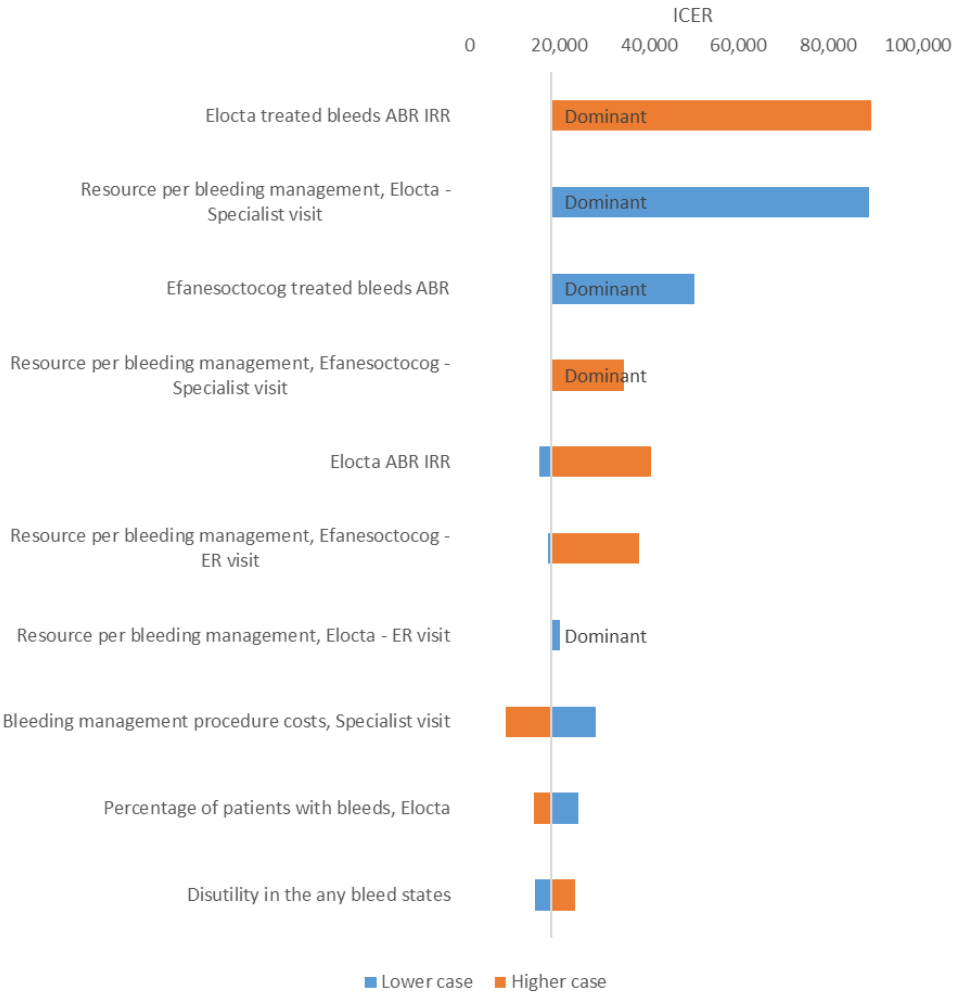
Figure 22: Cost-effectiveness acceptability curve, PTPs

Abbreviations: PTP, previously treated patients; WTP, willingness-to-pay.

B.3.10.2 Deterministic sensitivity analysis

Figure 23 presents the tornado diagram for the comparison with efmoroctocog alfa in PUPs. Results were sensitive to the ABRs for all bleeds and for treated bleeds, as well as the resource use associated with bleeds. However, the resource use associated with bleeds was varied independently for each comparator, which is likely to overestimate the uncertainty, as in reality, these parameters are likely to be correlated.

Figure 23: Tornado diagram efanesoctocog alfa vs efmoroctocog alfa, PUPs (net prices)



Abbreviations: ABR, annualised bleeding rate; ER, emergency room; ICER, incremental cost-effectiveness ratio; IRR, incidence rate ratio; PUPs, previously untreated patients.

Efanesoctocog alfa was dominant compared with emicizumab in both PUPs and PTPs, and remained so at the upper and lower value of all parameters, thus tornado diagrams were not produced. Instead, tornado diagrams for incremental costs and QALYs were produced for comparisons with emicizumab in PUPs and PTPs. Figure 24 and Figure 25 present the inputs that have the largest impact on incremental QALYs and costs in PUPs, respectively. Figure 26 and Figure 27 present the inputs that have the largest impact on incremental QALYs and costs in PTPs, respectively. For each population, the

list of influential factors was the same. The proportion of patients experiencing a bleed in each cycle was a driver of QALYs, as were the disutilities associated with bleeds, and the ABR for emicizumab. The number of bleeds and associated resource use were drivers of costs.

Figure 24: Tornado diagram for inputs impacting incremental QALYs vs emicizumab, PUPs

Abbreviations: ABR, annualised bleeding rate; IRR, incidence rate ratio; PUPs, previously untreated patients; QALY, quality-adjusted life year; Q2W, every 2 weeks.

Figure 25: Tornado diagram for inputs impacting incremental costs vs emicizumab, PUPs

Abbreviations: ABR, annualised bleeding rate; ER, emergency room; IRR, incidence rate ratio; PUPs, previously untreated patients; Q2W, every 2 weeks.

Figure 26: Tornado diagram for inputs impacting incremental QALYs vs emicizumab, PTPs

Abbreviations: ABR, annualised bleeding rate; IRR, incidence rate ratio; PTPs, previously treated patients; QALY, quality-adjusted life year; Q2W, every 2 weeks.

Figure 27: Tornado diagram for inputs impacting incremental costs vs emicizumab, PTPs

Abbreviations: ABR, annualised bleeding rate; ER, emergency room; IRR, incidence rate ratio; PTPs, previously treated patients; Q2W, every 2 weeks.

B.3.10.3 Scenario analysis

Table 69 summarises the different scenario analyses and Table 70 and Table 71 present the results for PUPs and PTPs, respectively.

In all scenarios, efanesoctocog alfa remains the most effective treatment option and remains dominant compared to emicizumab in all scenarios. The scenarios with the biggest impact on incremental QALYs are those that adjust the disutility associated with lower FVIII levels, or the proportion of patients experiencing a bleed.

Compared with efmoroctocog alfa, efanesoctocog alfa remained cost-effective at a WTP threshold of £30,000 per QALY in all but three of the scenarios. The first of these is the scenario without discounting, as the incremental cost associated with efanesoctocog alfa increased. The second in the scenario using a lower ABR, derived from HAVEN 3 Arm B. The lower bleed rate led to fewer incremental QALYs and a higher incremental cost due to smaller savings resulting from avoided bleeds. However, this scenario is based on emicizumab data, rather than data for efmoroctocog alfa. The third is the scenario that excluded the disutility for FVIII levels <20% (20 IU/dL). An increase in the ICER in this scenario was expected, as the benefits of sustained FVIII levels are a driver of QALYs for efanesoctocog alfa.

Table 69: Summary of scenario analyses

Scenario	Details
Discount rate of 6%	Discount rate for costs and outcomes set to 6%
No discounting	No discounting for costs or outcomes
Treated bleeds only	The ABR for treated bleeds is applied in the model, with all bleeds assumed to be treated
Baseline ABR from HAVEN 3 Arm B	The model used the baselines rates any bleeds (2.6) and treated bleed (1.3) for Arm B of Haven 3 to inform the emicizumab arm and calculates ABRs for comparators relative to this baseline
Baseline ABR from XTEND-1 Arm B	The baseline ABRs for any bleeds (0.88) and treated bleeds (0.61) were taken from Arm B of XTEND-1 during the prophylaxis period

Scenario	Details
Baseline ABR from HAVEN 3 Arm D	The model used the baselines rates any bleeds (3.3) and treated bleed (1.6) for Arm D of Haven 3 to inform the emicizumab arm, and calculated ABRs for comparators relative to this baseline
% of patients with bleeds on efanesoctocog alfa from XTEND-1 12-month data	12-month data from XTEND-1 was used to calculate the proportion of patients experiencing a bleed in each cycle for efanesoctocog alfa
% of patients with bleeds on emicizumab from HAVEN 3 Arm A	The proportion of patients experiencing a bleed in the emicizumab arm was taken from Arm A of HAVEN 3
% of patients with bleeds on emicizumab from HAVEN 3 Arm B	The proportion of patients experiencing a bleed in the emicizumab arm was taken from Arm B of HAVEN 3
Chromogenic assay for assessing FVIII levels	Chromogenic assay for assessing FVIII levels for efanesoctocog alfa and efmoroctocog alfa
No disutility associated with lower FVIII levels	Disutility values for FVIII below 20% were excluded
Disutility for FVIII <5%	Model 2 was used to generate utility values
Drug wastage for emicizumab	Drug wastage was included for emicizumab, using the method of moments

Abbreviations: ABR, annualised bleeding rates; FVIII, clotting Factor VIII.

Table 70: Scenario analyses, PUPs

Scenario	Vs efmoroctocog alfa			Vs emicizumab		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	£18,211	[redacted]	[redacted]	Dominant
Discount rate of 6%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No discounting	[redacted]	[redacted]	£54,211	[redacted]	[redacted]	Dominant
Treated bleeds only	[redacted]	[redacted]	£19,345	[redacted]	[redacted]	Dominant
Baseline ABR from HAVEN 3 Arm B	[redacted]	[redacted]	£36,995	[redacted]	[redacted]	Dominant
Baseline ABR from XTEND-1 Arm B	[redacted]	[redacted]	£20,593	[redacted]	[redacted]	Dominant
Baseline ABR from HAVEN 3 Arm D	[redacted]	[redacted]	£11,432	[redacted]	[redacted]	Dominant

Scenario	Vs efmoroctocog alfa			Vs emicizumab		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
% of patients with bleeds on efanesoctocog alfa from XTEND-1 12-month data	[redacted]	[redacted]	£18,028	[redacted]	[redacted]	Dominant
% of patients with bleeds on emicizumab from HAVEN 3 Arm A	[redacted]	[redacted]	£18,211	[redacted]	[redacted]	Dominant
% of patients with bleeds on emicizumab from HAVEN 3 Arm B	[redacted]	[redacted]	£18,211	[redacted]	[redacted]	Dominant
Chromogenic assay for assessing FVIII levels	[redacted]	[redacted]	£13,821	[redacted]	[redacted]	Dominant
No disutility associated with lower FVIII levels	[redacted]	[redacted]	£36,345	[redacted]	[redacted]	Dominant
Disutility for FVIII <5%	[redacted]	[redacted]	£10,648	[redacted]	[redacted]	Dominant
Drug wastage for emicizumab	[redacted]	[redacted]	£18,211	[redacted]	[redacted]	Dominant

Abbreviations: ABR, annualised bleeding rate; FVIII, clotting Factor VIII; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 71: Scenario analyses, PTPs

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	Dominant
Discount rate of 6%	[redacted]	[redacted]	Dominant
No discounting	[redacted]	[redacted]	Dominant
Treated bleeds only	[redacted]	[redacted]	Dominant
Baseline ABR from HAVEN 3 Arm B	[redacted]	[redacted]	Dominant
Baseline ABR from XTEND-1 Arm B	[redacted]	[redacted]	Dominant
Baseline ABR from HAVEN 3 Arm D	[redacted]	[redacted]	Dominant
% of patients with bleeds on efanesoctocog alfa from XTEND-1 pooled arms	[redacted]	[redacted]	Dominant

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
% of patients with bleeds on emicizumab from HAVEN 3 Arm A	[redacted]	[redacted]	Dominant
% of patients with bleeds on emicizumab from HAVEN 3 Arm B	[redacted]	[redacted]	Dominant
Chromogenic assay for assessing FVIII levels	[redacted]	[redacted]	Dominant
No disutility associated with lower FVIII levels	[redacted]	[redacted]	Dominant
Disutility for FVIII <5%	[redacted]	[redacted]	Dominant
Drug wastage for emicizumab	[redacted]	[redacted]	Dominant

Abbreviations: ABR, annualised bleeding rate; FVIII, clotting Factor VIII; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.10.4 Summary of sensitivity analyses results

Sensitivity analyses are mostly well aligned with the deterministic base-case results. Outputs of the PSA are well aligned with the deterministic base case and the model does not exhibit a large amount of non-linearity.

Deterministic sensitivity analysis and scenario analysis suggest that there is uncertainty introduced by the ABRs and proportion of patients experiencing bleeds. These are the key clinical inputs in the model, however, due to the lack of a control arm in XTEND-1, it was necessary to derive these inputs for comparators using the ITC. However, in all sensitivity analyses, efanesoctocog alfa remains the most effective treatment.

B.3.11 Subgroup analysis

No subgroup analyses have been implemented.

B.3.12 Benefits not captured in the QALY calculation

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.

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 (17). 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 (23). 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 (22).

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 (28). 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.

B.3.13 Validation

Quality control of the economic model was performed by the model developers and by health economists who were independent from the development of the model. This included cell-by-cell checks and logical checks.

The approach to modelling was validated with UK clinical experts (28). Expert input was sought on:

- The current treatment pathway and the positioning of efanesoctocog alfa
- Clinical data to be used in the model
- The impact of factor levels on HRQoL
- Durability of the treatment effect
- Resource use.

Additionally, the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) model validation assessment tool was completed (132), with results presented in Appendix Q.

B.3.14 Interpretation and conclusions of economic evidence

This cost-effectiveness analysis estimates that in PUPs, efanesoctocog alfa is more effective than emicizumab or efmoroctocog alfa, producing more QALYs than either comparator. Using the net prices for efanesoctocog alfa and efmoroctocog alfa, efanesoctocog alfa is associated with an incremental cost of £[redacted], leading to an ICER of £18,211, making it a cost-effective treatment option at a WTP threshold of £20,000 per QALY. Compared with emicizumab at list price, efanesoctocog alfa is cost saving and therefore dominant. In PTPs, efanesoctocog alfa is more effective than emicizumab and less costly, making it the dominant treatment option.

This analysis has been conducted in line with the NICE reference case and is based on data from the XTEND-1 study, which included patients in the UK and is considered generalisable to UK clinical practice.

A key weakness of this analysis is the lack of a comparator arm in XTEND-1, meaning the analysis relies on ITCs and naïve comparisons to inform outcomes for comparators. While appropriate methods have been used to address this, it introduces additional uncertainty into the analysis. The PSA demonstrates that results are stable to parameter uncertainty, with efanesoctocog alfa remaining dominant in all simulations across PUPs and PTPs when compared with emicizumab. Compared with efmoroctocog alfa, efanesoctocog alfa was cost-effective in [redacted]% of simulations at a WTP threshold of £30,000 per QALY.

A second weakness is the inability of the model to capture some of the long-term outcomes of severe haemophilia A, including the cumulative effect of bleeding into the joints, leading to deterioration of joint health and a reduction in quality of life over a patient's lifetime. This can also lead to requirement for joint replacement surgeries, which can lead to further reductions in QoL.

Overall, the base-case results and sensitivity analyses demonstrate that when using the PAS price, efanesoctocog alfa is a cost-effective treatment option for both PUPs and PTPs with severe haemophilia A.

Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Additional methodology information from XTEND-1

Appendix N: Additional efficacy data from XTEND-1

Appendix O: Efficacy and safety data from XTEND-Kids

Appendix P: Summary of pre-study 242HA201/OBS16221

Appendix Q: AdViSHE checklist

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Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Efanesoctocog alfa (brand name TBC)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

To treat and prevent bleeding episodes in patients with severe haemophilia A

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Efanesoctocog alfa does not yet have UK marketing authorisation for the indication in this submission. Food and Drug Administration (FDA) Breakthrough Therapy designation for haemophilia A was granted in February 2023 (1). A regulatory submission was made to the European Medicines Agency (EMA) in Q2 2023, with submission to the Medicines and Healthcare products Regulatory Agency (MHRA) anticipated in [redacted]. CHMP positive opinion is anticipated in Q1 2024 and MHRA regulatory approval in [redacted].

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

As part of an ongoing commitment to supporting people with haemophilia to lead the lives they want and deserve, we have engaged with or provided the following financial support to The Haemophilia Society in the form of grants and sponsorships provided in 2023:

Newly Diagnosed Weekends (£5,000)

Sponsorship provided by multiple partners to support the Haemophilia Society to deliver a series of 'Newly Diagnosed Weekends', designed to support families who have a child recently diagnosed with haemophilia.

Information days (£10,000)

Sponsorship provided by multiple partners to support the Haemophilia Society to deliver a series of information days, bringing together people diagnosed with different bleeding disorders to provide information and support.

Talking Red (£10,000)

Sponsorship provided by multiple partners to support the Haemophilia Society to launch a campaign raising awareness on the impact of bleeding disorders on women and girls.

Yorkshire 3 Peaks Challenge (£3,000)

Sponsorship provided by multiple partners to support the Haemophilia Society to host the 'Yorkshire 3 Peaks Challenge' for a group of people with haemophilia as part of a wider campaign to support physical activity in people with haemophilia.

Medical information requests

The Haemophilia Society requested a meeting with Sobi to discuss efanesoctocog alfa with regards to the health technology assessment (HTA) process. This was in terms of timelines and medical information support.

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Condition that the medicine treats

Haemophilia A is a rare bleeding disorder which results from the deficiency or absence of a protein known as factor VIII (FVIII), an essential component in the blood clotting process. Haemophilia A is the most common type of haemophilia, accounting for 80% of all cases (2), and is an X-linked recessive genetic disorder. This means that it is usually inherited from a mother who carries the genetic mutation on one of her X chromosomes (3). As males only have one X chromosome, the disorder most commonly affects males. Females tend to be carriers of the disease but may demonstrate bleeding symptoms requiring treatment (4).

Symptoms of severe haemophilia A often arise in the first months of life, whereas mild or moderate disease usually presents later in childhood or adolescence, often incidentally or following trauma (5). Patients with mild haemophilia A have FVIII plasma levels of >5–<40%, those with moderate disease have levels between 1–5%, and those with severe disease have FVIII levels <1% (5-7). Normal FVIII levels range between 50–150% (3).

As people with haemophilia A do not have enough FVIII, their blood cannot clot properly and they will experience excessive bleeding (8). Depending on severity of the disease, patients can present with easy bruising, bleeding into the joints and muscles, or bleeding into internal organs (5). Frequent bleeding into the joint (haemarthrosis) leads to irreversible disease of the joint (haemophilic arthropathy); a debilitating condition associated with inflammation, pain, and joint damage that significantly impacts mobility and the quality of life of patients (9).

Registry data from the UK Haemophilia Centres Doctors' Organisation (UKHCDO) suggests that in 2021–2022, there were 8,959 patients registered with haemophilia A in the UK (4).

What is the impact of haemophilia A on a person's quality of life?

Despite the availability of FVIII replacement and non-factor therapy, patients living with haemophilia A may still experience bleeding while receiving treatment (breakthrough bleeding), resulting in pain, joint problems, functional impairment, and impaired work and societal participation. An uncommon yet serious complication of haemophilia A is intracranial haemorrhage (bleeding into the brain), which can be devastating (10).

Studies have reported that patients experience depression, anxiety, and low self-esteem/self-autonomy (11-13), which can impact on normal daily activities, including travel, commuting, parenting, hobbies, physical activity, etc. One study reported that having one or more joint bleeds was associated with poorer quality of life scores compared with having no joint bleeds (14). Patients with moderate or severe haemophilia A have poorer quality of life scores compared with those with mild disease (15). In a 2021 UK survey conducted by the Haemophilia Society, 75% of patients with bleeding disorders stated that they avoided certain activities because they were too risky (16).

Haemophilia A can also impact employment and associated earnings. Patients are less likely to be employed than the general population (17), can experience a loss in wages, and are likely to undertake part-time work instead of full-time work (18).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How haemophilia A is diagnosed

If there is a family history of haemophilia A, a blood sample can be obtained from the baby's umbilical cord shortly after birth to measure FVIII levels (19).

If a patient has no family history of haemophilia A, then a diagnosis can be reached by looking at the patient's (19):

- history, signs and symptoms of bleeding
- family history of bleeding
- blood tests – a general test of blood clotting called a clotting screen, which can be performed at all hospitals, may suggest haemophilia and lead to referral for specific tests for FVIII.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

For patients with severe haemophilia A, the recommended treatment is regular replacement therapy (prophylaxis) with recombinant FVIII (rFVIII) or another suitable product to prevent bleeding (5). The aim of prophylaxis is to prevent spontaneous bleeding and joint damage (3). There are currently two types of rFVIII therapy; standard half-life (SHL) rFVIII or extended half-life (EHL) rFVIII therapy (20). SHLs may be administered from three times a week to every day, depending on the patient, whereas EHLs contain a molecule that has been modified in a way to delay the breakdown of FVIII in the body, resulting in higher levels of FVIII lasting longer in the blood, and leading to less frequent injections (21).

Patients may also receive non-factor replacement therapy, namely emicizumab (23). Emicizumab is a humanised monoclonal antibody that mimics the function of activated FVIII. It is indicated for prophylactic treatment of patients with haemophilia A who have FVIII inhibitors, or in patients without inhibitors who have severe haemophilia A or moderate haemophilia A with a severe phenotype. Patients receive emicizumab via injection under the skin (subcutaneously) initially at 3 mg/kg once weekly for 4 weeks, then as maintenance at either 1.5 mg/kg once weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks (22). Use of emicizumab is limited to prophylaxis, and therefore, additional

rFVIII therapy is required to treat bleeds resulting from trauma or surgical procedures in patients receiving emicizumab (23).

In the UK, prophylaxis is initiated at an increasingly early age, while adults who did not receive prophylaxis as a child commence treatment later in life to preserve musculoskeletal function (24). It is recommended that all children with severe haemophilia A, and patients of any severity who have had one or more spontaneous joint bleeds should receive prophylaxis (24).

Patients with haemophilia A may also receive rFVIII replacement therapy as needed, or 'on-demand'. On-demand treatment is the administration of rFVIII replacement therapy at the time of a bleeding event. While prophylactic treatments can reduce bleeding rates, on-demand therapies are still recommended on an 'as needed' basis for the treatment of sudden (acute) bleeds, and during surgery (3).

Some patients develop inhibitors to FVIII. For these patients, immune tolerance induction (ITI) therapy can be administered, with the aim to eliminate the inhibitor (3, 25). Guidelines recommend that ITI therapy should be given using the rFVIII therapy a patient is currently receiving (5).

Efanesoctocog alfa is anticipated to be suitable for treating and preventing bleeds in previously untreated patients and previously treated patients who have severe haemophilia A, and it is anticipated that previously treated patients who have insufficient bleed control will switch from existing rFVIII replacement therapy or emicizumab to efanesoctocog alfa.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Efanesoctocog alfa was studied in an open-label, multicentre Phase 3 trial, XTEND-1 (NCT04161495) in previously treated patients with severe haemophilia A.

During XTEND-1, 29 patients took part in a qualitative semi-structured interview within 6 months of exiting the study. Pain was the most common pre-study symptom, with 93% (28/29) of patients experiencing carrying degrees of pain in more than one joint (e.g. knees, ankles, elbows). Patients also reported that haemophilia A-related pain and other symptoms affected their day-to-day activities, particularly their physical functioning. Of the 28 patients who had pre-study pain, 25 (89%) reported meaningful improvements in joint pain after receiving efanesoctocog alfa. The remaining three patients who reported no change in joint pain intensity with efanesoctocog alfa noted that improvements were not expected, as they had sustained extensive cumulative joint damage over the years from repeated joint bleeds.

Patients with mild impairments before the study indicated that the level of improvement after the study was substantial in terms of overall functioning and quality of life.

All 29 patients who completed the exit questionnaire identified efanesoctocog alfa as their preferred haemophilia A treatment over their pre-study treatment. Patients noted that haemophilia-related pain is very impactful, and thus, an important concept to measure. Patients also expressed a preference for less frequent infusions required, convenience, greater feelings of confidence in projection, less fatigue, and improved quality of life.

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Efanesoctocog alfa is a new class of rFVIII replacement therapy, known as a high sustained factor (HSF), for the treatment of haemophilia A in adults and children. Existing rFVIII replacement therapies require frequent intravenous administration several times a week or every other day to maintain FVIII levels above a threshold of more than the historical target threshold of 1% (26).

Despite treatment advances in haemophilia A, patients continue to experience bleeds, pain, and disability, which have a major impact on physical, mental, and emotional health. World Federation of Haemophilia guidelines acknowledge that most clinicians treat haemophilia by aiming for FVIII trough levels (lowest levels) of 3–5%. However, there is increasing evidence that suggests factor levels of at least around 30% are necessary to substantially decrease bleeding risk. Indeed, a recent review highlighted that factor levels of up to 50% may be needed to achieve a near-zero joint bleed rate.

Consequently, there is a notable unmet need for a high-sustained FVIIII therapy that can control bleeds and provide optimal prevention of bleeding episodes by maintaining factor levels in the normal to near-normal range (>40%), while minimising treatment burden (27-29).

Due to its design and prolonged half-life, efanesoctocog alfa will be the only FVIII replacement therapy that will allow patients with severe haemophilia to maintain high FVIII activity levels within the normal to near-normal (>40%) range for up to 4 days after injection, and within the mild haemophilia range (15%) at 7 days after injection. With high FVIII levels, efanesoctocog alfa reduces bleeds, offers protection against joint damage, and improves pain and quality of life, aiding patients to live a more normal life (30).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☐ Yes

☒No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Not applicable.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

For prophylactic treatment, efanesoctocog alfa should be administered intravenously at a dose of 50 IU/kg once weekly. For on-demand treatment, efanesoctocog alfa should be administered intravenously at a dose of 50 IU/kg, as required.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical efficacy (how well the treatment works) and safety of efanesoctocog alfa was studied in two multicentre Phase 3 trials; XTEND-1 (NCT04161495) and XTEND-Kids (NCT04759131). There is one ongoing, long-term extension study investigating the safety and efficacy of efanesoctocog alfa in previously treated patients with haemophilia A (XTEND-ed). The study has enrolled 261 patients and is estimated to complete in February 2027.

XTEND-1 (30)

XTEND-1 completed in February 2022, and included patients with severe haemophilia A who were 12 years or over and who had previously received treatment. The study had two treatment arms:

- **Arm A** included patients who were assigned to receive efanesoctocog alfa at a dose of 50 IU/kg intravenously, once weekly on a prophylaxis treatment regimen for 52 weeks. To be included in Arm A, patients were required to have been receiving a prophylactic regimen prior to study enrolment.
- **Arm B** included patients who were on an on-demand treatment regimen prior to the study. To be included in Arm B, patients were required to have been receiving on-demand treatment with a marketed FVIII therapy, and to have had at least six bleeding episodes in the last 6 months or at least 12 bleeding episodes in the last 12 months. Arm B comprised two phases:
    - On-demand phase: patients received efanesoctocog alfa at a dose of 50 IU/kg intravenously as on-demand treatment of bleeding episodes for the first 26 weeks
    - Prophylaxis phase: patients switched to receive efanesoctocog alfa at a dose of 50 IU/kg intravenously, once weekly as a prophylaxis treatment regimen for a further 26 weeks.

A total of 159 patients were enrolled; 133 in Arm A, and 26 in Arm B.

XTEND-Kids (31)

XTEND-Kids completed in January 2023, and was a Phase 3, open-label, multicentre study evaluating the safety, efficacy, and pharmacokinetics (how the human body interacts with the drug) of efanesoctocog alfa in previously treated children (less than 12 years old) with severe haemophilia A.

To be included, patients needed to have received previous treatment with any FVIII therapy:

- Patients between the ages of 6–12 years were required to have at least 150 exposure days to prior therapy
- Patients under 6 years were required to have at least 50 exposure days to prior therapy.

In total, 74 male previously treated patients were treated with efanesoctocog alfa.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

XTEND-1 (30)

In XTEND-1, efanesoctocog alfa administered as weekly prophylaxis in adolescent and adult (aged 12 years or over) previously treated patients with severe haemophilia A demonstrated notable protection against bleeds and a clinically meaningful treatment effect. The mean annualised bleed rate (ABR) was 0.71 (Q1; Q3: 0.52; 0.97) and median ABR was 0.00 (Q1; Q3: 0.00; 1.04).

ABRs were consistently low across type of bleed (spontaneous or traumatic) and location of bleed (joint, muscle, internal, or skin/mucosa), when including untreated and treated bleeding episodes, as well as in all subgroups studied including patients aged 12 through 17 years. Weekly prophylaxis with efanesoctocog alfa had improved protection against bleeds vs pre-study FVIII prophylaxis (with currently available FVIII replacement therapy) – there was a 77% reduction in estimated mean ABR in patients already on a pre-study prophylactic treatment regimen.

Weekly prophylaxis with efanesoctocog alfa demonstrated statistically significant improvements in physical functioning and pain. Furthermore, prophylaxis with efanesoctocog alfa demonstrated statistically significant improvement in the clinical symptoms and signs of joint damage, reflected by a meaningful reduction in Haemophilia Joint Health Score (HJHS). Notably, taking into consideration that the majority of patients were already on prophylactic treatment prior to XTEND-1, changes from baseline observed in this study represent a clinically important benefit with efanesoctocog alfa over the existing standard-of-care prophylactic treatment.

Efanesoctocog alfa was effective for the treatment of bleeds. Most of the bleeds (96.7%) were controlled by a single injection with a mean dose per injection of 49.56 IU/kg, and the haemostatic efficacy in treatment of bleeds was rated by the participants as excellent or good in 94.9% of first injections.

Management of bleeds during surgery was assessed in 12 major surgical procedures in 11 patients. Responses with efanesoctocog alfa were rated as ‘excellent’ by investigators/surgeons in all 12 surgeries, indicating that blood loss was comparable to what would be expected for a patient who does not have haemophilia. A single dose of efanesoctocog alfa was sufficient to prevent bleeding during/post surgery. Efanesoctocog alfa maintained plasma FVIII activity in the normal to near-normal range (>40%) for 4 days post-administration. Plasma FVIII activity was maintained at 15% 7 days post-administration.

XTEND-Kids (31)

In XTEND-Kids, the development of inhibitors was monitored but inhibitors to FVIII were not detected in any patients (0% [95% confidence interval (CI)] 0, 4.9]). Efanesoctocog alfa maintained FVIII levels in the normal to near-normal range. Treatment with efanesoctocog alfa was associated with low bleed rates, with a median (interquartile range) and mean ABRs (95% CI) of 0.00 (0.00, 1.02) and 0.89 (0.56, 1.42), respectively. Most bleeds resolved with a single 50 IU/kg dose, and response to treatment was rated as excellent/good for 98% of evaluated injections. Prevention of bleeding during surgery (perioperative haemostasis) was rated as excellent in both major surgeries that occurred. In children <12 years old, efanesoctocog alfa maintained mean FVIII activity >40% for 3 days, >15% for around 5 days, and >10% for around 7 days.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life

for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

XTEND-1 evaluated the impact of efanesoctocog alfa treatment on health-related quality of life via a number of measures, including the Haem-A-QoL/Haemo-QoL, EQ-5D-5L, and PROMIS instruments (30).

Haem-A-QoL/Haemo-QoL

Quality of life data were collected in adult patients aged 17 years or older via the Haem-A-QoL questionnaire and in adolescent patients aged 13–16 years via the Haemo-QoL questionnaires. Lower scores represent better QoL; therefore, a negative change from baseline measurements represents improvement during the course of the study.

For patients aged 17 years and older, there was a notable improvement in Haem-A-QoL physical health score. In patients aged 13–16 years completing the Haemo-QoL questionnaire, the greatest improvements were in the domains of ‘perceived support’, ‘friends’, and ‘sports and school’.

EQ-5D-5L

The EQ-5D-5L was used to assess mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Overall, the percentages of patients who reported no problems generally increased from baseline to end of study in all domains except self-care and anxiety/depression which remained unchanged.

PROMIS

Patients had a statistically significant improvement in pain, as measured by the PROMIS Pain Intensity first item score, following 52 weeks of efanesoctocog alfa treatment. This was supported by an improvement in overall pain intensity.

Overall, weekly prophylaxis with efanesoctocog alfa was associated with improvements in physical functioning and pain. These findings were supported by the exit interviews that confirmed the magnitude of observed improvements in physical functioning and pain were important to patients with Haemophilia A.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

XTEND-1 (30)

Efanesoctocog alfa was generally well tolerated and reported side effects were generally consistent with what is expected in an adult and adolescent population treated for severe haemophilia A. Patients did not develop an inhibitor to FVIII, and there were no reports of serious allergic reaction, anaphylaxis, or vascular thrombotic events.

The most common side effects were headache (20.1% of patients), joint pain (arthralgia; 16.4% of patients), fall (6.3% of patients), and back pain (5.7% of patients).

XTEND-Kids (31)

The most common side effects occurring in more than 10% of patients included a positive SARS-CoV-2 test (14.9% of patients), upper respiratory tract infection (14.9% of patients), and fever (pyrexia; 12.2% of patients). No inhibitors or anti-drug antibodies were detected. No reports of serious allergic reactions, anaphylaxis, or embolic or thrombotic events.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Treatment with efanesoctocog alfa was associated with a clinically meaningful reduction in the number of bleeds compared with standard-of-care FVIII replacement products. Bleed rates were consistently low with weekly efanesoctocog alfa prophylaxis, regardless of the type (e.g. spontaneous, traumatic) or location (e.g. joint, skin) of bleed. Patients who switched from an on-demand treatment regimen to prophylaxis showed a clinically important 97% reduction in bleed rate.

A single dose of efanesoctocog alfa maintained FVIII activity levels in the normal to near-normal range for 3–4 days (>40%). The once-weekly administration of efanesoctocog alfa reduces the frequency that patients and/or caregivers need to administer therapy to maintain high activity levels of FVIII compared with current standard-of-care therapies. Maintenance of higher factor levels over a longer period of time reduces injection burden, and higher factor levels lead to increased protection from bleeding. Patients treated with efanesoctocog alfa had a combined dose and administration interval adherence of 98% (Group A, prophylaxis treatment) and 88% (Group B, on-demand treatment) (30).

One dose of efanesoctocog alfa successfully treated bleeds in 96.7% of cases. Patients rated the haemostatic response as excellent or good in 94.9% for all evaluable injections for treatment of a bleed. Physician’s assessment of response to prophylactic treatment was also rated as excellent in 95.7% of all study visits.

Prophylaxis with efanesoctocog alfa positively impacted patient joint health, improving signs and symptoms of joint damage (as measured by HJHS score), preventing joint bleeds, and resolving target joints in over half of patients presenting with at least one at baseline. Efanesoctocog alfa also improved physical functioning and pain. Joint damage and associated pain can be debilitating for patients; impacting daily physical functioning and being table to take part in activities. Improvement in joint bleeds, thus preventing joint damage and reducing pain, may have a positive effect on patient quality of life.

The safety profile of efanesoctocog alfa is generally consistent with that is expected in adults and adolescents who are treated with standard-of-care therapies for severe haemophilia A, and thus efanesoctocog alfa is not expected to be associated with any side effects above those seen with currently available treatments.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Patients and/or caregivers may need to learn how to administer efanesoctocog alfa at home as an intravenous injection if they are not already doing so with their current treatment or if they are newly diagnosed. In young children, this may sometimes require placement of a port-a-cath for easier venous (vein) access. However, compared with current FVIII replacement therapies, efanesoctocog alfa is only given once a week, while current FVIII therapies are administered intravenously on average, 3 times per week (32). Furthermore, despite significant advances in the treatment of haemophilia A, a notable number of patients will still experience bleeds on current FVIII replacement therapies (33).

While the current non-factor therapy, emicizumab, is administered subcutaneously, if a patient has a breakthrough bleed or requires surgery, they will still require FVIII replacement therapy via an intravenous injection to successfully treat acute bleeds.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

The model captures the impact of haemophilia A by modelling the number of bleeds patients have. The model has three health states, 'No bleeds', 'Any bleeds' and 'Death'. In each cycle, a proportion of living patients will have no bleeds, and the remainder will have at least one bleed.

Modelling how treatment extends life

Patients with haemophilia A have comparable life expectancy to the general population, and no difference in mortality is modelled between treatments.

Modelling how much a treatment improves quality of life

Each bleed is associated with a reduction in quality of life, captured as a short-term disutility reflecting the immediate impact of the bleed, and a longer-term disutility to reflect any longer-term impacts on quality of life. Additionally, the model accounts for improved

quality of life for people with higher factor levels, as peak factor levels may give people more freedom to undertake their usual activities.

Modelling how the costs of treatment differ with the new treatment

Most costs in the model come from the cost of prophylactic treatment. Efanesoctocog alfa is more expensive than some other FVIII products, however treatment costs with efanesoctocog alfa are either comparable with, or lower than, treatment costs for key comparators that are expected to be displaced. Overall, a net saving for the National Health Service (NHS) is expected. Additional savings due to a reduction in bleeds are also expected.

Uncertainty

There is uncertainty in the proportion of patients that bleed while on each treatment and the number of bleeds these patients will have. To assess the impact of this uncertainty, different sources were used to assess the number of bleeds for each treatment.

Scenario analyses that excluded differences in quality of life for patients with different factor levels were also explored, as well scenarios that explored different dosing regimens for comparators.

Cost-effectiveness results

When compared with emicizumab, efanesoctocog alfa produces more quality-adjusted life-years (QALYs) at a lower cost and is the dominant treatment option. With analyses against efmoroctocog alfa, efanesoctocog alfa was associated with higher costs and higher QALYs. Note, these results account for confidential discounts for efanesoctocog alfa and efmoroctocog alfa (two Sobi treatments), but do not include confidential discounts available for emicizumab.

Additional factors

Not all benefits of treatment have been captured in the model. Efanesoctocog alfa is associated with lower bleed rates than comparators, and while the direct impact of these bleeds on quality of life is captured, continued bleeds can lead to joint damage and eventually the need for surgical joint replacement. Over time, it is expected that joint health for patients treated with efanesoctocog alfa will be improved compared with other prophylactic treatments, however this has not been captured in the model.

It is difficult to measure QALY gains from the high FVIII levels obtained by patients treated with efanesoctocog alfa. In XTEND-1, once-weekly prophylaxis with efanesoctocog alfa provided mean FVIII activity of >40 IU/dL at Day 4 and >15 IU/dL at Day 7 (30). Mild haemophilia A is defined as FVIII activity of >5–<40 IU/dL (34) and near-normal FVIII levels are considered to be >40–50 IU/dL (29). Therefore, patients 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.

Efanesoctocog alfa has a once weekly dosing regimen, which alleviates some of the treatment burden for people being treated with existing FVIII prophylaxis. There is a need for a treatment which can maintain FVIII levels at the normal to near-normal range to reduce bleeding risk, and to help patients engage in activities that may otherwise be denied to them (e.g. work, hobbies, and physical activity).

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a ‘step change’ in treatment and/ or effectiveness compared with current

treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Clinicians who were interviewed stated that efanesoctocog alfa is a ‘game changer’ in the treatment of severe haemophilia A, as its once-weekly administration and efficacy in reducing bleed rates offers increased flexibility in terms of lifestyle. Efanesoctocog alfa is genuinely a once-a-week therapy, providing normal to near-normal factor levels for 3–4 days, and higher levels of protection from bleeding. Exposing patients to a FVIII replacement therapy earlier means they are less likely to develop an inhibitor as an adult.

During XTEND-1, perioperative (around the time of surgery) management of bleeds was assessed in 12 major surgical procedures in 11 patients. The procedures included surgeries such as joint replacements that can be associated with high intra- (during) and post-surgery bleeding. Responses with efanesoctocog alfa were rated as ‘excellent’ by investigators/surgeons in all 12 surgeries, indicating that blood loss was comparable to that expected for a patient without haemophilia. A single dose of efanesoctocog alfa was sufficient to prevent bleeding during/post-surgery. Patients currently receiving emicizumab must receive an infusion with current FVIII replacement therapies when receiving surgery or of they experience a breakthrough bleed on treatment. Current FVIII replacement therapies should be administered every 12 to 24 hours in order to stop a bleed (35, 36), whereas one dose of efanesoctocog alfa is typically recommended (30, 31).

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Not applicable.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on haemophilia A and treatment guidelines

- The Haemophilia Society: Understanding haemophilia
- APPG on Haemophilia and Contaminated Blood: Inquiry into Access to Treatment
- World Federation of Hemophilia: WFH Guidelines for the Management of Hemophilia, 3rd edition
- UKHCDO: Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B

Further information on efanesoctocog alfa

- XTEND-1 clinical trial information: A Phase 3 Open-label Interventional Study of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein, Efanesoctocog Alfa (BIVV001), in Patients With Severe Hemophilia A - Full Text View - ClinicalTrials.gov
- XTEND-Kids clinical trial information: Safety, Efficacy and PK of BIVV001 in Pediatric Patients With Hemophilia A - Full Text View - ClinicalTrials.gov

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Annualised bleeding rate: Is the number of reported bleeding events estimated over 12 months.

Confidence interval (CI): A range of values that you can be 95% certain contains the true mean of the population.

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease.

Disutility: Represents the decrement in utility (valued quality of life) due to a particular symptom or complication.

FVIII: Factor VIII is a protein important for the normal blood clotting process. It is deficient or absent in patients with haemophilia A, and therefore, their blood does not clot properly.

Intravenous: A medical technique that administers fluids, medications, and nutrients into a person's vein.

Mean: In statistics, the mean or average is the sum of numbers divided by the number of numbers. E.g. from adding the following seven numbers together and dividing by seven, the mean is 5.3: 1 + 3 + 3 + **6** + 7 + 8 + 9.

Median: In statistics, the median is the value separating the higher half from the lower half of a data sample. E.g. out of the following numbers, 6 is the median: 1, 3, 3, **6**, 7, 8, 9.

NICE: The National Institute for Health and Care Excellence. It is an independent organisation set up by the Government to decide which drugs and treatments are available on the NHS in England.

On-demand: Therapy received as required. For haemophilia A, on-demand treatment is given when a patient has a bleed.

Prophylaxis: Treatments given to prevent spread or worsening of a disease.

Quality of life: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living.

Quality adjusted life years (QALYs): QALYs are an overall measure of health outcome that weight the life expectancy of a patient with an estimate of their HRQoL (measured on a 0–1 scale).

Standard-of-care: Treatment that is accepted and widely used by medical experts and healthcare professionals for a certain type of disease.

Subcutaneous administration: Administration of a treatment under the skin via injection.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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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]

Clarification questions

13 November 2023

File name	Version	Contains confidential information	Date
ID6170 Efanesoctocog alfa_CQ response_v1.0 [CON]	1.0	Yes	5th December 2023

Section A: Clarification on effectiveness data

Literature searches

A 1. Please provide the search terms used and dates accessed for the searches of conference proceedings, trials registers and HTA organisations in company submission Appendix D.

Conferences

European Hematology Association (EHA) – EHA Congress

Conference: EHA 2023

Date of search: 07/09/2023

Source: https://journals.lww.com/hemasphere/Documents/EHA2023%20Abstract%20Book.pdf

Table 1: Search terms for EHA congress 2023

Keywords	# of hits	# of relevant hits
Hemophilia a	32	0
Haemophilia a	27	0
alfa	87	0
efanesoctocog	0	0
emicizumab	35	0
Hemlibra	0	0
fitusiran	32	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	0	0
Novoeight	0	0
Esperoct	0	0
simoctocog	0	0
Nuwiq	0	0
Lonoctocog	0	0
Afstyla	0	0
Efmoroctocog	1	0
damoctocog	0	0
Jivi	0	0
octocog	4	0
Advate	2	0
moroctocog	1	0
ReFacto	0	0

Keywords	# of hits	# of relevant hits
rurioctocog	1	0
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	0	0
viii	104	0

Conference: EHA 2022

Date of search: 12/09/2023

Source: https://journals.lww.com/hemasphere/Documents/EHA2022%20Congress%20Abstract%20Book.pdf

Table 2: Search terms for EHA congress 2022

Keywords	# of hits	# of relevant hits
Hemophilia a	22	0
Haemophilia a	0	0
alfa	79	0
efanesoctocog	0	0
emicizumab	9	0
Hemlibra	0	0
fitusiran	0	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	0	0
Novoeight	0	0
Esperoct	0	0
simoctocog	0	0
Nuwiq	0	0
Lonoctocog	0	0
Afstyla	0	0
Efmoroctocog	0	0
damoctocog	0	0
Jivi	0	0
octocog	2	0
Advate	0	0
moroctocog	0	0
ReFacto	1	0
rurioctocog	0	0
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	0	0
viii	82	0

Conference: EHA 2021

Date of search: 13/09/2023

Source: https://journals.lww.com/hemasphere/Documents/EHA2021%20Abstract%20Book%20Final.pdf

Table 3: Search terms for EHA congress 2021

Keywords	# of hits	# of relevant hits
Hemophilia a	27	0
Haemophilia a	9	0
Alfa	49	0
efanesoctocog	0	0
emicizumab	1	0
Hemlibra	0	0
fitusiran	0	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	2	0
Novoeight	0	0
Esperoct	0	0
simoctocog	0	0
Nuwiq	0	0
Lonoctocog	0	0
Afstyla	0	0
Efmoroctocog	0	0
damoctocog	0	0
Jivi	0	0
octocog	10	0
Advate	0	0
moroctocog	6	0
ReFacto	5	0
rurioctocog	0	0
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	0	0
viii	89	0

Conference: EHA 2020

Date of search: 14/09/2023

Source: https://journals.lww.com/hemasphere/toc/2020/06001

Table 4: Search terms for EHA congress 2020

Keywords	# of hits	# of relevant hits
Hemophilia a	24	0
Haemophilia a	8	0
Alfa	35	0
efanesoctocog	0	0
emicizumab	1	0
Hemlibra	0	0
fitusiran	0	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	0	0
Novoeight	0	0
Esperoct	0	0
simoctocog	0	0
Nuwiq	0	0
Lonoctocog	0	0
Afstyla	0	0
Efmoroctocog	0	0
damoctocog	0	0
Jivi	0	0
octocog	0	0
Advate	0	0
moroctocog	0	0
ReFacto	0	0
rurioctocog	0	0
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	0	0
viii	53	0

World Federation of Hemophilia (WFH) – World Congress

Conference: World Federation of Hemophilia, Virtual Summit – Connecting the Global Bleeding Disorders Community, June 2020

Date of search: 13/09/2023

Source: https://onlinelibrary.wiley.com/toc/13652516/2020/26/S4

Table 5: Search terms for WFH World Congress 2020

Keywords	# of hits	# of relevant hits
Alfa	53	0
efanesoctocog	0	0
emicizumab	102	0
Hemlibra	4	0
fitusiran	28	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	0	0
Novoeight	0	0
Esperoct	0	0
simoctocog	5	1?
Nuwiq	1	1?
Lonoctocog	0	0
Afstyla	0	0
Efmoroctocog	2	0
damoctocog	16	0
Jivi	1	0
octocog	52	1?
Advate	1	0
moroctocog	2	0
ReFacto	0	0
rurioctocog	16	0
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	3	0
viii	330	0

Conference: 13th Annual Congress of European Association for Haemophilia and Allied Disorders 2020, February 2020

Date of search: 13/09/2023

Source: https://onlinelibrary.wiley.com/toc/13652516/2020/26/S2

Table 6: Search terms for Annual Congress of European Association for Haemophilia and Allied Disorders 2020

Keywords	# of hits	# of relevant hits
Alfa	4	1
efanesoctocog	0	0
emicizumab	0	0
Hemlibra	0	0
fitusiran	7	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	0	0
Novoeight	0	0
Esperoct	0	0
simoctocog	0	0
Nuwiq	0	0
Lonoctocog	0	0
Afstyla	0	0
Efmoroctocog	0	0
damoctocog	0	0
Jivi	0	0
octocog	1	1
Advate	0	0
moroctocog	0	0
ReFacto	0	0
rurioctocog	1	1
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	0	0
viii	54	1

Conference: Virtual Congress of the European Association for Haemophilia and Allied Disorders 2021, February 2021

Date of search: 13/09/2023

Source: https://onlinelibrary.wiley.com/toc/13652516/2021/27/S2

Table 7: Search terms for Virtual Congress of the European Association for Haemophilia and Allied Disorders 2021

Keywords	# of hits	# of relevant hits
Alfa	117	2
efanesoctocog	0	0
emicizumab	209	1
Hemlibra	4	0
fitusiran	6	0
Kogenate	3	0
Kovaltry	3	0
turoctocog	15	0
Novoeight	2	0
Esperoct	1	0
simoctocog	0	0
Nuwiq	4	0
Lonoctocog	1	0
Afstyla	4	0
Efmoroctocog	7	0
damoctocog	8	1
Jivi	0	0
octocog	81	3
Advate	11	0
moroctocog	7	0
ReFacto	0	0
rurioctocog	40	2
ADYNOVATE	10	2
Xyntha	4	0
valoctocogene roxaparvovec	0	0
viii	1,003	5

Conference: 15th Annual Congress of European Association for Haemophilia and Allied Disorders 2022, February 2022, Virtual Meeting

Date of search: 13/09/2023

Source: https://onlinelibrary.wiley.com/toc/13652516/2022/28/S1

Table 8: Search terms for 15th Annual Congress of European Association for Haemophilia and Allied Disorders 2022

Keywords	# of hits	# of relevant hits
Alfa	27	0
efanesoctocog	8	0
emicizumab	143	0
Hemlibra	16	0
fitusiran	16	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	0	0
Novoeight	0	0
Esperoct	0	0
simoctocog	0	0
Nuwiq	0	0
Lonoctocog	0	0
Afstyla	0	0
Efmoroctocog	0	0
damoctocog	0	0
Jivi	0	0
octocog	30	2
Advate	0	0
moroctocog	0	0
ReFacto	1	0
rurioctocog	5	0
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	2	1
viii	269	1

Conference: 16th Annual Congress of European Association for Haemophilia and Allied Disorders 2023, February 2023

Date of search: 14/09/2023

Source: https://onlinelibrary.wiley.com/toc/13652516/2023/29/S1

Table 9: Search terms for 16th Annual Congress of European Association for Haemophilia and Allied Disorders 2023

Keywords	# of hits	# of relevant hits
Alfa	180	3
efanesoctocog	55	2
emicizumab	245	2
Hemlibra	1	0
fitusiran	11	0
Kogenate	0	0
Kovaltry	2	0
turoctocog	0	0
Novoeight	0	0
Esperoct	0	0
simoctocog	3	0
Nuwiq	6	0
Lonoctocog	10	0
Afstyla	0	0
Efmoroctocog	4	0
damoctocog	37	1
Jivi	5	1
octocog	142	3
Advate	5	0
moroctocog	4	0
ReFacto	4	0
rurioctocog	5	0
ADYNOVATE	2	0
Xyntha	0	0
Valoctocogene roxaparvovec	0	0

Conference: 12th BIC International Conference, September 2023

Date of search: 14/09/2023

Source: https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14844

Table 10: Search terms for 12th BIC International Conference, September 2023

Keywords	# of hits	# of relevant hits
Alfa	34	1
efanesoctocog	14	1
emicizumab	69	0
Hemlibra	1	0

Keywords	# of hits	# of relevant hits
fitusiran	0	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	1	0
Novoeight	0	0
Esperoct	0	0
simoctocog	12	0
Nuwiq	1	0
Lonoctocog	1	0
Afstyla	0	0
Efmoroctocog	5	0
damoctocog	7	0
Jivi	0	0
octocog	48	1
Advate	0	0
moroctocog	5	0
ReFacto	0	0
rurioctocog	0	0
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	3	0

Conference: WFH 2023 Comprehensive Care Summit: New Developments in Bleeding Disorders and MSK, May 2023

Date of search: 14/09/2023

Source: https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14781

Table 11: Search terms for WFH 2023 Comprehensive Care Summit: New Developments in Bleeding Disorders and MSK

Keywords	# of hits	# of relevant hits
Alfa	21	0
efanesoctocog	13	0
emicizumab	99	0
Hemlibra	1	0
fitusiran	0	0
Kogenate	0	0
Kovaltry	0	0
turoctocog	0	0
Novoeight	0	0
Esperoct	0	0
simoctocog	0	0
Nuwiq	0	0
Lonoctocog	0	0

Keywords	# of hits	# of relevant hits
Afstyla	0	0
Efmoroctocog	0	0
damoctocog	0	0
Jivi	0	0
octocog	20	1
Advate	1	0
moroctocog	0	0
ReFacto	0	0
rurioctocog	0	0
ADYNOVATE	0	0
Xyntha	0	0
Valoctocogene roxaparvovec	1	1

Health technology assessments

England: NICE

Date of search: 14/09/2023

Source: https://www.nice.org.uk/search?q=

Table 12: Search terms for NICE searches

Keywords	# of hits	# of relevant hits
Haemophilia	14	1

Scotland: Scottish Medicines Consortium (SMC)

Date of search: 14/09/2023

Source: https://www.scottishmedicines.org.uk/

Table 13: Search terms for SMC searches

Keywords	# of hits	# of relevant hits
Haemophilia	0	0

Ireland: National Centre for Pharmacoeconomics (NCPE)

Date of search: 14/09/2023

Source: https://www.ncpe.ie/category/drugs/

Table 14: Search terms for NCPE searches

Keywords	# of hits	# of relevant hits
Haemophilia	0	0

Australia: Pharmaceutical Benefits Advisory Committee (PBAC)

Date of search: 14/09/2023

Source: https://www.pbs.gov.au/pbs/home

Table 15: Search terms for PBAC searches

Keywords	# of hits	# of relevant hits
Haemophilia	0	0

Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)

Date of search: 14/09/2023

Source: https://www.cadth.ca/

Table 16: Search terms for CADTH searches

Keywords	# of hits	# of relevant hits
Haemophilia	20	3

France: Haute Autorité de Santé (HAS)

Date of search: 14/09/2023

Source: https://www.has-sante.fr/jcms/r_1455134/en/about-has

Table 17: Search terms for HAS searches

Keywords	# of hits	# of relevant hits
Haemophilia	18	3

Germany: German Institute for Quality and Efficiency in Health Care (IQWiG)

Date of search: 14/09/2023

Source: https://www.iqwig.de/en/

Table 18: Search terms for IQWiG searches

Keywords	# of hits	# of relevant hits
Haemophilia	18	5

Germany: Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])

Date of search: 14/09/2023

Source: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/

Searches: Under 'Therapiegebiet' (therapeutic area), select 'diseases of the blood and blood-forming organs' > filters > select 'show procedures with English translation only' > screen for haemophilia A > check for clinical trials

No. of hits: 25

No. of relevant hits: 5

United States of America: Institute for Clinical and Economic Review.

Date of search: 14/09/2023

Source: https://icer.org/explore-our-research/assessments/

Table 19: Search terms for ICER searches

Keywords	# of hits	# of relevant hits
Haemophilia	3	5

Clinical trial registries

World Health Organization International Clinical Trials Registry Platform (WHO ICTRP: **https://www.who.int/ictrp/search/en/**)

Date of search: 15/09/2023

Source: https://trialsearch.who.int/Default.aspx

Table 20: Search terms for WHO ICTRP searches

Keywords	# of hits	# of relevant hits
Haemophilia	73	23

United States National Institutes of Health (NIH) trial registry & results database (**https://clinicaltrials.gov/**).

Date of search: 15/09/2023

Source: https://clinicaltrials.gov/

Table 21: Search terms for National Institutes of Health (NIH) trial registry & results database searches

Keywords	# of hits	# of relevant hits
Haemophilia	92	47

A 2. The search methods in company submission Appendix G Table 1 report a single search strategy for both MEDLINE and Embase searches. Please confirm if this is a simultaneous search of both resources using a single strategy, or a single search of the Embase database conducted on the understanding that it now contains all records from MEDLINE. Please also provide details of the database coverage date(s) as appropriate.

This was a simultaneous search of both resources, which is why the deduplication process was added. The search was run by using the Ovid interface, on the 11th September 2023. Database coverage dates include:

- Embase:1974 to 2023 September 11
- Ovid MEDLINE ALL: 1946 to 2023 September 11.

A 3. Please provide the search terms used for searches of NHS EED, the HTA database and HTA organisations in company submission Appendix G.

NHS EED and HTA databases, as well as HTA agencies' websites were searched broadly, by using terms haemophilia and haemophilia, to ensure no relevant records were missed. The date of search of all of those information sources was the 18th September 2023.

A 4. Please provide the database coverage date for the MEDLINE search in company submission Appendix I.

For the MEDLINE search in Appendix I, the database coverage date included 2012 to current.

A 5. Please provide the search strategies used in company submission Appendix I for the following databases: CDSR, CENTRAL, CPCI-S, EconLit, SCHARRHUD.

The search strategies are outlined below in Table 22–Table 26.

Source: Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Information not found.

Issue searched: Issue 6 of 12, June 2022

Search date: 14 June 2022

Retrieved records: 4

Table 22: Search strategy for CDSR

No.	Search strings	# of hits
#1	[mh ^"hemophilia a"] or [mh ^"hemophilia b"]	486
#2	(hemophili* or haemophili*):ti,ab,kw	1678
#3	(subhemophili* or subhaemophili*):ti,ab,kw	0
#4	(antihemophili* or antihaemophili*):ti,ab,kw	39
#5	(hemophyli* or haemophyli*):ti,ab,kw	0
#6	(subhemophyli* or subhaemophyli*):ti,ab,kw	0
#7	(antihemophyli* or antihaemophyli*):ti,ab,kw	0
#8	(((factor* next viii) or (factor* next 8) or (factor* next eight) or F8 or ahf or ahg) near/5 (deficien* or disorder* or inhibit*)):ti,ab,kw	194
#9	(((factor* next ix) or (factor* next 9) or (factor* next nine) or F9) near/5 (deficien* or disorder* or inhibit*)):ti,ab,kw	33
#10	(christmas* next disease):ti,ab,kw	5
#11	((FIX or HEMB or P19 or THPH8 or christmas) near/5 (deficien* or disorder* or inhibit*)):ti,ab,kw	117
#12	((DXS1253E or F8B or F8C or FVIII or HEMA or THPH13) near/5 (deficien* or disorder* or inhibit*)):ti,ab,kw	207
#13	((("plasma thromboplastin" next component*) or PTC) near/5 (deficien* or disorder* or inhibit*)):ti,ab,kw	2
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	1814
#15	[mh ^"quality-adjusted life years"]	1467
#16	("quality adjusted" or (adjusted next life next year*)):ti,ab,kw	6116
#17	(qaly* or qald* or qale* or qtime*):ti,ab,kw	4273
#18	((illness or health) next state*):ti,ab,kw	1342
#19	(hui or hui1 or hui2 or hui3):ti,ab,kw	285
#20	(multiattribute* or (multi next attribute*)):ti,ab,kw	81
#21	(utility near/3 (score* or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)):ti,ab,kw	4377
#22	utilities:ti,ab,kw	1237
#23	(eq-5d or eq5d or eq-5 or eq5 or "euro qual" or euroqual or "euro qual5d" or euroqual5d or "euro qol" or euroqol or "euro qol5d" or	11533

No.	Search strings	# of hits
	euroqol5d or "euro quol" or euroquol or "euro quol5d" or euroquol5d or "eur qol" or eurqol or "eur qol5d" or "eur qol5d" or "eur qul" or "eur qul5d" or euroqul or euroqul5d or eurqul or eurqul5d or (euro* next "quality of life") or "european qol"):ti,ab,kw	
#24	(euro* near/3 (“5 d” or 5d or (5 next dimension*) or 5dimension* or (5 next domain*) or 5domain*)):ti,ab,kw	3336
#25	(sf36* or (sf next 36*) or "sf thirtysix" or "sf thirty six"):ti,ab,kw	12959
#26	((time next trade next off*) or (time next tradeoff*) or tto or timetradeoff*):ti,ab,kw	286
#27	[mh ^"quality of life"] and (("quality of life" or qol) next (score* or measure*)):ti,ab,kw	3040
#28	[mh ^"quality of life"] and [mh /EC]	1696
#29	[mh ^"quality of life"] and (health near/3 status):ti,ab,kw	2919
#30	("quality of life" or qol):ti,ab,kw and [mh ^"cost-benefit analysis"]	2428
#31	((qol or hrqol or "quality of life"):ti or [mh ^"quality of life"]) and ((qol or hrqol* or "quality of life") near/2 (increas* or decrease* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change* or impact* or impacted or deteriorat*)):ab14677	
#32	[mh ^"cost-benefit analysis"] and (("cost-effectiveness ratio" or "cost-effectiveness ratios") and (perspective* or (life next expectanc*))):ti,ab,kw	666
#33	[mh ^"quality of life"] and ("quality of life" or qol):ti	6784
#34	[mh ^"quality of life"] and (("quality of life" or qol) near/3 (improv* or chang*)):ti,ab,kw	6831
#35	[mh ^"quality of life"] and "health-related quality of life":ti,ab,kw	5493
#36	[mh ^"models, economic"]	259
#37	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36	49252
#38	((utility next loss*) or disutilit* or (short next form*) or shortform* or sf-12 or sf12 or "15-d" or 15d or fifteen-d or fifteend or (15 next dimension*) or (fifteen next dimension*) or sf-6 or sf6 or sf-6d or sf6d or sf-six or sfsix or sf-sixd or sfsixd or (6 next dimension*) or (six next dimension*)):ti,ab,kw	19748
#39	(Euroqol5 or EQoL-5D or EQol5 or EQol5D or EQ5D3L or sf-20 or sf20 or sf-16 or sf16 or sf-8 or sf8):ti,ab,kw	358
#40	#37 or #38 or #39	59337
#41	#14 and #40 with Cochrane Library publication date Between Jan 2012 and Dec 2022, in Cochrane Reviews, Cochrane Protocols	4

Source: Cochrane Central Register of Controlled Trials (CENTRAL)

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Information not found.

Issue searched: Issue 6 of 12, June 2022

Retrieved records: 82

Table 23: Search strategy for CENTRAL

No.	Search strings	# of hits
#1	[mh ^"hemophilia a"] or [mh ^"hemophilia b"]	486
#2	(hemophili* or haemophili*)	1879
#3	(subhemophili* or subhaemophili*)	0
#4	(antihemophili* or antihaemophili*)	46
#5	(hemophyli* or haemophyli*)	0
#6	(subhemophyli* or subhaemophyli*)	0
#7	(antihemophyli* or antihaemophyli*)	0
#8	(((factor* next viii) or (factor* next 8) or (factor* next eight) or F8 or ahf or ahg) near/5 (deficien* or disorder* or inhibit*))	240
#9	(((factor* next ix) or (factor* next 9) or (factor* next nine) or F9) near/5 (deficien* or disorder* or inhibit*))	45
#10	christmas* next disease	10
#11	((FIX or HEMB or P19 or THPH8 or christmas) near/5 (deficien* or disorder* or inhibit*))	111
#12	((DXS1253E or F8B or F8C or FVIII or HEMA or THPH13) near/5 (deficien* or disorder* or inhibit*))	215
#13	((("plasma thromboplastin" next component*) or PTC) near/5 (deficien* or disorder* or inhibit*))	3
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	1999
#15	[mh ^"quality-adjusted life years"]	1467
#16	("quality adjusted" or (adjusted next life next year*))	6555
#17	(qaly* or qald* or qale* or qtime*)	4457
#18	((illness or health) next state*)	1479
#19	(hui or hui1 or hui2 or hui3)	2178
#20	(multiattribute* or (multi next attribute*))	91
#21	(utility near/3 (score* or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*))	4732
#22	utilities	1305
#23	(eq-5d or eq5d or eq-5 or eq5 or "euro qual" or euroqual or "euro qual5d" or euroqual5d or "euro qol" or euroqol or "euro qol5d" or euroqol5d or "euro quol" or euroquol or "euro quol5d" or euroquol5d or "eur qol" or eurqol or "eur qol5d" or "eur qol5d" or "eur qul" or "eur qul5d" or euroqul or euroqul5d or eurqul or eurqul5d or (euro* next "quality of life") or "european qol")	12372
#24	(euro* near/3 (“5 d” or 5d or (5 next dimension*) or 5dimension* or (5 next domain*) or 5domain*))	3661
#25	(sf36* or (sf next 36*) or "sf thirtysix" or "sf thirty six")	14502
#26	((time next trade next off*) or (time next tradeoff*) or tto or timetradeoff*)	303
#27	[mh ^"quality of life"] and (("quality of life" or qol) next (score* or measure*))	3390
#28	[mh ^"quality of life"] and [mh /EC]	1696
#29	[mh ^"quality of life"] and (health near/3 status)	3151
#30	("quality of life" or qol) and [mh ^"cost-benefit analysis"]	2433
#31	((qol or hrqol or "quality of life"):ti or [mh ^"quality of life"]) and ((qol or hrqol* or "quality of life") near/2 (increas* or decrease* or improv* or declin* or reduc* or high* or low* or effect or effects or	

No.	Search strings	# of hits
	worse or score or scores or change* or impact* or impacted or deteriorat*)):ab14677	
#32	[mh ^"cost-benefit analysis"] and (("cost-effectiveness ratio" or "cost-effectiveness ratios") and (perspective* or (life next expectanc*)))	678
#33	[mh ^"quality of life"] and ("quality of life" or qol):ti	6784
#34	[mh ^"quality of life"] and (("quality of life" or qol) near/3 (improv* or chang*))	7084
#35	[mh ^"quality of life"] and "health-related quality of life"	5646
#36	[mh ^"models, economic"]	259
#37	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36	53175
#38	(utility next loss*) or disutilit* or (short next form*) or shortform* or sf-12 or sf12 or "15-d" or 15d or fifteen-d or fifteend or (15 next dimension*) or (fifteen next dimension*) or sf-6 or sf6 or sf-6d or sf6d or sf-six or sfsix or sf-sixd or sfsixd or (6 next dimension*) or (six next dimension*)	24673
#39	(Euroqol5 or EQoL-5D or EQol5 or EQol5D or EQ5D3L or sf-20 or sf20 or sf-16 or sf16 or sf-8 or sf8)	386
#40	#37 or #38 or #39	66278
#41	#14 and #40 with Publication Year from 2012 to 2022, in Trials	82

Interface / URL: Web of Science

Database coverage dates: 1990 to present

Search date: 10 June 2022

Retrieved records: 32

Search strategy:

All search lines run in the advanced search interface using exact search. The final search line below was limited by publication date. It is not possible to export this in a format that displays in Word. The limit applied was: 2012-01-01 to 2022-12-31

Table 24: Search strategy for CPCI-S

No.	Search strings	# of hits
1	TS=(hemophili* OR haemophili*)	3,297
2	TS=(subhemophili* OR subhaemophili*)	0
3	TS=(antihemophili* OR antihaemophili*)	44
4	TS=(hemophyli* OR haemophyli*)	1
5	TS=(subhemophyli* OR subhaemophyli*)	0
6	TS=(antihemophyli* OR antihaemophyli*)	0
7	TS=(("factor$ viii" OR "factor$ 8" OR "factor$ eight" OR F8 OR ahf OR ahg) NEAR/5 (deficien* OR disorder* OR inhibit*))	377
8	TS=(("factor$ ix" OR "factor$ 9" OR "factor$ nine" OR F9) NEAR/5 (deficien* OR disorder* OR inhibit*))	80

No.	Search strings	# of hits
9	TS="christmas* disease"	6
10	TS=((FIX OR HEMB OR P19 OR THPH8 OR christmas) NEAR/5 (deficien* OR disorder* OR inhibit*))	62
11	TS=((DXS1253E OR F8B OR F8C OR FVIII OR HEMA OR THPH13) NEAR/5 (deficien* OR disorder* OR inhibit*))	158
12	TS=(("plasma thromboplastin component*" OR PTC) NEAR/5 (deficien* OR disorder* OR inhibit*))	15
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	3,595
14	TS=("quality adjusted" OR "adjusted life year*")	692
15	TS=(qaly* OR qald* OR qale* OR qtime*)	422
16	TS=("illness state$" OR "health state$")	1,307
17	TS=(hui OR hui1 OR hui2 OR hui3)	253
18	TS=(multi-attribute* OR multiattribute*)	2,800
19	TS=(utility NEAR/3 (score$ OR valu* OR health* OR cost* OR measur* OR disease* OR mean OR gain OR gains OR index*))	4,712
20	TS=utilities	11,622
21	TS=(eq-5d OR eq5d OR eq-5 OR eq5 OR "euro qual" OR euroqual OR "euro qual5d" OR euroqual5d OR "euro qol" OR euroqol OR "euro qol5d" OR euroqol5d OR "euro quol" OR euroquol OR "euro quol5d" OR euroquol5d OR "eur qol" OR eurqol OR "eur qol5d" OR eurqol5d OR eur$qul OR eur$qul5d OR "euro* quality of life" OR "european qol")	400
22	TS=(euro* NEAR/3 ("5 d" OR 5d OR "5 dimension*" OR "5dimension*" OR "5 domain*" OR 5domain*))	125
23	TS=(sf36* OR "sf 36*" OR "sf thirtysix" OR "sf thirty six")	1,236
24	TS=("time trade off$" OR "time tradeoff$" OR tto OR timetradeoff$)	514
25	TS=(("quality of life" OR qol) NEAR/0 (score$ OR measure$))	1,138
26	TS=("quality of life" AND (health NEAR/3 status))	889
27	TS=(("quality of life" OR qol) AND "cost-benefit analys*")	40
28	TS=("quality of life" AND economic*)	1,605
29	TS=(("quality of life" OR qol OR hrqol*) NEAR/2 (increas* OR decrease* OR improv* OR declin* OR reduc* OR high* OR low* OR effect OR effects OR worse OR score OR scores OR change$ OR impact$ OR impacted OR deteriorat*))	10,503
30	TS=("cost-benefit analys*" AND ("cost-effectiveness ratio*" AND (perspective* OR "life expectanc*")))	2
31	TI=("quality of life" OR qol)	20,507
32	TS=(("quality of life" OR qol) NEAR/3 (improv* OR chang*))	7,160
33	TS="health-related quality of life"	4,799
34	TS=(economic* NEAR/1 model*)	4,284
35	TS=("utility loss*" OR disutilit* OR "short form*" OR shortform* OR sf-12 OR sf12 OR 15-d OR 15d OR fifteen-d OR fifteend OR "15 dimension*" OR "fifteen dimension*" OR sf-6 OR sf6 OR sf-6d OR sf6d OR sf-six OR sfsix OR sf-sixd OR sfsixd OR "6 dimension*" OR "six dimension*")	7,107
36	TS=(Euroqol5 OR EQoL-5D OR EQol5 OR EQol5D OR EQ5D3L OR sf-20 OR sf20 OR sf-16 OR sf16 OR sf-8 OR sf8)	47

No.	Search strings	# of hits
37	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	61,102
38	#37 AND #13	84
39	(#36 AND #13) AND LA=(English)	32

Source: Econlit

Interface / URL: OvidSP

Database coverage dates: 1886 to 6 June 2022

Search date: 9 June 2022

Retrieved records: 6

Table 25: Search strategy for Econlit

No.	Search strings	# of hits
1	(hemophili$ or haemophili$).af.	11
2	(subhemophili$ or subhaemophili$).af.	0
3	(antihemophili$ or antihaemophili$).af.	0
4	(hemophyli$ or haemophyli$).af.	0
5	(subhemophyli$ or subhaemophyli$).af.	0
6	(antihemophyli$ or antihaemophyli$).af.	0
7	((factor$1 viii or factor$1 8 or factor$1 eight or F8 or ahf or ahg) adj5 (deficien$ or disorder$ or inhibit$)).af.	0
8	((factor$1 ix or factor$1 9 or factor$1 nine or F9) adj5 (deficien$ or disorder$ or inhibit$)).af.	0
9	christmas$ disease.af.	0
10	((FIX or HEMB or P19 or THPH8 or christmas) adj5 (deficien$ or disorder$ or inhibit$)).af.	4
11	((DXS1253E or F8B or F8C or FVIII or HEMA or THPH13) adj5 (deficien$ or disorder$ or inhibit$)).af.	0
12	((plasma thromboplastin component$ or PTC) adj5 (deficien$ or disorder$ or inhibit$)).af.	0
13	or/1-12	15
14	limit 13 to english	14
15	limit 14 to yr="2012 -Current"	7

Source: ScHARRHUD

Interface / URL: https://www.scharrhud.org/

Database coverage dates: Information not found.

Search date: 9 June 2022

Retrieved records: 5

Table 26: Search strategy for ScHARRHUD

No.	Search strings	# of hits
1	hemophili* OR haemophili*	6
2	subhemophili* OR subhaemophili*	0
3	antihemophili* OR antihaemophili*	0
4	hemophyli* OR haemophyli*	0
5	subhemophyli* OR subhaemophyli*	0
6	antihemophyli* OR antihaemophyli*	0
7	(factor* viii OR factor* 8 OR factor* eight OR F8 OR ahf OR ahg) AND (deficien* OR disorder* OR inhibit*)	1
8	(factor* ix OR factor* 9 OR factor* nine OR F9) AND (deficien* OR disorder* OR inhibit*)	1
9	christmas* disease	0
10	(FIX OR HEMB OR P19 OR THPH8 OR christmas) AND (deficien* OR disorder* OR inhibit*)	0
11	(DXS1253E OR F8B OR F8C OR FVIII OR HEMA OR THPH13) AND (deficien* OR disorder* OR inhibit*)	0
12	(plasma thromboplastin component* OR PTC) AND (deficien* OR disorder* OR inhibit*)	0
13	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)	6
14	#13 AND 2012 > 2022:YR	6

A 6. The HRQoL and cost/resource use searches (company submission Appendices H and I) were conducted in June 2022. Please update these searches to bring them into line with the clinical- and cost-effectiveness searches (company submission Appendices D and G) which were last run in September 2023.

The Company contacted NICE on the 28th November 2023 with regard to providing the SLR updates. As the Company are pending a response, in summary, the health economics vendor supporting the Company submission have advised that they can provide the updated SLR updates by January 2024. However, the Company would appreciate NICE's view on the necessity of updating the HCRU, as requested by the EAG at clarification stage. The original SLR only identified 17 primary studies, but given the model structure, none of the findings were used to parameterise the cost-effectiveness model. This will not change following any updated review; it should be noted that resource use other than relating to replacement therapy (which the model predicts) represented [redacted] of incremental costs in most scenarios.

A 7. The clinical effectiveness database searches (company submission Appendix D) have been limited to search for English language studies only. Please explain

the effect that this limit may have had on the results found, in terms of potential publication bias.

With regard to evidence selection bias, there may be other published research on this topic in languages other than English. However, given that the majority of high-quality international research is published in English language journals, a pragmatic decision was made to search only the English language literature.

Decision problem

A 8. Priority question. The company states that there is no evidence for the previously untreated population. Please explain how a cost effectiveness analysis in this population is feasible in the absence of evidence.

No studies have assessed the use of efanesoctocog alfa in previously untreated patients (PUPs) and the cost-effectiveness analysis is based on data from previously treated patients (PTPs). However, clinical opinion supports the extrapolation of safety and efficacy data to PUPs. This reflects the way that clinicians have utilised emicizumab in PUPs despite there being no evidence historically. Consequently, the same efficacy data is applied for both the PUP and PTP populations.

It is also worth noting that since 2018, the guideline on the clinical investigation of recombinant and human plasma-derived FVIII products no longer requires PUPs data as part of the clinical development programme to gain a license in this indication (1). However, as with all new products to market, there will be additional safety monitoring under the MHRA's Black Triangle scheme.

A 9. Priority question. The NICE Final Scope specified "people with haemophilia A" as the relevant population, however the company selected "patients with severe haemophilia A". Please clarify the deviation away from the NICE scope: is this to be consistent with the XTEND-1 trial? Please confirm that you would therefore not expect efanesoctocog alfa to be used to treat patients with mild or moderate disease.

The Company confirms that this is to maintain consistency with the XTEND-1 trial and aligns with clinical feedback received; indicating use in severe population. The Company would not expect efanesoctocog alfa to be routinely used to treat patients with mild or moderate haemophilia A.

A 10. Priority question. The XTEND-1 trial includes patients from age 12 upwards. Could the company please confirm that the decision problem (DP) population should be correspondingly narrowed? If not, then please present evidence for a younger population.

Top-line results from XTEND-Kids (patients under the age of 12 years who were previously treated with prophylaxis) demonstrate the efficacy of efanesoctocog alfa within the under 12 years population and support the clinical evidence base for such. The Company do not believe the decision problem population should be narrowed to patients over 12 years of age only. Clinicians agreed that in the absence of data in PUPs, PTP data would be the next best alternative (2).

XTEND-Kids was not used in the cost-effectiveness analysis, as data from XTEND-Kids was not available in time to inform the indirect treatment comparison or economic model. Furthermore, an indirect treatment comparison (ITC) to compare efanesoctocog alfa with emicizumab was deemed unfeasible in the absence of any paediatric data for the non-inhibitor population for emicizumab.

Extrapolation of data between XTEND-1 and XTEND-Kids was considered, as haemophilia A is a condition where the underlying defect (a deficiency in clotting FVIII) is the same in children and adults. Treatment with efanesoctocog alfa in XTEND-1 and XTEND-Kids was considered generalisable across the adult and paediatric populations. Patients across both trials had similar ABRs, a comparable PK profile (with a shorter half-life expected in younger individuals), and similar rates of zero bleeds. The safety profile of efanesoctocog alfa was also comparable between the two trial populations.

A 11. Priority question: Please justify the exclusion of prophylactic Factor VIII replacement therapy as a comparator in the DP when only just over half (55%) of patients were receiving emicizumab and a quarter (26%) of patients were documented as still using the standard half-life (SHL) form of FVIII replacement at end of 2022 (company submission Document B, Table 1, “Comparators”).

Given that it still appears to be standard UK clinical practice for many patients, please include it as a comparator in all clinical and cost effectiveness analyses.

To reiterate, the justification for the exclusion of SHL/EHL factor therapies as a comparator in the PTP population is based on the proposed positioning of efanesoctocog alfa in the treatment pathway.

In PTPs, efanesoctocog alfa is positioned for patients who would otherwise be offered emicizumab, this being previously treated factor patients (Document B, Figure 2). Therefore, the point in the treatment pathway where efanesoctocog alfa will be offered is when emicizumab is the only other alternative treatment option.

In PUPs, efmoroctocog alfa (Elocta) is licensed for use in patients under the age of 12 years (3) and is an additional comparator included in the analysis.

Regarding SHLs in general, since Q2 2019, the use of SHLs has declined from [redacted]% to [redacted]% at the end of 2022 (4), and clinical opinion suggests that SHL use will be minimal in 5 years' time (2). The beginning of a significant decrease in rFVIII issued from 2020/21 is attributable to the introduction of emicizumab prophylaxis from September of 2018/19 (4). It is also important to note that the figure of [redacted]% is an overrepresentation of market share, since patients on emicizumab require additional rFVIII for at home contingency stock, breakthrough bleeding management (at home or in hospital), and surgery. The UKHCDO comment on this data limitation and indicate that there is some double counting in this chart since people may be issued with more than one product type in any given year (4).

A recent investor report from Roche, the manufacturers of emicizumab, indicates that the market share of the product may be up to 70% as of September 2023 (5).

A 12. The NICE Final Scope defines established clinical management (ECM) as Factor VIII replacement therapy (prophylactic and on-demand) or emicizumab. The company's DP distinguishes by previous treatment, indicating that emicizumab should be regarded as the comparator for previously-treated patients (PTPs) and "Emicizumab and efmoroctocog alfa" for previously untreated patients (PUPs). Please clarify whether the comparator for PUPs is:

emicizumab in combination with efmoroctocog alfa; or a choice between emicizumab or efmoroctocog alfa.

In the PUP population, the comparator is a choice between emicizumab or efmoroctocog alfa. Patients receiving emicizumab will receive a supply of FVIII treatment in case of break-through bleeding, however this is usually in the form of an SHL factor therapy.

A 13. The EAG noted a reliance on clinical opinion to substantiate some arguments presented in company submission Document B. The methodological details of the elicitation exercise (available from the Clinical Consultation Report) were scant beyond saying that clinical opinion was derived from interviewing five UK-based consultant haematologists.

a) Please provide full methodological details of the interviews conducted with the clinical experts. In particular, please explain the degree of independence between the clinical experts and the company.

The clinical interviews were not conducted as an elicitation exercise, and so this particular methodology was not followed. Each interview was held in a 1:1 format via Microsoft® Teams to ascertain expert clinical opinion. In terms of independence between the clinicians and the Company, the clinicians were interviewed under a consultancy agreement only. Given the highly specialised nature of haemophilia and the level of experience required in the clinicians interviewed, it is very difficult to find participants who have not provided consultancy activity for any company.

This is a well-established activity that has been used in numerous other NICE appraisals.

b) According to the company submission, the clinical experts endorsed the extrapolation of efficacy and safety data for the non-factor therapy emicizumab to PUPs and previously treated paediatric populations despite a lack of data for these groups (p.12 & p.117 of Document B). Given that emicizumab was launched in 2019 (Table 1 of Document B), please confirm whether relevant empirical data are now available to support this extrapolation. If they are available, please provide them.

No studies have assessed the use of efanesoctocog alfa in PUPs, and the cost-effectiveness analysis is based on data from PTPs. However, clinical opinion supports the extrapolation of safety and efficacy data to PUPs. Consequently, the same efficacy data are applied for both the PUP and PTP populations.

The company acknowledges that there is an ongoing Phase 3b study evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in PUPs and minimally treated patients (MTPs; defined as ≤5 exposure days to FVIII) aged ≤12 months (HAVEN 7) (6). Interim results from HAVEN 7 are published (7).

At the interim analysis cut-off date, 54 patients had more than one dose of emicizumab. Of these, 30 (55.6%) were minimally treated prior to the study, and 24 (44.4%) were previously untreated. Median (range) of emicizumab treatment duration was 42.1 (1–60) weeks.

Mean model-based ABR for treated bleeds was 0.4 (95% CI: 0.23, 0.65), and was 1.9 (95% CI: 1.23, 2.68) and 0.1 (95% CI: 0.01, 0.22) for all bleeds and treated joint bleeds, respectively. Zero treated bleeds were reported in 42 patients (77.8%), while 23 patients (42.6%) had no bleeds at all. PK data were evaluable in 52 patients. Mean trough concentrations of emicizumab increased with loading doses, with concentrations of 63.2 µg/mL (95% CI: 59.5, 66.8) at Week 5; steady-state concentrations were maintained at 60–65 µg/mL thereafter. None of the 48 patients evaluable for immunogenicity analysis tested positive for anti-drug antibodies.

Fifty patients (92.6%) had more than one AE, and nine (16.7%) had more than one treatment-related AE (all injection-site reactions). No AEs leading to treatment withdrawal/modification/interruption occurred. Eight patients reported 12 serious AEs (SAEs); none of which were considered treatment-related.

c) Some statements supported by clinical opinion seemed to focus on predicting future aspects of standard of care: e.g., SHL use will be minimal in 5 years (p.14 & p.120 of company submission) and efanesoctocog alfa (EFA) will be used in patients who would otherwise be offered emicizumab (p.14 & p.27-8). Please clarify the details of current standard of care in the UK NHS as opposed to predicting future trends.

Emicizumab is now considered the standard-of-care in the NHS for the treatment of haemophilia A, as most patients who switch from a recombinant FVIII (rFVIII) treatment move to emicizumab therapy. This is aligned with the proposed positioning of efanesoctocog alfa in PTPs. Clinical opinion suggests there are several issues which may lead clinicians to consider switching from rFVIII to emicizumab (28):

- Haemostasis is inadequately controlled and the patient experiences breakthrough bleeds with rFVIII prophylaxis
- FVIII levels are not sufficiently controlled on rFVIII (i.e. poor pharmacokinetic coverage due to reduced area under curve [AUC] and shorter half-life)
- Prophylaxis with multiple weekly intravenous (IV) injections with rFVIII is inconvenient or not possible (i.e. frequent injections can lead to poor adherence to rFVIII therapy)
- The patient is seeking better quality of life or to live a life as 'normal' as is possible. Aligned to UK guidelines, healthcare practitioners (HCPs) will utilise shared decision-making to tailor prophylaxis with the patient, basing therapy on PK data, patient activity, lifestyle, and patient preferences (29).

Since launch in 2019 (Figure 1), the proportion of patients receiving emicizumab has rapidly increased and continues to do so, with it now being the standard of care in the UK for the treatment of PUPs and PTPs (4). The proportion of patients with severe haemophilia A receiving emicizumab has increased from x% in 2019, to xx% at the end of 2022 (4). Furthermore, since Q2 2019, the use of SHLs has declined from xx% to xx% at the end of 2022 (4), and clinical opinion suggests that SHL use will be minimal in 5 years time , irrespective of the availability of efanesoctocog alfa(2).

A recent investor report from Roche, the manufacturers of emicizumab, indicates that the market share of the product may be up to 70% as of September 2023 (5).

If a patient on emicizumab prophylaxis experiences a breakthrough bleed or undergoes surgery, they will still require rFVIII (factor replacement therapy) to treat acute bleeds. Typically, patients are offered an SHL to treat breakthrough bleeds,

and therefore, the proportion of rFVIII issued to patients is overrepresented, as it includes a notable number of patients who receive emicizumab who have a contingency stock of rFVIII at home, or patients who have received rFVIII to treat a bleed in hospital/during a surgical procedure. (Note: the data represents “treatment issued” as opposed to “patients treated with”. This is a nuance of the data collected within the database).

Figure 1: The Proportion of people with severe haemophilia A and no inhibitor issued treatment by product type 2019 Q2 - 2022 Q4

Source: National Haemophilia Database, Real World Evidence report (4)
Abbreviations: EMI, emicizumab; FVIII, clotting Factor VIII.

Systematic review

A 14. In Document B of the company submission, the company states that “overall, 177 publications corresponding to 105 unique studies were identified, of which, a full data extraction was performed on 62 publications comprising 49 unique studies.” However, in company submission Appendix D, the company states that “overall, the systematic literature reviews (SLRs) identified 176 publications reporting 105 unique studies, of which full data extraction was performed on 65 publications comprising 49 unique studies.” Therefore, the EAG requests that the company clarify this discrepancy and identify which set of numbers is correct.

The correct number of included publications is 65 – Document B should read: “full data extraction was performed on **65** publications comprising 49 unique studies.”

A 15. Section D.1.4.2 in company submission Appendix D describes the data extraction process however, the output of this is not included in the submission. Please provide:

a) Details of the data extraction template

A data extraction template was developed to extract study design, baseline characteristics and outcomes. Mean, median, standard deviation, standard error, and range were extracted for continuous variables where possible. For categorical variables, frequency and percentage were extracted. Key characteristics and data elements that were captured are presented in Table 27.

Table 27: Data elements captured during data extraction

Study Design Characteristics	Baseline Characteristics	Treatment Characteristics	Outcomes
• Author, study title, journal, and publication year • Trial number and acronym • Trial phase • Setting (e.g. country, study period) • Study population • Inclusion/exclusion criteria • Intervention/ comparators • Study methods (e.g. randomisation ratio, stratification factors, cross-over) • Trial duration/ follow-up • Blinding • Sample size • Relevant statistical methods used in studies (e.g. handling of missing data) • Proportion of patients with hemophilia A (only for trials that include mixed populations and subgroup results for the hemophilia A subgroup)	• Age • Sex • Race • Weight and/or body mass index • Previous regimen (i.e. on-demand, prophylaxis) • Number of bleeds prior to study entry • Disease severity • Gilbert score • FVIII levels • Number of target joints • FVIII inhibitor status • Infections (e.g. HIV, HCV)	• Treatment • Dose • Schedule • Prior treatments • SHL/EHL • Plasma-derived/recombinant • Prophylaxis/on-demand	• ABR • AsBR • AjBR • Factor usage/ consumption • Target joints • Development of inhibitors • Available PRO measures (e.g. Haem-A-QoL) • HJHS/mHJHS

Study Design Characteristics	Baseline Characteristics	Treatment Characteristics	Outcomes
• Quality assessment			

Abbreviations: ABR, annualised bleed rate; AjBR, annualised joint bleed rate; AsBR, annualised spontaneous bleed rate; EHL, extended half-life; FVIII, clotting Factor VIII; Haem-A-QoL; Haemophilia Quality of Life Questionnaire for Adults; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HJHS, Haemophilia Joint Health Score; mHJHS, modified Haemophilia Joint Health Score; PRO, patient-reported outcome; SHL, standard half-life.

b) The extracted data for the 62 (or 65) publications reporting 49 unique studies

Please refer to the accompanying document "ID6170 Efanesoctocog alfa_CQ response_Question A15_clinical-SLR-DET [CON]", which contains the full data extraction.

A 16. Section D.1.5 of company submission Appendix D outlines the criteria used to assess risk of bias in the included randomised controlled trials (RCTs). A later section of the same appendix (D.4) shows a tabulation of the output of risk of bias assessment for RCTs. However, some information is lacking. Please provide:

a) Details of the tool(s) used to assess risk of bias in the included non-randomised studies (e.g., XTEND-1)

Quality appraisal was not conducted for the non-randomised studies. It was expected that the risk of bias is similar between single-arm prospective trials and there is no accepted standard method to assess risk of bias in single-arm studies specifically. Therefore, no risk of bias assessment was attempted for these studies.

b) The output of assessing the risk of bias in the non-randomised studies

Quality appraisal was not conducted for the non-randomised studies.

c) Information on how many reviewers performed the assessment of risk of bias (for all study designs) and the approach used for resolving disagreements.

Quality appraisal was conducted (using the primary publication for each RCT identified) by one reviewer and validated for accuracy by a second reviewer. Any discrepancies that arose between the two reviewers were reconciled by both reviewers and/or a third reviewer, if needed, to reach consensus.

A 17. Table 8 of company submission Appendix D suggests a mismatch between outcomes listed in the NICE Final Scope and DP and those listed for the clinical effectiveness SLR. For example, change in Factor VIII levels, durability of response to treatment, joint surgeries, adverse effects and mortality are all listed in the Scope but not for the SLR. Please justify these exclusions.

As the clinical SLR was originally planned and conducted before the draft scope was published, these outcomes were not captured when the original searches were conducted. When the searches were updated in 2023, a pragmatic decision was made to focus on the outcomes already extracted, as:

- Changes in FVIII levels were not considered relevant, as the Company believe it is more appropriate to measure FVIII levels in response to treatment, in contrast to monitoring changes in factor levels over time, which would be more appropriate for a gene therapy (8)
- Durability of response to treatment was not considered relevant for FVIII replacement therapy. The Company consider that response to treatment is best measured following each administration, as FVIII levels are likely to fluctuate over time between treatments
- Joint surgery was not considered relevant for FVIII replacement therapy studies, as the number of surgeries a patient may have over their lifetime is minimal. On average, a patient would require a surgery every 152 years according to the assumptions made in previous models (9). Furthermore, this was not captured in the economic model
- Adverse effects were not considered relevant for these types of study, as there is a wealth of evidence supporting the safety profile of factor replacement therapies (3, 10, 11)
- Mortality was not considered relevant, as treated patients typically have survival rates in line with the general population.

A 18. Related to question A.7, study eligibility has been restricted to English language only. Please explain the impact of excluding non-English language publications on the findings of the SLR.

With regard to evidence selection bias, there may be other published research on this topic in languages other than English, however, given that the majority of high-quality international research is published in English language journals, a pragmatic decision was made to search only the English language literature.

Clinical effectiveness evidence

A 19. Priority question: Please comment on whether the trial population is representative of the target population in the UK.

XTEND-1 enrolled [redacted] patients from three UK sites, and XTEND-Kids enrolled [redacted] patients from three sites across the UK and ROI. Demographically, 51% of patients in XTEND-1 were in Europe (81/159) and 16% were in North America (26/159) (12, 13). In XTEND-Kids, 37% (27/74) of patients were in Europe and 38% (28/74) in North America (14). Given the similarities between these populations and that of the UK, the trial populations in XTEND-1 and XTEND-Kids can be considered broadly representative of the severe haemophilia A population in the UK.

A 20. Priority question. Company submission Appendix D mentions that the HAVEN-3 and A-LONG RCTs provide comparison data for the indirect treatment comparison (ITC) however, only provides brief data on patient disposition and population matching with XTEND-1 for these two trials. Please provide full details of HAVEN-3 and A-LONG including a description of trial design, methods, participant eligibility and interventions as well as full details of baseline and outcome data.

The publications for A-LONG (Mahlangu et al, 2014 (10)) AND HAVEN 3 (Mahlangu et al, 2018 (15)), are available in the Company submission reference pack. For convenience, please also find a summary of the trials below.

A-LONG

Summary

A-LONG was a Phase 3, open-label, multicentre, partially randomised study evaluating the efficacy, safety, and pharmacokinetics of efmoroctocog alfa (recombinant FIII FC fusion protein [rFVIIIFc]) for prophylaxis, on-demand treatment, and perioperative management of previously treated adults and adolescents (aged ≥12 years) with severe haemophilia A (10).

Study participants

Previously treated male patients aged 12 years or older with severe haemophilia A (defined as <1% endogenous FVIII activity or severe genotype) were eligible if previously treated prophylactically or episodically with a history of ≥12 bleeding events in the 12 months prior to the study. Exclusion criteria included a history of inhibitors, history of hypersensitivity associated with any FVIII concentrate or IV immunoglobulin, or other coagulation disorders.

Study design

The study enrolled 165 patients into 1 of 3 treatment arms:

- Arm 1: Individualised prophylaxis (twice-weekly dosing; 25 IU/kg on Day 1 and 50 IU/kg on Day 4 to start, followed by 25–65 IU/kg every 3–5 days, n=118)
- Arm 2: Weekly prophylaxis (65 IU/kg, n=24)
- Arm 3: Episodic (on-demand) treatment as needed for bleeding episodes (10–50 IU/kg, depending on bleeding severity, n=23)

In Arm 1, pharmacokinetic parameters were used to guide individual adjustments to dosing interval (down to 3 days or up to 5 days), and dose (up to 65 IU/kg) to target a steady-state trough FVIII level of 1 to 3 IU/dL or higher as needed to maintain good control of breakthrough bleeding. All patients on a prophylactic regimen prior to study entry were enrolled into Arm 1.

Patients on an episodic regimen prior to study entry had the option to enter into Arm 1 or be randomised into either Arm 2 or Arm 3. Baseline rFVIIIFc pharmacokinetic measures were evaluated in all patients.

Baseline rFVIIIFc pharmacokinetic measures were evaluated in all patients. A subgroup of patients in Arm 1 had sequential pharmacokinetic evaluations for comparison with a commercially available rFVIII product (octocog alfa [Advate]). An injection of 50 IU/kg of rFVIIIFc was administered, and pharmacokinetic measures were assessed for 72 hours; following a washout period, an injection of 50 IU/kg of rFVIIIFc was administered, and pharmacokinetic measures were assessed for 120 hours. rFVIIIFc pharmacokinetics were reassessed 12 to 24 weeks later.

Study termination occurred after completion of the specified pharmacokinetic assessments and achievement of the prespecified rFVIIIFc exposure required to ensure acceptable inhibitor detection. Trough and peak levels of rFVIIIFc were checked for all patients at each visit to verify subjects maintained targeted troughs.

Outcome measures

The primary efficacy endpoints were ABR in Arm 1 vs Arm 3, and assessment of FVIII activity based on primary pharmacokinetic parameters. Primary safety endpoints were inhibitor development and adverse events (AE). Secondary efficacy end points included ABR in Arm 2 vs Arm 3, and the number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode.

Baseline characteristics

Table 1. Subject demographics and baseline characteristics

	Arm 1: individualized prophylaxis (n = 118)	Arm 2: weekly prophylaxis (n = 24)	Arm 3: episodic treatment (n = 23)	Total (n = 165)
Age, y, median (min, max)	29 (12, 65)	31.5 (18, 59)	34 (13, 62)	30 (12, 65)
Weight, kg, median (min, max)	71.65 (42.0, 127.4)	75.85 (50.0, 105.0)	70.00 (48.0, 110.4)	71.60 (42.0, 127.4)
Race, n (%)				
White	79 (66.9)	12 (50.0)	16 (69.6)	107 (64.8)
Black	7 (5.9)	1 (4.2)	2 (8.7)	10 (6.1)
Asian	27 (22.9)	11 (45.8)	5 (21.7)	43 (26.1)
Other	5 (4.2)	0 (0)	0 (0)	5 (3.0)
Geographic location, n (%)				
Europe	34 (28.8)	3 (12.5)	4 (17.4)	41 (24.8)
North America	44 (37.3)	5 (20.8)	7 (30.4)	56 (33.9)
Other*	40 (33.9)	16 (66.7)	12 (52.2)	68 (41.2)
Genotype, n (%)				
Intron 22 inversion	41 (35.0)	7 (33.3)	9 (39.1)	57 (35.4)
Frameshift	24 (20.5)	4 (19.0)	6 (26.1)	34 (21.1)
Missense mutation	22 (18.8)	4 (19.0)	1 (4.3)	27 (16.8)
Nonsense mutation	19 (16.2)	6 (28.6)	1 (4.3)	26 (16.1)
Splice site change	7 (6.0)	0 (0)	4 (17.4)	11 (6.8)
Intron 1 inversion	3 (2.6)	0 (0)	1 (4.3)	4 (2.5)
Duplication	1 (0.9)	0 (0)	0 (0)	1 (0.6)
NA	0 (0)	0 (0)	1 (4.3)	1 (0.6)
VWF antigen, IU/dL, median (IQR)	118.0 (85, 151)	129.0 (86, 166)	131.0 (83, 155)	118.0 (85, 153)
Prestudy FVIII regimen, n (%)				
Prophylaxis	87 (73.7)	0 (0)	0 (0)	87 (52.7)
Episodic	31 (26.3)	24 (100)	23 (100)	78 (47.3)
Estimated bleeding events in prior 12 mo, median (IQR)†				
Prior prophylaxis	6.0 (2, 15)	—	—	6.0 (2, 15)
Prior episodic	27.0 (17, 41)	29.5 (19, 44)	24.0 (15, 36)	27.0 (18, 40)
1 or more target joint, n (%)				
Prior prophylaxis	47 (39.8)	—	—	47 (28.5)
Prior episodic	26 (22.0)	22 (91.7)	18 (78.3)	66 (40.0)
HIV-positive, n (%)	25 (21.2)	4 (16.7)	7 (30.4)	36 (21.8)
HCV-positive, n (%)	55 (46.6)	14 (58.3)	13 (56.5)	82 (49.7)

—, none; HCV, hepatitis C virus; NA, not applicable.
*Other included Australia, New Zealand, Brazil, Hong Kong, India, Japan, Russia, and South Africa.
†Calculation was based on available data.

Source: Mahlangu et al, 2014 (10).

Pharmacokinetics

Comparative pharmacokinetic data for rFVIIIFc vs rFVIII were available for 28/30 patients in the sequential pharmacokinetics subgroup. The terminal half-life of rFVIIIFc was significantly longer than that of rFVIII (geometric mean: 19.0 vs 12.4 hours, respectively; p<0.001).

Efficacy

ABR was significantly reduced with prophylaxis by 92% (Arm 1) and 76% (Arm 2) compared with episodic treatment, based on estimates from a negative binomial regression model (2.91, 8.92, and 37.25 for Arms 1, 2, and 3, respectively; p<0.001). The median (IQR) observed ABRs in Arms 1, 2, and 3 were 1.6 (0.0, 4.7), 3.6 (1.9, 8.4), and 33.6 (21.1, 48.7), respectively.

Among patients receiving individualised prophylaxis, over the last 3 months on the study, the median dosing interval was 3.50 days (mean, 3.87 days) and the median weekly dose was 77.70 IU/kg.

Across all arms, 757 bleeding episodes were treated with rFVIIIFc during the efficacy period. Overall, 87.3% of bleeding episodes were resolved with 1 injection, and 97.8% were controlled with ≤2 injections. The median dose per injection to treat a bleeding episode was 27.35 IU/kg.

Safety

No inhibitors were detected in any patients with an evaluable inhibitor test, including 110 patients with ≥50 exposure days, for whom the inhibitor incidence was 0% (95% CI, 0, 3.3); the inhibitor incidence overall was also 0% (95% CI, 0, 2.2).

Of the 164 patients exposed to rFVIIIFc (1 patient received only rFVIII on study), 108 (65.9%) reported at least one AE (excluding the perioperative period). The types of AEs were representative of events occurring in the general haemophilia population. AEs judged by the investigator to be related to rFVIIIFc treatment occurred in 10 (6.1%) patients; of these, arthralgia and malaise were reported in more than 1 patient (2 patients each).

HAVEN 3

Summary

HAVEN 3 was a Phase 3, multicentre study evaluating the use of emicizumab (bispecific monoclonal antibody bridging activated Factor IX and Factor X) as prophylaxis in adults and adolescents (aged 12 years or older) with severe haemophilia A without inhibitors (15).

Study participants

Eligible patients were 12 years of age or older with severe congenital haemophilia A (defined as <1% endogenous FVIII activity), without current FVIII inhibitors (defined as <0.6 Bethesda units/mL), who were receiving episodic or prophylactic FVIII infusions.

Study design

Two emicizumab prophylactic maintenance regimens were evaluated, following on from four initial loading doses of 3.0 mg/kg:

- A dose of 1.5 mg/kg every week (QW) – Group A
- A dose of 3.0 mg/kg every 2 weeks (Q2W) – Group B.

Patients receiving previous episodic therapy with FVIII were randomly assigned in a 2:2:1 ratio to receive emicizumab QW (Group A) or Q2W (Group B) or to receive no prophylaxis (Group C). Randomisation was conducted centrally by means of an interactive voice–Web-response system and was stratified according to the number of bleeding events (<9 or ≥9) that had occurred in the preceding 24 weeks. Patients who had been receiving adequate prophylactic FVIII, as determined by the investigator, were assigned to receive QW emicizumab (Group D) and could continue FVIII prophylaxis until the second loading dose of emicizumab. At least 40 patients were required to complete 24 weeks or more of observation in a non-interventional study before they could be enrolled in Group D.

After 24 weeks or longer, patients in Group C could switch to receiving emicizumab Q2W (and remain in Group C). All the patients could continue emicizumab therapy at or after 24 weeks.

The primary analysis occurred after the last randomly assigned patient and at least 40 patients from Group D had completed 24 weeks in the trial or had withdrawn, whichever occurred first.

Outcome measures

The primary endpoint was the difference in the rate of treated bleeding events over a period of at least 24 weeks between randomly assigned groups of patients (Group A vs Group C and Group B vs Group C).

Secondary endpoints for the randomised comparisons included all bleeding events (treated and untreated), spontaneous and joint bleeding events, and Haem-A-QoL physical health subscale.

Baseline characteristics

Table S1. Demographic and Clinical Characteristics of the Participants.

	Study Group*				
	Previous Episodic Treatment (randomized)			Previous Prophylactic Treatment	
Participant Characteristics	**A: Emicizumab once-weekly prophylaxis (N = 36)**	**B: Emicizumab every-2-weeks prophylaxis (N = 35)**	**C: No prophylaxis (N = 18)**	**D: Emicizumab once-weekly prophylaxis (N = 63)**	**Total (N = 152)**
Sex, n (%)					
Male	36 (100)	35 (100)	18 (100)	63 (100)	152 (100)
Age, yr					
Median	36.5	41.0	40.0	36.0	38.0
Range	19–77	20–65	16–57	13–68	13–77
<18 yr, no. (%)	0	0	1 (5.6)	7 (11.1)	8 (5.3)
<9 bleeding events in 24 weeks before trial entry, n (%)	9 (25.0)	5 (14.3)	4 (22.2)	53 (84.1)	71 (46.7)
Target joints†					
None, no. (%)	2 (5.6)	8 (22.9)	3 (16.7)	37 (58.7)	50 (32.9)
Yes, no. (%)	34 (94.4)	27 (77.1)	15 (83.3)	26 (41.3)	102 (67.1)
>1, no./total no. (%)	20/34 (58.8)	22/27 (81.5)	14/15 (93.3)	18/26 (69.2)	74/102 (72.5)
FVIII product used before trial entry					
Patients, n	36	34‡	18	63	151‡
Standard half-life, n (%)	31 (86.1)	31 (91.2)	15 (83.3)	53 (84.1)	130 (86.1)
Extended half-life, n (%)	4 (11.1)	2 (5.9)	2 (11.1)	10 (15.9)	18 (11.9)
Both, n (%)	1 (2.8)	1 (2.9)	1 (5.6)	0	3 (2.0)

* Participants who had received episodic treatment with FVIII before trial entry were randomly assigned in a 2:2:1 ratio to receive subcutaneous emicizumab prophylaxis (group A or B) or no emicizumab prophylaxis (group C). Participants who had previously received prophylactic treatment with FVIII were assigned to emicizumab prophylaxis in group D. (Fig. S1 in the Supplementary Appendix).

† All values are based on electronic case-report forms and not on data from the noninterventional study.

‡ In group B, one patient reported 'Other' as the product used. Therefore, percentages are based on 34 participants in group B and 151 participants in the Total column.

Source: Mahlangu et al, 2018 (15).

Efficacy

The ABR was 1.5 (95% CI: 0.9, 2.5) with the QW emicizumab regimen (Group A) and 1.3 (95% CI: 0.8, 2.3) with the regimen of emicizumab Q2W (Group B), compared with 38.2 events (95% CI: 22.9, 63.8) with no prophylaxis (Group C). The bleeding rate was 96% lower in Group A than in Group C (rate ratio: 0.04; 95% CI: 0.02, 0.08; p<0.001), and 97% lower in Group B than in Group C (rate ratio: 0.03; 95% CI: 0.02, 0.07; p<0.001).

No treated bleeding events were reported in 56% of the patients in Group A and in 60% of those in Group B, as compared with those in Group C, who all had bleeding events.

In an intraindividual comparison involving the 48 patients in Group D who had participated in the non-interventional study, the ABR was 1.5 (95% CI: 1.0, 2.3) with QW emicizumab therapy, compared with 4.8 events (95% CI: 3.2, 7.1) during FVIII prophylaxis.

Safety

Overall, 543 AEs were reported in 127/150 patients who received emicizumab. The most common AE was injection-site reaction, occurring in 25% of patients.

One patient discontinued treatment owing to several low-grade AEs that were considered by the investigator to be related to emicizumab. No deaths, thrombotic microangiopathy, or thrombotic events occurred.

No new FVIII inhibitors developed in participants receiving emicizumab. One patient had undergone induction of immune tolerance in 1987 and subsequently had intermittent detectable inhibitor. This patient had a detectable inhibitor titre at Week 13 (1.6 Bethesda units/mL) that spontaneously declined at Week 25.

A 21. According to the Company submission (page 38 of Document B), the XTEND-Kids study was included as part of the clinical effectiveness evidence but did not inform the economic evaluation. Please explain exactly how the XTEND-Kids study contributed to the submission. Please explain why there is a mismatch between the clinical effectiveness and cost-effectiveness evidence in this respect.

The XTEND-Kids study was presented on page 38 of Document B, and Appendix O, for information purposes only and the data were not used to inform the economic model. The Company has not completed an ITC in the paediatric population, and therefore, data from XTEND-Kids was not able to inform the economic model. Rather, it was the adult ITC that informed the economic evaluation for all ages.

Haemophilia is a condition where the underlying defect (a deficiency in clotting FVIII) is the same in children and adults, and so it is felt that extrapolating data can be considered. Treatment with efanesoctocog alfa in XTEND-1 and XTEND-Kids was considered generalisable across the adult and paediatric populations. Patients across both trials had similar ABRs, a comparable PK profile (with a shorter half-life expected in younger individuals), and similar rates of zero bleeds. The safety profile of efanesoctocog alfa was also comparable between the two trial populations.

Efanesoctocog alfa is a factor replacement therapy, a treatment class that has extensive historical data. This wealth of data provides a strong foundation for understanding how these treatments are likely to perform in all age groups. In

addition, factor replacement therapies have a relatively predictable efficacy and safety profile, which has been extensively documented in both adults and children. Again, supporting the rationale to extrapolate data from adults to children and agreeing that the effects of the drug are sufficiently similar across all age groups.

A 22. The Pre-study to XTEND-1 is mentioned in several places in company submission Document B. Please explain how the data from this study were used to inform clinical effectiveness and cost-effectiveness estimates for this submission.

In terms of clinical effectiveness, the observational pre-study was used to inform the key secondary endpoint, i.e. intrapatient comparison of ABR with efanesoctocog alfa prophylaxis versus ABR with pre-study FVIII prophylaxis. This included patients enrolled into Group A following on from the observational pre-study (n=78). Switching from pre-study FVIII prophylaxis to efanesoctocog alfa prophylaxis demonstrated a significant reduction in mean ABR from 2.96 to 0.69, a reduction of 77% (rate ratio 0.23; 95% CI: 0.13, 0.42; p<0.001).

The pre-study was not used to inform the cost-effectiveness estimates, and this was considered a conservative approach, given the statistically significant reduction in ABR.

A 23. Please provide separate baseline and outcome data for the UK subgroup of patients in XTEND-1.

As discussed during the clarification call on Monday 27th November 2023, Sobi plans to request the UK subgroup data from our partners Sanofi however we are unable to provide this data in time for our response. The Company's global medical team is liaising with our partners Sanofi to determine timelines with regard to obtaining these data and these can be provided at a later date.

However, it is worth noting that the UK-based patients in XTEND-1 are considered broadly comparable with the population of patients with severe haemophilia A within the UK. Demographically, 51% of patients in XTEND-1 were in Europe (81/159) and 16% were in North America (26/159) (12, 13). Given the similarities between these populations and that of the UK, the trial populations in XTEND-1 can be considered

broadly representative of the severe haemophilia A population in the UK, and as such any subgroup analysis is expected to show very similar results.

A 24. Please explain how the data from XTEND-1, HAVEN-3 and A-LONG can address the NICE Final Scope given the narrower populations in all three trials (people with severe haemophilia A) versus the Scope ("People with haemophilia A").

The Company is submitting within the narrower population (people with severe haemophilia A), and as such the data from the three studies (XTEND-1, HAVEN-3, and A-LONG) align to this narrower population for the appraisal. While the Company would not expect efanesoctocog alfa to be routinely used to treat patients with mild or moderate haemophilia A, efmoroctocog alfa, for example, has been approved to treat the wider population of patients by regulatory bodies (e.g. Medicines & Healthcare products Regulatory Agency and European Medicines Agency), despite the clinical evidence base being focussed on patients with severe haemophilia A only (3, 16).

Indirect treatment comparison (ITC)

A 25. Priority question. The company submission lists two trials for conducting the ITC, HAVEN 3 to compare with emicizumab, and A-LONG, to compare with efmoroctocog alfa. However, it is unclear how these trials were selected from the SLR. Please provide evidence from the SLR that there are no other trials of these two comparators that could have been used for the ITC.

The following studies were identified through the SLR:

- For efmoroctocog alfa:
  - **A-LONG** – the study was used for the ITC
  - **PUPs A-LONG** – the study was excluded due to inadequate population regarding age: previously untreated patients <6 years
  - **Kids A-LONG** - the study was excluded due to inadequate population regarding age: previously treated patients <12 years

- For emicizumab:
    - **HAVEN 1** – the study was excluded due to an inadequate population regarding history of inhibitors: patients with a history of inhibitors
    - **HAVEN 2** - the study was excluded due to an inadequate population regarding history of inhibitors: paediatric patients (<12 years) with a history of inhibitors
    - **HAVEN 3** - the study was used for the ITC
    - **HAVEN 4** - the study was excluded due to inadequate population regarding history of inhibitors: adults or adolescents with or without a history of inhibitors
    - **HAVEN 5** - the study was excluded due to inadequate population regarding history of inhibitors: adults or adolescents with a history of inhibitors
    - **HAVEN 6** - the study was excluded due to inadequate population regarding severity: no patients with severe hemophilia
    - **HAVEN 7** - the study was excluded due to inadequate population regarding age: a subset of newborns and infants.

A 26. Priority question. A matching adjusted indirect comparison (MAIC) was used for the comparison with emicizumab. However, NICE technical support document (TSD) 18 suggests that a MAIC might be an extremely unreliable method of adjusting for bias in an unanchored treatment comparison.

a) Please provide a justification for why a MAIC as opposed to any other method of population adjustment was chosen.

Haemophilia A is a rare disease, which limits the possibility of conducting randomised control trials. All the trials for efanesoctocog alfa and comparators were disconnected; therefore, neither traditional network meta-analysis nor anchored comparisons were possible. Thus, the following methods were selected in compliance with NICE TSD 18:

- Unanchored population-adjusted indirect comparison when only aggregated data were available for the comparator trials
- Methods for the comparison of individual patient data (IPD), when IPD were also available for the comparator trial.

NICE TSD 18 recommends two methods for unanchored comparisons: MAIC and simulated-treatment comparison (STC) (17). Both methods require the assumption that all prognostic factors and effect modifiers are accounted for.

For this analysis, MAIC was used due to the following reasons:

- MAIC accounts for mean and medians, as well as for the associated standard deviations and ranges. On the contrary, STC is less flexible, and usually only central tendencies are used to predict outcomes in the outcome regression models
- STC should be conducted using the identity link function and may potentially cause bias on other scales (18)
- MAIC was more frequently used by the researchers, including NICE submissions (19, 20).

b) Please employ at least one other method of population adjustment, such as simulated treatment comparison (STC).

Due to time constraints, it was considered not feasible to rerun the entire analysis using a STC. Nevertheless, STC was run for the most important comparator (emicizumab) regarding ABR for any bleeds in the following subpopulations:

- Patients receiving prior prophylaxis:
  - XTEND-1 Arm A versus HAVEN 3 Arm D (QW)
  - STC was run using the same set of variables as for MAIC:
    - Age
    - Body weight
    - Race: proportion of White patients, Asians and Other

        - Target joints (no target joints, 1, 2+)

- Patients receiving prior on-demand:
    - XTEND-1 Arm B versus HAVEN 3 Arm A (QW)
    - XTEND-1 Arm B versus HAVEN 3 Arm B (QW)
    - STC was attempted using the same set of variables as for MAIC:
        - Age
        - Body weight
        - Target joints (no target joints, 1+).

The analysis with all above listed variables was not feasible since all patients with zero target joints at baseline did not experience bleeding events during the study; therefore, the STC model was reduced to age and body weight as covariates.

The results of the STC are presented in Table 28.

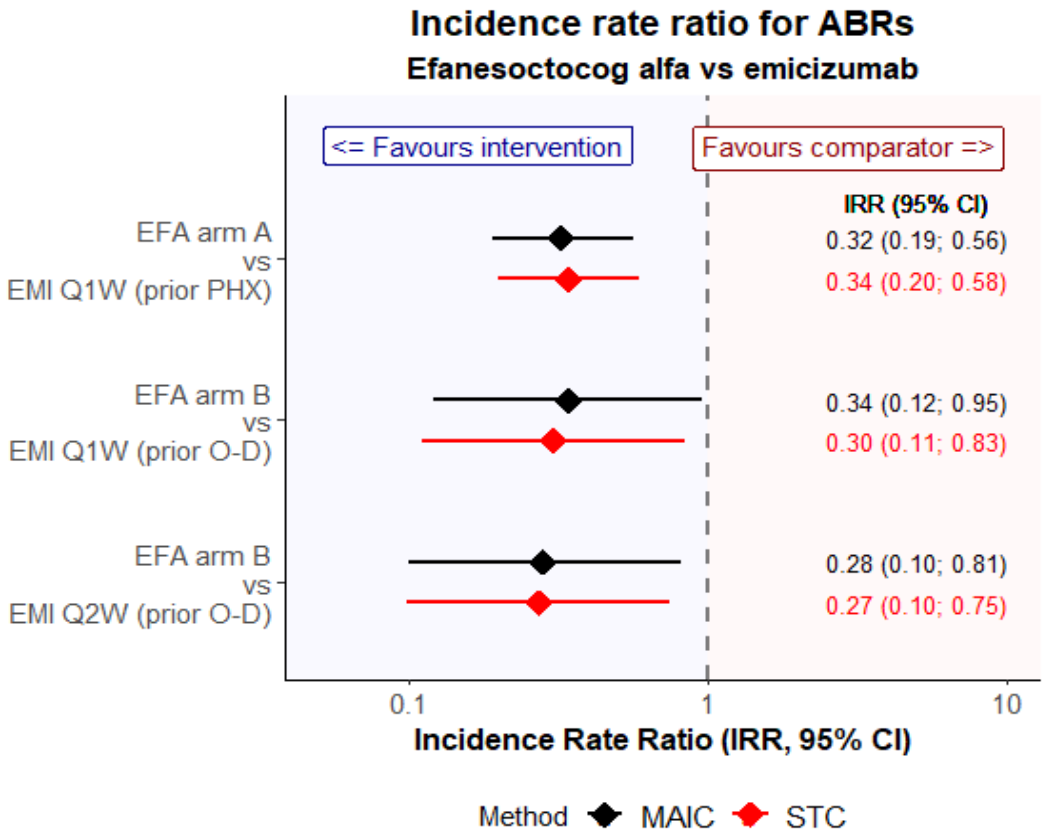
Table 28: STC-adjusted estimates for annualised bleed rate (any bleeding)

STC model	ABR for any bleeding [95% CI]		
	HAVEN 3 Arm D	**XTEND-1 Arm A**	**IRR [95% CI]**
Age + Weight + White + Asian + 0 Target Joint + 1 Target Joint + 2+ Target joint	3.30 [2.23; 4.87]	1.12 [0.78; 1.63]	**0.34 [0.20; 0.58]**
	HAVEN 3 Arm A	**XTEND-1 Arm B**	**IRR [95% CI]**
Age + Weight	2.50 [1.60; 3.90]	0.76 [0.31; 1.87]	**0.30 [0.11; 0.83]**
	HAVEN 3 Arm B	**XTEND-1 Arm B**	**IRR [95% CI]**
Age + Weight	2.60 [1.59; 4.26]	0.71 [0.29; 1.70]	**0.27 [0.10; 0.75]**

Underlined - favours efanesoctocog alfa; **Bold** - statistically significant.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; IRR, incidence rate ratio

The results of the STC were highly consistent with those received using MAIC in the original analysis regarding point estimates and confidence intervals, which is reflected in the forest plot in Figure 2.

Figure 2: Comparison of ABR (any bleeding) between efanesoctocog alfa and emicizumab



Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; EFA, efanesoctocog alfa; EMI, emicizumab; QxW, every x weeks; PHX, prophylaxis; O-D, on-demand; vs, versus; IRR, Incidence rate ratio.

c) As recommended in TSD 18, please provide evidence:

i. that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects, and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison.

NICE TSD 18 recommends the quantification of systematic error and presents initial suggestions on the methods for this analysis. However, the expectations for the additional analyses should be confronted with the rare nature of haemophilia A and the limited quality of the evidence.

The first approach proposed by NICE TSD 18 (out-of-sample validation) was not feasible, since XTEND-1 is the only trial designed to assess the efficacy and safety of efanesoctocog alfa in the target population (21).

As indicated by Hu et al, 2018 (22), the in-sample k-fold cross-validation may overestimate the prediction error in small samples. In our analyses, the available

number of patients used for MAIC was even smaller than those tested by Hu et al, 2018, which raises serious concerns regarding the use of the k-fold method.

As outlined by NICE TSD 18, the methods for estimating the likely error are still under development. Since the credibility of these estimations remains unknown, they are usually avoided in submissions (20).

ii. of sufficient covariate overlap

Each analysis was preceded by a table summarizing the distributions of available variables before and after matching, together with the associated estimates for the effective sample size (ESS). The overlapping was generally sufficient to conduct matching, even despite very limited samples. In particular, the ESS after matching versus emicizumab QW remained at a relatively high level (65% of the initial sample), indicating good overlapping between populations. Of note, TSD 18 indicates that an average reduction of ESS by 80% is not uncommon.

iii. of effect modifier and prognostic status

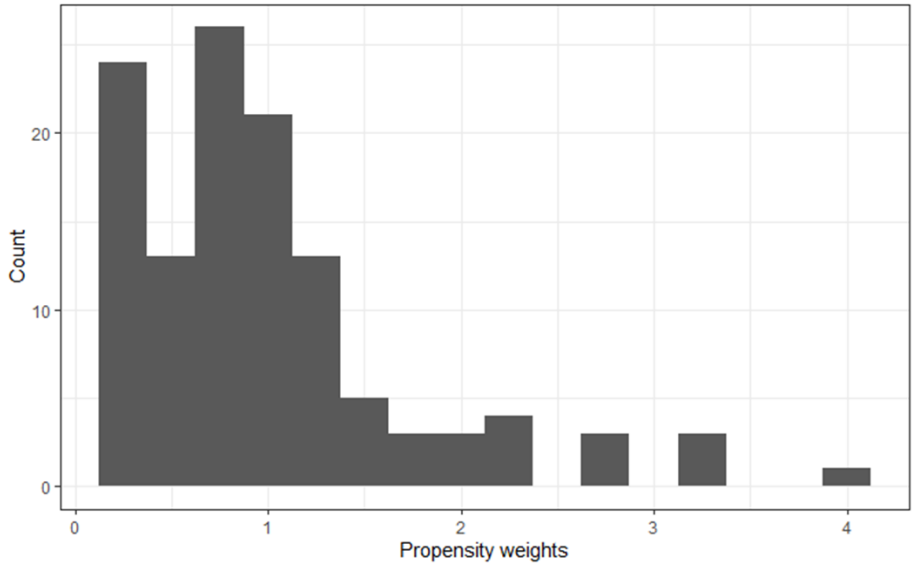
NICE TSD 18 recommends that unanchored population-adjusted indirect comparisons should adjust for all effect modifiers and prognostic variables. To best meet this recommendation, the comparison was adjusted to all available variables reported in the respective comparator studies.

Therefore, in case of unanchored comparison, the distinction between effect modifiers and prognostic factors is not that important since this status does not influence the selection of variables.

iv. of the distribution of weights

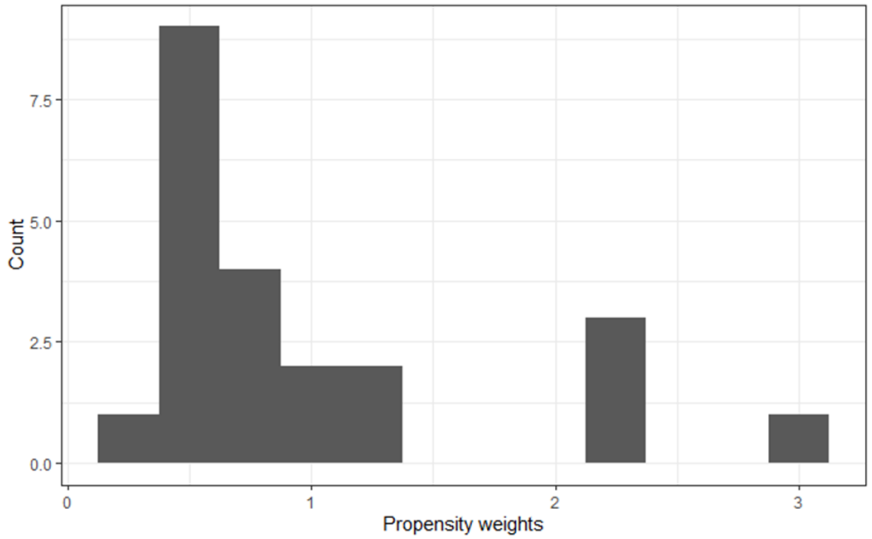
The distribution of weights for each analysis is presented in Figure 3 to Figure 7.

Figure 3: Histogram of weights from MAIC adjustments comparing with HAVEN 3 Arm D



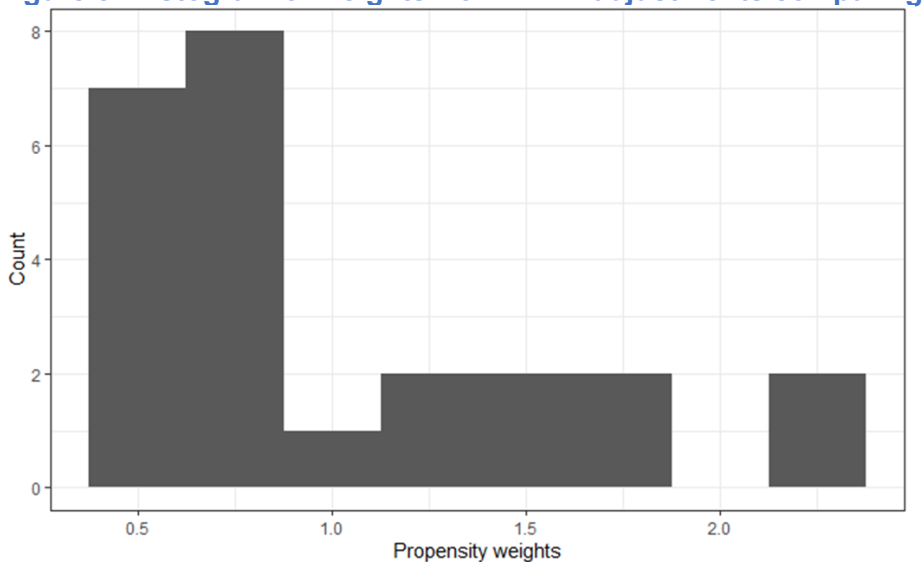
Abbreviations: MAIC, matching-adjusted indirect comparison.

Figure 4: Histogram of weights from MAIC adjustments comparing to HAVEN 3 Arm A



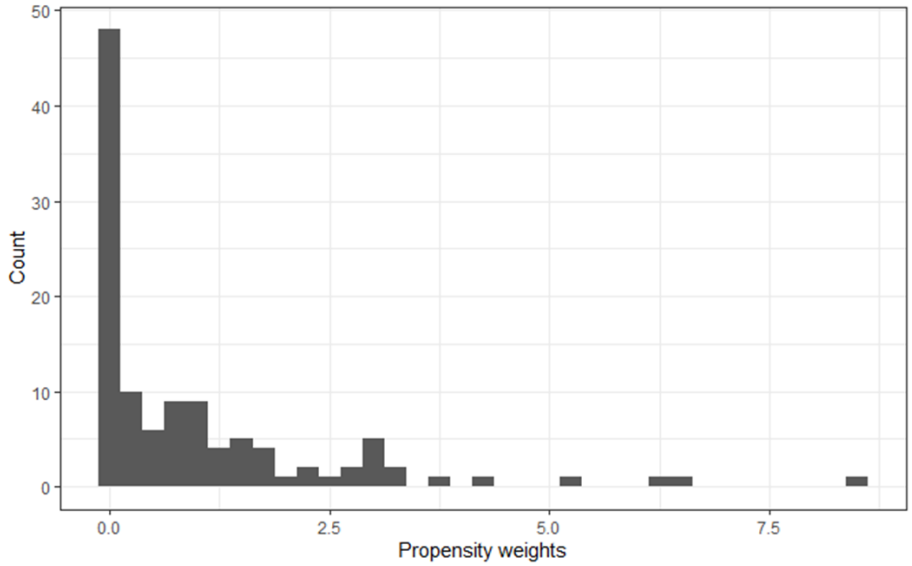
Abbreviations: MAIC, matching-adjusted indirect comparison

Figure 5: Histogram of weights from MAIC adjustments comparing to HAVEN 3 Arm B



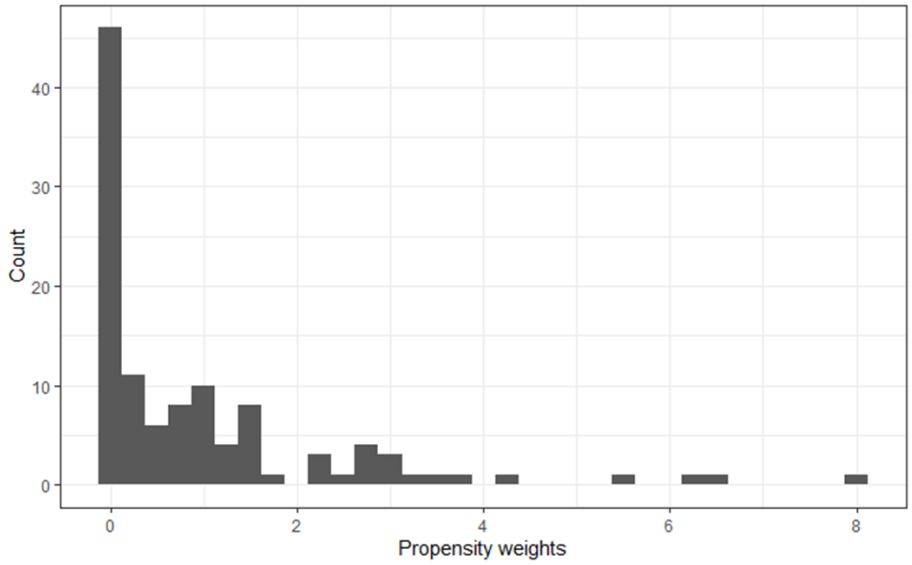
Abbreviations: MAIC, matching-adjusted indirect comparison.

Figure 6: Histogram of weights for the MAIC comparison with pooled HAVEN 3 arms, HJHS joint score



Abbreviations: HJHS, Haemophilia Joint Health Score; MAIC, matching-adjusted indirect comparison.

Figure 7: Histogram of weights for the MAIC comparison with pooled HAVEN 3 arms, HJHS total score



Abbreviations: HJHS, Haemophilia Joint Health Score; MAIC, matching-adjusted indirect comparison.

A 27. Priority question. A propensity score matching (PSM) analysis was used for the comparison with efmoroctocog alfa. However, NICE TSD 17 indicates that other methods, including inverse probability weighting (IPW), regression adjustment and doubly robust methods are options.

a) Please provide a justification for why a PSM analysis as opposed to any other method of population adjustment was chosen.

NICE TSD 17 recommends that regression adjustment can be considered if there are no problems with overlapping (23), however, there were significant differences between XTEND-1 and A-LONG regarding the proportion of patients who had been receiving prophylaxis prior to enrolment, the proportion of patients with target joints, the mean number of target joints at baseline, the mean number of prior bleeds, and the proportion of patients with hepatitis C virus (HCV) at baseline. The between-study difference regarding the mean body weight at baseline was at the border of statistical significance. This raised a concern regarding the degree of overlapping between samples; therefore, in compliance with NICE TSD 17, matching was conducted to improve overlap. Following matching, there were no significant differences between XTEND-1 and A-LONG. Full matching was considered for this analysis, since there is some evidence suggesting a better performance of PSM over IPTW (24-26).

b) Please employ at least one other method of analysis, such as IPW.

An IPW analysis was performed, with patient characteristics for XTEND-1 and A-LONG before and after weighting presented in Table 29. Due to time constraints, it was not feasible to rerun all analyses from the PSM approach, however an analysis of ABRs and of safety data has been performed.

Table 29: Matching of baseline characteristics between XTEND-1 pooled arms and A-LONG for models assessing bleeding outcome and safety outcomes

Variables in IPW model used for ABR and safety	Before weighting					After weighting				
	XTEND-1 (Arm A&B)		A-LONG (Individual PHX)		P-value for difference	XTEND-1 (Arm A&B)		A-LONG (Individual PHX)		P-value for difference
	Estimate mean (SD)/%	N	Estimate mean (SD)/%	N		Estimate mean (SD)/%	ESS (%)	Estimate mean (SD)/%	ESS (%)	
IPW model :Age + Weight + Prior regimen + Target Joint + Prior bleeds + HIV + HCV										
Mean age	35.36 (15.56)	145	33.05 (12.74)	116	*0.187*	34.91 (15.22)	117 (81%)	34.47 (13.44)	98 (84%)	0.803
Mean weight	77.42 (18.95)		73.35 (15.08)		*0.054*	75.55 (18.83)		75.06 (15.53)		0.817
Prior prophylaxis	84.1%		73.3%		***0.031***	73.9%		72.4%		0.786
Mean number of TJ	0.938 (1.735)		1.672 (2.063)		***0.002***	1.217 (1.832)		1.387 (1.777)		0.450
% pts with 0 TJs	70.3%		37.9%		***<0.001***	.60.3%		42.5%		**0.004**
Mean number of prior bleeds	8.34 (15.49)		18.31 (22.28)		***<0.001***	13.99 (22.11)		14.59 (17.93)		0.807
% HIV	13.8%		21.6%		*0.099*	14.0%		15.3%		0.769
% HCV	34.5%		47.4%		***0.034***	40.4%		41.1%		0.899

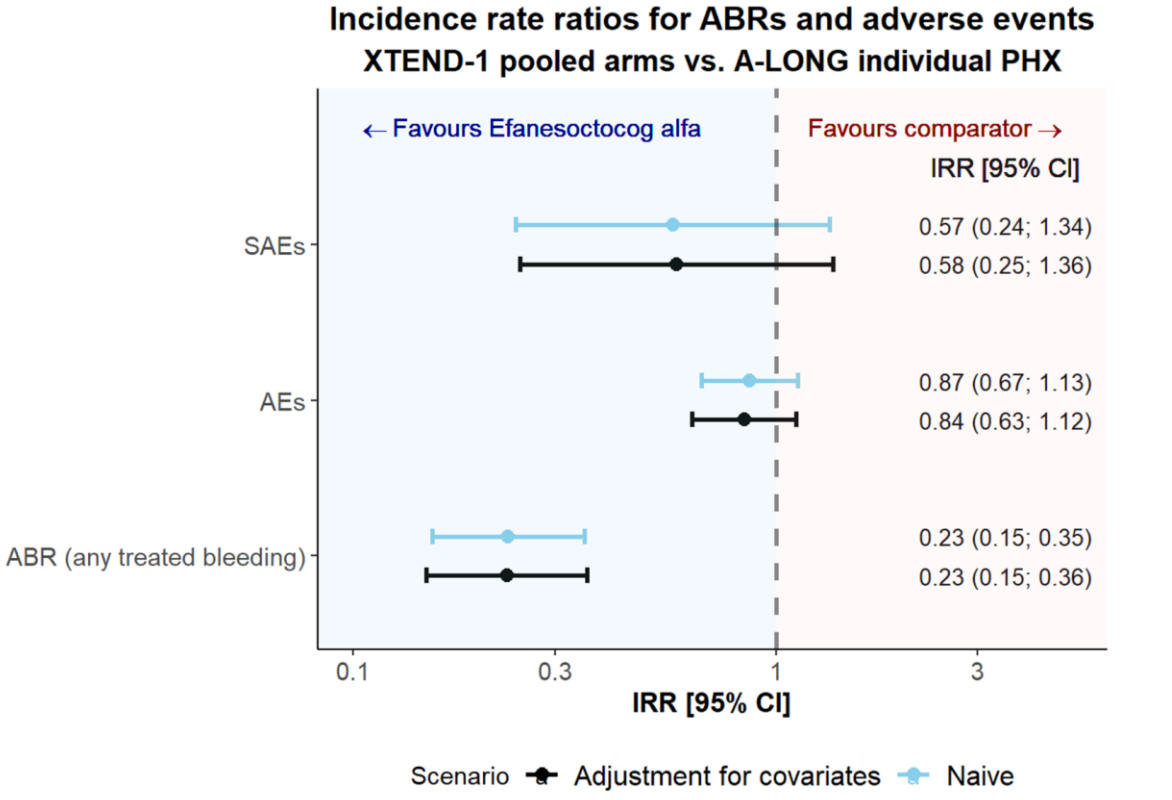
Statistical test: two sample t-test for continuous variables, 2-sample test for equality of proportions for binary variable.
Bold – statistically significant difference in baseline characteristic between studies; italics – in favour of efanesoctocog alfa.
Abbreviations: ABR, annualised bleed rate; ESS, effective sample size; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IPW, Inverse Probability Weighting; PHX, prophylaxis; SD, standard deviation; TJ, target joint.

ABR data were analysed as rates using negative binomial regression model with weights from IPW and log follow-up duration as offset. Safety data were analyzed using two different approaches:

- As rates, using weighted quasi-Poisson model, number of respective events as dependent variable, and log follow-up duration as offset (Figure 8)
- As hazards, using weighted binomial model with complementary log-log link, presence of at least one bleed during follow-up as categorical dependent variable, and log follow-up duration as offset (Figure 9).

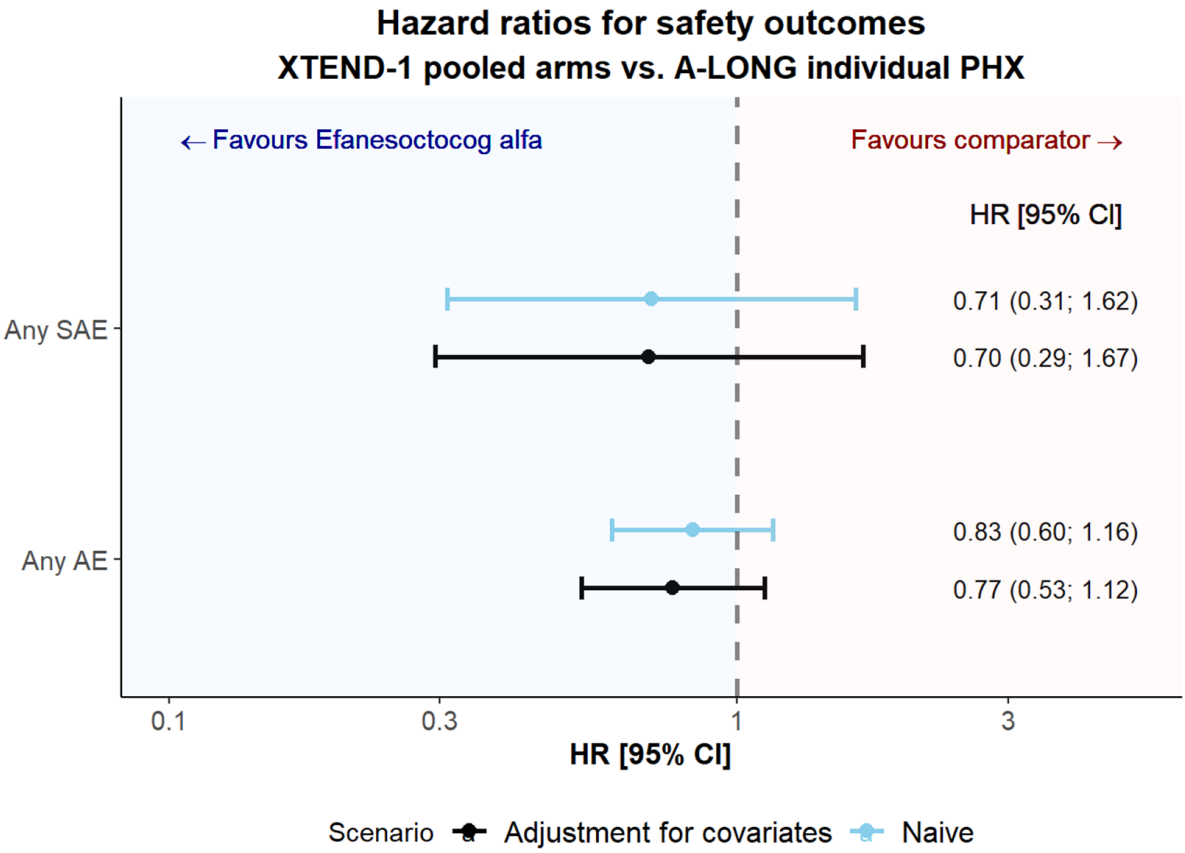
The IPW analysis for ABR is highly consistent with the PSM analysis, while safety analysis indicates that there are no significant differences regarding safety profiles between XTEND and A-LONG.

Figure 8: Incidence rate ratios for ABRs and AEs



Abbreviations: ABR, annualised bleed rate; AE, adverse event; CI, confidence interval; IRR, incident rate ratio; PHX, prophylaxis; SAE, serious adverse event.

Figure 9: Hazard ratios for safety outcomes



Abbreviations: ABR, annualised bleed rate; AE, adverse event; CI, confidence interval; HR, hazard ratio; PHX, prophylaxis; SAE, serious adverse event.

c) Please complete the Quality of Effectiveness Estimates from Non-randomised Studies (QuEENS) checklist as recommended in TSD 17, including an analysis of overlap.

The QuEENS checklist is provided in Table 30.

Table 30: QuEENS checklist

Questions	Answer	Comment
Q1: Have different methods been compared within the study?	No	The selection was based on the decision algorithm proposed in TSD 17. Matching was conducted due to overlapping issues (Figure 3, TSD 17)
Q2: Have the results of the study been compared to others in the literature?	Not compared	Efanesoctocog alfa is a novel technology and there were no other indirect comparisons available
Q3: Is there a discussion of what treatment effect is identified and of the assumptions needed?	No discussion of either	
Q4: Is the model chosen consistent with the outcome	Yes	Negative binomial regression model was used to estimate ABR

Questions	Answer	Comment
variable if using a parametric method?		Binomial regression model with complementary log-log function was used to estimate odds for zero bleeds Linear regression was used to estimate the change in Haem-A-QoL
Q5: Were any checks conducted on the model specification?	No checks reported	
Q6: On selection: Is the assumption of selection on observables assessed?	No	Limited variables were available, therefore all of the were included
Q7: What checks were conducted to assess overlap?	Yes, thorough checks	Distributions were characterised, tabularized and compared using statistical tests
Q8: Has balancing of the covariates been checked after matching and propensity score methods?	Yes, thorough checks	Balancing was checked for all variables using statistical tests
Q9: Is the propensity score function sufficiently flexible?	Unclear	The model included all variables but the complexity and flexibility was limited by the low number of available patients
Q10: Are potential IVs excluded from the set of conditioning variables?	Yes	No clear instrumental variables were available and considered
Q11: Data quality: Are there data quality issues?	a) Data and definitions comparable for treated and control groups	Yes
	b) Treated and controls come from the same area or environment	Yes
	c) Rich set of variables used for matching	Yes (all relevant variables were included)
	d) Reasonable sample sizes	Yes. The samples were sufficient to balance the characteristics although
Q12: For Nearest Neighbour: Has bias adjustment been conducted if more than one variable was included when matching on covariates?	Not applicable	
Q13: Is the choice of replacement (with/without) reasonable?	Yes	Full matching was used
Q14: Is the choice of the number of matches/calliper matching/radius matching reasonable?	Yes	Callipers of reasonable width were selected

A 28. Priority question. Company submission Appendix D describes the methods of conversion of mean difference (MD) to ratio of means (RoM) and incidence rate ratio (IRR) to MD. However, relative bleeding rate in the ITC was reported as IRR or odds ratio (OR). Also, terms for MD and IRR appear to be absent from the equations presented.

a) Please explain why conversion to RoM and MD were required and precisely which data from which trials were converted.

The methods used to re-estimate the effects of efanesoctocog alfa were always consistent with the ones used in the respective comparator trials. So that:

- log incidence rates were the output of negative binomial regression or Poisson regression models. In this case, the between-treatment comparison was calculated as an incidence rate ratio (IRR).

The weighted arithmetic mean number of annual bleeds was sometimes estimated for consistency. In that case, the mean difference was calculated to compare the treatments.

The re-estimation between IRR and mean differences was not necessary for comparisons with emicizumab.

a) Please expand on or provide further explanation of the expository equations.

Mean difference to ratio of means conversion was calculated using method proposed by Friedrich et al, 2008 (27). Specifically, given the outcomes following the normal distribution and reported on the continuous scale, the point estimate of the ratio of means can be derived using a formula:

$$\mathrm{RoM} = \frac{mean(exp)}{mean(contr)},$$

where *mean(exp)* is the mean effect size in the experimental group and *mean(contr)* is the mean effect size in the control group. Given the availability of standard error estimates in the experimental (*SE(exp)*) and control (*SE(contr)*) group, the variance of natural logarithm of RoM can be estimated as:

$$\mathrm{Var}[\ln(\mathrm{RoM})] = \left[\frac{SE(exp)}{mean(exp)}\right]^2 + \left[\frac{SE(contr)}{mean(contr)}\right]^2$$

The pooled transformed ratio can be then back transformed to obtain a pooled ratio and 95% confidence interval (CI), as follows:

$$95\%\mathrm{CI} = \exp\{[\ln(\mathrm{RoM}] \pm 1.96 * sqrt(\mathrm{Var}[\ln(\mathrm{RoM})])\}$$

The negative binomial model implemented in glm.nb() function from MASS package (28) reports log link-transformed estimates on the linear scale, i.e. the effects are additive on the link scale, while the response scale is nonlinear. Thus, the estimated effects are multiplicative on the response scale, which poses a challenge in the effort of estimating mean difference in treatment effects, based on data reported using the relative measures.

The approximation of IRR with normal distribution with parameters mean *E[X]* and variance *Var[X]* can be achieved employing delta method using Taylor expansion, assuming existence of transformation function *g(x)* of specific value *x* and *g(x)* is continuously differentiable (29).

Here, using the second-order terms of Taylor's series expansion to the $g(x)=e^x$ function of log-transformed treatment-effect estimates for intervention (*X*) and comparator (*Y*) can be used to approximate expectation of mean difference in bleeding rates as follows:

$$\mathrm{E}[MD] =$$

$$\mathrm{E}[\exp(\ln(\mathrm{X})) - exp(\ln(\mathrm{Y}))] =$$

$$\exp(\ln(\mathrm{X})) + \frac{1}{2}\exp(\ln(\mathrm{X}))SE(\ln(X))^2 - (\exp(\ln(\mathrm{Y})) + \frac{1}{2}\exp(\ln(\mathrm{Y}))SE(\ln(Y))^2$$

And the approximation of variance of MD can be estimated as:

$$\mathrm{Var}[MD] =$$

$$\mathrm{Var}[\exp(\ln(\mathrm{X})) - \exp(\ln(\mathrm{Y}))] =$$

$$\exp(\ln(\mathrm{X}))^2 SE(\ln(X))^2 + \exp(\ln(\mathrm{Y}))^2 SE(\ln(Y))^2$$

The 95% CI of the mean difference in between-treatment effect estimate can be calculated, as follows:

$$95\%\mathrm{CI} = \mathrm{E}[\mathrm{MD}] \pm 1.96 * sqrt(\mathrm{Var}[\mathrm{MD}])\}$$

A 29. Please confirm whether the A-LONG and HAVEN 3 data was from patients with severe haemophilia like the patients in the XTEND-1 trial or whether the cohort of patients were of mixed disease severity (mix of severe, moderate and mild).

In both trials, eligible patients had to have been diagnosed with severe hemophilia A, defined as <1IU/dL (<1%) of endogenous FVIII.

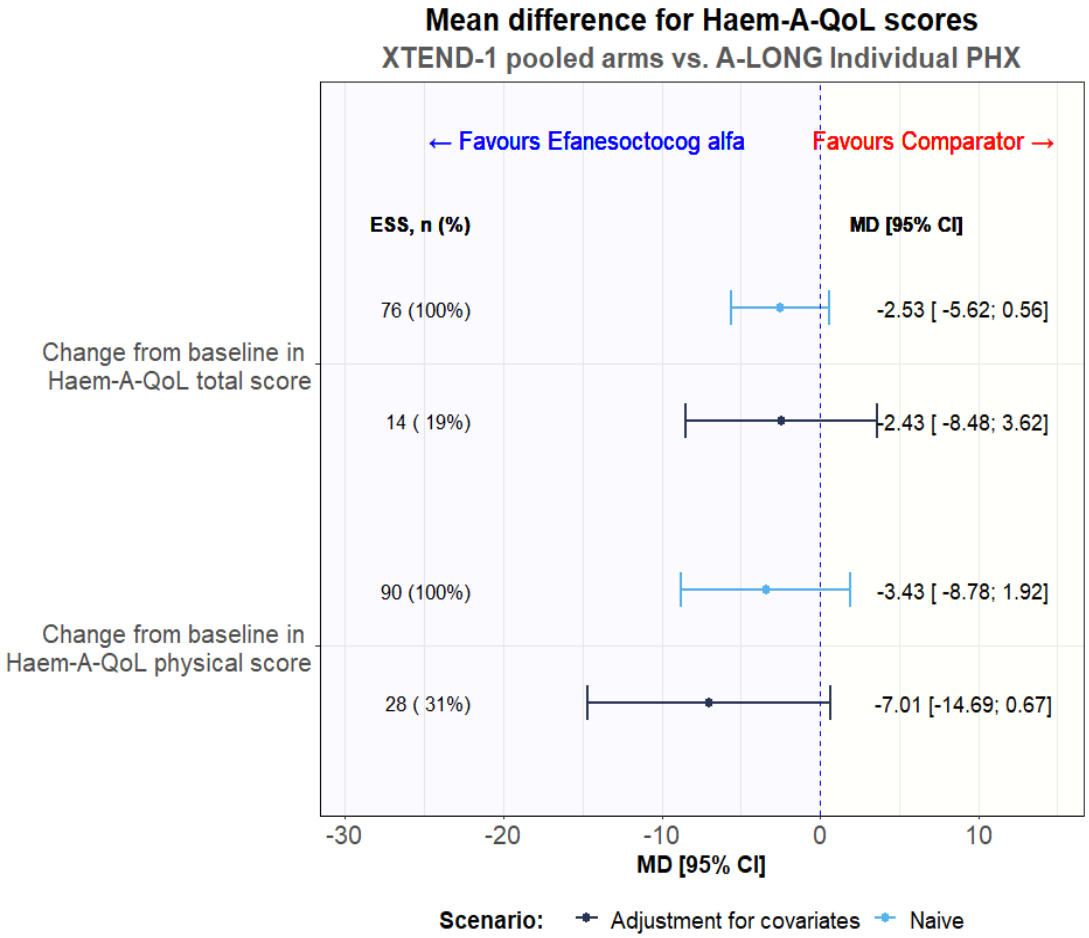
A 30. Please provide ITCs of both HAVEN-3 and A-LONG trials vs. XTEND-1 trials for adverse events of treatment, health related quality-of life (HRQoL) and mortality.

ITCs for mortality were not considered feasible, as there was a single death observed in A-LONG, and no deaths observed in either HAVEN 3 or XTEND-1.

Change from baseline in Haem-A-QoL total score and physical score were considered in the ITC comparing with efmoroctocog alfa. Results are presented in Figure 10. Efanesoctocog alfa compared with efmoroctocog alfa individualised prophylaxis was associated with:

- Favourable estimate for change from baseline in Haem-A-QoL Total score (greater reduction in measures of impairment in quality of life)
- Favourable estimate for change from baseline in Haem-A-QoL Physical domain score (greater reduction in measures of impairment in quality of life)
- The estimated MDs for Haem-A-QoL score was not statistically significant.

Figure 10 Comparison of Haem-A-QoL scores between efanesoctocog alfa and efmoroctocog alfa Individualized prophylaxis



Abbreviations: CI, confidence interval, ESS, effective sample size, Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults, MD, Mean difference; PHX, prophylaxis.

Further discussion of AEs is given in the responses to questions A30 and A31.

Adverse events

A 31. Priority question. There are no data provided in the company submission relating to adverse events (AEs) experienced by patients treated with comparators evaluated in the HAVEN-3 and A-LONG RCTs

a) Please provide the necessary data and appropriate comparative analyses.

Table 31 presents an overview of AEs across HAVEN 3, A-LONG and XTEND-1. In XTEND-1, efanesoctocog alfa was well tolerated and reported treatment-emergent adverse events (TEAEs) that were generally consistent with what is anticipated in an adult and adolescent population with severe haemophilia A (13). Across all trials, few serious adverse events (SAEs) were observed, and the rate of discontinuation due to adverse events was low. No deaths related to study treatment, as determined by Investigators, were observed across the trials. A comparative analysis of XTEND-1 and HAVEN 3 is not considered appropriate due to notable differences of the durations of efficacy periods between the trials. For the base case cost effectiveness analysis, patients in Group D HAVEN 3 were followed up for a median of 29 weeks (63 patients), compared to 52 weeks in Arm A of XTEND-1 (133 patients). An analysis of safety data for XTEND-1 and A-LONG is presented in response to Question 27.

Table 31: Comparison of AEs between HAVEN 3, A-LONG, and XTEND-1

Variable	HAVEN 3			A-LONG			XTEND-1		
	Group A	Group B	Group D	Arm 1	Arm 2	Arm 3	Arm A	Arm B On-demand	Arm B Prophylaxis
Number of patients	36	35	63	117	24	23	133	26	
Duration of exposure period (weeks), median [range]	29.3 [17.3-49.1]	30.1 [6.1-50.1]	33.1 [18.0-48.1]	32.6 [8.6-56.3]	28.0 [0.0001-38.4]	27.9 [14.8-31.1]	52.1 [1.1–55.1]	50.9 [27.1–53.1]	52.1 [27.1–53.1]
No. of adverse events	143	145	236	219	46	23	361	22	11

Variable	HAVEN 3			A-LONG			XTEND-1		
	Group A	Group B	Group D	Arm 1	Arm 2	Arm 3	Arm A	Arm B On-demand	Arm B Prophylaxis
Most common adverse events, N (%)									
Injection-site reaction	9 (25)	7 (20)	20 (32)	0 (0)	0 (0)	1 (4.3)	3 (2.3)	0 (0)	0 (0)
Upper respiratory tract infection	4 (11)	4 (11)	8 (13)	6 (5.1)	0 (0)	3 (13)	3 (2.3)	0 (0)	0 (0)
Nasopharyngitis	2 (6)	6 (17)	10 (16)	16 (13.7)	1 (4.2)	3 (13)	6 (4.5)	0 (0)	0 (0)
Arthralgia	7 (19)	6 (17)	14 (22)	10 (8.5)	2 (8.3)	1 (4.3)	25 (18.8)	1 (3.8)	0 (0)
Headache	3 (8)	4 (11)	8 (13)	5 (4.3)	6 (25)	2 (8.7)	26 (19.5)	5 (19.2)	1 (3.8)
Influenza	1 (3)	3 (9)	5 (8)	5 (4.3)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)
Patients with 1 or more serious adverse events				10 (8.5)	2 (8.3)	0 (0)	13 (9.8)	2 (7.7)	0 (0)
No. of serious adverse events	1	3	10	–	–	–	16	2	0
Adverse event leading to discontinuation of treatment, N (%)	0 (0)	1 (3)	0 (0)	1 (0.9)	1 (4.2)	1 (4.3)	2 (1.5)	0 (0)	0 (0)

A 32. The EAG noted that the evidence base for the ITC to compare with emicizumab is HAVEN 3 trial, which reported AEs experienced by patients treated with any of the comparators (company submission reference 100), but the AEs were not reported in the company submission. Please explain why these data were not reported and provide the necessary data.

As presented in Question A30, a summary of AEs experienced by patients treated with emicizumab in HAVEN 3 is also presented in Table 32. As outlined in the response to Question A30, an ITC of AEs was not performed as the exposure times in each study were not comparable. However, the rate of SAEs was low across both HAVEN-3 and XTEND-1 and there were very few AEs leading to discontinuations.

Table 32: Summary of AEs, HAVEN 3

Variable	HAVEN 3		
	Group A	Group B	Group D
Number of patients	36	35	63
Duration of exposure period (weeks), median [range]	29.3 [17.3-49.1]	30.1 [6.1-50.1]	33.1 [18.0-48.1]
No. of adverse events	143	145	236
Most common adverse events, n (%)			
Injection-site reaction	9 (25)	7 (20)	20 (32)
Upper respiratory tract infection	4 (11)	4 (11)	8 (13)
Nasopharyngitis	2 (6)	6 (17)	10 (16)
Arthralgia	7 (19)	6 (17)	14 (22)
Headache	3 (8)	4 (11)	8 (13)
Influenza	1 (3)	3 (9)	5 (8)
No. of serious adverse events	1	3	10
Adverse event leading to discontinuation of treatment, n (%)	0 (0)	1 (3)	0 (0)

Source: Mahlangu et al, 2018 (15).

Section B: Clarification on cost-effectiveness data

Patient population

B 7. B 1. In the electronic model all patients are assumed to be only males.

a) Please confirm if the target patient population of efanesoctocog alfa is only males. Table 47 of the company submission states that 99.4% is males but this does not align with the input in the model.

The population of XTEND-1 was 99.4% male, and this is representative of severe haemophilia A, as the UKHCDO annual report indicates that 99.8% of patients with severe haemophilia A in the UK are male (30). For simplicity, in the model it has been assumed that the population is 100% male.

b) Emicizumab and efanesoctocog alfa are not licenced for patients below the age of 12. Please comment on the validity of the assumption to use these treatments for patients below the age of 12.

Emicizumab is licensed for use in all age groups, and efanesoctocog alfa is also expected to be licensed for use in all age groups.

Model Structure

B 8. Priority questions: In company submission section B.3.2.2, it is noted that the model structure in the economic analysis matches with that used in similar economic models referring to four sources (numbered 111-114). However, the economic SLR identified 24 studies which were included to the extraction process, with additional information reported in company submission Appendix G. The following questions relate to the use of bleed and non-bleed health states in the model:

B 2. Please explain the reasoning for using the health states of bleed and no bleed only, and not incorporating joint damage (as done in half of the studies identified

in the SLR), or any other relevant health states such as target joint, arthropathy or joint replacement surgery as done in other economic analysis.

Evaluations using health states that incorporated factors such as joint damage have typically been those evaluating prophylactic therapy compared with on-demand therapy or comparing prophylaxis with EHLs or emicizumab with prophylactic SHLs (9). In these evaluations, the progression of joint damage with comparator therapies would have been an important factor, however, as the use of effective prophylaxis has become more widespread, it has become less relevant.

For example, in the ICER evaluation that included health states based on the Pettersson score (PS) (9), it was assumed that the score would progress by 1 for every 6.52 joint bleeds. In HAVEN 3, the ABR for joint bleeds for patients treated with emicizumab prophylaxis varied between 0.9 and 1.2, compared with 0.51 in XTEND-1, meaning that on average, the PS would progress by 1 point every 5 and a half years at its fastest, and it would take 152 years to progress from no arthropathy to a joint replacement surgery (PS: 28). The study also had limited evidence to differentiate utility values between PS based health states.

Input from clinical experts who were asked to assess the model structure suggested that progression of joint disease was a less meaningful outcome to consider when comparing efanesoctocog alfa and emicizumab or efmoroctocog alfa, and that the impact of not experiencing bleeds for a longer period would be more relevant for patients (2).

B 3. Using the bleed and no bleed health states may miss granularity in terms of bleeding levels and locations. For instance, low, mild and severe levels of bleeding, or intra-cranial or joint bleeding might be expected to require different treatment paths for patients and lead to different HRQoL levels. Please comment on the impact the severity and location of the bleeding may have on health outcomes and resource use and explain why these pathways were not structurally incorporated in the model.

As outlined in the response to Question B8, the majority of bleeds observed in XTEND-1 were joint or muscle bleeds, and 96.7% were controlled by a single injection of efanesoctocog alfa. No intracranial bleeds were observed. The Company expect that the majority of bleeds for patients treated prophylactically with

efanesoctocog alfa to be controlled using efanesoctocog alfa alone, in line with current therapies. The model does account for some differences in resource use by bleed severity via the modelling of treated and untreated bleeds, as untreated bleeds are likely to be those of lower severity, for example a cut while shaving. More severe bleeds, such as bleeds following joint impact during exercise, will require treatment, but typically can be controlled with FVIII alone (a treated bleed). While more complicated bleeds can require additional treatment, beyond that included in the model, this is typically associated with events such as surgery, or major trauma, the rate of which is not expected to differ between treatment arms. As such, the cost of such complications is expected to be equal between arms and has not been included in the model.

Any variation in the disutility associated with different bleed severities is expected to be implicitly captured in the utility analysis. While the overall bleed rate may vary between treatments, the distribution of bleeds across different sites or levels of severity is not expected to vary between therapies.

B 4. Please explain why differentiation of patients across different FVIII levels was only used to assess HRQoL and not treatment effectiveness (e.g. bleeding levels).

An approach using different bleed rates by FVIII level was initially explored in the model using data from Benson et al, 2021 (31) and Groth et al, 2016 (32) to inform ABRs, and Chowdary et al, 2020 (33) to inform the proportion of patients experiencing a bleed. The proportion of time patients spend in each FVIII level state was computed form the PK profile of each drug. However, the results of this analysis showed poor concordance between the predicted ABRs values based on FVIII levels over time, and values from the MAIC (Table 33 and Table 34). In both analyses, the data used to derive ABRs by FVIII level was based on PK and outcome data for a single therapy, with Groth et al, 2016 using data on turoctocog alfa from guardian™ 1 and guardian ™ 3, and Benson et al, 2021 using data on turoctocog alfa pegol from the pathfinder2 trial. Therefore, it is unclear how well the FVIII level analyses generalise to other treatments with differing PK and pharmacodynamic properties. It was also unclear if analysis of bleed rates by FVIII level would be applicable to emicizumab, where FVIII equivalence is used.

Table 33: Comparison of predicted ABRs using FVIII levels and MAIC outputs

Treatment	Groth 2016	Benson 2021	ABR from MAIC
Efanesoctocog alfa (chromogenic substrate assay)	0.89	1.76	1.07
Efanesoctocog alfa (one-stage assay)	1.40	2.44	1.07
Efmoroctocog alfa (chromogenic substrate assay)	2.56	3.72	3.70
Efmoroctocog alfa (one-stage assay)	2.54	3.69	3.70
Emicizumab QW	2.86	4.05	3.25
Emicizumab Q2W	2.86	4.05	3.83
Emicizumab Q4W	2.86	4.05	4.87

Abbreviations: ABR, annualised bleed rate; MAIC, matching adjusted indirect comparison; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 34: Comparison of the proportion of patients experiencing bleeding in a 6 months period using FVIII levels and the ITC/clinical trials

Treatment	Chowdary 2020 pragmatic	Chowdary 2020 conservative	Proportion of patients with bleedings from MAIC
Efanesoctocog alfa (chromogenic substrate assay)	3.7%	3.7%	44.1%
Efanesoctocog alfa (one-stage assay)	12.1%	12.1%	44.1%
Efmoroctocog alfa (one-stage assay)	30.2%	32.1%	61.1%
Efmoroctocog alfa (chromogenic substrate assay)	30.5%	32.5%	61.1%
Emicizumab QW†	39.7%	39.7%	55.6%
Emicizumab Q2W†	39.7%	39.7%	55.6%
Emicizumab Q4W†	39.7%	39.7%	55.6%

†As the proportion of patients experiencing bleeding was not evaluated in the MAIC comparing to emicizumab, values presented here are HAVEN 3 values for Arm D as used in the company submission.
Abbreviations: FVIII, clotting Factor VIII; ITC, indirect treatment comparison; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

To account for these differences, an additional calibration of health outcomes for each FVIII activity level group was attempted. The data from the aforementioned publications used as the basis for evaluating the general relationship between assessed parameters.

Two approaches were undertaken to calibrate the health outcomes in relation to FVIII activity level data:

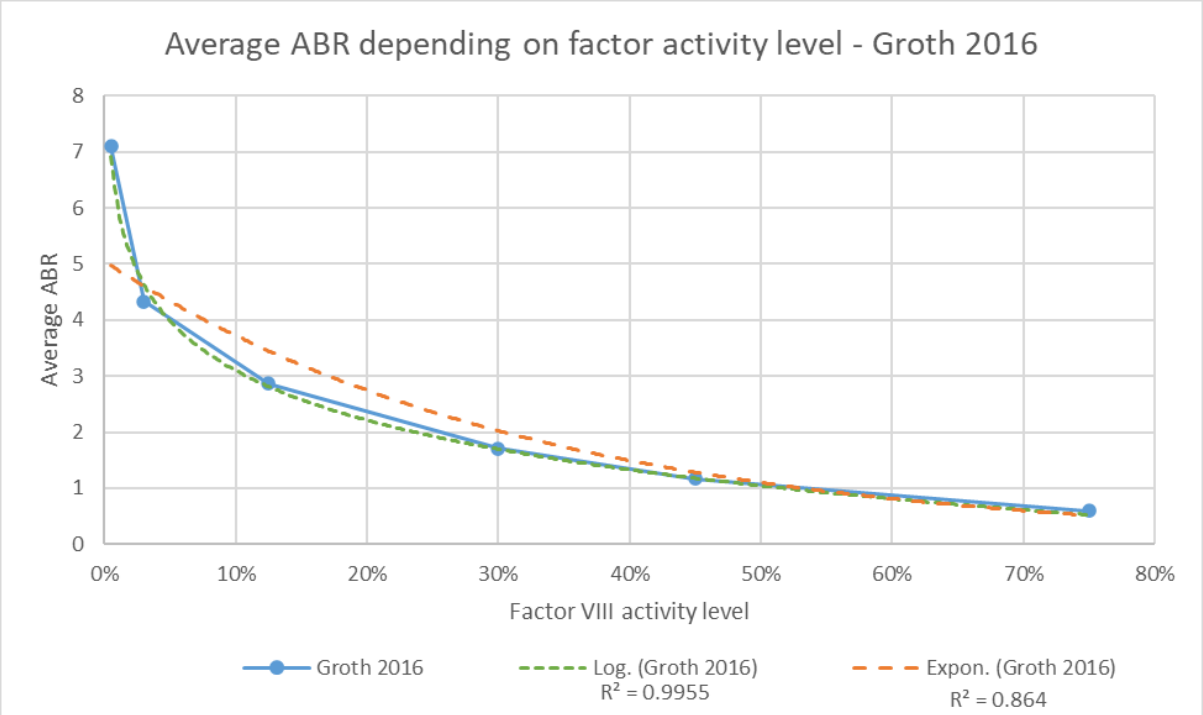
- Using data from source publications (Groth et al, 2016 and Benson et al, 2021 for ABR and Chowdary et al, 2020 for the proportion of patients with no bleeds) multiplied by a constant value
- Estimation based on the distribution with the best fit to the published data.

To ascertain the best fitting distribution, data from publications was plotted and a simple fit based on a coefficient of determination was attempted:

- For both Groth et al, 2016 (Figure 11) and Benson et al, 2021 (Figure 12), the logarithmic function has shown the best fit; however, the exponential function could also be viable
- As described previously, two data sets were presented in the publication by Chowdary et al, 2020: conservative and pragmatic
- Fitting was performed for both data sets and the logarithmic function has shown the best fit, with a closer fit for the conservative vs pragmatic data set (Figure 13 and Figure 14, respectively).

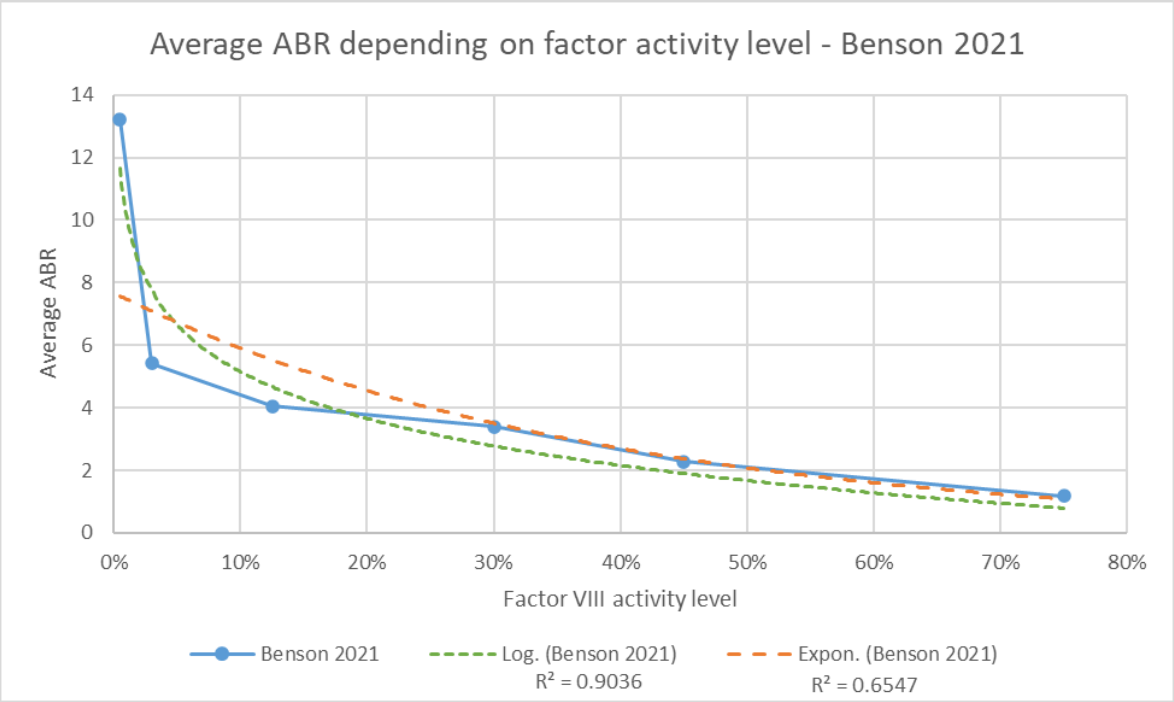
However, when considering the proportion of patients with bleeds instead of the proportion of patients without bleeds, the exponential function provided a fit superior to the logarithmic function for both conservative and pragmatic data set (Figure 15 and Figure 16, respectively).

Figure 11: ABR depending on factor activity level – Groth 2016



Abbreviations: ABR, annualised bleeding rate.

Figure 12. ABR depending on factor activity level – Benson 2021



Abbreviations: ABR, annualised bleeding rate.

Figure 13. Proportion of patients with no bleedings depending on factor activity level – Chowdary 2020 (conservative data set)

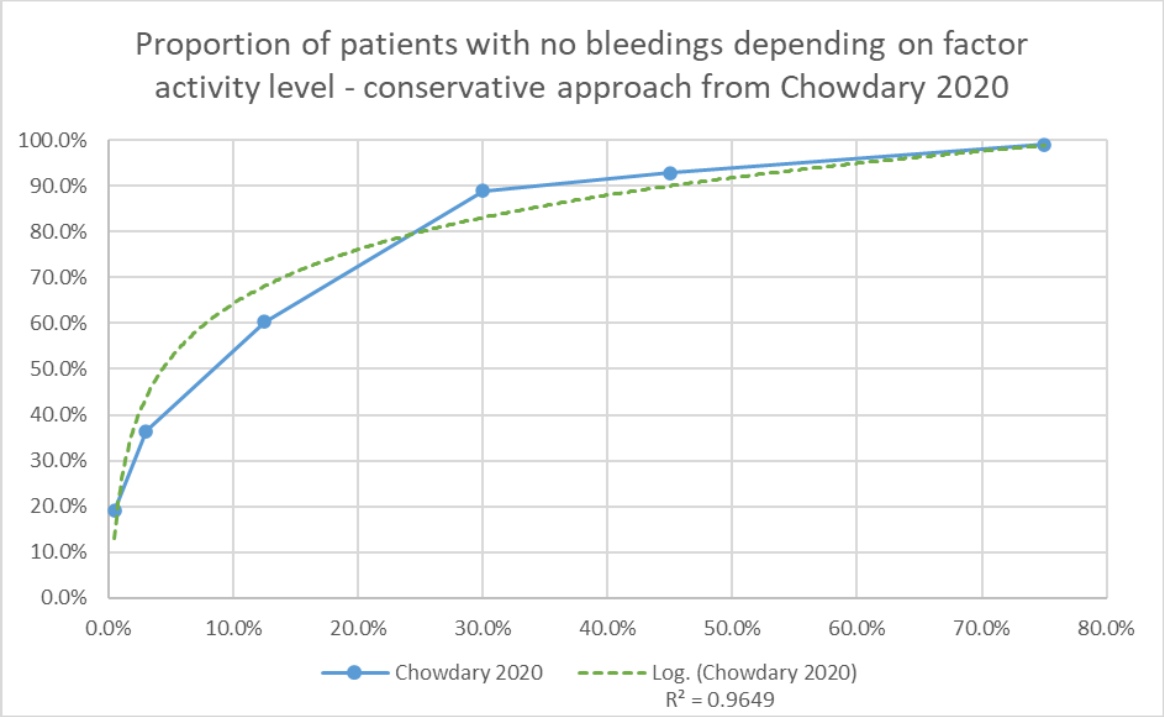


Figure 14. Proportion of patients with no bleedings depending on factor activity level – Chowdary 2020 (pragmatic data set)

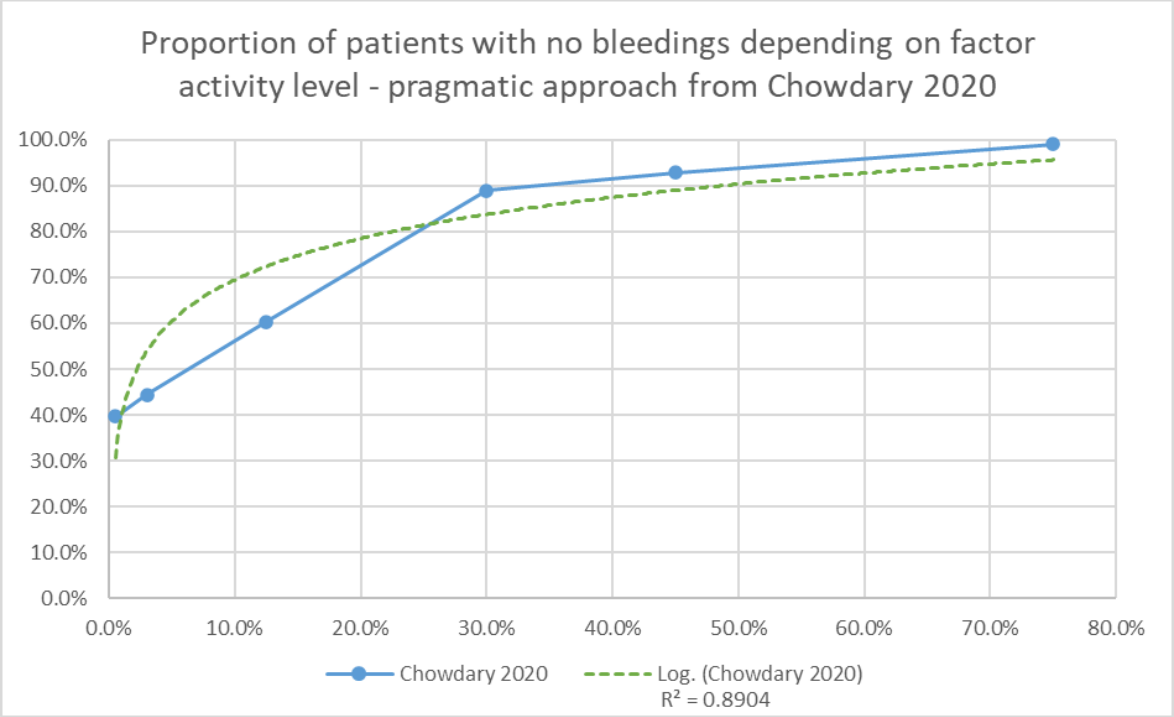


Figure 15. Proportion of patients with bleedings depending on factor activity level – Chowdary 2020 (conservative data set)

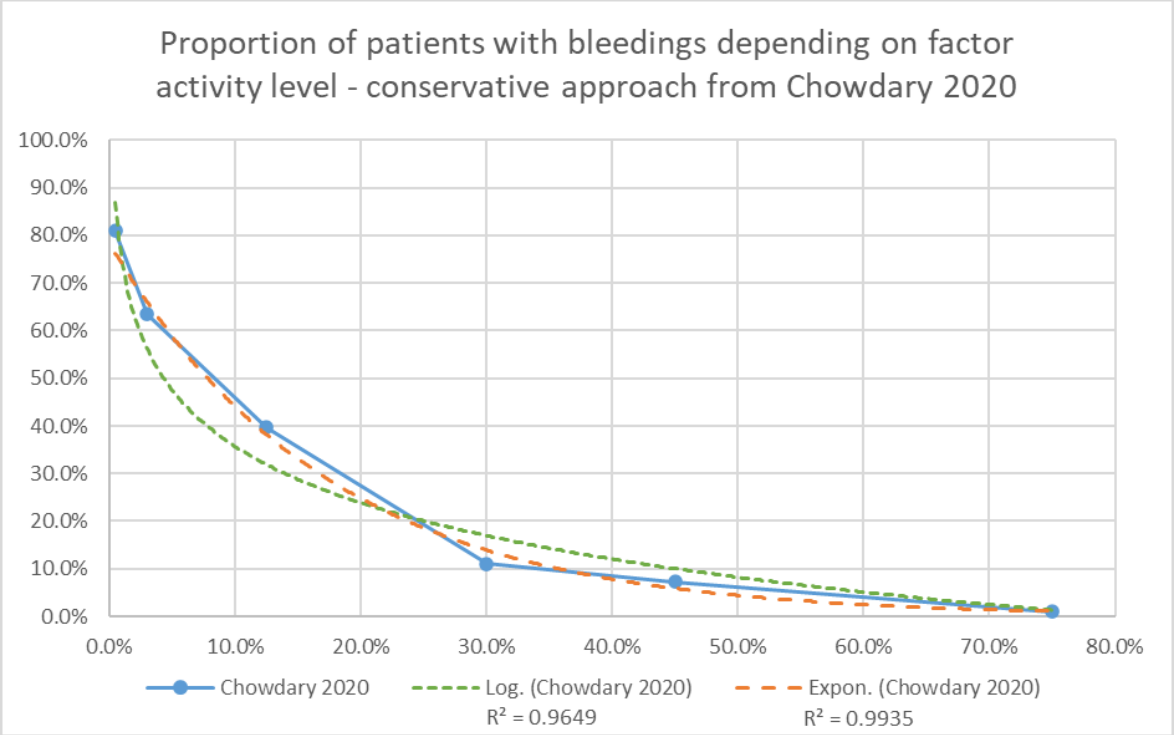
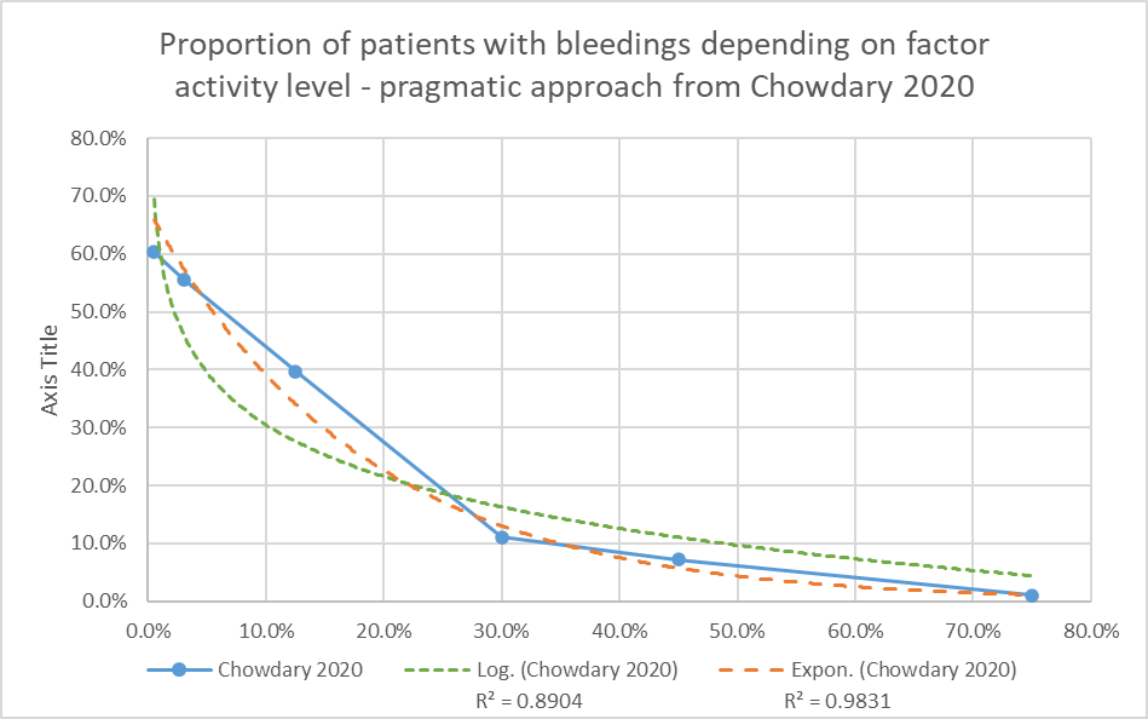


Figure 16. Proportion of patients with bleedings depending on factor activity level – Chowdary 2020 (pragmatic data set)



Finally, logarithmic and exponential functions were assessed for both ABR data and the proportion of patients with bleedings:

$$Outcome = \alpha * Publication\ Data$$

$$Outcome = \alpha * Ln(FVIII) + \beta$$

$$Outcome = \alpha * e^{\beta * FVIII}$$

Where:

a) $Outcome$ is outcome of interest (ABR, proportion of patients with no bleedings) based on FVIII activity level,

b) α, β are searched parameters and,

c) $FVIII$ is Factor VIII activity level.

Residual sum of squares (RSS) was used as a measure of data fit. It was calculated with the following equation:

$$RSS = \sum (Outcome_{calculated} - Outcome_{MAIC})^2$$

Where:

- $Outcome_{calculated}$ is the average value of the outcome (ABR, proportion of patients with no bleedings) calculated for each treatment based on the distribution of FVIII activity level data and values of outcome for each FVIII activity level group estimated in the course of the calibration,
- $Outcome_{MAIC}$ is the average value of the outcome estimated in MAIC.

In most cases logarithmic and exponential calibrations had shown the best results. Multiplying ABR values from Groth et al, 2016 by a constant gave values closer to the ones reported in the MAIC than for Benson et al, 2021.

The results of pairwise calibration were based on one-stage assay for efanesoctocog alfa and chromogenic assay for efmoroctocog alfa. Those assay were conservatively assumed as one-stage assay showed poorer FVIII distribution data for efanesoctocog alfa and chromogenic assay showed better distribution for efmoroctocog alfa. As the exponential calibration showed less ABR values equal to 0

for high FVIII levels, it was deemed as more reliable option. Summary of ABR values used in this analysis is presented in Table 35. Table 36 presents the results of the calibration for proportion of patients with bleeds. This includes a scenario that adjusts the bleed proportion for emicizumab to 46.5% to reflect 26 weeks (6 months) of follow-up, compared to 33.7 weeks in HAVEN 3.

Table 35: Summary of ABR calibration results

Treatment	Factor VIII activity level					
	<1%	1–5%	5–20%	20–40%	40–50%	>50%
Efanesoctocog alfa vs						
Efmoroctocog alfa	10.50	8.54	3.89	0.91	0.26	0.02
Emicizumab	9.98	8.17	3.83	0.95	0.29	0.03

Abbreviations: ABR, annualised bleed rate.

Table 36: Summary of proportion of patients with bleeds calibration results

Treatment	Factor VIII activity level					
	<1%	1–5%	5–20%	20–40%	40–50%	>50%
Efanesoctocog alfa vs						
Efmoroctocog alfa	83.37%	80.30%	69.64%	53.57%	42.78%	27.28%
Emicizumab†	68.50%	65.60%	55.60%	40.90%	31.50%	18.60%
Emicizumab‡ (scenario)	52.90%	51.50%	46.50%	38.60%	32.90%	23.90%

†As the proportion of patients experiencing bleeding was not evaluated in the MAIC comparing to emicizumab, values presented here are calibrated to HAVEN 3 values for Arm D.
‡A scenario analysis in which the proportion of patients experiencing a bleed in HAVEN 3 is adjusted to reflect 26 weeks of follow-up.

However, the results of this analysis give and overall ABR and bleed proportion that is matched to the MAIC and return similar results to the analyses without ABRs by FVIII level. As such, this analysis was excluded from the model base case.

B 5. Page 116 of the company submission states that ‘in each cycle, the model estimates the proportion of time a patient will spend with FVIII in different ranges. The model can divide FVIII levels into six groups: ≤1%, 1–5%, 5–20%, 20–40%, 40–50%, and >50%, however in the base-case analysis, the model only differentiates between people with FVIII above or below 20%, with scenario analysis considering a 5% threshold.’ Please explain if this categorization is applied for the HRQoL analysis only or also for the annualised bleeding rate (ABR) that was used to distribute patients across health states. Please also

explain how ‘the proportion of time a patient will spend with FVIII in different ranges’ is exactly estimated in the model and how is this used in the model. Please provide an example of computations if possible.

In the model base case, and as outlined in response to Question B4, FVIII levels are applied for the HRQoL analysis only. The amount of time spent in each state was calculated according to the PK profile of each drug, using the formula from Benson et al, 2021 for efanesoctocog alfa and efmoroctocog alfa (31).

For FVIII therapies, the time from infusion to reaching a given FVIII level is given by the formula

$$t = Ln\left(\frac{D * IR}{Breakpoint * \left(1 - e^{-\frac{\tau}{MRT}}\right)}\right) * MRT$$

Where:

- D is the dose of a given treatment,
- IR is the incremental recovery, set to 1 divided by Vss
- MRT is the mean residence time, calculated as Vss divided by clearance
- t is the time since the dose,
- τ is the dosing interval.

This is calculated for each of the breakpoints included in the model and if this is more than the time between doses, then it is assumed that patients will spend no time with FVIII below this level. Otherwise, this is used to calculate the proportion of time a patient will spend with FVIII above this level, by dividing the time by the dosing interval.

These calculations are included in the model, on the sheet ‘Activity level’.

B 6. Page 116 of the company submission also mentions that ‘*the model also includes an option to specify ABRs by FVIII level, however this has not been applied in this analysis’*. Please make the necessary model modifications to allow the user to make this switch in the model in order to assess the impact of efanesoctocog alfa using the FVIII level instead of the bleed/no bleed

categorization. Please run a scenario analysis and present results using the implemented option in the model.

A scenario analysis using the ABRs and bleed proportions by FVIII level presented in Table 35 and Table 36 has been provided in Appendix A. As highlighted in the response to B4, the impact of these scenarios is minimal, with only minor differences in costs and QALYs observed.

B 7. In the Markov model (B.3.2.2.2), a 6-month cycle length was used. In general, the cycle length chosen should be short enough that it is unlikely that 2 transitions may occur within one cycle. Considering this, please justify why you consider 6 months an appropriate length given that severe haemophilia A patients could suffer from multiple bleeding events within 6-month time. Otherwise, please refine the model accordingly.

While patients may have more than one bleed in 6 months, the acute impact of this can be adequately captured using 6-month cycle. This was tested during the QC of the model, the model was rebuilt, including a model using a 1-week cycle length, which gave comparable results. However, to capture the longer-term impact of bleeds using the shorter cycle length would require the use of entail tunnel states. As such, it was concluded that a shorter cycle length would add complexity to the model without adding granularity.

Clinical effectiveness inputs

B 8. Priority question: On page 121 of Document B of the company submission it is noted that '*as per study protocol, all reported ABRs were treated in XTEND-1'*.To compare efanesoctocog alfa with efmoroctocog alfa in PUPs, the company submission mentions on page 122 that the IRR from the MAIC for treated bleeds was applied because 'an analysis of any bleeds (treated and untreated) was not possible, as these data were not collected in the A-LONG study (as per study

protocol, all reported ABRs were treated in A-LONG)'. However, in Table 49 the % of treated bleeds (64%) seems to be informed from the XTEND-1 trial.

a. Please clarify the inconsistency in the statements and clarify if all bleeds were treated or not in the XTEND-1 trial.

This statement should read "ABRs for all bleeds and treated bleeds were reported in XTEND-1". Not all bleeds were treated in XTEND-1.

b. Please provide detailed information on the number of bleeds that were treated in the XTEND-1 trial and the treatment used for these bleeds.

Bleeding episodes were treated with a single dose of efanesoctocog alfa 50 IU/kg. For minor/moderate bleeding episodes occurring within 2 to 3 days after a recent prophylactic dose, an initial 30 IU/kg dose could instead be used. If the bleeding episode did not resolve, additional doses of 30 or 50 IU/kg could be administered every 2 or 3 days, as needed. In total, across the 2 treatment arms, 362 bleeds were treated with efanesoctocog alfa, with 74% (268 of 362) occurring in Arm B during the on-demand treatment phase. Analysis per bleeding episode showed that overall, 99.7% were controlled with ≤2 injections of efanesoctocog alfa, with 96.7% controlled by only one injection. No bleeding episode required more than three injections. One who had right arm fracture on Day 126 had three injections (between Day 126 and Day 130) to treat a traumatic bleed; the patient received six additional injections between Day 134 and Day 163, i.e. more than 72 hours after previous injection to treat a bleeding episode. The mean (SD) number of injections (including initial and follow-up injections) required for resolution of a bleeding episode was 1.0 (0.2).

c. Please comment on whether the inconsistency between bleeds treated and not treated between the XTEND-1, the A-LONG and the HAVEN 3 study would mean that patients in A-LONG are more severe patients, assuming all bleeds were treated in A-LONG but not in the XTEND-1/HAVEN 3 trial(s). If so, please discuss the implications for the model outcomes.

It is not the case that all bleeds were treated in the A-LONG study, however the study only reports treated bleeds. As such, it was necessary to assume that the ratio

of treated to untreated bleeds in A-LONG was equal to that seen in XTEND-1. There is not expected to be any difference in the severity of patients included in XTEND-1 and A-LONG.

d. From section B.3.3.2.1, it is unclear whether the treated versus no treated bleeds were estimated using baseline values from the XTEND-1 trial or the HAVEN 3 trial, and then on which values were the IRR used. Please provide details on the order of the computations.

The model uses the rates of treated and untreated bleeds in XTEND-1 to calculate the baseline rate of bleeds for efanesoctocog alfa, then applies the IRRs from the MAIC to calculate bleed rates for comparators. Further details of these calculations can be found on the 'MAIC ABRs' sheet of the economic model.

B 9. Priority question: Page 123 of the company submission states that 'due to differing assessment periods between trials, the proportion of patients experiencing a bleed was not assessed in the MAIC comparing efanesoctocog alfa with emicizumab. As such, the proportion of patients experiencing a bleed in each cycle was taken directly from the relevant clinical trials for efanesoctocog alfa and emicizumab.'

a. Table 50 reports the proportions of patients with bleeds used in the base case. Please clarify if these proportions are used for each cycle of the model or only to inform the baseline distribution of bleeds.

The Company can confirm that the proportion of bleeds reported in Table 50 are used in each cycle.

b. Please explain why differing assessment periods prohibit the use of the MAIC for estimation of the proportion of patients experiencing a bleed, when the company was able to derive the 6 month estimate for efanesoctocog alfa and the emicizumab estimate encompassed 6 months of treatment.

The comparison of absolute effects for binary outcomes, such as the experience of a bleeding event, is reasonable only when both trials have comparable follow-up periods. Otherwise, the cumulative risk at the end of the trial may be higher in a longer study, even if the underlying rates were comparable.

The truncation of the follow-up duration in the XTEND-1 trial to match the follow-up in HAVEN 3 would only be feasible if HAVEN 3 was a study with a fixed duration of follow-up. Unfortunately, the duration of exposure in the HAVEN 3 trial was flexible, with a median duration ranging from 29.3 weeks to 33.1 weeks in the respective arms of emicizumab prophylaxis. It was reported that the respective patients were treated from 6.1 weeks to even 50.1 weeks. Taking this variability into account, the selection of one time threshold for re-estimation of the probability of patients with zero bleeds could not be justified.

c. Please comment on the implications for using the raw trial data to inform these parameters without adjusting for differences in the patient population between trials.

XTEND-1 Arm A was the longest trial, therefore the cumulative risk of bleed at the end of the trial was highest. Thus, the comparisons with shorter studies are conservative. Additionally, when the proportion of patients experiencing a bleed was adjusted to account for the MAIC weights with HAVEN 3 Arm D, the proportion of patients in Arm A of XTEND-1 that experienced a bleed by Month 12 was reduced from 39.25% to 36.03%. As such, the use of unadjusted rates is expected to be conservative for efanesoctocog alfa.

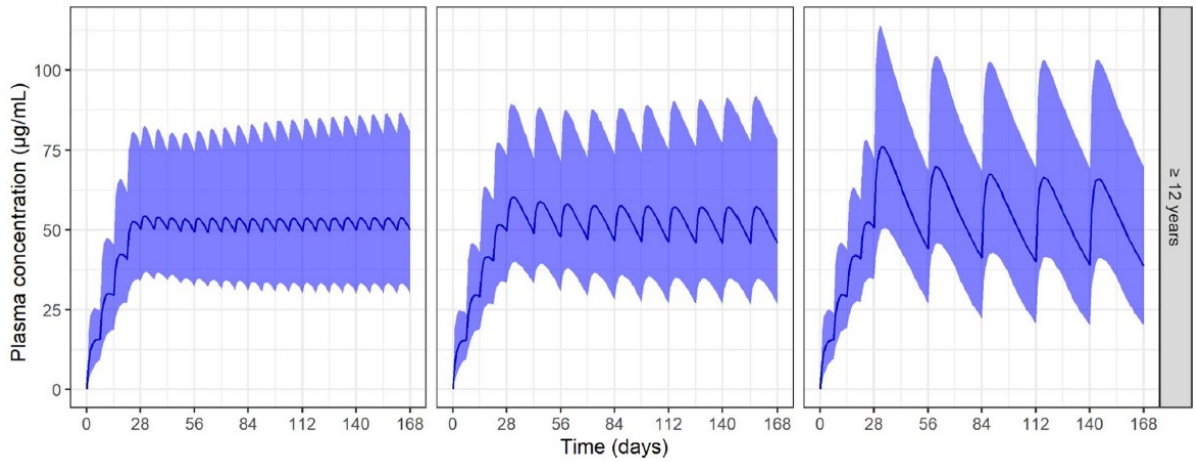
B 10. Priority question: In Table 52 of the company submission, document B, for emicizumab it is assumed that 100% of patients fall into 5-20% FVIII activity level group. In the company submission, the assumption is made with reference to Windyga et al. (company submission ref 120). In the paper by Windyga et al. a reference is made to Yoneyama et al.(34) when stating that the emicizumab dosage corresponds to 15% factor VIII activity. However, when reading the paper by Yoneyama, this statement is part of the discussion rather than a result of their study. Following the trail of references, we found that the statement in their discussion "...t*he maintenance dose of 1.5 mg/kg QW is expected to constantly provide an equivalent FVIII activity of at least 15 IU/dL, which should minimize the risk of joint bleeding and may prevent hemophilic arthropathy*" originates from a study in nonhuman primates.(35) In that study, a 61 µg (first dose) or 36 µg (at 16 hours thereafter) dose of plasma emicizumab per milliliter exerted similar hemostatic activity against on-going bleeds to the estimated

levels in porcine factor VIII: 25 U (first dose) or 7.4 U (at 16 hours thereafter, trough) per deciliter. From these data, a factor for the conversion of micrograms of emicizumab per milliliter to units of equivalent factor VIII hemostatic activity per deciliter was estimated to be 0.2 to 0.4 (around 0.3).(36) Considering the above:

a) **Please indicate if this is the only source of evidence to support the assignment of all patients in the emicizumab group in 5-20 in every cycle.**

FVIII activity level over time was also calculated for emicizumab in a similar method to those used for efanesoctocog alfa and efmoroctocog alfa, using pharmacokinetic data from Summary of Product Characteristics (SmPC) and Retout et al, 2020 (37). This resulted in 100% of time spent in the 5–20% FVIII activity level group for patients on QW and Q2W regimen, when conversion rate of 0.3 for emicizumab → FVIII level. Applying the 0.3 conversion rate to C_{max} and $C_{through}$ values from the SmPC results in values within the range of 5–20% for FVIII activity for all but the C_{max} value for Q4W regimen, which ends in 20.04%.

The stable level of emicizumab's plasma concentration is also shown in Retout et al, 2020:



Source: Retout et al, 2020 (37).

The 0.3 conversion rate is widely used in across different studies within the literature(34, 38, 39).

In addition, in two recent Haute Autorité de Santé (HAS) appraisals of treatments for haemophilia A, clinical experts have stated that FVIII equivalence levels emicizumab are around 15% (40, 41). In an appraisal of valoctocogene roxaparvovec a clinical

expert stated that *"Since 2020, this prophylaxis can be performed with emicizumab, which is a monoclonal antibody anti-Factor IX Factor X, which is a Factor VIII mimetic, and which allows a stable coagulation, equivalent to the one observed in mild hemophilia. It is estimated around 15%"*. Similarly, in an appraisal of emicizumab, a clinical expert stated patients treated with emicizumab had the profile of a patient with mild haemophilia with FVIII of 10–15%.

b) Please indicate what the distribution of emicizumab patients across FVIII activity groups would be if the range of the conversion factor is used, rather than the mean.

Table 37, Table 38 and Table 39 compare the percentage of time spent in different factor level states for conversion rates of 0.2, 0.3 and 0.4 respectively.

Table 37: Conversion rate = 0.2

	<1%	1-5%	5-20%	20-40%	40-50%	50%+
QW	0%	0%	100%	0%	0%	0%
Q2W	0%	0%	100%	0%	0%	0%
Q4W	0%	0%	100%	0%	0%	0%

Abbreviations: QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 38: Conversion rate = 0.3

	<1%	1-5%	5-20%	20-40%	40-50%	50%+
QW	0%	0%	100%	0%	0%	0%
Q2W	0%	0%	100%	0%	0%	0%
Q4W	0%	0%	84%	16%	0%	0%

Abbreviations: QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 39: Conversion rate = 0.4

	<1%	1-5%	5-20%	20-40%	40-50%	50%+
QW	0%	0%	0%	100%	0%	0%
Q2W	0%	0%	13%	87%	0%	0%
Q4W	0%	0%	35%	65%	0%	0%

Abbreviations: QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

B 11. The ABRs applied in the model were obtained from Arm A of the XTEND-1 for efanesoctocog alfa and from the MAIC for emicizumab and efmoroctocog alfa. However, as also noted in the company submission not all bleeds may require treatment and for the economic analysis it is important to count the number of treated bleeds and treatment paths of these bleeds. Please provide detailed

information from XTEND-1 on the treated bleeds and treatments used for these bleeds.

Please see response to Question B8.

B 12. On company submission, document B, page 126, it is noted that 'long-term survival data suggest that patients with haemophilia A receiving efanesoctocog alfa have comparable survival with the age-adjusted general population'. However, in the company submission, section B 1.3.2.1, it is stated: 'The most recent UKHCDO report stated that five out of 52 patients with haemophilia A presenting with cerebral haemorrhage between 2021–2022 died as a result of the complication.'

a) Please provide a source for the assumption that survival is comparable with the age-adjusted population.

b) Please explain the discrepancy between the two quoted sentences.

A study of mortality amongst Italian patients with haemophilia between 1990 and 2007 (42) reported that life expectancy increased over the duration of the study period, and for the period between 2000 and 2007, mortality for patients with haemophilia did not differ significantly from the general population (SMR: 1.08; CI: 0.83, 1.40). A similar study in the Netherlands found a comparable trend for decreasing excess mortality amongst patients with severe haemophilia A (43). While this study still finds a significant difference between patients with severe haemophilia A and the general population in the 2001–2018 cohort (SMR 1.4; CI 1.2, 1.7), treatment for haemophilia A has evolved rapidly over the last decade and this trend for reduced excess mortality is expected to continue. All clinical experts consulted agreed that it was reasonable to assume general population mortality rates for patients included in this appraisal (2), however an additional scenario including an SMR of 1.4 has been included in Appendix A.

These scenarios demonstrate a small decrease in life-years of 0.3 in PUPs and 0.81 in PTPs, and thus a small decrease in QALYs, however this change in the ICERs is small and there is no change in the conclusions of the analysis.

The UKHCDO report states that between 2021 and 2022 of the 52 deaths in patients with Haemophilia A, five were due to cerebral haemorrhage. Amongst severe patient's cerebral haemorrhage accounted for two of nine deaths. In the 2022/23 UKHCDO report published in November 2023, cerebral haemorrhage accounted for one of six deaths amongst severe patients. While cerebral haemorrhage remains a risk for patients with severe haemophilia A, this risk is low for patients managed with effective prophylaxis (30).

Comparators

B 13. Priority question: On page 25 of the company submission, it is noted that rFVIII (SHLs and extended half-life (EHL)s) are used prophylactically in the UK. Please explain why these treatments were not included as comparators in the cost effectiveness analysis for the previously untreated population.

A comparison with efmoroctocog alfa, an EHL licensed for use in patients under 12 years, has been included in the economic analysis for PUPs.

As per the response to Question A11, since Q2 2019, the use of SHLs has declined from xx% to xx% at the end of 2022 (4), and clinical opinion suggests that SHL use will be minimal in 5 years' time (2). It is not expected that it will be standard practice for clinicians to start treatment with SHLs in the future, regardless of the introduction of efanesoctocog alfa, and so they are not considered relevant comparators.

B 14. On page 26 of the company submission, it is mentioned that 'almost all patients with severe haemophilia A who are prescribed emicizumab will, in addition, be issued a small stock of FVIII for breakthrough bleeding, should it occur. Furthermore, given the limitation of emicizumab being limited to prophylaxis only, some clinicians seek to tolerise their patients to FVIII to ensure it can be used effectively on-demand and to avoid future development of inhibitors'. Based on the aforementioned, please comment if emicizumab treatment is combined with use of small stock of FVIII in the economic analysis in case of breakthrough bleeding only or if FVIII treatment is also assumed to be used as method to avoid future development of inhibitors'.

The stock of FVIII provided to patients treated with emicizumab is for the management of acute bleeds only.

B 15. In Tables 51 and 52 of the company submission, document B, there is a distinction made for efmoroctocog alfa and efanesoctocog alfa into ‘chromogenic substrate assay’ and ‘one-stage assay’. Please explain these definitions and explain how these are used in the economic analysis.

The base case analysis utilised data from the one stage assay, however for completeness, the Company have conducted a scenario using the chromogenic results.

The terms "chromogenic substrate assay" and "one-stage assay" are often used in the context of biochemistry and clinical diagnostics, particularly in the field of coagulation and haemostasis.

Chromogenic substrate assay

A chromogenic substrate assay is a type of biochemical test that uses a chromogenic (colour-changing) substrate to measure the activity of certain enzymes. This assay is particularly useful in the field of coagulation where it's used to measure the activity of specific clotting factors or enzymes. In this assay, a specific substrate is added that the target enzyme (such as a clotting factor) can act upon. This substrate is designed so that when it is cleaved or modified by the enzyme, it releases a chromophore, a molecule that produces a colour change. The intensity of the colour change can be measured, usually spectrophotometrically, and is proportional to the activity of the enzyme. This allows for quantification of the enzyme's activity in the sample. For example, in the diagnosis of haemophilia or monitoring of certain anticoagulant therapies (like factor replacement therapies), chromogenic substrate assays can be used to measure the activity of specific clotting factors.

One-stage assay

The one-stage assay, often referred to in the context of clotting factor assays, is a traditional and widely used method for measuring the activity of certain clotting factors, particularly FVIII and Factor IX. This assay is important in the diagnosis and management of bleeding disorders like haemophilia.

In a one-stage assay, patient plasma is mixed with a reagent that contains all the necessary components for clot formation except for the factor being tested. When calcium (which initiates clotting) is added, the time taken for a clot to form is measured. The clotting time is inversely proportional to the activity of the clotting factor in the patient's plasma. If the clotting factor is deficient or defective, the clotting time will be prolonged.

This assay is called "one-stage" because it involves a single step of adding all reagents together and then measuring the clotting time, as opposed to more complex, multi-stage assays.

Comparison

While both assays are used in the context of blood coagulation:

Chromogenic substrate assays are more specific and can be more sensitive, as they directly measure the activity of an enzyme based on the cleavage of a synthetic substrate. They are particularly useful for cases where standard clot-based assays might be affected by other factors or when testing the efficacy of specific anticoagulant drugs.

One-stage assays are more traditional and are typically used for routine screening and diagnosis of clotting disorders. They are generally easier to perform but can sometimes be less specific, as they rely on the overall clotting ability of the plasma rather than on the activity of a specific enzyme. Both assays have their own advantages and are chosen based on the specific clinical context and the information needed.

B 16. Regarding the PUPs population it is noted that severe haemophilia A will present early in life and therefore patients starting treatment with an EHL will be administered efmoroctocog alfa, considering it is the only treatment licenced for patients below the age of 12 years. Please comment if there is a stopping rule implemented in the model for efmoroctocog alfa. Would patients switch treatment after the age of 12 or will they continue the treatment for lifetime?

There is no stopping rule for efmoroctocog alfa, and in the economic model, it was assumed that patients would continue treatment with efmoroctocog alfa for life.

B 17. The dosing schedule of efmoroctocog alfa was assumed to be every 2 weeks (Q2W) based on clinical expert opinion suggesting that this is the most frequent option. Please adapt the model to include the observed distribution of patients across the three dosing schedules (every week (QW), Q2W, every 4 weeks (Q4W)) instead of using the most frequent option for all patients.

There is not currently data available to inform the distribution of patients across the different dosing schedules for emicizumab, however scenario analyses for the QW and Q4W doses have been incorporated into the scenario analyses presented in Appendix A.

As emicizumab QW was included in the MAIC, ABRs for the QW population have been applied in the scenarios for emicizumab QW. Emicizumab Q4W was not included in the MAIC, as patients treated with emicizumab Q4W may or may not have had an inhibitor (compared with XTEND-1 population, who had no inhibitors to therapy). Outcomes have been assumed to be equivalent to emicizumab Q2W used in the base case. Results for emicizumab QW show a small increase in QALYs and a small decrease in costs, however the magnitude of these changes is not large enough to change conclusions. There is no difference in outcomes for emicizumab Q4W compared to emicizumab Q2W.

B 18. In previously treated patients (company submission, section B.3.2.4.2.2), it is clearly indicated that patients who received emicizumab as prophylaxis treatment are patients with difficulties in achieving treatment target. Please explain to what extent the PTPs who use emicizumab and PTPs who would use efanesoctocog alfa are comparable patients.

Prior to being offered emicizumab or efanesoctocog alfa, patients only have the option of recombinant FVIII (rFVIII; SHL or EHL). Thus, together with clinical opinion, that is why efanesoctocog alfa is positioned for patients who would otherwise be offered emicizumab.

The patients would be similar, as current treatment options are unable to reach the same level of haemostatic protection that emicizumab and efanesoctocog alfa can offer. This contrasts with rFVIII (SHL or EHL), where protection can vary depending on the timing of the last infusion and the specific pharmacokinetics of the product

used. Clinical opinion suggests there are several issues which may lead clinicians to consider switching from currently available rFVIII prophylaxis to emicizumab (28):

- Haemostasis is inadequately controlled and the patient experiences breakthrough bleeds with rFVIII prophylaxis
- FVIII levels are not sufficiently controlled on rFVIII (i.e. poor pharmacokinetic coverage due to reduced area under curve [AUC] and shorter half-life)
- Prophylaxis with multiple weekly IV injections with rFVIII is inconvenient or not possible (i.e. frequent injections can lead to poor compliance or adherence to rFVIII therapy)
- The patient is seeking better quality of life or to live a life as 'normal' as is possible. Aligned to UK guidelines, HCPs will utilise shared decision-making to tailor prophylaxis with the patient, basing therapy on PK data, patient activity, lifestyle, and patient preferences (29).

It will be the same rationale that may lead a physician to switch from rFVIII to emicizumab or efanesoctocog alfa.

Currently, if there is no clinical (or otherwise) rationale for switching from rFVIII (EHL/SHL) to emicizumab then the patient is unlikely to switch and will remain on rFVIII (EHL/SHL) long term.

Quality of life

B 19. Priority question: Considering quality of life, on page 10 of document B of the company submission it is noted that 'UK-based patients with haemophilia reported an average health state of 0.59. This is notably lower than the UK national population average of 0.85'. Nonetheless, on page 127 it is noted that 'baseline utility values for people without a bleed were derived from age-adjusted general population utility values from the UK'. Please justify the inconsistency in these statements. If patients at baseline have a health-related quality of life equal to that of the general population, would that imply that patients in the analysis are actually better off than those in clinical practice? And would the

economic analysis then match with the patient population as defined in the decision problem?

0.59 is the average value for a patient with severe haemophilia A, whereas 0.85 is assumed to be the value for a person with FVIII >20% who has not experienced a bleed in the last 6 months. General population utility is applied only to patients in the best modelled health states (No bleeds and FVIII >20%).

This approach is aligned with previous analyses, which found that utility values for patients in this health state were comparable to the general population (31). A scenario analysis has been performed using the baseline utility value observed in XTEND-1 (0.7760).

This scenario shows a reduction in total QALYs across all arms, but this is not associated with a change in incremental QALYs as adjusting this baseline does not impact the differences between health states.

B 20. Priority question: In the electronic model, the sheet presenting utility values does not include the sources for each of the inputs.

a. Please include the sources used for each of the inputs.

The model has been amended to include the source for each input.

b. Please explain where the utility of 0.91 used in the model does come from for patients with a FVIII level > 50% and explain how this is used in the economic model as, in relative terms, results seem to be insensitive to changes in this parameter.

The model uses age-adjusted general population utility values report by Hernandez Alava et al, 2022 (44) as the baseline utility value for patients with no bleeds and FVIII above 50%. 0.91 is the age-adjusted utility value for men in the general population at age 35, which is the age at the start of the model time horizon. The model is insensitive to this parameter as it is primarily used as the baseline value, to which disutilities are applied and adjusting this baseline does not impact the differences between health states.

c. Page 127 of the company submission, document B mentions that the study of Benson et al, 2021(31) reported a value of 0.94 for general population

utility, and that this value was applied in this analysis. Please indicate how this relates to the value of 0.91 found in the model (see also sub-question b.).

The value of 0.94 was reported in error. This value was used in earlier versions of the model but was updated prior to submission to better reflect UK general population values.

B 21. Priority question: The SLR identified 22 publications reporting 20 studies on utilities. Please compare the utility values used in the current economic analysis to the ones reported in other studies. Please also comment on whether the validity was assessed of the utility values estimated in the present analysis and used in the model. Finally, please present alternative utility values from other studies that could be an alternative appropriate source to inform utility scores in the present analysis and run a scenario analysis using these scores.

Amongst the studies identified, there were five cost-effectiveness studies that reported data on patients with haemophilia A, either without inhibitors or in a mixed population:

- Cook, 2020 (45)
- ICER 2020 (9, 46)
- Machin, 2018 (47)
- Benson, 2021 (31)
- Coppola, 2017 (48).

Across these studies, the utility values for patients in the best health was typically high, ranging from 0.82 to 0.94, in line with the value used in the current economic analysis. In the published studies, these values represented patients without bleeds, either on FVIII prophylaxis, or in health states with minimal joint damage.

Three studies reported disutilities associated with bleeds:

- In Cook, 2020, disutilities for non-joint bleeds ranged from 0.15 to 0.17, and for joint bleeds from 0.25 to 0.29

- ICER, 2020 reports a disutility for bleeds not into target joints of 0.002
- Benson, 2021 reported a disutility for a spontaneous bleed of 0.02 and for a trauma bleed of 0.26.

Again, the disutility associated with a bleed applied in the present analysis falls within the range of those reported in the literature, with a disutility of 0.0663 applied in the short-term (7 days) and a disutility of 0.0435 applied in the 6 months beyond this. None of the identified studies make the differentiation between short- and long-term impacts of bleeds. While the impact of bleeds used in the present analysis is within the range of reported values, it is on the lower end of the spectrum. However this is expected, as the majority of bleeds for patients receiving prophylactic treatment are expected to be of lower severity. While there was a larger disutility reported in the literature for traumatic bleeds, as outline in the response the question B3, the rate of traumatic bleed is not expected to vary between treatments, and the impact of this is on cost-effectiveness is expected to be minimal.

No identified studies differentiated QoL by FVIII level, though Benson, 2021 does differentiate by severity of haemophilia. Patients with mild haemophilia had utility values 0.12 higher than those with moderate haemophilia. Patients with severe haemophilia had utility values 0.06 lower than those with moderate haemophilia. These values exceed those used in the model base case, though alternate models fit to XTEND-1 data did find larger disutilities, especially for patients with FVIII less than 5% (disutility of 0.0782 in Model 2 and 0.1231 in Model 4), which is the breakpoint between mild and moderate haemophilia.

To test the impact of the variance in disutilities, the following additional scenario analyses have been performed:

- A disutility of 0.15 for bleeds in the short-term
- A disutility of 0.25 for bleeds in the short-term
- Using Model 4 in the fit to XTEND-1 data to inform bleed disutilities and the impact of lower FVIII levels.

Applying a larger disutility for bleeds leads to a reduction QALYs across all arms, but an increase in incremental QALYs for efanesoctocog alfa, as it is associated with the lowest bleed rate. Using model 4 for utility leads to a decrease in QALYs for efmoroctocog alfa, but an increase for efanesoctocog alfa and emicizumab. This is because model 4 has a disutility for FVIII below 5% rather than below 20%, which only impacts efmoroctocog alfa. However, in both PUPs and PTPs, efanesoctocog alfa remains the most effective treatment and it is cost-effective in both populations.

B 22. In company submission, document B, page 128, below table 53, it states that "Disutility due to age was incorporated in the general population mortality (Section B.3.3.3); therefore, the result of disutility due to age was not applied to avoid double counting." Please clarify why the age-related mortality and age-related disutility are overlapping.

This is a mistake in the company submission, which should state that the disutility due to age is captured in the general population utility values, therefor the disutility due to age from the regression model used to estimate the impact of bleeds and FVIII levels has not been included.

B 23. In company submission, document B, Table 53, please clarify to what extend the inclusion of 7-days bleeding and 6-month bleeding as explanatory variables leads to problems with multicollinearity.

Variance inflation factor (VIF) analysis was performed and found no evidence of multicollinearity in the models used for utility. The VIF for each of the independent variables in the model used in the base case is presented in Table 40. In all cases, the VIF is close to one, which indicates that multicollinearity is not a problem.

Table 40: VIF analysis for the utility model used in the base-case

Variable	VIF
Baseline utility	1.213
7-day bleed disutility	1.043
6-month bleed disutility	1.132
Days since study initiation	1.107
Age	1.160
Proportion of time in <20%	1.050

Abbreviations: VIF, variance inflation factor.

Additionally, utility models with interactions between the 7-day and 6-month disutilities were tested and no interaction was found between these variables.

Resource use

B 24. Priority question: Please explain why treatment administration costs were not considered in the economic analysis.

Treatment administration costs have not been included in this submission, as any costs related to administration are expected to be negligible. Patients treated with FVIII products or emicizumab would self-administer treatment. While there may be a small cost up front for training patients to self-administer, this is not expected to vary between treatments and would be negligible compared with the cost of treatment.

B 25. Priority question: Company submission, document B, table 58 presents the costs of bleeding management procedures used in the economic analysis. The cost of a specialist visit is set at £193.24 based on the average *Outpatient Attendances Data for Clinical Haematology* (service code 303) in Table 58. However, in the economic model this cost is assumed to be £538.9 (on the 'Costs' sheet), and when looking at the NHS 2021/2022 costs, the *Outpatient Attendances Data for Clinical Haematology* (service code 303) code cost is £194.01. Please explain which of the three cost values is correct. If the value in the model is incorrect, please provide a revised version of the model, and in Word a complete set of revised results (base case, sensitivity analyses, and scenario analyses).

The value used in the model is the weighted average cost of consultant-led Outpatient Attendances for Haemophilia services. In the latest NHS 2021/2022 costs, this figure has changed to £531.53, and this value has been used for the updated analyses.

B 26. In company submission, document B, table 58, only the cost of an emergency room (ER) visit, specialist visit, and nurse visit were included. Please explain why resource use related to severe bleedings (e.g. intra-cranial, joints) were not included.

Severe intracranial bleed is a rare occurrence, notably since the introduction of regular prophylactic treatment in the 1970s, when more concentrated clotting factor concentrates became available for patients. This event is now witnessed infrequently and more commonly attributed to traumatic situations. The economic impact of an

intracranial haemorrhage over a patient's lifetime was felt to have marginal impact to the cost effectiveness analysis and was therefore not included. No intracranial bleeds were reported in XTEND-1, HAVEN 3, or A-LONG.

It was felt that the cost of an emergency room (ER) visit, specialist visit, and nurse visit were sufficient to cover occurrences of a severe bleed, such as a knee bleed following impact during sport, ankle bleed following a long hike or accidently tripping over and landing awkwardly are some examples of situations that may cause a bleed that requires treatment. In addition to the resource costs, severe bleeding was captured during pivotal clinical studies as a "treated bleed" and therefore the additional drug cost to treat a bleed is also associated with this occurrence in the cost effectiveness evaluation.

B 27. For patients on emicizumab treatment, a FVIII replacement therapy may be needed in case of breakthrough bleeds. Please explain why octocog alfa was chosen to treat bleeds for patients on emicizumab in the economic analysis. Is this reflecting UK practice? What are the alternative treatment options in such cases?

In clinical practice, patients treated with emicizumab will keep a stock of whichever FVIII therapy they were using prior to initiating treatment with emicizumab. Octocog alfa was selected as a representative therapy.

Section C: Textual clarification and additional points

C 7. C 1. A RIS file was included with the submission but this does not appear to be the full file (i.e., does not include all references). Please provide the full file.

The Company apologise for this error. As per NICE's request, the full RIS file was provided on Tuesday 14th November 2023.

C 2. The contents of company submission Appendix Q (results of using the AdViSHE model validation assessment tool) were mentioned in Section B.3.13 ("*Validation*") but were not included with the submission. Please provide Appendix Q.

As per NICE's request, Appendix Q was uploaded onto NICE docs on Tuesday 14th November 2023.

C 3. The clinical study report (CSR) for the XTEND-1 study does not appear to be the fully detailed document as some links do not work (e.g., “16-1-1-protocol [8.1.4]” on p.21, “16-1-9-sap” on p.27, “16-2-1-disposition [16.2.1.6]” on p.32 and many other similar instances throughout the document. Please provide a different version of the CSR with all links active.

Regarding the CSR, the Company were unfortunately unable to provide the CSR with full links due to our joint collaboration with Sanofi. However, if you have any particular questions within the CSR, the Company would be happy to try and respond to these individually.

C 4. Relating to the reference list for Document B, several pdfs are missing from the reference pack, details as follows. Please could these be provided?

a) #14 Gualtierotti R, Solimeno LP, Peyvandi F. Hemophilic arthropathy: Current knowledge and future perspectives. J Thromb Haemost. 2021;19(9):2112-21.

b) #17 National Heamophilia Database. Data on file [CON]. Real world evidence – UK National Haemophilia Database – UKHCDO. August 2023. 2023.

c) #88 Malec L, Peyvandi F, Chan A, Königs C, Zulfikar B, et al. Efanesoctocog Alfa Prophylaxis for Previously Treated Patients < 12 Years of Age With Severe Hemophilia A ISTH Academy. 06/25/23; 395388; LB 01.1

d) #93 Chowdary P, Khoo L, Wang M, Chambost H, Chan A, Moryusef A, et al. PB1249 - Prospective, Observational Study of the Clinical Characteristics of Adults and Adolescents With Severe Hemophilia A. Presented at ISTH June 2023. 2023.

e) #98 Sanofi and Sobi. Indirect treatment comparison (ITC) between efanesoctocog alfa and selected comparators in patients with hemophilia A without inhibitors - Technical report. 2023.

f) #101 Shapiro AD, Mahlangu JN, Perry D, Pasi J, Quon DV, Chowdary P, et al. Treatment of bleeding episodes with recombinant factor VIII Fc fusion protein in A-LONG study subjects with severe haemophilia A. Haemophilia. 2017;23(3):392-9.

As per NICE's request, missing references were uploaded onto NICE docs on Tuesday 14th November 2023.

References

1.European Medicines Agency. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2_en.pdf. 2018.

2.Sobi. Data on file [CON]. Efanesoctocog alfa Health Technology Appraisal: Clinical consultation report. 2023.

3.MHRA. ELOCTA 250 IU powder and solvent for solution for injection. Summary of Product Characteristics. Available at: https://products.mhra.gov.uk/search/?search=elocta&page=1.

4.National Haemophilia Database. Data on file [CON]. Real world evidence – UK National Haemophilia Database – UKHCDO. August 2023. 2023.

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Appendix A: Appendix of updated model results

Updated results from the original submission

Table 41: Base-case results, PUPs (efanesoctocog alfa PAS price, efmoroctocog alfa PAS price) [Update to Document B, Table 63]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Original submission								
Efmoroctocog alfa	xxxxxxxxx	27.054	22.940	–	–	–	–	–
Efanesoctocog alfa	xxxxxxxxx	27.054	23.500	xxxxxxx	0.000	0.560	xxxxxxx	xxxxxxx
Emicizumab	xxxxxxxxx	27.054	22.806	xxxxxxxxx	0.000	–0.134	xxxxxxxxx	xxxxxxxxx
With corrected data								
Efmoroctocog alfa	xxxxxxxxx	27.054	22.940	–	–	–	–	–
Efanesoctocog alfa	xxxxxxxxx	27.054	23.500	xxxxxxx	0.000	0.560	xxxxxxx	xxxxxxx
Emicizumab	xxxxxxxxx	27.054	22.806	xxxxxxxxx	0.000	–0.134	xxxxxxxxx	xxxxxxxxx

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 42: Net health benefit, PUPs (efanesoctocog alfa PAS price, efmoroctocog alfa PAS price) [Update to Document B, Table 64]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Original submission						
Efmoroctocog alfa	[redacted]	22.940	–	–	–	–
Efanesoctocog alfa	[redacted]	23.500	[redacted]	0.560	[redacted]	[redacted]
Emicizumab	[redacted]	22.806	[redacted]	–0.134	[redacted]	[redacted]
With corrected data						
Efmoroctocog alfa	[redacted]	22.940	–	–	–	–
Efanesoctocog alfa	[redacted]	23.500	[redacted]	0.560	[redacted]	[redacted]
Emicizumab	[redacted]	22.806	[redacted]	–0.134	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 43: Base-case results, PTPs (efanesoctocog alfa PAS price) [Update to Document B, Table 65]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Original submission								
Efanesoctocog alfa	[redacted]	22.369	19.007	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.434	[redacted]	0.000	–0.574	[redacted]	[redacted]
With corrected data								
Efanesoctocog alfa	[redacted]	22.369	19.007	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.434	[redacted]	0.000	–0.574	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 44: Net health benefit, PTPs (efanesoctocog alfa PAS price) [Update to Document B, Table 66]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Original submission						
Efanesoctocog alfa	xxxxxxxxxx	19.007	–	–	–	–
Emicizumab	xxxxxxxxxxx	18.434	xxxxxxxxxx	–0.574	xxxxxxx	xxxxxxx
With corrected data						
Efanesoctocog alfa	xxxxxxxxxx	19.007	–	–	–	–
Emicizumab	xxxxxxxxxxx	18.434	xxxxxxxxxx	–0.574	xxxxxxx	xxxxxxx

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 45: Probabilistic results, PUPs (efanesoctocog alfa PAS price) [Update to Document B, Table 67]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Original submission						
Efmoroctocog alfa	xxxxxxxxxx	22.942	–	–	–	–
Efanesoctocog alfa	xxxxxxxxxx	23.503	xxxxxxx	0.561	xxxxxxx	xxxxxxx
Emicizumab	xxxxxxxxxx	22.791	xxxxxxxxxx	–0.151	xxxxxxxxx	xxxxxxxxx
With corrected data						
Efmoroctocog alfa	xxxxxxxxxx	22.934	-	-	-	-
Efanesoctocog alfa	xxxxxxxxxx	23.499	xxxxxxx	0.565	xxxxxxx	xxxxxxx
Emicizumab	xxxxxxxxxx	22.780	xxxxxxxxxx	–0.153	xxxxxxxxx	xxxxxxxxx

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PUP, previously untreated patients; QALYs, quality-adjusted life years.

Table 46: Probabilistic results, PTPs (efanesoctocog alfa PAS price) [Update to Document B, Table 68]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Original submission						
Efanesoctocog alfa	[redacted]	19.008	–	–	–	–
Emicizumab	[redacted]	18.419	[redacted]	–0.589	[redacted]	[redacted]
With corrected data						
Efanesoctocog alfa	[redacted]	19.007	-	-	-	-
Emicizumab	[redacted]	18.415	[redacted]	–0.592	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PTP, previously treated patients; QALYs, quality-adjusted life year.

Table 47: Scenario analyses, PUPs [Update to Document B, Table 70]

Scenario	Vs efmoroctocog alfa			Vs emicizumab		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Original submission						
Base case	[redacted]	0.560	[redacted]	[redacted]	0.694	[redacted]
Discount rate of 6%	[redacted]	0.359	[redacted]	[redacted]	0.445	[redacted]
No discounting	[redacted]	1.564	[redacted]	[redacted]	1.939	[redacted]
Treated bleeds only	[redacted]	0.527	[redacted]	[redacted]	0.625	[redacted]
Baseline ABR from HAVEN 3 Arm B	[redacted]	0.529	[redacted]	[redacted]	0.661	[redacted]
Baseline ABR from XTEND-1 Arm B	[redacted]	0.541	[redacted]	[redacted]	0.674	[redacted]
Baseline ABR from HAVEN 3 Arm D	[redacted]	0.545	[redacted]	[redacted]	0.678	[redacted]
% of patients with bleeds on efanesoctocog alfa from XTEND-1 12-month data	[redacted]	0.566	[redacted]	[redacted]	0.552	[redacted]
% of patients with bleeds on emicizumab from HAVEN 3 Arm A	[redacted]	0.560	[redacted]	[redacted]	0.589	[redacted]

Scenario	Vs efmoroctocog alfa			Vs emicizumab		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
% of patients with bleeds on emicizumab from HAVEN 3 Arm B	[redacted]	0.560	[redacted]	[redacted]	0.777	[redacted]
Chromogenic assay for assessing FVIII levels	[redacted]	0.738	[redacted]	[redacted]	0.758	[redacted]
No disutility associated with lower FVIII levels	[redacted]	0.281	[redacted]	[redacted]	0.354	[redacted]
Disutility for FVIII <5%	[redacted]	0.958	[redacted]	[redacted]	0.350	[redacted]
Drug wastage for emicizumab	[redacted]	0.560	[redacted]	[redacted]	0.694	[redacted]
With corrected data						
Base case	[redacted]	0.560	[redacted]	[redacted]	0.694	[redacted]
Discount rate of 6%	[redacted]	0.359	[redacted]	[redacted]	0.445	[redacted]
No discounting	[redacted]	1.564	[redacted]	[redacted]	1.939	[redacted]
Treated bleeds only	[redacted]	0.527	[redacted]	[redacted]	0.625	[redacted]
Baseline ABR from HAVEN 3 Arm B	[redacted]	0.529	[redacted]	[redacted]	0.661	[redacted]
Baseline ABR from XTEND-1 Arm B	[redacted]	0.541	[redacted]	[redacted]	0.674	[redacted]
Baseline ABR from HAVEN 3 Arm D	[redacted]	0.545	[redacted]	[redacted]	0.678	[redacted]
% of patients with bleeds on efanesoctocog alfa from XTEND-1 12-month data	[redacted]	0.566	[redacted]	[redacted]	0.552	[redacted]
% of patients with bleeds on emicizumab from HAVEN 3 Arm A	[redacted]	0.560	[redacted]	[redacted]	0.589	[redacted]
% of patients with bleeds on emicizumab from HAVEN 3 Arm B	[redacted]	0.560	[redacted]	[redacted]	0.777	[redacted]

Scenario	Vs efmoroctocog alfa			Vs emicizumab		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Chromogenic assay for assessing FVIII levels	[redacted]	0.738	[redacted]	[redacted]	0.758	[redacted]
No disutility associated with lower FVIII levels	[redacted]	0.281	[redacted]	[redacted]	0.354	[redacted]
Disutility for FVIII <5%	[redacted]	0.958	[redacted]	[redacted]	0.350	[redacted]
Drug wastage for emicizumab	[redacted]	0.560	[redacted]	[redacted]	0.694	[redacted]

Abbreviations: ABR, annualised bleeding rate; FVIII, clotting Factor VIII; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 48: Scenario analyses, PTPs [Update to Document B, Table 71]

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Original submission			
Base case	[redacted]	0.574	[redacted]
Discount rate of 6%	[redacted]	0.406	[redacted]
No discounting	[redacted]	1.120	[redacted]
Treated bleeds only	[redacted]	0.518	[redacted]
Baseline ABR from HAVEN 3 Arm B	[redacted]	0.547	[redacted]
Baseline ABR from XTEND-1 Arm B	[redacted]	0.558	[redacted]
Baseline ABR from HAVEN 3 Arm D	[redacted]	0.561	[redacted]
% of patients with bleeds on efanesoctocog alfa from XTEND-1 pooled arms	[redacted]	0.463	[redacted]
% of patients with bleeds on emicizumab from HAVEN 3 Arm A	[redacted]	0.489	[redacted]
% of patients with bleeds on emicizumab from HAVEN 3 Arm B	[redacted]	0.640	[redacted]
Chromogenic assay for assessing FVIII levels	[redacted]	0.614	[redacted]
No disutility associated with lower FVIII levels	[redacted]	0.286	[redacted]
Disutility for FVIII <5%	[redacted]	0.283	[redacted]
Drug wastage for emicizumab	[redacted]	0.574	[redacted]

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
With corrected data			
Base case	[redacted]	0.574	[redacted]
Discount rate of 6%	[redacted]	0.406	[redacted]
No discounting	[redacted]	1.120	[redacted]
Treated bleeds only	[redacted]	0.518	[redacted]
Baseline ABR from HAVEN 3 Arm B	[redacted]	0.547	[redacted]
Baseline ABR from XTEND-1 Arm B	[redacted]	0.558	[redacted]
Baseline ABR from HAVEN 3 Arm D	[redacted]	0.561	[redacted]
% of patients with bleeds on efanesoctocog alfa from XTEND-1 pooled arms	[redacted]	0.463	[redacted]
% of patients with bleeds on emicizumab from HAVEN 3 Arm A	[redacted]	0.489	[redacted]
% of patients with bleeds on emicizumab from HAVEN 3 Arm B	[redacted]	0.640	[redacted]
Chromogenic assay for assessing FVIII levels	[redacted]	0.614	[redacted]
No disutility associated with lower FVIII levels	[redacted]	0.286	[redacted]
Disutility for FVIII <5%	[redacted]	0.283	[redacted]
Drug wastage for emicizumab	[redacted]	0.574	[redacted]

Abbreviations: ABR, annualised bleeding rate; FVIII, clotting Factor VIII; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Figure 17: Cost-effectiveness plane vs efmoroctocog alfa, PUPs [Update to Document B, Figure 18]

Abbreviations: PUP, previously untreated patients; QALYs, quality-adjusted life years.

Figure 18: Cost-effectiveness plane vs emicizumab, PUPs [Update to Document B, Figure 19]

Abbreviations: PUP, previously untreated patients; QALYs, quality-adjusted life years.

Figure 19: Cost-effectiveness acceptability curve, PUPs [Update to Document B, Figure 20]

Abbreviations: PUP, previously untreated patients; WTP, willingness-to-pay.

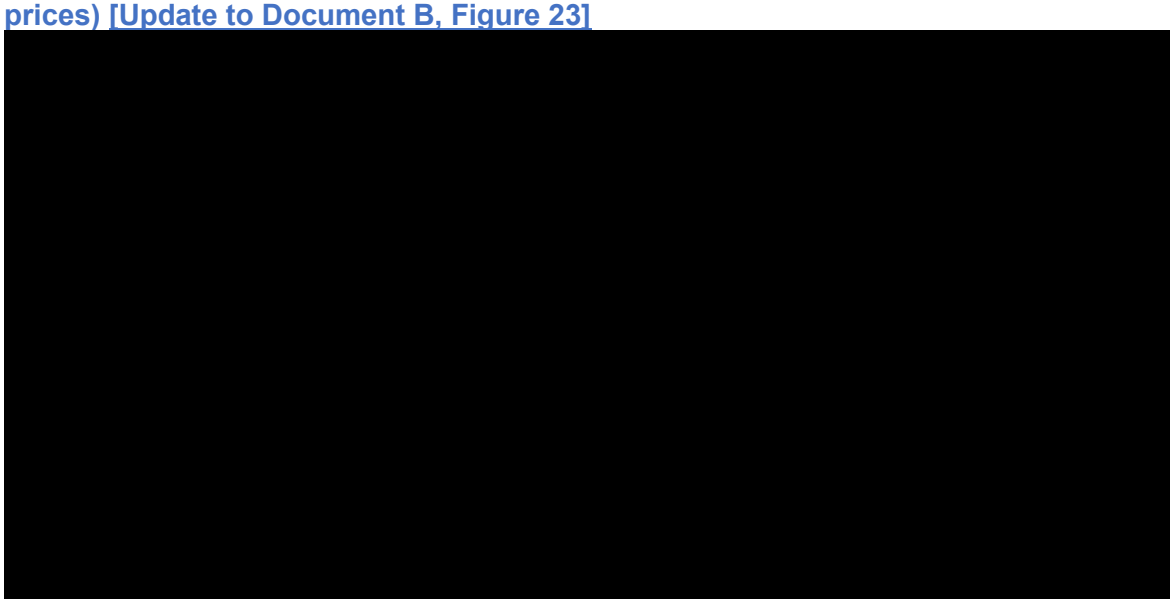
Figure 20: Cost-effectiveness plane vs emicizumab, PTPs [Update to Document B, Figure 21]

Abbreviations: PUP, previously untreated patients; WTP, willingness-to-pay.

Figure 21: Cost-effectiveness acceptability curve, PTPs [Update to Document B, Figure 22]

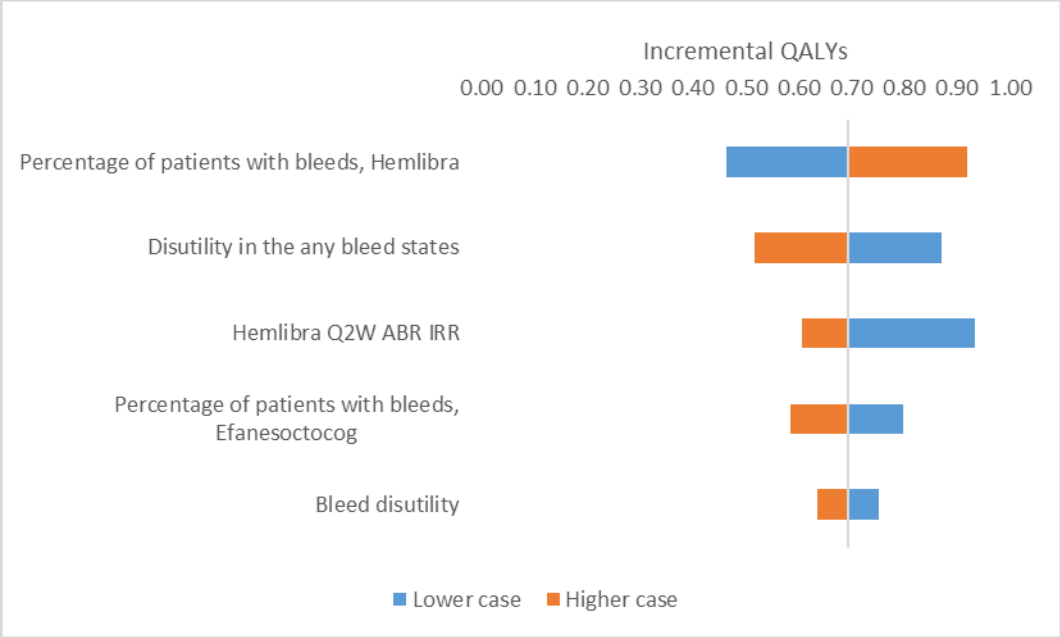
Abbreviations: PTP, previously treated patients; WTP, willingness-to-pay.

Figure 22: Tornado diagram efanesoctocog alfa vs efmoroctocog alfa, PUPs (net prices) [Update to Document B, Figure 23]



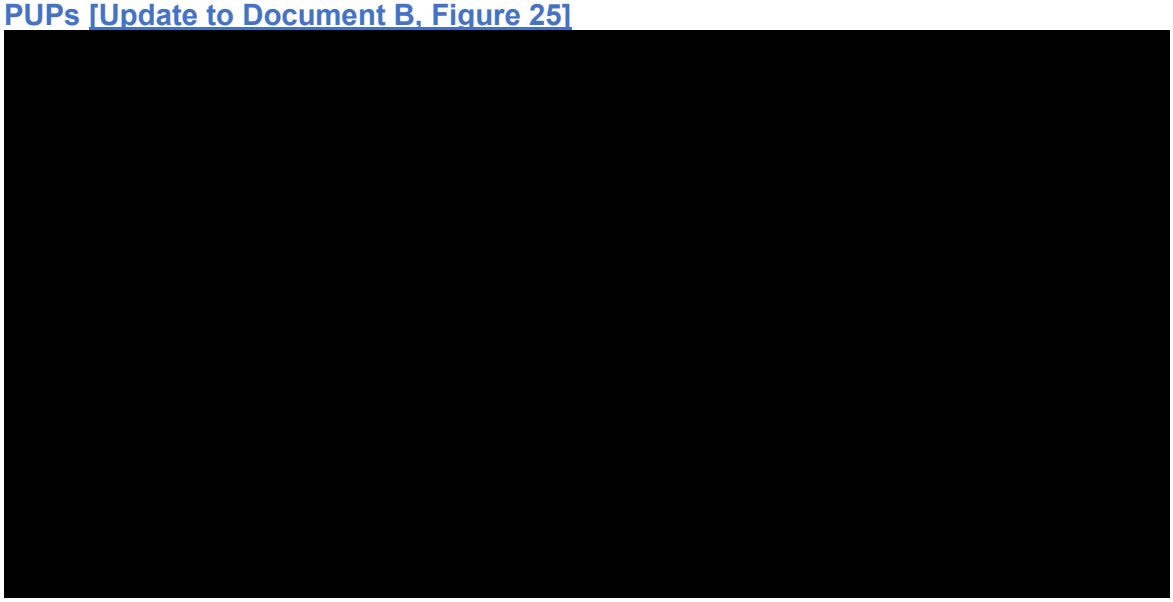
Abbreviations: ABR, annualised bleeding rate; ER, emergency room; ICER, incremental cost-effectiveness ratio; IRR, incidence rate ratio; PUPs, previously untreated patients.

Figure 23: Tornado diagram for inputs impacting incremental QALYs vs emicizumab, PUPs [Update to Document B, Figure 24]



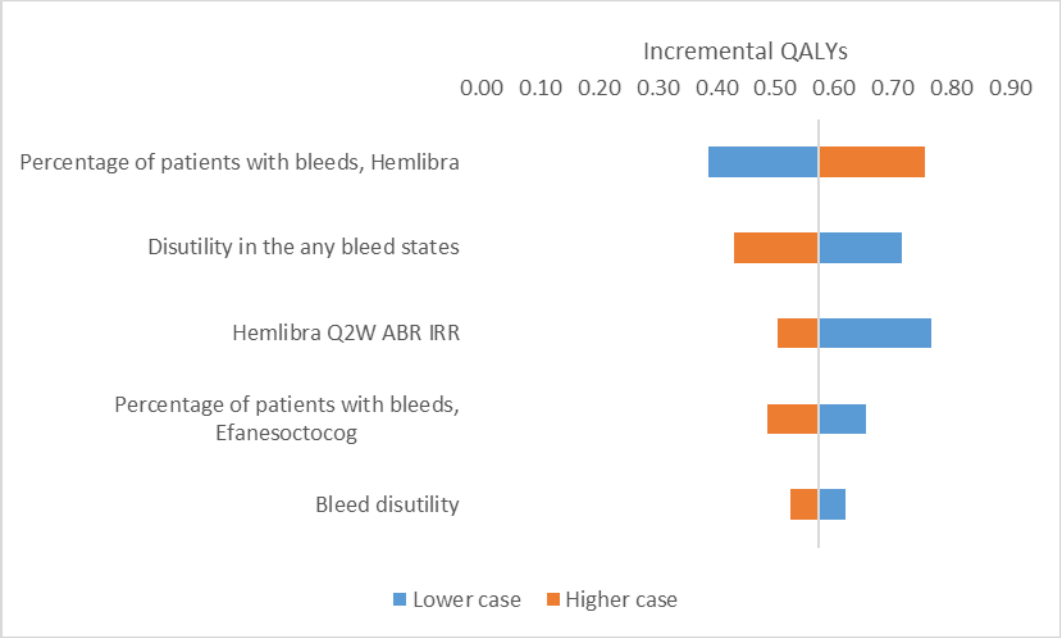
Abbreviations: ABR, annualised bleeding rate; IRR, incidence rate ratio; PUPs, previously untreated patients; QALY, quality-adjusted life year; Q2W, every 2 weeks.

Figure 24: Tornado diagram for inputs impacting incremental costs vs emicizumab, PUPs [Update to Document B, Figure 25]



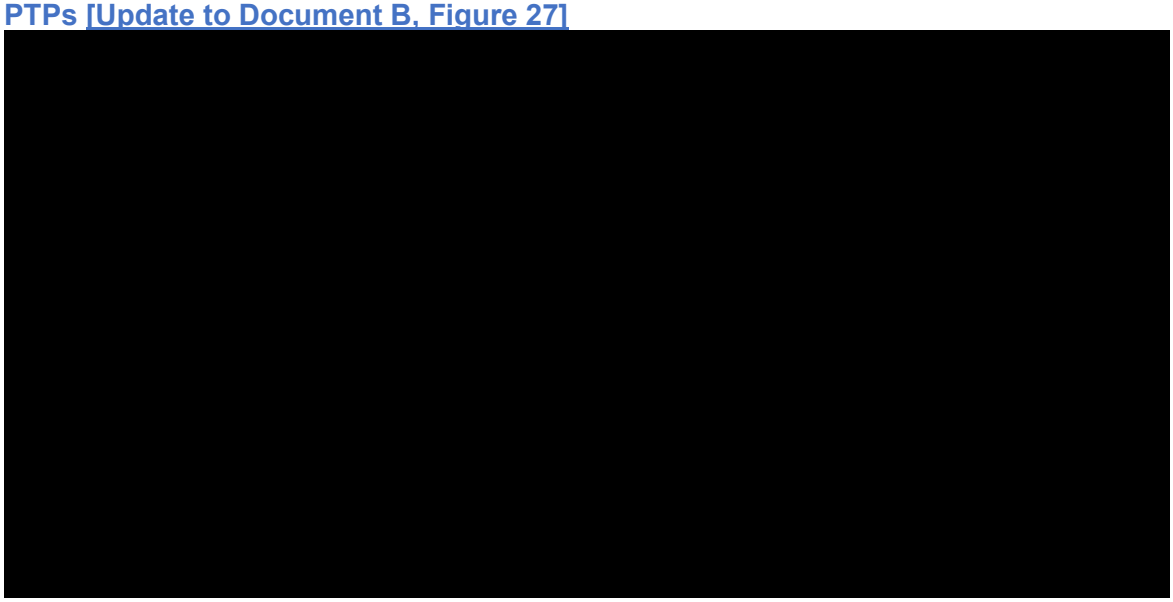
Abbreviations: ABR, annualised bleeding rate; ER, emergency room; IRR, incidence rate ratio; PUPs, previously untreated patients; Q2W, every 2 weeks.

Figure 25: Tornado diagram for inputs impacting incremental QALYs vs emicizumab, PTPs [Update to Document B, Figure 26]



Abbreviations: ABR, annualised bleeding rate; IRR, incidence rate ratio; PTPs, previously treated patients; QALY, quality-adjusted life year; Q2W, every 2 weeks.

Figure 26: Tornado diagram for inputs impacting incremental costs vs emicizumab, PTPs [Update to Document B, Figure 27]



Abbreviations: ABR, annualised bleeding rate; ER, emergency room; IRR, incidence rate ratio; PTPs, previously treated patients; Q2W, every 2 weeks.

Additional scenario analysis

Base case

Table 49: Base-case results, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	22.940	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.500	[redacted]	0.000	0.560	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	22.806	[redacted]	0.000	–0.134	[redacted]	[redacted]

Table 50: Base case results, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	19.007	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.434	[redacted]	0.000	–0.574	[redacted]	[redacted]

Results for scenarios using outcomes by FVIII level (Question B6)

Table 51: Results using FVIII level outcomes calibrated for EFA vs ELO, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	22.763	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.337	[redacted]	0.000	0.574	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	22.618	[redacted]	0.000	–0.145	[redacted]	[redacted]

Table 52: Results using FVIII level outcomes calibrated for EFA vs EMI, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	22.919	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.468	[redacted]	0.000	0.548	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	22.856	[redacted]	0.000	–0.064	[redacted]	[redacted]

Table 53: Results using FVIII level outcomes calibrated for EFA vs EMI, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	19.008	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.465	[redacted]	0.000	–0.544	[redacted]	[redacted]

Table 54: Results using FVIII level outcomes calibrated for EFA vs EMI (scenario for proportion with bleed), PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	23.003	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.477	[redacted]	0.000	0.475	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	23.009	[redacted]	0.000	0.006	[redacted]	[redacted]

Table 55: Results using FVIII level outcomes calibrated for EFA vs EMI (scenario for proportion with bleed), PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	19.008	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.592	[redacted]	0.000	–0.416	[redacted]	[redacted]

Results for scenarios applying an SMR for mortality (Question B12)

Table 56: Results using an SMR of 1.4, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	26.754	22.714	–	–	–	–	–
Efanesoctocog alfa	[redacted]	26.754	23.269	[redacted]	0.000	0.555	[redacted]	[redacted]
Emicizumab	[redacted]	26.754	22.582	[redacted]	0.000	–0.133	[redacted]	[redacted]

Table 57: Results using an SMR of 1.4, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	21.559	18.372	–	–	–	–	–
Emicizumab	[redacted]	21.559	17.818	[redacted]	0.000	–0.554	[redacted]	[redacted]

Results for emicizumab QW and Q4W (Question B17)

Table 58: Results using emicizumab QW, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	22.940	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.500	[redacted]	0.000	0.560	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	22.823	[redacted]	0.000	–0.117	[redacted]	[redacted]

Table 59: Results using emicizumab QW, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	19.007	-	-	-	-	-
Emicizumab	[redacted]	22.369	18.447	[redacted]	0.000	–0.560	[redacted]	[redacted]

Table 60: Results using emicizumab Q4W, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	22.940	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.500	[redacted]	0.000	0.560	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	22.806	[redacted]	0.000	–0.134	[redacted]	[redacted]

Table 61: Results using emicizumab Q4W, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	19.007	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.434	[redacted]	0.000	–0.574	[redacted]	[redacted]

Results using the baseline utility value from XTEND-1 (Question B19)

Table 62: Results using the baseline utility value form XTEND-1, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	19.303	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	19.863	[redacted]	0.000	0.560	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	19.169	[redacted]	0.000	–0.134	[redacted]	[redacted]

Table 63: Results using the baseline utility value form XTEND-1, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	16.071	–	–	–	–	–
Emicizumab	[redacted]	22.369	15.498	[redacted]	0.000	–0.574	[redacted]	[redacted]

Results of scenarios using alternative utility data (Question B21)

Table 64: Results with a bleed disutility of –0.15, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	22.778	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.453	[redacted]	0.000	0.675	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	22.638	[redacted]	0.000	–0.140	[redacted]	[redacted]

Table 65: Results with a bleed disutility of –0.15, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	18.969	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.298	[redacted]	0.000	–0.671	[redacted]	[redacted]

Table 66: Results with a bleed disutility of –0.25, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	22.585	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.397	[redacted]	0.000	0.813	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	22.438	[redacted]	0.000	–0.147	[redacted]	[redacted]

Table 67: Results with a bleed disutility of –0.25, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	18.924	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.136	[redacted]	0.000	–0.788	[redacted]	[redacted]

Table 68: Results using utility model 4, PUPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efmoroctocog alfa	[redacted]	27.054	22.327	–	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	23.692	[redacted]	0.000	1.365	[redacted]	[redacted]
Emicizumab	[redacted]	27.054	23.323	[redacted]	0.000	0.996	[redacted]	[redacted]

Table 69: Results using utility model 4, PTPs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Efanesoctocog alfa	[redacted]	22.369	19.122	–	–	–	–	–
Emicizumab	[redacted]	22.369	18.824	[redacted]	0.000	–0.298	[redacted]	[redacted]

Regarding clarification question A6, we encourage you to provide responses to all of the clarification questions wherever possible. However, we note your comments about the potentially modest impact of the requested SLR update on the appraisal. If you are not able to provide a response in the available timeframe, we note that this might have an impact later in the appraisal and recommend you provide an explanation or rationale in your response, if not provided already.

As indicated in our previous response to Question A6, Sobi are unable to update the HCRU and HSUV SLRs within the available time frame. The Company will be in the position to provide these updates by the end of January 2024, if NICE consider this acceptable.

Please explain why no adverse events have been included in the CE model?

Adverse events (AEs) have been excluded from the model because in XTEND-1, efanesoctocog alfa was well tolerated and reported treatment-emergent adverse events (TEAEs) were generally consistent with what is anticipated in an adult and adolescent population with severe haemophilia A (1). A total of 18 TEAEs were deemed by the Investigator as related to efanesoctocog alfa in 8 (5.0%) participants, all in Arm A. Related TEAEs included coagulation factor VIII level increased (3 [1.9%] participants), headache (2 [1.3%] participants), and CD4 lymphocytes decreased, protein urine present, injection site dermatitis, malaise, and dysphoria (1 [0.6%] participant, each). There were a total of 18 serious AES (SAEs) in 15 patients (9.4%), the majority of which were assessed as being mild to moderate in severity and not related to efanesoctocog alfa. Additionally, there were only 2 instances of patients reporting an adverse event of special interest (AESI), both of which were pregnancies in partners of participants. AESIs were chosen for their relevance to hemophilia A or treatment and in accordance with European Medicines Agency (EMA) guidelines (AEs considered medically important) were pre-specified in the study protocol. These AEs included development of inhibitors, Grade 3 or higher allergic reactions or anaphylactic reactions (per CTCAE Version 5.0), and embolic or thrombotic events (except for injection site thrombophlebitis).

This approach is consistent with previous modelling in haemophilia. Of the 24 studies identified by the SLR, eight refer to AEs. Three of these studies state that AEs were not included (2-4), while one states that the cost of AEs was assumed to be zero (5). The Institute for Clinical and Economic Review (ICER) analysis stated the following regarding the main comparators relevant to this appraisal (emicizumab and factor VIII replacement therapies) (6):

"Serious adverse event data reported in the HAVEN trials for emicizumab, particularly in HAVEN 3, were not significantly associated with the drug. Serious adverse events (SAEs) in data available for factor VIII inhibitors were few and mainly bleed-related. […] Consequently, the models here do not include SAEs."

In the other four models, the cost of adverse events treatment was included (7-10).

Two of these studies were evaluations of gene therapies, where AEs are expected to be of more interest due to the considerable number of unknowns regarding new treatments such as gene therapy and because patients will likely also experience an elevation in the alanine aminotransferase level requiring immunosuppression with corticosteroids (11), as was modelled in the ICER review of gene therapies for hemophilia (10). This is in stark contrast to the wealth of knowledge and data concerning the safety and efficacy of clotting factor replacement therapies.

Only two studies considering emicizumab as the key treatment of interest included AEs. One study included the cost of SAEs as a one-off cost at the start of the model (7), however, given the relative cost of SAEs applied ($930 for emicizumab, $1,429 for clotting Factor VIII [FVIII] (7)) compared with the cost of treatment and the similarity in the rate of SAEs between treatments in this analysis (see response to question A31), the impact of modelling AEs in this analysis is expected to be negligible. The second study reporting costs associated with AEs included them only in the first year of treatment and noted that the model was not sensitive to parameter relating to AEs (8).

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	The Haemophilia Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Haemophilia Society (THS) is the only UK-wide charity and free membership organisation for everyone affected by a bleeding disorder. We have over 5,000 members. At THS we want to empower everyone affected by a bleeding disorder to live life to the full, whatever stage they are at. We offer free member events, a local group network and online communities to share advice and experiences, as well as the latest news and access to specialist resources. THS also campaigns and advocates for what matters to our community; lobbying government, the NHS and clinicians to demand excellent care and safe and effective treatment which is available to everyone affected by a genetic bleeding disorder.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	Yes. The Haemophilia Society receives funding from companies involved in the development, manufacture, marketing, and distribution of treatments for haemophilia and other bleeding disorders. I have included the companies, total amounts and projects funded for the financial year 22/23 below: CSL Behring £60,000 – Communications, Core Funding LFB £10,000 – Women's Project Novo Nordisk £16,000 – Conference Attendance, Member Magazine, Information Days Octapharma £10,000 – Women's Project Pfizer £20,000 – Youth Ambassador Project, Publications Roche/Chugai £15,000 – Transition Project, Newly Diagnosed Weekends Sobi £25,000 – Publications, Conference Attendance, Information Days

amount, and purpose of funding.	Takeda £19,000 - Women's Project, Publications
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Haemophilia Society regularly speaks to a range of members at our events in person, by phone through our helpline and via social media. This allows us to understand in depth a broad range of views of our membership. We have a board of trustees, a series of sub-committees and working groups that give direct feedback on our work and steer our priorities. Staff members, trustees and ambassadors with haemophilia have contributed directly to the submission.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Haemophilia A is a lifelong, inherited bleeding disorder. People with severe and moderate haemophilia A take longer than normal for bleeding to stop. They may have bleeding into joints and muscles without having had an injury, so prophylactic treatment is aimed at reducing spontaneous bleeding. Bleeds may also be caused by minor trauma, bumps, trips and accidents requiring further treatment and potential hospital visits. Our ambassadors describe how living with haemophilia is difficult, having bleeds are not only painful physically but cause great mental distress. You have to adapt your life and this means stopping or not being able to do certain things in life including certain sports, travelling and a number of jobs. This includes not being able to move to certain places for fear of being too far away from a treatment centre. On a day-to-day level even walking in a major crowd can be worrying too for fear of a knock causing a bleed. The time and money spent on the condition should not be forgotten. Going to a treatment centre even if only for regular appointments a few times a year can cost hundreds of pounds and take you away from work, school and other events. Then, when things go wrong, which on average occurs 3-4 times a year you end up with multiple trips or days spent in hospital. Even with modern standards of treatment and care most people with haemophilia still develop joint damage over time which has a substantial impact on their quality of life (https://onlinelibrary.wiley.com/doi/full/10.1111/hae.14766) . Analysis of the CHESS data concluded that it “has shown the negative impact of increasing joint morbidity on HRQoL and costs for children, adolescents and adults with moderate or severe HA”. Analysis from the PROBE study (https://probestudy.org/headlines/) showed that “Haemophilia has a significant negative impact on work life. [People with severe haemophilia] report a higher rate of retiring early or working part-time due to health than age-matched controls. Use of mobility aids, acute / chronic pain, difficulty with ADL and history of joint surgery are associated with retiring early or working part-time.” And it concluded that “The lifetime impact of haemophilia on employment should be more fully considered within health technology assessments.”

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	While current treatments can prevent most haemophilia related mortality living with severe and moderate haemophilia A still causes substantial restrictions on day-to-day living. People with haemophilia A will still have so-called microbleeds which can cause pain and reduce joint health. Even with lower numbers of major bleeds haemophilia Current treatments do not prevent or reduce pain from existing joint damage and still allow joint damage to worsen over time. Current treatments allow for reduced attendance at hospital, greater ability to take part in work and travel but this new technology would allow less frequent dosing, increasing independence and greater protection from bleeds and resulting joint damage. Many people with haemophilia speak of seeking a haemophilia-free mindset. This is not current possible with current available treatments.
8. Is there an unmet need for patients with this condition?	An extensive study published by the All-Party Parliamentary Group on Haemophilia and Contaminated Blood concluded that “The submissions to the APPG, and the available literature, confirm that UK PwBD have substantial unmet needs. Health-related quality of life for UK-based PwBD falls far behind their peers in France, Germany and Italy and indicates that PwBD in the UK have worse outcomes including higher annual bleed rates, a greater degree of joint deterioration, greater levels of mental health problems and a greater loss of work productivity and school achievement.” The inquiry showed that under the current treatment paradigm, even when fully compliant with treatment, this has not been sufficient to achieve life free from bleeds for most people with haemophilia and does not remove the negative impacts of living with a bleeding disorder noted above. The full report is available at: https://haemophilia.org.uk/appg-on-haemophilia-and-contaminted-blood-launch-final-report/

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	This technology with weekly dosing and much greater protection from bleeds does offer the potential of not needing to worry as much about their haemophilia A. While current treatments have been able to achieve trough factor levels between 1-5% which has traditionally been associated with preventing almost all spontaneous bleeding. Trough factor levels of over 15% are thought to be required to prevent almost all joint bleeding (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4111811/). Having the higher trough levels as this technology would offer also means they can take part in activities that they may not have been able to do before without preplanning. This may also have a positive impact on career choice where a degree of activity is involved and being able to participate fully in social situations.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	This technology is clearly superior to prophylaxis with existing commissioned factor replacement products both standard half-life and so-called extended half-life products, notably Elocta. This is because the treatment method and burden of treatment is the same, yet a given dose will last for far longer in the patient's blood stream allowing for higher trough levels (a key driver of outcomes, www.ncbi.nlm.nih.gov/pmc/articles/PMC4111811/) as well as less frequent dosing. Compared to Emicizumab one disadvantage of the technology is that it is administered intra-venously which can be more difficult for people with venous-access issues, those who are less experienced in self-treatment or who have needle-phobia. This may particularly affect newly diagnosed people, older people or younger children.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This treatment will provide the most benefit to people who have or want more active lifestyles with fewer of the restrictions faced by people with haemophilia A. Compared to Emicizumab it allows for peaks in factor levels to coincide with sport and other activities and greater protection while levels remain in the normal or near-normal range. It is also particularly benefit people who have not been able to satisfactorily control bleeds and raise factor levels on existing factor replacement products as the longer half-life leads to greater factor levels throughout the week and higher trough levels which provide more protection. Some people with venous-access issues may be able to maintain factor replacement prophylaxis more easily on this product due to the lower frequency of injections.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None, that we are aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The technology will reduce burden of treatment through fewer injections than current factor products • Higher trough levels will allow greater activity and slow development of joint damage • The product is clearly superior to current commissioned factor products • Some patients may prefer to remain on Emicizumab due to the greater ease of administration • At good dosing levels the product can provide near-normal factor levels which lead to better health-related quality of life, better joint health and less pain.

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Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or **representative** of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The United Kingdom Haemophilia Doctors organisation (UKHCDO) is a professional membership organisation that brings together Haematologists focusing on patients with inherited bleeding disorders. The organisation aims to consider the contemporaneous uncertainties in managing individuals with bleeding disorders, enhance the understanding of inherited bleeding disorders and their management and improve the quality of care for this group of people. The UKHCDO aims to provide guidance where reliable evidence is available, either as a stakeholder in other organisations or under the auspices of the British Society of Haematology and works with other organisations in this space, including professional and patient organisations. In the absence of good evidence, it provides a forum for examining existing information, exchanging opinions and experience and articulating a consensus on the potential approaches to deal with challenges reported in routine clinical practice. Moreover, deliberations within UKHCDO facilitate the characterisation of the unmet needs or issues that require the attention and focus of the organisation and the broader scientific community. The organisation is a registered charity, and expenses are met through income generated from hosting the UKHCDO annual general body meeting, which receives sponsorship from the pharmaceutical industry.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	The UKHCDO also owns the UKHCDO Limited, which runs the national haemophilia database (NHD). The NHD receives funds from commissioners and unrestricted grants from the industry for research projects and undertakes an analysis of NHD data for specific questions funded by the industry.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The treatment aims to reduce mortality and morbidity. The primary morbidity is joint damage due to recurrent bleeds, resulting in severe disabling arthropathy. Weekly injections through the reduction of joint bleeds prevent the onset of joint damage in young children and older adults, reducing progression. The trials show excellent outcomes compared to current therapies. The treatment prevents further progression of arthropathy by preventing joint bleeds and confers protection against bleed-related mortality.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In the context of the severity classification of Haemophilia and the current management principles, factor levels in the mild and moderate range results in significant reduction of bleeds. Clinically significant response (CSR) is zero treated bleeds over 12 months in the majority of patients.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	See 9c.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Haemophilia A is an X-linked inherited bleeding disorder characterised by a deficiency of factor VIII (FVIII); the degree of deficiency largely determines a patient's clinical bleeding phenotype, with those with severe

	haemophilia (FVIII <1 IU/dL) typically presenting with recurrent joint and muscle bleeds; these patients may also experience spontaneous and potentially fatal bleeds in any tissue. The classification of disease severity has been established for over 20 years and is detailed below. Severe: <1% of normal (<1 IU/dL) Spontaneous bleeding Joints or muscles Predominantly in the absence of identifiable haemostatic challenge Bleeding into any tissue and organ Post-trauma and surgical bleeding Moderate: 1–5%, (1–5 IU/dL) Occasional spontaneous bleeding Prolonged bleeding with minor trauma or surgery Mild: 5 to <40% (5–40 IU/dL) Spontaneous bleeding is rare Prolonged bleeding with major trauma or surgery The current standard of care for patients with severe deficiency is prevention of bleeding, i.e., prophylaxis. Numerous studies have established its benefits in children and adults. People with severe haemophilia and those with moderate haemophilia with FVIII <3% at risk of spontaneous bleeding are encouraged to have regular prophylaxis. The primary goal of prophylaxis is the prevention of joint damage in addition to the prevention of fatal bleeds. This requires, at a minimum, zero spontaneous bleeds; ideally, patients should have no bleeds concerning regular physical activity. Despite an improved understanding of the factors underpinning an excellent prophylactic outcome, patients on prophylaxis can still experience breakthrough bleeds that impact joint health, so there is considerable potential to improve treatment effectiveness. Some challenges that contribute to poor outcomes include access to adequate treatment, treatment burden and the impact of the disease on mobility, pain, participation in society and quality of life.

	Prophylaxis must start under the age of 2 yrs and is often necessary within the first few months of life. There is evidence that subclinical joint bleeds can occur as soon as a child is standing/walking and the majority of spontaneous bleeding in the brain in children occurs within the first year of life in non-mobile babies without prophylaxis. Treatment is typically given on-demand in patients with mild haemophilia (and some with moderate haemophilia and a mild bleeding phenotype), i.e., as needed for prevention of bleeding in relation to surgery or management of bleeding in relation to trauma or other activities. Prophylactic options in patients with Haemophilia A with FVIII deficiency include: 1. Replacement therapy – i.e., like with like where the missing FVIII is provided as an intravenous infusion. This can be used for prophylaxis and management of bleeds and surgery but is ineffective in the presence of inhibitors. There is scope for treatment intensification if patients have responded poorly. 2. Emicizumab is a bispecific monoclonal antibody administered underneath the skin every 1 to 4 weeks. It is effective for prophylaxis in patients with and without inhibitors and provides fixed protection and markedly reduced treatment burden. There is no scope for treatment intensification, and it cannot be used to manage bleeds and surgery. Parents of babies and young children started on this treatment, do not learn to treat with FVIII and hence management of a bleed or trauma has to involve hospital attendance for that group (in contrast to adult patients who will have learned to self-treat with FVIII.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes UK guidelines: Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. Rayment R et al; British Journal of Haematology 2020. World Federation of Haemophilia Guidelines (WFH): WFH Guidelines for the Management of Haemophilia, 3rd edition. Srivastava et al; Haemophilia 2020.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the	Yes, there is consensus on the implementation of the most appropriate treatment regimen as per disease severity and the most appropriate follow-up. The challenges are related to adherence and funding for comprehensive care at individual centres.

NHS? (Please state if your experience is from outside England.)	
9c. What impact would the technology have on the current pathway of care?	As detailed in 9, the two options available are replacement therapy and FVIIIa mimetics. Replacement therapy whilst enabling individualised treatment and outcomes is associated with a treatment burden (intravenous infusions require skill and time, and frequency of these infusions). Further, some patients have challenges with venous access, requiring more than one infusion attempt. In babies and young children treatment with FVIII 2-3 times a week almost always necessitates a central venous access device which is associated with a small but present risk of infection. As mentioned, whilst the treatment burden is markedly decreased with emicizumab, there is minimal scope for treatment intensification, and it cannot be used for the management of bleeds and surgery. With current prophylaxis regimens, patients continue to have spontaneous or minimally provoked bleeds, which may be due to less than adequate regimens or adherence and the treatment burden of more intense regimens. There is an increasing understanding of the concept of rationalised non-adherence or 'treatment breaks or holidays' as a coping mechanism from patients. Further, an often quoted definition of good adherence is 80 to 85% of the prescribed medication which we know is ineffective in Haemophilia. Efanesoctocog alfa offers an opportunity for excellent protection with reduced treatment burden particularly in patients who are very physically active. The clinical trial outcomes have demonstrated marked improvement over current standard of care. It also offers the possibility of avoiding or shortening the length of need for central venous access devices in babies and small children, whilst retaining the ability for families to give additional doses following trauma or in the event of a bleed.
10. Will the technology be used (or is it already used) in the same way as current	Yes.

care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Better disease control means reduced health care resource utilisation in the long run. The only requirement is set up of lab assays.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Designated Haemophilia comprehensive care centres
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Lab assays need to be set up for efanesoctocog alfa.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – better disease control with reduced treatment burden for all severities of haemophilia
11a. Do you expect the technology to increase length of life more than current care?	Yes, as it will address adherence issues.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, patients with good responses are delighted with the outcomes from a disease perspective and quality of life. They believe the guessing – is this a bleed or not a bleed, has decreased, and they can focus all their energies on their professional and personal life.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Some patients struggle with regular infusions, and this group is likely to benefit more than others. Families with babies and young children will have the benefit of not only reduced treatment burden, but the ability to remove central venous access devices at an earlier age than previously possible and in some cases, it may be possible to avoid a central access device entirely and thus avoid two surgical procedures (for insertion and removal) and the small but on-going risk of an infection.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Same as current technologies
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will be screened for inhibitors to FVIII
15. Do you consider that the use of the technology will result in any	Yes, elaborated in 11b.

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. The drug is excellent example of exploitation of the understanding of basic science. It is truly a designer molecule, and incredible to see basic science exploited for patient benefit.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, in HA it offers truly reduced treatment burden with better bleed cover as a result of substantially higher trough FVIII levels.
16b. Does the use of the technology address any particular unmet need of the patient population?	11b
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most important side effects are the scope for developing antibodies against the infused factor VIII.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	Not applicable
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Bleed rate, infusion frequency, improvement in pain, reduction in target joints, reduced need for central venous catheters in young children
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes, reference included. The threshold at which an individual becomes bleed free is variable and related to multiple factors. Modeling to Predict Factor VIII Levels Associated with Zero Bleeds in Patients with Severe Hemophilia A Initiated on Tertiary Prophylaxis. Chowdary P, Fischer K, Collins PW, Cotterill A, Konkle BA, Blanchette V, Pipe SW, Berntorp E, Wolfsegger M, Engl W, Spotts G. Thromb Haemost. 2020 May;120(5):728-736. doi: 10.1055/s-0040-1709519. Epub 2020 May 5. PMID: 32369844 Clinical Trial.
20. How do data on real-world experience	None are available at the moment

compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

22. Do you consider 'on-demand' therapies to be a suitable comparator?	No
23. Do you expect efanesoctocog alfa to be offered to people who have not previously taken factor VIII treatments?	We expect efanesoctocog alfa to be available for patients previously treated with emicizumab and other factor VIII products and for previously untreated babies and young children starting prophylaxis.
24. Do you expect efanesoctocog alfa to be suitable for varying severity levels of haemophilia, for example a mild and or a moderate population? • **If efanesoctocog alfa is expected to be clinically effective in the severe haemophilia population, do you expect it to have a similar impact for the mild or moderate population?** • **What are the advantages and disadvantages of using data from the severe population for the mild/moderate population?**	As efanesoctocog alfa is replacement therapy, it can be used in any situation where FVIII can be used, i.e., for the prevention and management of bleeds in patients with mild, moderate, and severe HA. It cannot be used in patients with current inhibitors to FVIII as the inhibitors will neutralise the treatment. The drug has the highest impact in severe HA patients where patients can now receive weekly prophylaxis and maintain factor VIII levels in the mild range for most of the week, reducing bleeds and enabling most of the activities. In patients with mild HA unable to self-treat, this will offer an opportunity for true ambulatory care as it can be administered every two to four days when required. Currently patients require admission to enable once daily and twice daily administration of FVIII. The data from severe patients can be used for mild and moderate for management of bleeds. The indication of prevention of bleeds is individualised, with majority of severe patients requiring prophylaxis and minority of mild HA requiring targeted prophylaxis.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Efanesoctocog alfa is an ultra-long half FVIII, which for the first time delivers weekly prophylaxis with a much higher trough FVIII level than previously achievable. • In addition to a long half-life, the time in mild and moderate haemophilia range is increased over a 7 day period due to slope of the PK. This increases the protection provided over rolling seven day period. • The treatment is effective for prevention and management of bleeds in mild, moderate, and severe HA patients without inhibitors. • In patients unable to self-treat, it opens options for ambulatory care or administration by district nurses

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

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

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Contributions of authors

Susan O'Meara acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Venetia Qendri and Yi Hsuan Chen acted as health economists, critiqued the company's economic evaluation and contributed to the writing of the report. Nigel Armstrong acted as health economist and systematic reviewer on this assessment, critiqued the company's clinical effectiveness evidence and economic evaluation and contributed to the writing of the report. Jiongyu Chen and Mubarak Patel acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ABR	Annualised bleeding rate
A&E	Accident & Emergency
AdViSHE	Assessment of the Validation Status of Health-Economic decision models
AE	Adverse effect/event
AESI	Adverse event of special interest
AiC	Academic in Confidence
AIC	Akaike Information Criterion
AjBR	Annualised joint bleeding rate
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AsBR	Annualised spontaneous bleeding rate
AST	Aspartate aminotransferase
AUC	Area under the curve
BU/ml	Bethesda Unit per millitre
BIC	Bayesian Information Criterion
BMI	Body mass index
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CD4	Cluster of differentiation 4
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CL	Clarification letter
CMU	Commercial medicines unit
COVID-19	Coronavirus disease 2019
CRD	Centre for Reviews and Dissemination
CQ	Clarification question
CS	Company submission
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effects
DP	Decision problema
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECM	Established clinical management
ED	Exposure day
EFA	Efanesoctocog alpha
EFM	Efmoroctocog alpha
EFMO	Efmoroctocog alpha
EHL	Extended half-life
EMA	European Medicines Agency
EMI	Emicizumab
EmiPref	Emicizumab Preference (survey)
EOS	End of study
EQ-5D	European Quality of Life-5 dimensions
EQ-5D-5L	European Quality of Life-5 dimensions 5 levels
ER	Emergency Room
ESHPM	Erasmus School of Health Policy & Management

ESS	Effective sample size
ET	Early termination
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FDA	Food and Drug Administration
FVIII	Clotting factor VIII
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAL	Haemophilia Activities List
HAS	Haute Autorité de Santé
HCP	Health care professional
HCRU	Health care resource use
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICTRP	International Clinical Trials Registry Platform
Incr.	Incremental
IPD	Individual Patient Data
IPW	Inverse probability weighting
IQR	Interquartile range
IQWiG	German Institute for Quality and Efficiency in Health Care.
IRC	Independent Review Committee
IRR	Incidence rate ratios
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IU	International unit
IU/dl	International unit per decilitre
IU/kg	International units per kilogram (body weight)
IV	Intravenous
JBI	Joanna Briggs Institute
Kg	Kilogram
KSR	Kleijnen Systematic Reviews Ltd
LS	Least squares
LYG	Life years gained
MA	Marketing authorisation
MAIC	Matching-adjusted indirect comparison
Max	Maximum
MD	Mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
mg/kg	Milligrams per kilogram (body weight)
mg/kg/wk	Milligrams per kilogram body weight per week
mHJHS	modified Haemophilia Joint Health Score
MHRA	Medicines and Healthcare Products Regulatory Agency
µg	Microgram
Min	Minimum
ml	Millilitre
MMRM	Mixed-effect model of repeated measures
MTP	Minimally treated patient
NA	Not applicable
N/A	Not applicable
NC	Not calculable

NCPE	National Centre for Pharmacoeconomics
NHD	National Haemophilia Database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIS	Non-interventional study
NL	Netherlands
No.	Number
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
O-D	On-demand
OR	Odds ratio
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
pedHAL	Paediatric Haemophilia Activities List
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PICOS	Population, intervention, comparator, outcomes and study design
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
pts	Patients
PTP	Previously treated patient
PUP	Previously untreated patient
QALY	Quality-adjusted life year
QoL	Quality of life
QW	Once weekly
Q2W	Once every two weeks
Q4D	Every four days
Q4W	Once every four weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
rFVIII	Recombinant clotting factor VIII
rFVIIIFc	recombinant clotting factor VIII Fc fusion protein
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety analysis set
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SHL	Standard half-life
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class

STA	Single Technology Appraisal
STC	Simulated treatment comparison
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TESAE	Treatment-emergent serious adverse event
TSD	Technical Support Document
TSQM-9	Treatment Satisfaction Questionnaire for Medication
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centres Doctors' Organisation
ULN	Upper limit of normal
UMC	University Medical Centre
URTI	Upper respiratory tract infection
USA	United States of America
VWF	von Willebrand Factor
WHO	World Health Organization
WTP	Willingness-to-pay
wk	Week
y	Year

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem; Section 1.4 relates to the clinical effectiveness evidence whilst Section 1.5 outlines issues related to the cost effectiveness evidence. Other key issues are discussed in Section 1.6 and a summary of the EAG's view is presented in Section 1.7.

The following Sections are presented after the Executive Summary: Sections 2 (decision problem), 3 (clinical effectiveness), 4 (cost effectiveness methods), 5 (cost effectiveness results), and 6 (the EAG's additional cost-effectiveness analyses).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID6170	Summary of issue	Report Section
1	The DP population (people with severe haemophilia A) was defined as narrower than that of NICE Final Scope and SmPC (people with haemophilia A) in order to align with the sample in the XTEND-1 trial (PTPs aged ≥12 years with severe haemophilia A and without FVIII inhibitors). The populations in the two comparator studies (HAVEN 3 and A-LONG) are similar to that of XTEND-1. Since all three study populations are narrower than both the NICE Final Scope and the DP, there is uncertainty as to whether the CS can fully address either of the latter as the findings may not apply to those younger than 12 years or people with mild or moderate haemophilia A or presence of inhibitors.	2.1, 3.2.2, 3.3.1.2 and 3.3.2.2
2	The DP excludes FVIII replacement therapy (prophylactic and O-D treatment) as a comparator, listing emicizumab for PTPs and a choice between emicizumab and efmoroctocog alfa for PUPs. This may mean that the comparators included in the CS do not reflect current standard of care in the UK NHS.	2.3
3	There are problems with the clinical effectiveness SLR methods meaning that relevant studies could have been missed. This is partly due to omission of non-English language studies from the search and study selection process. In addition, the documentation of included and excluded records suggests that studies may have been excluded from the SLR for reasons that were not pre-specified.	3.1.2 and 3.2.1
4	It is not clear whether the population in XTEND-1 is representative of the UK target population.	3.2.5
5	ITC methods: there is a lack of justification as to the choice of arms pooled, outcomes, trimming and covariate choice.	3.4
6	The ABRs for emicizumab were estimated using data from the comparison of the XTEND-1 Arm B and HAVEN 3 Arm B, since the dosing schedule in the latter was once every 2 weeks (in line with the schedule chosen for the model). However, weekly and bi-	4.2.6

ID6170	Summary of issue	Report Section
	weekly doses of emicizumab had similar efficacy in the HAVEN 3 trial and for the proportion of patients with a bleed, arm D from the HAVEN 3 study was selected as most appropriate. The EAG prefers to use the outcomes based on XTEND-1 Arm A and HAVEN 3 Arm D to estimate the ABRs for emicizumab.	
7	In the cost effectiveness model, a disutility is applied each time (between two dosages of prophylaxis) that the FVIII activity level falls below 20%, arguably to reflect the expectation that patients with lower FVIII levels are less capable of undertaking certain activities due to the fear of a bleeding event.	4.2.8
8	When a bleeding event occurs, the company assumed that one dose of 25 IU/kg would suffice for patients using efanesoctocog alfa treatment, whereas for patients using efmoroctocog alfa or emicizumab treatments dose of 50 IU/kg would be needed. This assumption is justified by referring to expert opinion whereas the data from XTEND-1 shows that the large majority of patients received 50 IU/kg to treat a bleeding event, and the others around 30 IU/kg.	4.2.9
ABR = annualised bleeding rate; CS = company submission; DP = decision problem; EAG = External Assessment Group; FVIII = clotting factor VIII; ITC = indirect treatment comparison; IU/kg = international units per kilogram (body weight); NHS = National Health Service; NICE = National Institute for Health and Care Excellence; O-D = on-demand; PTP = previously treated patient; PUP = previously untreated patient; SLR = systematic literature review; SmPC = summary of product characteristics; UK = United Kingdom		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, treatment with efanesoctocog alfa is modelled to affect QALYs by:

- Reducing the number of bleedings
- Improving the time spent in with higher activity levels of clotting factor VIII (FVIII)

Overall, treatment with efanesoctocog alfa is modelled to affect costs by:

- The costs of the treatment (efanesoctocog alfa, efmoroctocog alfa, and emicizumab)
- The costs of treating bleedings

The modelling assumptions that have the greatest effect on the ICER are:

- The choice of baseline annualised bleeding rate (ABR) (i.e. from which treatment option) to which the incidence rate ratios (IRR) are applied
- The choice of treatment arms being compared from the various trials
- The assumption that all patients with a FVIII activity level below 20% have a decreased QoL, regardless of a bleeding in the last 6 months.

1.3 The decision problem: summary of the EAG's key issues

Details of key issues relating to the company's decision problem (DP) are summarised in Tables 1.2 and 1.3.

Table 1.2: Key issue 1: Mismatch between populations in the Scope, DP and included studies

Report Sections	2.1, 3.2.2, 3.3.1.2 and 3.3.2.2
Description of issue and why the EAG has identified it as important	The DP population (people with severe haemophilia A) was defined as narrower than that of NICE Final Scope and SmPC (people with haemophilia A) This was supposedly in order to align with the sample in the XTEND-1 trial. However, the population of XTEND-1 was narrower again (PTPs aged ≥12 years with severe haemophilia A and without FVIII inhibitors). The populations in the two comparator studies (HAVEN 3 and A-LONG) are similar to that of XTEND-1. Since all three study populations are narrower than both the NICE Final Scope and the DP, there is uncertainty as to whether the CS can fully address the Scope or DP as the findings may not apply to those younger than 12 years or people with mild or moderate haemophilia A or presence of inhibitors.
What alternative approach has the EAG suggested?	Limit the DP population to the study populations.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	As above.
CS = company submission; DP = decision problem; EAG = External Assessment Group; FVIII = clotting factor VIII; NICE = National Institute for Health and Care Excellence; PTP = previously treated patient; SmPC = summary of product characteristics	

Table 1.3: Key issue 2: Mismatch of comparators between the Scope and the DP

Report Sections	2.3
Description of issue and why the EAG has identified it as important	The DP excludes FVIII replacement therapy (prophylactic and O-D treatment) as a comparator, listing emicizumab for PTPs and a choice between emicizumab and efmoroctocog alfa for PUPs. This may mean that the comparators included in the CS do not reflect current standard of care in the UK NHS.
What alternative approach has the EAG suggested?	Include FVIII replacement therapy as a comparator.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	As above.
CS = company submission; DP = decision problem; EAG = External Assessment Group; FVIII = clotting factor VIII; O-D = on-demand; NHS = National Health Service; PTP = previously treated patient; PUP = previously untreated patient; UK = United Kingdom	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The methods and documentation of the systematic literature review (SLR) were suboptimal and the EAG is concerned that relevant evidence could have been missed (the details are presented in Table 1.4). Furthermore, it is uncertain whether the XTEND-1 study population is representative of the

UK target population (Table 1.5). Issues with the indirect treatment comparison (ITC) methods are summarised in Table 1.6.

Table 1.4: Key issue 3: Suboptimal SLR methods and documentation

Report Sections	3.1.2 and 3.2.1
Description of issue and why the EAG has identified it as important	There are problems with the clinical effectiveness SLR methods meaning that relevant studies could have been missed. This is partly due to omission of non-English language studies from the search and study selection process. In addition, the documentation of included and excluded records suggests that studies may have been excluded from the SLR for reasons that were not pre-specified.
What alternative approach has the EAG suggested?	Provide information on relevant studies published in languages other than English. Provide a clear set of documentation describing the inclusion and exclusion of studies together with full explanations of colour coding and categorisation terms used. Ensure congruence between the SLR protocol (the study eligibility table) and reasons given for exclusion.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	As above.
EAG = External Assessment Group; SLR = systematic literature review	

Table 1.5: Key issue 4: Uncertain applicability of XTEND-1 to the UK target population

Report Sections	3.2.5
Description of issue and why the EAG has identified it as important	It is not clear whether the population of XTEND-1 is representative of the UK target population since data on the subgroup of UK patients was unavailable.
What alternative approach has the EAG suggested?	Provide data on the subgroup of UK patients for XTEND-1. These data were requested during the clarification process but were not made available to the EAG.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	As above.
EAG = External Assessment Group; UK = United Kingdom	

Table 1.6: Key issue 5: ITC methods: lack of justification as to the choice of arms pooled, outcomes, trimming and covariate choice

Report Section	3.4
Description of issue and why the EAG has identified it as important	The following choices for the ITC versus emicizumab were not clearly justified: • How the various arms from HAVEN 3 were chosen given that only Arm D contained patients with the same experience i.e., prior prophylaxis. In fact, although Arms A and B were chosen for a comparison in the prior O-D population, the majority of

Report Section	3.4
	patients had received prophylaxis previously. It is also unclear whether prior experience (O-D or prophylaxis) makes much of a difference to effectiveness of prophylaxis given that the difference between Arm A (previous prophylaxis) and Arm B (previous O-D) in XTEND-1 in mean (SD) ABR seems negligible: 0.71 [redacted] and 0.69 (1.35) respectively. • Why outcomes assessed varied by whether arms were pooled or not. • Why patients were removed from XTEND-1 (population trimmed) prior to matching and how the baseline characteristics were chosen for this purpose. • How baseline characteristics were chosen for matching (this also applies to the adjustment of individual patient data for the comparison with efmoroctocog).
What alternative approach has the EAG suggested?	Further justification, based on empirical evidence and/or clinical expert opinion is provided as well as sensitivity analysis be conducted, which uses the pooled arms for all ABR outcomes and without any trimming.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Further justification, based on empirical evidence and/or clinical expert opinion is provided as well as sensitivity analysis be conducted, which uses the pooled arms for all ABR outcomes, based on a set of baseline characteristics with adequate justification, and without any trimming.
ABR = annualised bleeding rate; EAG = External Assessment Group; ITC = indirect treatment comparison; O-D = on-demand; SD = standard deviation	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The main EAG results are presented with list prices for emicizumab and octocog alfa and reproduced using confidential patient access schemes (for emicizumab and octacog alfa) in a confidential appendix.

The key issues in the cost effectiveness evidence are discussed in Tables 1.7 to 1.9.

Table 1.7: Key issue 6: Using ABRs from XTEND-1 Arm A and HAVEN 3 Arm D

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG did not agree with the company's choice to estimate the ABR for emicizumab using data from the comparison of the XTEND-1 Arm B and HAVEN 3 Arm B. The main reason behind their choice was the dosing schedule for emicizumab (Q2W). However, the CS commented themselves that weekly and bi-weekly doses of emicizumab had similar efficacy in the HAVEN 3 trial, and for the proportion of patients with a bleeding the

Report Section	4.2.6
	company had already selected Arm D from the HAVEN 3 study as most appropriate.
What alternative approach has the EAG suggested?	The EAG prefers to use the outcomes based on XTEND-1 Arm A and HAVEN 3 Arm D, which involved patients with previous prophylactic treatment and a dosing schedule of once per week for emicizumab. The added benefit of this choice is that the percentage of patients with a bleeding event were also estimated from these study arms and that the estimated IRRs are now based on a much larger sample increasing the robustness of the estimates.
What is the expected effect on the cost effectiveness estimates?	The impact on the estimated ABR for any bleed for emicizumab is modest, decreasing from 3.96 to 3.47. At the same time, the percentage of bleeds being treated slightly increases from 38.1% to 40.9%. This leads to an even more modest decrease in cost savings (though this might be relatively less modest if confidential prices for emicizumab are used) and decrease in QALY gain.
What additional evidence or analyses might help to resolve this key issue?	None required
ABR = annualised bleeding rate; CS = company submission; EAG = External Assessment Group; QALY = quality-adjusted life year; Q2W = once every 2 weeks	

Table 1.8: Key issue 7: Only include disutility related to FVIII <5%

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	In the regression model for the utility of patients receiving efanesoctocog alfa, FVIII activity level below 20% was included as a covariate. The company argued that the disutility for patients with an FVIII activity level below 20% would reflect the expectation that patients with lower FVIII levels are less capable of undertaking certain activities due to the fear of a bleeding event. This issue is potentially important as the model classifies patients receiving emicizumab as having a FVIII activity level between 5-20% all the time, whereas efanesoctocog alfa patients spent the majority of the time at FVIII activity levels >20%. It should be noted that these FVIII levels are modelled as being high immediately after administration of the treatment, after which it decreases until the next dosage. Thus, they do not reflect the (hypothetical?) concept that some patients might show more response to their treatment than others, leading to some patients spending most time at low FVIII activity levels.
What alternative approach has the EAG suggested?	The EAG thinks the argument of being less capable of undertaking certain activities is not convincing as most patients will not be aware of their FVIII level as it appears that this is not monitored regularly/frequently. At this moment, the EAG suggests to only

Report Section	4.2.8
	include disutility related to FVIII <5%, though even that assumption is debatable**.**
What is the expected effect on the cost effectiveness estimates?	Not including a disutility for FVIII activity level 5-20% has a very large impact on the incremental QALYs. For efanesoctocog alfa versus efmoroctocog alfa, the QALY gain increases, whereas for efanesoctocog alfa versus emicizumab the QALY gain decreases.
What additional evidence or analyses might help to resolve this key issue?	Any evidence from literature and/or experts whether patients are hindered in their activities in the periods where the FVIII activity level is between 5-20%, leading to a reduced QoL in that period compared to patients (others or themselves) with an FVIII activity level >20%, independent from bleedings.
EAG = External Assessment Group; FVIII = clotting factor VIII; QALY = quality-adjusted life year; QoL = quality of life	

Table 1.9: Key issue 8: Using 50 IU/kg to treat bleeding events with efanesoctocog alfa

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	When a bleeding event occurs, the company assumes that one dose of 25 IU/kg would suffice for patients using efanesoctocog alfa treatment, whereas for patients using efmoroctocog alfa or emicizumab treatments one dose of 50 IU/kg would be needed. To justify this assumption the company referred to expert opinion whereas the data from XTEND-1 clearly shows that the large majority of patients received 50 IU/kg to treat a bleeding event, and the others around 30 IU/kg. No data other than expert opinion was provided to support the claim that in clinical practice only 25 IU/kg would be used and would be sufficient.
What alternative approach has the EAG suggested?	The EAG suggests using one dose of 50 IU/kg to treat bleeding events for patients in the efanesoctocog alfa arm, similar to the efmoroctocog alfa and emicizumab treatment and to what was done in the XTEND-1 study.
What is the expected effect on the cost effectiveness estimates?	The impact for the comparison of efanesoctocog alfa versus efmoroctocog alfa is large, as it increases the ICER from £18,899 per QALY gained to £43,798 per QALY gained. For the comparison of efanesoctocog alfa versus emicizumab, this change leads to a relatively small decrease in cost-savings for efanesoctocog alfa.
What additional evidence or analyses might help to resolve this key issue?	Data from studies where the dosage of efanesoctocog alfa is varied in the treatment of acute bleedings.
EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; IU/kg = international unit per kilogram (body weight); QALY = quality-adjusted life year	

1.6 Summary of the EAG's view

Tables 1.10 and 1.11 summarise the ICERs of both the company's and EAG's preferred base-cases, as well as the impact of each EAG preferred assumption applied separately to the company base-case.

For the comparison of efanesoctocog alfa versus efmoroctocog alfa, only the EAG preferred assumption regarding the dosage of efanesoctocog alfa for bleedings has an impact, more than doubling the ICER.

For the comparison of efanesoctocog alfa versus emicizumab, both for previously untreated patients (PUPs) and previously treated patients (PTPs), the impact is quite minimal, with efanesoctocog alfa being the dominant treatment. The impact of the changes is so small, relatively speaking, as there is an immense difference in costs between efanesoctocog alfa and emicizumab, as for the first the Patient Access Scheme (PAS) price is used whereas for emicizumab in this report the list price is used. In a confidential appendix the EAG will explore the relative impact of the changes when confidential prices for all treatments in the model have been applied.

When looking at the probabilistic EAG analyses, for the comparison between efanesoctocog alfa and efmoroctocog alfa, the probability of efanesoctocog alfa being cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted] respectively, whilst it was dominant in [redacted] of simulations. Unsurprisingly, in the comparison between efanesoctocog alfa and emicizumab all probabilistic sensitivity analysis (PSA) iterations show an increase in QALYs whilst saving costs; hence, the cost effectiveness acceptability curves (CEACs) for these comparisons show a flat line at 100% probability of being acceptable.

Various scenarios were explored, both by the company and the EAG. Of these, only a few stood out. For the comparison of efanesoctocog alfa versus efmoroctocog alfa, we notice an impact on the ICER of the choice of baseline bleeding rates (from the emicizumab arm informed by Arm B of Haven 3, instead of Arm A from XTEND-1) and ABRs for comparators calculated relative to this baseline. Though the impact on incremental costs and incremental QALYs is modest, as they work in opposite directions the ICER increases substantially. The ICER also substantially increases for scenarios where the costs of non-medicine management of a bleeding decrease. In contrast, the ICER substantially decreases (by almost 50%) when the disutility for patients with an FVIII activity level between 5% and 20% is omitted.

For the comparison between efanesoctocog alfa and emicizumab, scenarios that mostly or only influenced the costs did not show much impact, due to the very high treatment costs and the large cost savings projected for efanesoctocog alfa. Again, this relates to the fact that for efanesoctocog alfa the PAS price is used whereas for emicizumab here the list price is used. Not including a disutility for FVIII activity level 5% to 20% (by applying utility model 4) has a very large impact on the incremental QALYs, these drop from [redacted] to [redacted] for PUPs and from [redacted] to [redacted] for PTPs.

Table 1.10: Deterministic EAG base-case versus company base-case, PUPs, full incremental

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Efmoroctocog alfa	[redacted]	[redacted]	–		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£18,211
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CS base-case following the clarification phase					
Efmoroctocog alfa	[redacted]	[redacted]	–		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£18,899
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base-case					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£43,798
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CS and Only correction error					
Efmoroctocog alfa	[redacted]	[redacted]	–		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£18,899
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Correction error and ABRs from XTEND-1 Arm A and HAVEN 3 Arm D					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£18,899
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Correction error and one dose of 50 IU/kg to treat bleeding events with efanesoctocog alfa					
Efmoroctocog alfa	[redacted]	[redacted]			
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£43,798
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ABR = annualised bleeding rate; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; IU/kg = International units per kilogram (body weight); PUPs = previously untreated patients; QALYs = quality-adjusted life years					

Table 1.11: Deterministic EAG base-case versus company base-case, PTPs, full incremental

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CS base-case following the clarification phase					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base-case					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CS and Only correction error					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Correction error and ABRs from XTEND-1 Arm A and HAVEN 3 Arm D					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Correction error and one dose of 25 IU/kg to treat bleeding events with efanesoctocog alfa					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ABR = annualised bleeding rate; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; IU/kg = international units per kilogram (body weight); PTPs = previously treated patients; QALYs = quality-adjusted life years

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the DP (as presented by the company)

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE Scope	EAG Comment
Population	People with haemophilia A	Patients with severe haemophilia A	The anticipated license for efanesoctocog alfa is [redacted] The evidence base for this submission comes from the Phase 3 XTEND-1 trial, which recruited PTPs with severe haemophilia A. No studies have assessed the use of efanesoctocog alfa in patients with mild/moderate haemophilia A or in PUPs.	The company defined the DP population as "*patients with severe haemophilia A*". Given the discrepancy between this and the NICE Final Scope ("*People with haemophilia A*"),[1] the company were asked to confirm whether this was done in order to be consistent with the population in the XTEND-1 trial. The company were also asked to confirm whether efanesoctocog alfa would not be expected to be administered to patients with mild or moderate disease (CQ A 9). The company confirmed both points.[2] The EAG noted that the XTEND-1 trial only included participants age ≥12 years.[3] The company were asked whether the

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE Scope	EAG Comment
				DP population should be limited to this age group and if not, to provide evidence relating to participants age <12 years (CQ A 10). The company asserted that the DP should not be restricted age-wise as data could be generalised across different age groups.[2] The company were asked to explain how a CEA in PUPs with haemophilia A is feasible in the absence of evidence (CQ A 8). The company replied that clinical opinion supported the extrapolation of data between PTPs and PUPs.[2]
Intervention	Efanesoctocog alfa	As per Final Scope	–	The intervention is in line with the NICE Final Scope.[1]
Comparator(s)	Established clinical management, including:	• PTPs: emicizumab • PUPs: emicizumab and efmoroctocog alfa	The aim of prophylaxis with replacement therapy for patients with severe haemophilia is to decrease the frequency of bleeding, thereby preventing subsequent joint damage (by preventing bleeding into the joints) and related sequalae.[4] The majority	The EAG asked the company to justify the exclusion of prophylactic FVIII replacement therapy as a comparator

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE Scope	EAG Comment
	• Prophylaxis and O-D treatment with FVIII replacement therapy • Emicizumab		of people with severe haemophilia A in the UK receive prophylaxis, and it is considered the treatment approach of choice by the UKHCDO and World Federation of Haemophilia. Any consideration of O-D treatment should only be within the context of a prophylactic regimen, as an additional requirement following a bleed (e.g., following trauma or during surgery). In the UK, very few patients with severe haemophilia are treated with O-D therapy, as it does not prevent bleeding and therefore results in significant joint damage (the rationale for prophylaxis). The minority of patients with severe haemophilia A who are currently treated with O-D therapy are thought to be doing so for historical reasons/personal choice, or who have a milder clinical phenotype. Since launch in 2019, the proportion of patients receiving emicizumab has rapidly increased[5] and continues to do so, with it now being the standard of care in the UK for the treatment of PUPs and PTPs.[6] The proportion of patients with severe haemophilia A receiving emicizumab has increased from [redacted] in 2019, to [redacted] at the end of 2022.[6] Furthermore, since Q2 2019, the use of SHLs has declined from [redacted] to [redacted] at the end of 2022,[6] and clinical opinion suggests that SHL use will be minimal in 5 years' time.[7] **PTPs** Sobi propose that the relevant comparator for PTPs is emicizumab, given it is now standard of	in the DP; or to include it as a comparator in all clinical and CEAs (CQ 11). In their reply, the company maintained their original view and continued to highlight the declining use of FVIII replacement therapy in clinical practice as the rationale.[2] Regarding the DP comparator for PUPs, the EAG asked the company to clarify whether emicizumab and efmoroctocog alfa are alternative treatments or used in combination (CQ A 12). The company clarified that emicizumab and efmoroctocog alfa are alternative treatments for PUPs.[2] The company stated that clinical opinion endorsed the extrapolation of efficacy and safety data for emicizumab to PUPs and previously treated

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE Scope	EAG Comment
			care in patients with severe haemophilia A. Aligning to clinical opinion, it is anticipated that efanesoctocog alfa will be used in patients who would otherwise be offered emicizumab. Amongst PTPs, patients may switch away from rFVIII therapy for the following reasons: • haemostasis is inadequately controlled and the patient experiences breakthrough bleeds with rFVIII prophylaxis. • FVIII levels are not sufficient on rFVIII (i.e., poor pharmacokinetic coverage due to reduced AUC and shorter half-life). • prophylaxis with multiple weekly IV injections with rFVIII is inconvenient or not possible (i.e., frequent injections results in poor compliance or adherence to rFVIII therapy). • the patient is seeking better QoL or to live a life that is as 'normal' as is possible. Aligned to UK guidelines, the HCP will utilise shared decision-making to tailor prophylaxis with the patient, basing therapy on PK data, patient activity, lifestyle, and patient preferences.[4] **PUPs** Clinical advice provided to the Company stated that for PUPs, the choice of treatment results from parental decision. All patients with severe disease/bleeding phenotype will require prophylaxis, and the majority of parents select emicizumab.[7] Some parents will select treatment with a FVIII therapy, often because their child has presented with a severe bleed that required	paediatric populations despite a lack of data for these groups.[3] Given that emicizumab was launched in 2019, the EAG asked the company to confirm whether the statements made could now be supported by relevant empirical data (CQ 13b). By way of reply,[2] the company outlined data from an interim analysis of the HAVEN 7 study which recruited PUPs and MTPs (discussed further in Section 2.3 below). The EAG asked the company to define current SoC in the UK NHS rather than predict future trends (CQ 13c). The company reiterated several of their existing arguments, stating that emicizumab is now considered SoC for prophylaxis in the UK NHS plus use of rFVIII for breakthrough bleeds.

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE Scope	EAG Comment
			emergency treatment with FVIII replacement therapy. In this instance, clinicians stated that an EHL would be the first choice of treatment for prophylaxis in newly diagnosed patients, among which, only efmoroctocog alfa is licensed for use in patients under the age of 12 years. As patients with severe haemophilia A will present early in life, any patients starting treatment with an EHL will be administered efmoroctocog alfa.	The company also asserted that the use of rFVIII is overestimated within the available documentation.[2]
Outcomes	The outcome measures to be considered include: • ABR • Change in FVIII levels • Need for further treatment with FVIII injections • Durability of response to treatment • Complications of the disease (for example joint problems or joint surgeries) • Adverse effects of treatment • Mortality • HRQoL	As per Final Scope.	–	The company stated that the outcomes in the DP are in line with the NICE Final Scope;[1] however, no details were provided.[3]
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be	As per Final Scope	–	No comment; as per NICE Final Scope

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE Scope	EAG Comment
	expressed in terms of incremental cost per QALY. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and PSS perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups to be considered	If evidence allows, subgroups will be considered based on: • severity of haemophilia • presence or development of inhibitors	No subgroups were considered in the CS.	In XTEND-1, all patients had severe haemophilia A and therefore subgroup analysis based on the severity of haemophilia was not possible. Furthermore, no inhibitors to efanesoctocog alfa were detected during XTEND-1 or XTEND-Kids. With regard to previous treatment status, patients who had prior prophylaxis were enrolled into Arm A, while those with prior O-D therapy were enrolled into Arm B of XTEND-1.	None of the subgroups defined in the NICE Final Scope[1] were addressed in the DP. The CS included data on subgroups in XTEND-1 according to age group, bleeding phenotype at baseline, number of

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE Scope	EAG Comment
	• previous treatment status			target joints at screening, dosing and dosing interval compliance for the outcome of ABR. In addition, haemostatic response to treatment was assessed in the subgroup of patients who underwent major surgery during the XTEND-1 trial.[3] For the cost effectiveness analysis, only previous treatment status was used for subgroup analysis, with evidence from XTEND-1 Arm A used to inform both the PTPs and the PUPs. The only difference between these 2 subgroups was the starting age, and the associated weight, baseline utilities and mortality.
Special considerations including issues related to equity or equality	None specified.	None identified.	No comment made.	The CS (Section B1.4) stated that there are no equality considerations for efanesoctocog alfa treatment in patients with severe haemophilia A.[3]

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE Scope	EAG Comment
				However, this is not the same as the population defined in the NICE Final Scope.[1]

Based on Table 1 and Section B.1.1 of Document B of the CS.[3]

ABR = annualised bleeding rate; AUC = area under the curve; CEA = cost-effectiveness analysis; CQ = clarification question; CS = company submission; DP = decision problem; EAG = External Assessment Group; EHL = extended half-life; FVIII = clotting factor VIII; HCP = health care professional; HRQoL = health-related quality of life; IV = intravenous; MTP = minimally treated patient (defined as no more than 5 exposure days to FVIII[2]); NHS = National Health Service; NICE = National Institute of Health and Care Excellence; O-D = on-demand; PK = pharmacokinetics; PSS = Personal Social Services; PTP = previously treated patient; PUP = previously untreated patient; QALY = quality-adjusted life year; QoL = quality of life; rFVIII = recombinant clotting factor VIII; SHL = standard half-life; SoC = standard of care; UK = United Kingdom; UKHCDO = United Kingdom Haemophilia Centres Doctors' Organisation

2.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) Final Scope is "*People with haemophilia A*"[1] which broadly aligns with information under "*Therapeutic indications*" in the summary of product characteristics (SmPC) and the company's anticipated license for efanesoctocog alfa: "[redacted]."[8] However, the company describes a narrower population for the decision problem (DP) namely, "*Patients with severe haemophilia A*".[3] In their rationale for the DP population, the company mentions that: "*The evidence base for this submission comes from the Phase 3 XTEND-1 trial, which recruited previously treated patients (PTPs) with severe haemophilia A. No studies have assessed the use of efanesoctocog alfa in patients with mild/moderate haemophilia A or in previously untreated patients (PUPs).*"[3]

The company was asked to clarify (clarification question [CQ] A 9) whether the DP population was defined as narrower than that of the NICE Final Scope[1] in order to align with the sample in the XTEND-1 study which restricted inclusion to participants aged 12 years or older with previously treated severe haemophilia A (Table 7 of Document B of the company submission [CS]).[3] The company replied that "*…this is to maintain consistency with the XTEND-1 trial and aligns with clinical feedback received; indicating use in severe population. The Company would not expect efanesoctocog alfa to be routinely used to treat patients with mild or moderate haemophilia A.*"[2] However, the SmPC for efanesoctocog alfa describes the therapeutic indication as "*Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)*" and does not specify disease severity.[8]

In light of the XTEND-1 study limiting participant inclusion to those aged 12 years or older, the company was asked to confirm whether the DP population should be narrowed correspondingly (CQ A 10). In their reply, the company referred to the XTEND-Kids study (that recruited participants younger than 12 years previously treated prophylactically) and expressed a view that the DP population should not be narrowed to those aged at least 12 years, making the following additional statements:[2]

"*Clinicians agreed that in the absence of data in PUPs, PTP data would be the next best alternative.*[7]"

"*XTEND-Kids was not used in the cost-effectiveness analysis, as data from XTEND-Kids was not available in time to inform the indirect treatment comparison or economic model. Furthermore, an indirect treatment comparison (ITC) to compare efanesoctocog alfa with emicizumab was deemed unfeasible in the absence of any paediatric data for the non-inhibitor population for emicizumab.*"

"*Extrapolation of data between XTEND-1 and XTEND-Kids was considered, as haemophilia A is a condition where the underlying defect (a deficiency in clotting FVIII) is the same in children and adults. Treatment with efanesoctocog alfa in XTEND-1 and XTEND-Kids was considered generalisable across the adult and paediatric populations. Patients across both trials had similar ABRs, a comparable PK profile (with a shorter half-life expected in younger individuals), and similar rates of zero bleeds. The safety profile of efanesoctocog alfa was also comparable between the two trial populations.*"

Finally, the External Assessment Group (EAG) asked the company to explain how a cost-effectiveness analysis (CEA) in previously untreated patients (PUPs) with haemophilia A would be feasible in the absence of evidence in this population group (CQ A 8). The company replied that "*…clinical opinion supports the extrapolation of safety and efficacy data to PUPs…Consequently, the same efficacy data is applied for both the PUP and PTP populations" and also that "It is also worth noting that since 2018, the guideline on the clinical investigation of recombinant and human plasma-derived FVIII*

products no longer requires PUPs data as part of the clinical development programme to gain a license in this indication."[2]

EAG comment: The company has defined the DP population to correspond to that in the XTEND-1 study rather than the NICE Final Scope. There is persisting uncertainty as to whether the efficacy and safety data from XTEND-1 can be extrapolated to people with mild or moderate haemophilia A or to participants younger than 12 years of age. Similarly, it is still unclear whether data derived from previously treated patients (PTPs) can be applied to PUPs. Therefore, the relevant population for this appraisal is currently unclear. This has been highlighted as a key issue.

2.2 Intervention

The intervention (efanesoctocog alfa) as defined in the company's DP[3] is in line with the NICE Final Scope.[1]

Efanesoctocog alfa is described as "*a novel fusion protein designed to decouple recombinant Factor VIII (rFVIII) from endogenous von Willebrand Factor (VWF) in circulation.*"[9] It is provided as a powder and solvent (water for injection) and administered as an intravenous (IV) injection over several minutes at a rate determined by the patient's comfort level.[8] The recommended prophylactic dose for adults and children is 50 international units per kilogram (IU/kg) administered QW. It is recommended that on-demand (O-D) treatment starts with a single dose of 50 IU/kg with additional doses and their timing varying according to the severity of the clotting factor VIII (FVIII) deficiency, the location and extent of bleeding and the patient's clinical condition. For instances of resumption of prophylaxis following O-D treatment of a bleed, it is recommended that an interval of at least 72 hours should elapse between the last 50 IU/kg O-D dose and the resumption of routine prophylactic treatment.[8]

In terms of testing and monitoring, the SmPC states that: "*In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered.*"[8]

The company outlined the following information regarding current marketing authorisation (MA) for the intervention: *"Efanesoctocog alfa does not yet have UK marketing authorisation for the indication in this submission. Food and Drug Administration (FDA) Breakthrough Therapy designation for haemophilia A was granted in February 2023.[10] A regulatory submission was made to the European Medicines Agency (EMA) in* [redacted]*, with submission to the Medicines and Healthcare projects Regulatory Agency (MHRA) anticipated in* [redacted]*. Committee for Medicinal Products for Human Use (CHMP) positive opinion is anticipated in* [redacted] *and MHRA regulatory approval in* [redacted]*"* (Table 2 of Document B of the CS).[3]

2.3 Comparators

The NICE Final Scope defined the comparator as established clinical management (ECM), indicating that this could consist of prophylactic and O-D treatment with FVIII replacement therapy or emicizumab, an extended half-life (EHL) therapy.[1] The company's DP distinguished between comparators for PTPs (emicizumab) and PUPs ("*Emicizumab and efmoroctocog alfa*", the latter being another EHL therapy).[3] The EAG queried whether the comparator for PUPs was emicizumab in combination with efmoroctocog alfa; or a choice between the two products (CQ A 12). The company confirmed that the comparator in this patient group is a choice between emicizumab or efmoroctocog alfa

and suggested that "*Patients receiving emicizumab will receive a supply of FVIII treatment in case of break-through bleeding, however this is usually in the form of an SHL factor therapy.*"[2]

In 2019, NHS England published a Clinical Commissioning Policy to make emicizumab available as prophylactic therapy for people of all ages with congenital haemophilia A without FVIII inhibitors.[11] Efmoroctocog alfa was licenced in the United Kingdom (UK) in 2020 for the O-D treatment and prophylaxis of bleeding in patients of all age groups and all severities of haemophilia A.[12]

In their rationale for the discrepancy between the scope and DP comparators, the company stated that:[3] "*The majority of people with severe haemophilia A in the UK receive prophylaxis, and… Any consideration of on-demand treatment should only be within the context of a prophylactic regimen, as an additional requirement following a bleed*".[3] The company also stated that:[3] "*Since launch in 2019, the proportion of patients receiving emicizumab has rapidly increased*[5] *and continues to do so, with it now being the standard of care in the UK for the treatment of PUPs and PTPs.*[6] *The proportion of patients with severe haemophilia A receiving emicizumab has increased from* [redacted] *in 2019, to* [redacted] *at the end of 2022.*[6] *Furthermore, since Q2 2019, the use of SHLs has declined from* [redacted] *to* [redacted] *at the end of 2022,*[6] *and clinical opinion suggests that SHL use will be minimal in 5 years time.*[7]"[3]

In the context of PTPs, the company asserted that:[3] "*the relevant comparator for PTPs is emicizumab, given it is now standard of care in patients with severe haemophilia A. Aligning to clinical opinion, it is anticipated that efanesoctocog alfa will be used in patients who would otherwise be offered emicizumab.*[7]"[3] Regarding PUPs, the company outlined the following:[3] "*Clinical advice… stated that for PUPs, the choice of treatment results from parental decision. All patients with severe disease/bleeding phenotype will require prophylaxis, and the majority of parents select emicizumab.*[7] *Some parents will select treatment with a FVIII therapy, often because their child has presented with a severe bleed that required emergency treatment with FVIII replacement therapy. In this instance, clinicians stated that an EHL would be the first choice of treatment for prophylaxis in newly diagnosed patients, among which, only efmoroctocog alfa is licensed for use in patients under the age of 12 years. As patients with severe haemophilia A will present early in life, any patients starting treatment with an EHL will be administered efmoroctocog alfa.*"[3]

EAG comment: The EAG asked the company to justify the exclusion of prophylactic FVIII replacement therapy as a comparator in the DP when [redacted] of patients were receiving emicizumab and [redacted] were still using the standard half-life (SHL) FVIII replacement therapy at the end of 2022 (CS Document B, Table 1, "Comparators"[3]). The company were also asked to include it as a comparator in all clinical and CEAs given that it still appears to be standard UK clinical practice for many patients (CQ A 11). The company's reply was as follows:[2]

- "*To reiterate, the justification for the exclusion of SHL/EHL factor therapies as a comparator in the PTP population is based on the proposed positioning of efanesoctocog alfa in the treatment pathway.*"
- "*In PTPs, efanesoctocog alfa is positioned for patients who would otherwise be offered emicizumab, this being previously treated factor patients (Document B, Figure 2*[3]*). Therefore, the point in the treatment pathway where efanesoctocog alfa will be offered is when emicizumab is the only other alternative treatment option.*"
- "*In PUPs, efmoroctocog alfa (Elocta) is licensed for use in patients under the age of 12 years*[12] *and is an additional comparator included in the analysis.*"
- "*Regarding SHLs in general, since Q2 2019, the use of SHLs has declined from* [redacted] *to* [redacted] *at the end of 2022,*[6] *and clinical opinion suggests that SHL use will be minimal in 5 years' time.*[7]

The beginning of a significant decrease in rFVIII issued from 2020/21 is attributable to the introduction of emicizumab prophylaxis from September of 2018/19.[6] *It is also important to note that the figure of* [redacted] *is an overrepresentation of market share, since patients on emicizumab require additional rFVIII for at home contingency stock, breakthrough bleeding management (at home or in hospital), and surgery. The UKHCDO comment on this data limitation and indicate that there is some double counting in this chart since people may be issued with more than one product type in any given year.*[6]"

- "*A recent investor report from Roche, the manufacturers of emicizumab, indicates that the market share of the product may be up to 70% as of September 2023.*"[13]

The EAG noted a reliance on clinical opinion to substantiate some arguments relating to the choice of comparators.[3] Details of the approach taken to elicit clinical opinion were minimal beyond saying that five UK-based consultant haematologists were interviewed: therefore, the EAG requested further information (CQ A 13a). the company's response was as follows:[2]

- "*The clinical interviews were not conducted as an elicitation exercise, and so this particular methodology was not followed. Each interview was held in a 1:1 format via Microsoft® Teams to ascertain expert clinical opinion. In terms of independence between the clinicians and the Company, the clinicians were interviewed under a consultancy agreement only. Given the highly specialised nature of haemophilia and the level of experience required in the clinicians interviewed, it is very difficult to find participants who have not provided consultancy activity for any company.*"

According to the CS, the clinical experts endorsed the extrapolation of efficacy and safety data for the non-factor therapy emicizumab to PUPs and previously treated paediatric populations despite a lack of data for these groups (p.12 and p.117 of Document B of the CS). Given that emicizumab was launched in 2019 (Table 1 of Document B of the CS),[3] the EAG asked the company to confirm whether relevant empirical data are now available to support this extrapolation, and to provide data if feasible (CQ A13b). The company outlined the following explanation:[2]

- "*No studies have assessed the use of efanesoctocog alfa in PUPs, and the cost-effectiveness analysis is based on data from PTPs. However, clinical opinion supports the extrapolation of safety and efficacy data to PUPs. Consequently, the same efficacy data are applied for both the PUP and PTP populations.*"
- "*The company acknowledges that there is an ongoing Phase 3b study evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in PUPs and minimally treated patients (MTPs; defined as ≤5 exposure days to FVIII) aged ≤12 months (HAVEN 7).*[14] *Interim results from HAVEN 7 are published.*[15]"
- "*At the interim analysis cut-off date, 54 patients had more than one dose of emicizumab. Of these, 30 (55.6%) were minimally treated prior to the study, and 24 (44.4%) were previously untreated. Median (range) of emicizumab treatment duration was 42.1 (1–60) weeks.*"
- "*Mean model-based ABR for treated bleeds was 0.4 (95% CI: 0.23, 0.65), and was 1.9 (95% CI: 1.23, 2.68) and 0.1 (95% CI: 0.01, 0.22) for all bleeds and treated joint bleeds, respectively. Zero treated bleeds were reported in 42 patients (77.8%), while 23 patients (42.6%) had no bleeds at all. PK data were evaluable in 52 patients. Mean trough concentrations of emicizumab increased with loading doses, with concentrations of 63.2 µg/mL (95% CI: 59.5, 66.8) at Week 5; steady-state concentrations were maintained at 60–65 µg/mL thereafter. None of the 48 patients evaluable for immunogenicity analysis tested positive for anti-drug antibodies.*"

- "*Fifty patients (92.6%) had more than one AE, and nine (16.7%) had more than one treatment-related AE (all injection-site reactions). No AEs leading to treatment withdrawal/modification/interruption occurred. Eight patients reported 12 serious AEs (SAEs); none of which were considered treatment-related.*"

The EAG noted statements made in Document B of the CS, supported by clinical opinion, that focused on predicting future aspects of standard of care (SoC), e.g., SHL use will be minimal in 5 years (p.14 and p.120) and efanesoctocog alfa will be used in patients who would otherwise be offered emicizumab (p.14 and p.27-8).[3] The EAG asked the company to clarify the details of current SoC in the UK National Health Service (NHS) as opposed to predicting future trends (CQ A 13c).

The company began their response[2] with information about their rationale for choice of comparators as already shown in the DP table (Table 1 of Document B of the CS[3] and reproduced in this report, see Table 2.1 above). In brief, this includes the assertion that "*Since launch in 2019…the proportion of patients receiving emicizumab has rapidly increased and continues to do so, with it now being the standard of care in the UK for the treatment of PUPs and PTPs.*[6]"[2, 3] The company went on to say that the documented use of rVIII therapy may be overestimated: "*If a patient on emicizumab prophylaxis experiences a breakthrough bleed or undergoes surgery, they will still require rFVIII (factor replacement therapy) to treat acute bleeds. Typically, patients are offered an SHL to treat breakthrough bleeds, and therefore, the proportion of rFVIII issued to patients is overrepresented, as it includes a notable number of patients who receive emicizumab who have a contingency stock of rFVIII at home, or patients who have received rFVIII to treat a bleed in hospital/during a surgical procedure. (Note: the data* [in Figure 1 below] *represents "treatment issued" as opposed to "patients treated with". This is a nuance of the data collected within the database).*"

Figure 2.1: The proportion of people with severe haemophilia A and no inhibitor issued treatment by product type 2019 Q2 – 2022 Q4

Source is the company's response to CQ A 13c[2] which in turn cites the National Haemophilia Database Real World Evidence Report[6]
CQ = clarification question; EMI = emicizumab; FVIII = clotting factor VIII; Q = quarter

The company maintains that SoC focuses on prophylactic treatment with EHL products plus O-D use of recombinant clothing factor VIII (rFVIII) in cases of breakthrough bleeds or requirement for surgery. However, given the evidence of continued use of prophylactic FVIII, despite a decline, it remains

uncertain whether this view is reflected in current UK clinical practice. This therefore constitutes a key issue.

2.4 Outcomes

The NICE Final Scope[1] lists the following outcome measures:

- Annualised bleeding rate (ABR)
- Change in FVIII levels
- Need for further treatment with FVIII injections
- Durability of response to treatment
- Complications of the disease (e.g., joint problems or joint surgery)
- Adverse effects (AEs) of treatment
- Mortality
- Health-related quality of life (HRQoL)

The company stated that the outcomes in the DP were in line with the NICE Final Scope but did not provide any further details.[3] When comparing the above list of outcomes with those specified for the XTEND-1 study (the sole source of clinical efficacy and safety evidence for the use of efanesoctocog alfa in the CS), the EAG noted that two were not covered by the study (change in FVIII levels and need for further treatment with FVIII injections, as listed in Table 9 in Document B of the CS). The XTEND-1 study included several outcomes that were not specified in the NICE Final Scope:[3]

- prophylactic dose and dosing interval (for efanesoctocog alfa)
- number of injections and dose of efanesoctocog alfa to treat a bleeding episode
- assessment of response to efanesoctocog alfa treatment of bleeding episodes
- annualised joint bleeding rate
- target joint resolution
- Haemophilia Joint Health Score
- treatment satisfaction/preference
- physical activity
- ultrasound measures
- healthcare resource utilisation

In addition, the XTEND-1 study reported the following for a subgroup who underwent surgery during the study period:[3]

- Investigator or surgeon's assessment of patient haemostatic response to efanesoctocog alfa
- number of injections and dose to maintain haemostasis for major surgery
- total efanesoctocog alfa consumption for major surgery
- estimated blood loss for major surgery
- number and type of blood component transfusions for major surgery

2.5 Subgroups

The NICE Final Scope[1] specified consideration of subgroups based on:

- severity of haemophilia
- presence or development of inhibitors
- previous treatment status

In the DP, the company indicated that no subgroups were considered in the CS.[3] The rationale for this was that all patients in the XTEND-1 study had severe haemophilia A and none had inhibitors. In addition, patients were allocated to different treatment arms according to previous treatment status. Therefore, analysis according to the subgroups defined in the NICE Final Scope[1] was addressed in the DP.

The CS included data on subgroups in XTEND-1 according to age group, bleeding phenotype at baseline, number of target joints at screening, dosing and dosing interval compliance for the outcome of ABR. In addition, haemostatic response to treatment was assessed in the subgroup of patients who underwent major surgery during the XTEND-1 study.[3]

2.6 Other relevant factors

According to the company, efanesoctocog alfa has the potential to resolve unmet needs in relation to prevention of bleeding episodes and reducing the treatment burden: "*Due to its high-sustained and further prolonged half-life compared with EHLs, efanesoctocog alfa addresses these unmet needs by providing high-sustained FVIII activity levels for the majority of the week, improving bleed prevention, and offering greater protection against joint damage.*" (Section B2.12 of Document B of the CS).[3]

The CS (Section B1.4) stated that there are no equality considerations for efanesoctocog alfa treatment in patients with severe haemophilia A.[3] However, the EAG notes that this is not the same as the population defined in the NICE Final Scope.[1]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[3, 16] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[17, 18] The CS[3] was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[19] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the systematic literature review (SLR) conducted to identify relevant phase 3 trials of FVIII replacement therapies and non-factor replacement therapies for the treatment of haemophilia A.[16] The searches were conducted in February 2021, and updated in September 2023.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-10/2/21 10/2/21-6/9/23	10/2/21 6/9/23
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	Inception - 10/2/21 10/2/21-6/9/23	10/2/21 6/9/23
CENTRAL	Ovid	To January 2021 2021-6/9/23	10/2/21 6/9/23
CDSR	Ovid	To January 2021 2021-6/9/23	10/2/21 6/9/23
DARE	Ovid	To Q1 2016	10/2/21
HTA Database	Ovid	To Q4 2016	10/2/21
Conferences			
• European Hematology Association • World Federation of Hemophilia • Annual Congress of European Association for Haemophilia and Allied Disorders • BIC International Conference • Comprehensive Care Summit: New Developments in Bleeding Disorders and MSK	Internet	2020-2023 2020-2023 2020-2023 2023 2023	Sept 2023
Trials registries			
• ClinicalTrials.gov	Internet	Not stated	Sept 2023

Resource	Host/Source	Date Ranges	Date searched
• WHO ICTRP			
HTA Organisations			
• NICE • SMC • NCPE • PBAC • CADTH • HAS • IQWiG • Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA]) • ICER	Internet	Not stated	Sept 2023

CADTH = Canadian Agency for Drugs and Technologies in Health; CENTRAL: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; HAS = Haute Autorité de Santé; ICER = Institute for Clinical and Economic Review; IQWiG = German Institute for Quality and Efficiency in Health Care; NCPE = National Centre for Pharmacoeconomics; HTA: Health Technology Assessment; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform

EAG comment:

- Searches were undertaken in February 2021, and updated in September 2023 to identify relevant phase 3 trials of FVIII replacement therapies and non-factor replacement therapies for the treatment of haemophilia A. The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 3, 16]
- A good range of bibliographic databases, conferences, trials registers and Health Technology Assessment (HTA) resources were searched. Reference checking was conducted. Searches were well structured, transparent and reproducible.
- The database searches for the clinical effectiveness SLR contained a population facet for haemophilia A. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials. Animal-only studies were excluded.
- Database searches were limited to studies from 1980-date and were restricted to English language studies only. Limiting the results to only studies published in English may have introduced language bias. Current best practice states that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"[20] and that "research related to language bias supports the inclusion of non-English studies in systematic reviews".[21, 22] In response to clarification (CQ A.7) the company stated that:

  "With regard to evidence selection bias, there may be other published research on this topic in languages other than English. However, given that the majority of high-quality international research is published in English language journals, a pragmatic decision was made to search only the English language literature".[2]
- The study design filter for the Embase search contained a number of MEDLINE subject heading terms (MeSH), rather than the EMTREE terms which should have been used for this database. In the MEDLINE search, the 'animal study' exclusion facet contained EMTREE terms rather than MeSH. Although some mapping between indexing terms does take place on MEDLINE and

Embase, it is possible that as the appropriate subject heading terms were not used, potentially relevant records could have been missed.

- Additional synonyms could have been added to the population facet to increase recall, such as *type A h?emophilia* and *h?emophilia adj2 classic$.* In addition, truncation would have been useful on *h?emophilia$* in order to retrieve records which contained *h?emophiliac* or *h?emophiliacs* as text words. The exclusion of the phrase *(acquired hemophilia).ab,ti.* using the Boolean NOT operator runs the risk of missing records which contain mention of both congenital and acquired haemophilia. The range of resources included in this SLR however may have mitigated against these limitations in the search strategies.

3.1.2 Inclusion criteria

An SLR was conducted to identify relevant clinical evidence. Full details of the SLR search strategy, study selection process and results were reported in Appendix D of the CS.[16] The eligibility criteria used in the SLR is presented in Table 3.2.

Table 3.2: Eligibility criteria used in the SLR

	Inclusion criteria	Exclusion criteria
Population	Patients or patient subgroup with haemophilia A with or without inhibitors	• Acquired haemophilia • Patients with conditions other than haemophilia A with or without inhibitors • Not in humans • Subpopulations (e.g., undergoing surgery, undergoing knee replacement, hemarthroses, dental extraction, circumcision, pregnancy, obesity)
Interventions	Prophylaxis or O-D use of: • non-factor replacement therapies (e.g., emicizumab, fitusiran, anti-tissue factor pathway inhibitor and gene therapies), and • FVIII-replacement therapies, including SHL and EHL recombinant therapies (e.g., BIVV001, antihemophilic factor [recombinant], PEGylated; GlycoPEGylated-exei; single chain)	Interventions others than prophylaxis or O-D use of: • non-factor replacement therapies (e.g., emicizumab, fitusiran, anti-tissue factor pathway inhibitor and gene therapies), and FVIII-replacement therapies, including SHL and EHL recombinant therapies (e.g., BIVV001, antihemophilic factor [recombinant], PEGylated; GlycoPEGylated-exei; single chain) • plasma derivates and supportive therapies, including alternative medicines such as healing systems, manipulation, touch, energy therapies, dietary studies with herbs, vitamins, mineral supplements etc.

	Inclusion criteria	Exclusion criteria
Outcomes	• ABR • AsBR • AjBR • Factor usage/consumption • Target joints • Development of inhibitors • PROs (e.g., Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL])	Not reporting any of the outcomes listed in the inclusion criteria
Study design	Phase III RCTs and non-RCTs (single arm trials, and open label extension trials)	• observational studies • SLRs, meta-analyses (for bibliography check only) • case reports or editorial comments • non-Phase 3 studies (including Phase 1, 1/2, 2, and 4)
Language restrictions	English language publications	Non-English language publications

Based on Table 8 in Appendix D of the CS[16]
ABR = annualised bleeding rate; AjBR = annualised joint bleeding rate; AsBR = annualised spontaneous bleeding rate; CS = company submission; EHL = extended half-life; FVIII = clotting factor VIII; O-D = on-demand; PICOS = population, intervention, comparator, outcomes, and study design; PRO = patient reported outcomes; RCT = randomised controlled trial; SHL = standard half-life; SLR = systematic literature review

EAG comment:

- The EAG noted that the eligibility criteria suggest a mismatch between outcomes listed in the NICE Final Scope and DP and those listed for the clinical effectiveness SLR. For example, change in FVIII levels, durability of response to treatment, joint surgeries, AEs and mortality are all listed in the Scope but not for the SLR. The company was asked to justify these exclusions (CQ A.17). The company responded to this question with the following explanation:[2] "*As the clinical SLR was originally planned and conducted before the draft scope was published, these outcomes were not captured when the original searches were conducted. When the searches were updated in 2023, a pragmatic decision was made to focus on the outcomes already extracted, as:*
    1. *Changes in FVIII levels were not considered relevant, as the Company believe it is more appropriate to measure FVIII levels in response to treatment, in contrast to monitoring changes in factor levels over time, which would be more appropriate for a gene therapy.*[23]
    2. *Durability of response to treatment was not considered relevant for FVIII replacement therapy. The Company consider that response to treatment is best measured following each administration, as FVIII levels are likely to fluctuate over time between treatments.*
    3. *Joint surgery was not considered relevant for FVIII replacement therapy studies, as the number of surgeries a patient may have over their lifetime is minimal. On average, a patient would require a surgery every 152 years according to the assumptions made in previous models.*[24] *Furthermore, this was not captured in the economic model.*
    4. *Adverse effects were not considered relevant for these types of study, as there is a wealth of evidence supporting the safety profile of factor replacement therapies.*[12, 25, 26]
    5. *Mortality was not considered relevant, as treated patients typically have survival rates in line with the general population."*[2]

The EAG does not agree with all of these statements, especially as the choice of outcomes for the submission seems to be driven by data availability rather than any scientific protocol. In particular, the EAG is concerned regarding the suggestion that safety-related outcomes could be overlooked and related to this, appreciates the provision of further information provided during the clarification process (discussed further in Sections 3.2.8 and 3.3).

- Related to question CQ A.7 (discussed in Section 3.1.1 above), study eligibility has been restricted to English language only. The company was asked to explain the impact of excluding non-English language publications on the findings of the SLR (CQ A.18). The company stated that:[2] *"With regard to evidence selection bias, there may be other published research on this topic in languages other than English, however, given that the majority of high-quality international research is published in English language journals, a pragmatic decision was made to search only the English language literature."*[2] The company did not provide the impact of these omissions on clinical effectiveness estimates. This means that the potential impact of language bias cannot be discounted.

3.1.3 Critique of study selection and data extraction

The following details about the SLR process were provided in Appendix D of the CS.[16]

Two reviewers, working independently, reviewed all title/abstract and full-text screening. Only the reasons for exclusion at full-text screening were documented and reported. Any discrepancies in study selection between reviewers were resolved with the help of a third, more senior reviewer.[16]

Data were extracted by one reviewer and checked for accuracy by a second reviewer. Any discrepancies between reviewers were resolved by discussion and/or referral to a third reviewer.[16]

EAG comment: The EAG noted that Section D.1.4.2 in Appendix D of the CS mentions the data extraction process, however full details of the template were lacking, and the output was not included in the submission. The EAG asked the company to provide details of the data extraction template (CQ A.15a). The company responded that *"A data extraction template was developed to extract study design, baseline characteristics and outcomes. Mean, median, standard deviation, standard error, and range were extracted for continuous variables where possible. For categorical variables, frequency and percentage were extracted."*[2] These details were tabulated and shown below in Table 3.3. The EAG is satisfied with this response and appreciates the additional information.

The company was also asked to provide the extracted data for the included and extracted studies (CQ A.15b). The company presented an accompanying document by way of response to this[27] (discussed further in Section 3.2.1).

Table 3.3: Data elements captured during data extraction

Study design characteristics	Baseline characteristics	Treatment characteristics	Outcomes
• Author, study title, journal, and publication year • Trial number and acronym • Trial phase • Setting (e.g., country, study period) • Study population	• Age • Sex • Race • Weight and/or body mass index • Previous regimen (i.e., O-D, prophylaxis)	• Treatment • Dose • Schedule • Prior treatments • SHL/EHL • Plasma-derived/recombinant	• ABR • AsBR • AjBR • Factor usage/consumption • Target joints • Development of inhibitors

Study design characteristics	Baseline characteristics	Treatment characteristics	Outcomes
• Inclusion/exclusion criteria • Intervention/comparators • Study methods (e.g., randomisation ratio, stratification factors, cross-over) • Trial duration/follow-up • Blinding • Sample size • Relevant statistical methods used in studies (e.g., handling of missing data) • Proportion of patients with hemophilia A (only for trials that include mixed populations and subgroup results for the hemophilia A subgroup) • Quality assessment	• Number of bleeds prior to study entry • Disease severity • Gilbert score • FVIII levels • Number of target joints • FVIII inhibitor status • Infections (e.g., HIV, HCV)	• Prophylaxis/O-D	• Available PRO measures (e.g., Haem-A-QoL) • HJHS/mHJHS

Based on Table 27 of the CQ[2]
ABR = annualised bleed rate; AjBR = annualised joint bleed rate; AsBR = annualised spontaneous bleed rate; CQ = clarification question; EHL = extended half-life; FVIII = clotting Factor VIII; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HJHS = Haemophilia Joint Health Score; mHJHS = modified Haemophilia Joint Health Score; O-D = on-demand; PRO = patient reported outcome; SHL = standard half-life

3.1.4 Quality assessment

The company provided details of the methods and results of risk of bias assessment for randomised controlled trials (RCTs) in Appendix D of the CS,[16] stating that this was conducted using guidelines from NICE.[28] The assessment consisted of the following seven questions: 1) Was the method used to generate random allocations adequate? 2) Were the groups similar at the outset of the study in terms of prognostic factors (e.g., severity of disease)? 3) Was the treatment allocation sequence adequately concealed? 4) Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? 5) Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? 6) Is there any evidence to suggest that the authors measured more outcomes than they reported? 7) Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

The CS did not provide a risk of bias assessment for non-randomised studies (e.g., XTEND-1) and did not report details of the quality assessment process for any study design (i.e., the number of reviewers involved and the approach for resolving disagreements).

EAG comment:

- In CQs A16a and 16b, the company was asked to provide details of the tool(s) and the output of assessing the risk of bias in the non-randomised studies (e.g., XTEND-1). The company responded

that "*Quality appraisal was not conducted for the non-randomised studies. It was expected that the risk of bias is similar between single-arm prospective trials and there is no accepted standard method to assess risk of bias in single-arm studies specifically. Therefore, no risk of bias assessment was attempted for these studies."*[2] The EAG does not agree with this approach and therefore conducted its own risk of bias assessment of the XTEND-1 study using the Joanna Briggs Institute (JBI) critical appraisal checklist for quasi-experimental studies as more appropriate tool.[29] The results of the EAG's risk of bias assessment are provided in Section 3.2.6 and Table 3.10 of this report.

- The company were also asked to provide details of the process of risk of bias assessment (CQ A.16c). The company clarified that: *"Quality appraisal was conducted (using the primary publication for each RCT identified) by one reviewer and validated for accuracy by a second reviewer. Any discrepancies that arose between the two reviewers were reconciled by both reviewers and/or a third reviewer, if needed, to reach consensus."*[2] The EAG is satisfied with this response.

3.1.5 Evidence synthesis

The company stated that a meta-analysis was not applicable.

EAG comment: Given that the XTEND-1 trial was not an RCT, a direct head-to-head meta-analysis would not have been appropriate. Instead, to permit comparison with comparators in the DP, an indirect treatment comparison (ITC) has been performed using two Phase 3 RCTs, A-LONG, and HAVEN 3. These studies and the ITC methods used are discussed in Sections 3.3 and 3.4 respectively.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

In Document B of the CS,[3] the company states that "*overall 177 publications corresponding to 105 unique studies were identified, of which, a full data extraction was performed on 62 publications comprising 49 unique studies*". This is discrepant with Appendix D of the CS,[16] which states that "*overall, the systematic literature review (SLR) identified 176 publications reporting 105 unique studies, of which full data extraction was performed on 65 publications comprising 49 unique studies*". Related to this, the EAG noted that the CS did not include any record of data extraction for the included studies within the submission documents.

EAG comment: The EAG requested that the company clarify the discrepancy around the numbers of included studies (CQ A 14). The company responded by stating that, "*The correct number of included publications is 65 – Document B should read: "full data extraction was performed on 65 publications comprising 49 unique studies*."[2]

The EAG also requested the data extraction record for the included studies (CQ A 15b). By way of a reply, the company provided a supplement to their main clarification response file and the remaining EAG comments in this Section pertain to this document unless otherwise stated.[27] The EAG noted some further discrepancies in terms of numbers of included studies. Table 1 (which appears to be the eligible and data extracted studies, "*Study characteristics*") listed 50 records whereas Appendix 3.1.1 of the same document ("*Publications [N=39 + 26 in update] included and data extracted*") presented 65 records. The EAG are satisfied with the number of studies included but not extracted (n=112) tabulated in Appendix 3.1.2. However, details in Appendix 3.1.3 ("*Publications [N=85 + 39 in update] excluded in level 2 full text screening*") regarding the reasons as to why papers were excluded are also unclear. Many studies were excluded for the reason "*superseded*", with no explanation of what is meant by this; similarly, one study was excluded for the reason "*LANG*", again with no key as to the full term. In the

same appendix, the EAG noted two more specific instances of excluded studies which could have been eligible for inclusion:[27]

- Dargaud Y (2018) "*Individual thrombin generation and spontaneous bleeding rate during personalized prophylaxis with Nuwiq R (human-cl rhFVIII) in previously treated patients with severe haemophilia A.*" The reason for exclusion was given as "*Outcome*" however the title suggests the possibility of a relevant outcome being reported.
- Horling FM (year not provided) "*Immunogenicity of BAX 855 in previously treated patients with congenital severe hemophilia A.*" The reason for exclusion was given as "*Publication type*" but there is not mention of this being a study selection criterion in the SLR details (Appendix D of the CS[16]).

Since full bibliographic details were lacking for both references, the EAG could not explore further to verify the eligibility of the records.[27]

Finally, the EAG noted the use of colour coding in tables throughout the clarification response document which was not explained (and clearly did not correspond to the usual academic in confidence [AiC] or commercial in confidence [CiC] mark-up).[27]

Overall, the discrepancies in the number of included studies across different files and the lack of clarity within the documentation overall means that the EAG does not have confidence in the account of study flow provided and is concerned that there is a risk that eligible studies (particularly in relation to comparator evaluations) may have been omitted from the submission. The potential for the SLR to miss eligible studies has been highlighted as a key issue.

3.2.2 Details of the included trial

One study was identified as being eligible for inclusion: the XTEND-1 study which recruited PTPs of at least 12 years of age with severe haemophilia A. A second study was identified which provided data for patients under 12 years of age (XTEND-Kids) however, this did not inform the economic model for the submission.[3]

Details outlined in Section B.2.2 of the CS[3] indicated that XTEND-1 was a Phase 3 study and was used to determine the primary clinical effectiveness and safety evidence for the use of efanesoctocog alfa for the treatment of severe haemophilia A. The clinical effectiveness data for XTEND-1 were available from a clinical study report (CSR)[30] and a published paper, von Drygalski *et al*. (2023).[31] Outcomes of the study included: the ABR, need for further treatment with FVIII injections, change in FVIII activity levels, pharmacokinetics, adverse events (AEs) of treatment, mortality and HRQoL. The XTEND-1 study was conducted across 19 countries, including Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Spain, South Korea, Taiwan, the UK and the United States of America (USA), at 51 active centres. Due to screen failure, patients were enrolled in 48 of the 51 active centres. It should be noted that in total [redacted] patients were enrolled from the UK. Table 3.4 highlights the study details from the clinical effectiveness evidence for the XTEND-1 and XTEND-Kids studies.

Table 3.4: Clinical effectiveness evidence for XTEND-1 and XTEND-Kids

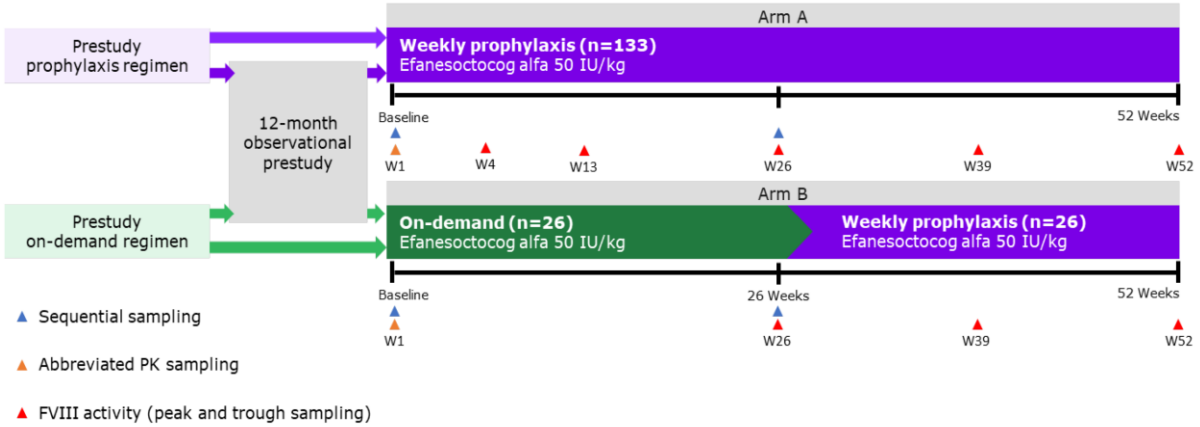
Study	XTEND-1 (NCT04161495)	XTEND-Kids (NCT04759131)
Study design	Phase 3, open-label, multinational, multicentre study	Phase 3, open-label, non-randomised study

Study	XTEND-1 (NCT04161495)	XTEND-Kids (NCT04759131)
Population	Previously treated patients ≥12 years old with severe haemophilia A (defined as <1 IU/dl [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia)	Previously treated patients younger than 12 years of age with severe haemophilia (defined as <1 IU/dl [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia)
Intervention(s)	Efanesoctocog alfa	Efanesoctocog alfa
Comparator(s)	N/A	N/A
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	No
Reported outcomes specified in the decision problem	ABR Need for further treatment with FVIII injections Change in FVIII activity levels Complications of the disease e.g. joint problems or surgeries to treat joint problems) Pharmacokinetics AEs of treatment Mortality HRQoL	ABR Change in FVIII activity levels Complications of the disease e.g. joint problems AEs of treatment Pharmacokinetics HRQoL
All other reported outcomes	N/A	N/A

Based on Table 6 of Document B of the CS[3]
ABR = annualised bleeding rate; AEs = adverse effects; CS = company submission; FVIII = clotting factor VIII; HRQoL = health-related quality of life; IU/dl = international unit per decilitre; N/A = not applicable

XTEND-1 included PTPs aged 12 years or older, with severe haemophilia A, which was defined as endogenous FVIII activity <1 IU/dl [<1%]. There was an 8-week screening period, a maximum of 52 weeks open-label treatment period and a follow-up safety period of 2- to 3-weeks, which was only for patients that did not continue into an open label extension study (Figure 3.1).

Figure 3.1: Schematic of XTEND-1 trial design



Based on Figure 4 of Document B of the CS[3]
CS = company submission

The study had two arms:

- Arm A: where patients received efanesoctocog alfa at a dose of 50 IU/kg IV once weekly (QW) on a prophylaxis treatment for 52 weeks. A prerequisite for Arm A was that patients were required to be receiving a prophylactic regimen prior to study enrolment.
- Arm B: where patients were required to be receiving an O-D treatment with a marketed FVIII therapy prior to the study and to have had ≥6 bleeding episodes in the last 6 months or ≥12 bleeding episodes in the last 12 months. Arm B comprised of two phases:
    - an O-D regimen: where patients received a dose of 50 IU/kg IV efanesoctocog alfa as O-D treatment of bleeding episodes for the first 26 weeks.
    - and a prophylaxis regimen where patients switched to receive a dose of 50 IU/kg IV QW efanesoctocog alfa as a prophylaxis treatment regimen for another 26 weeks.

The key inclusion exclusion criteria for XTEND-1 are listed in Table 3.5.

Table 3.5: Key inclusion and exclusion criteria of XTEND-1

Key inclusion criteria	Key exclusion criteria
Previously treated[a] patients with severe haemophilia A (defined as <1 IU/dl [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia A). Aged 12 years or older. Platelet count ≥100,000 cells/µL at screening. Patients who are HIV-positive must have a CD4 lymphocyte count >200 cells/mm^3 and a viral load of <400 copies/ml. Willingness and ability of patient or caregiver to complete training in the use of the study electronic patient diary.	Patients with a history of a positive inhibitor test or with a positive inhibitor test result (defined as ≥0.6 BU/ml) at screening. Clinical signs or symptoms of a decreased response to FVIII. Any concurrent, clinically significant liver disease (e.g. cirrhosis, portal hypertension, and acute hepatitis). Serious active bacterial or viral infection present within 30 days of screening (other than chronic hepatitis or HIV). Other known coagulation disorders in addition to haemophilia A. History of anaphylaxis or hypersensitivity associated with any FVIII product. Abnormal renal function, defined as serum creatinine >2.0 mg/dl at screening. Serum ALT or AST >5x ULN at screening.

Key inclusion criteria	Key exclusion criteria
	Serum total bilirubin >3x ULN at screening. Prohibited concomitant therapies (listed in Table 3.6 below) Treatment with an investigational product within 30 days or 5.5 half-lives prior to screening. Major surgery within 8 weeks prior to screening. Pregnant or breastfeeding females.
Arm A only	
Prophylactic treatment regimen with a marketed FVIII product or prophylactic emicizumab for ≥6 months during the previous 12 months, with appropriate washout time	–
Arm B only	
At least 12 bleeding episodes in the previous 12 months or ≥6 bleeding episodes in the previous 6 months prior to study enrolment	–
Based on Table 7 of Document B of the CS[3] [a]Previous treatment for haemophilia A was defined as any treatment with any recombinant and/or plasma derived FVIII product, or cryoprecipitate for at least 150 EDs. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BU/ml = Bethesda units per millilitre; CS = company submission; EDs = exposure days; FVIII = clotting Factor VIII; HIV = human immunodeficiency virus; ULN = upper limit of normal	

The permitted and prohibited concomitant medications in XTEND-1 are detailed in Table 3.6.

Table 3.6: Permitted and prohibited concomitant medications in XTEND-1

Permitted
Local, topical, and/or inhaled steroids
Prohibited
• Vaccination within 30 days of screening. • Acetylsalicylic acid or non-NSAID anti-platelet therapies within 2 weeks prior to screening. • NSAIDs above the maximum dose specified in the regional prescribing information within 2 weeks of screening • Systemic treatment within 12 weeks prior to screening with chemotherapy and/or other immunosuppressive drugs (except for treatment of HCV or HIV) • Systemic corticosteroid treatment given daily or on alternate days for >14 days • Emicizumab use within 20 weeks prior to screening
Based on Table 8 of the CS [3] CS = company submission; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NSAID = non-steroidal anti-inflammatory drug

The efficacy endpoints from the XTEND-1 study are presented in Table 3.7.

Table 3.7: Efficacy endpoints in XTEND-1

Primary endpoint
ABR in Arm A
Key secondary endpoint
Intra-patient comparison of ABR during the efanesoctocog alfa weekly prophylaxis treatment period versus the historical prophylaxis ABR was performed using non-inferiority testing for patients in Arm A

Other secondary endpoints
• ABR by type and location • ABR for all bleeding episodes • Intra-patient comparison of ABR in Arm B • Percentage of patients who maintain FVIII activity levels • Prophylactic dose and dosing interval • Number of injections and dose of efanesoctocog alfa to treat a bleeding episode • Assessment of response to efanesoctocog alfa treatment of bleeding episodes • AjBR • Target joint resolution • HJHS • Haem-A-QoL and Haemo-QoL • PROMIS Pain Intensity and Physical Function
Surgery endpoints
• Investigator or surgeon's assessment of patient haemostatic response to efanesoctocog alfa • Number of injections and dose to maintain haemostasis for major surgery • Total efanesoctocog alfa consumption for major surgery • Estimated blood loss for major surgery • Number and type of blood component transfusions for major surgery
Exploratory endpoints
• HAL (in patients ≥18 years of age) and paediatric HAL (pedHAL; in patients <18 years of age) questionnaires • Treatment Satisfaction Questionnaire for Medications • EQ-5D-5L • PGIC • PGIS • Treatment preference survey • Physical Activity Monitor • Ultrasound measures, if applicable • Healthcare resource utilisation
Based on Table 9 of the CS[3] ABR = annualised bleeding rate; AjBR = annualised joint bleeding rate; CS = company submission; ED-5D = European Quality of Life-5 Dimensions; FVIII = clotting factor VIII; HAL = Haemophilia Activities List; HJHS = Haemophilia Joint Health Score; PGIS = Patient Global Impression of Severity; PGIC = Patient Global Impression of Change; PROMIS = Patient-Reported Outcomes Measurement Information System

The CS made several mentions of two other studies that were linked to XTEND-1: XTEND-Kids and the Pre-study to XTEND-1.[3] Since the contribution of these studies to the clinical effectiveness and cost effectiveness evidence was not clear from the CS, the EAG asked for further information (CQs A 21 and A 22 respectively).

According to the CS (p.38 of Document B),[3] the XTEND-Kids study was included as part of the clinical effectiveness evidence but did not inform the economic evaluation. The company were asked to explain exactly how the XTEND-Kids study contributed to the submission, and to elaborate on the reason for the mismatch between the clinical effectiveness and cost effectiveness evidence in this respect (CQ A 21). The company responded by stating that, "*The XTEND-Kids study was presented on page 38 of Document B, and Appendix O, for information purposes only and the data were not used to inform the*

economic model. The Company has not completed an ITC in the paediatric population, and therefore, data from XTEND-Kids was not able to inform the economic model. Rather, it was the adult ITC that informed the economic evaluation for all ages. Haemophilia is a condition where the underlying defect (a deficiency in clotting FVIII) is the same in children and adults, and so it is felt that extrapolating data can be considered. Treatment with efanesoctocog alfa in XTEND-1 and XTEND-Kids was considered generalisable across the adult and paediatric populations. Patients across both trials had similar ABRs, a comparable PK profile (with a shorter half-life expected in younger individuals), and similar rates of zero bleeds. The safety profile of efanesoctocog alfa was also comparable between the two trial populations. Efanesoctocog alfa is a factor replacement therapy, a treatment class that has extensive historical data. This wealth of data provides a strong foundation for understanding how these treatments are likely to perform in all age groups. In addition, factor replacement therapies have a relatively predictable efficacy and safety profile, which has been extensively documented in both adults and children. Again, supporting the rationale to extrapolate data from adults to children and agreeing that the effects of the drug are sufficiently similar across all age groups."[2] Some discussion of the XTEND-Kids study is shown earlier in this section.

The pre-study to XTEND-1 is mentioned in several places in Document B of the CS.[3] As for the above, the company was asked to explain how the data from this study were used to inform clinical effectiveness and cost effectiveness estimates for the submission (CQ A 22). The company stated that, "*In terms of clinical effectiveness, the observational pre-study was used to inform the key secondary endpoint, i.e. intrapatient comparison of ABR with efanesoctocog alfa prophylaxis versus ABR with pre-study FVIII prophylaxis. This included patients enrolled into Group A following on from the observational pre-study (n=78). Switching from pre-study FVIII prophylaxis to efanesoctocog alfa prophylaxis demonstrated a significant reduction in mean ABR from 2.96 to 0.69, a reduction of 77% (rate ratio 0.23; 95% CI: 0.13, 0.42; p<0.001). The pre-study was not used to inform the cost-effectiveness estimates, and this was considered a conservative approach, given the statistically significant reduction in ABR."*[2]

EAG comment: The EAG notes that the population in XTEND-1 is narrower (PTPs aged ≥12 years with severe haemophilia A and without inhibitors) than those specified in the NICE Final Scope (people with haemophilia A)[1] and the company's DP (people with severe haemophilia A).[3] The EAG remains uncertain as to whether the clinical effectiveness results from XTEND-1 can be applied in a valid way to patients younger than 12 years, those with mild or moderate disease and those with a history or current presence of FVIII inhibitors. This has been highlighted as a key issue.

3.2.3 Statistical analysis of the included studies

Document B of the CS provided the following details relating to statistical analysis methods used for the XTEND-1 study.[3]

3.2.3.1 Sample size and power calculation

Section B.2.4.2 in Document B of the CS reported the following:[3] "*The sample size was estimated to rule out a greater-than-acceptable risk of immunogenicity. Assuming a drop-out rate of approximately 15%, a sample size of 124 patients in the prophylaxis arm was expected to provide 104 evaluable patients with at least 50 exposure days (ED). An ED is defined as a 24-hour period in which one or more efanesoctocog alfa injections are administered… Approximately 124 patients who were previously on a prophylaxis treatment regimen were estimated to enrol in Arm A, a 52-week prophylaxis arm, of which approximately 16 patients were enrolled in the sequential pharmacokinetics (PK) subgroup. In addition, approximately 26 patients who were previously on an on-demand treatment*

regimen were estimated to enrol in Arm B, received efanesoctocog alfa on-demand for 26 weeks, followed by weekly prophylaxis for 26 weeks. Thus, the overall sample size was estimated at 150 patients (i.e. 124 in Arm A and 26 in Arm B)."[3]

3.2.3.2 Statistical analysis of the primary efficacy endpoint

The company outlined the following points in Section B.2.4.3 of Document B of the CS:[3] "*The primary endpoint of mean ABR in the weekly prophylaxis treatment arm (Arm A) was analysed using an estimation approach. The mean ABR and one-sided 97.5% confidence interval was estimated using a negative-binomial regression model for the weekly prophylaxis treatment arm (Arm A). Based on currently marketed FVIII products, mean ABR during clinical trials typically ranges from two to five bleeds per year, but can be as high as six bleeding episodes per year.*[25, 32-34]"[3]

"*To demonstrate adequate control of bleeding consistent with currently marketed FVIII products, and to account for this variability, a clinically meaningful treatment effect may be claimed if the upper bound of the confidence interval of the estimated ABR is ≤6. In a Phase 3 study of recombinant factor VIII Fc fusion protein (rFVIIIFc), the mean ABR for an individualised prophylaxis arm was 2.9 and the dispersion factor was estimated at 2.3.*[25] *Based on 2,000 simulations of a negative binomial regression model with mean ABR of 2.9 and dispersion factor of 2.3, a sample size of 124 patients was estimated to provide at least 90% power for the upper bound of the one-sided 97.5% confidence interval to exclude an ABR >6, assuming a 15% drop out rate.*"[3]

3.2.3.3 Statistical analysis of the key secondary endpoints

Section B.2.4.4 of Document B of the CS[3] included the following points and further information was available from Appendix M of the CS:[35] "*For the key secondary efficacy endpoint, an intra-patient comparison of ABR during the efanesoctocog alfa weekly prophylaxis treatment period vs the historical prophylaxis ABR was performed using non-inferiority testing for patients in Arm A who had at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221.*[36] *The non-inferiority margin was estimated based on the known treatment effect between on-demand and prophylaxis treatment. A meta-analysis of Phase 3 registrational studies for recombinant FVIII products that include both on-demand and prophylaxis treatment arms estimated an average reduction of 31 bleeds per year between on-demand and prophylaxis treatment regimens (Appendix M).*[35] *The lower bound of this treatment effect was 27 bleeds per year. Using a fixed margin approach to maintain a substantial amount (85%) of the treatment effect results in a non-inferiority margin of four bleeds. For a non-inferiority test of the null hypothesis (median difference in ABR exceeds or is equal to non-inferiority margin) vs the alternative hypothesis (median difference in ABR is less than non-inferiority margin), a sample size of 63 achieves 90% power to detect non-inferiority using a one-sided paired Wilcoxon Signed Rank test at a 0.025 significance level when the actual mean of paired differences is 0 and the non-inferiority margin is four. Without prior knowledge of the standard deviation of the paired differences, a conservative estimate of 10 was assumed. In order to account for drop-out and the use of the Per Protocol Set, at least 75 patients who have completed at least 6 months of participation in observational Study 242HA201/OBS166221 will be enrolled in Arm A.*"[3]

"*If non-inferiority was achieved, then superiority was evaluated sequentially using a negative-binomial regression model. The paired ABR ratio and 95% CI was estimated using the full analysis set, and the treatment was considered superior if the upper limit of the 1-sided 97.5% CI of the intra-patient ABR difference is <1.*"[3]

An outline of statistical methods for other secondary endpoints (as listed in Table 3.7 of this report) is available from Appendix M of the CS.[35]

A consideration of multiplicity issues is presented in Section B.2.4.6 of Document B of the CS.[3]

3.2.3.4 Analysis sets

The populations for analysis are described in Document B of the CS as follows:[3]

- "***All-enrolled analysis set:*** *all patients who were enrolled in the study, regardless of whether they were dosed with efanesoctocog alfa or not. Patients were considered enrolled when the investigator had verified that they were eligible according to the eligibility criteria. Patient disposition and enrolment summaries were based on the all-enrolled analysis set*
- ***Full analysis set (FAS):*** *all patients who received ≥1 dose of efanesoctocog alfa. All analyses of demographics, baseline characteristics, and efficacy were based on the FAS, unless otherwise specified*
- ***Per protocol set (PPS):*** *a subset of the FAS, including patients who did not have important protocol deviations potentially impacting efficacy. The PPS was used for analysis of the key secondary efficacy endpoint, as well as sensitivity analysis of the primary endpoint*
- ***Safety analysis set (SAS):*** *the SAS was the same as the FAS. All analyses of safety were based on the SAS, unless otherwise specified*
- ***PK analysis set (PKAS):*** *all patients who had completed adequate blood sample collection to assess key PK parameters, as determined by the PK scientist. All analyses of PK were based on the PKAS, unless otherwise specified*
- ***Sequential PK subgroup:*** *all patients who had evaluable PK profiles for both baseline and repeat PK profiles, as determined by the PK scientist*
- ***Surgery subgroup:*** *all patients who underwent major surgery after the first dose of study drug*."

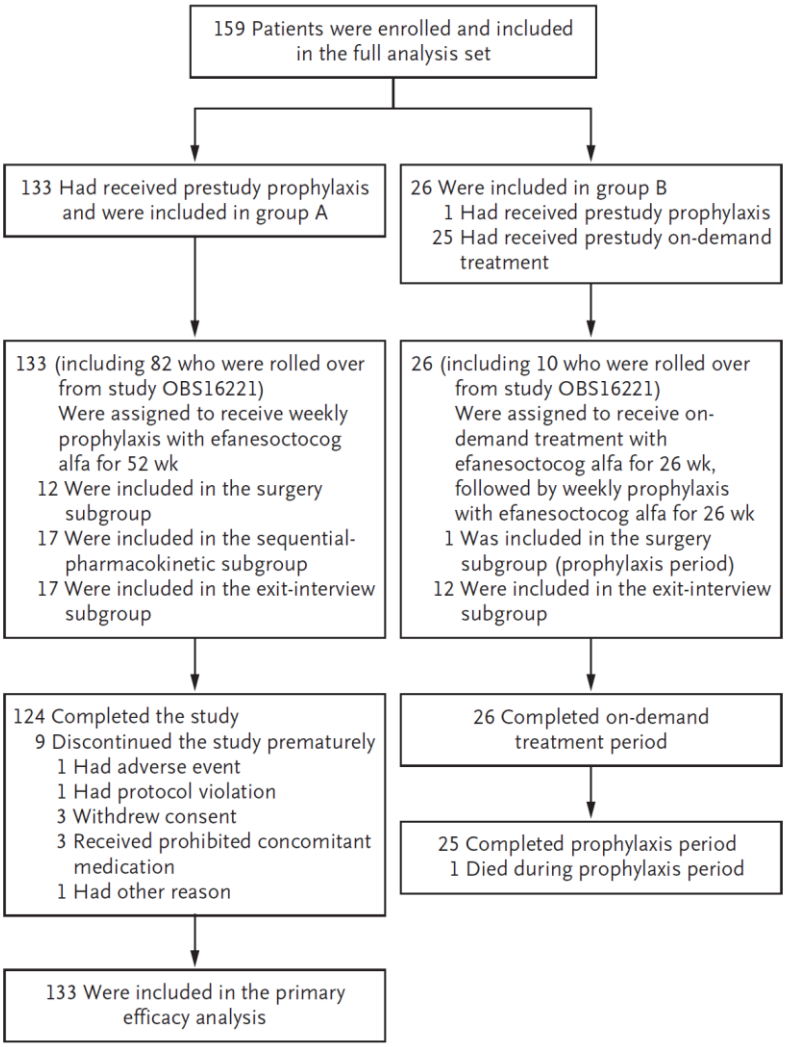
3.2.4 Patient disposition

There were 170 patients who were screening for the study, of which 11 (6.5%) were excluded during the screening process. The most reported reason for screening failure was related to the study inclusion criteria for severe haemophilia A, which was three patients (1.8%).

There was a total of 159 patients enrolled in the study, of which 133 patients in Arm A, and 26 patients in Arm B, respectively. A dose of ≥1 of efanesoctocog alfa was administered to all patients. Ten (6.3%) patients discontinued from the study, whilst 149 (93.7%) of patients completed the study. The use of prohibited concomitants medication and the withdrawal of consent were the most frequently reported reasons for discontinuation in Arm A, in three (1.9%) patients each, respectively. In Arm B one patient had been receiving pre-study prophylaxis but was incorrectly assigned to receive O-D treatment and was deemed as a major deviation away from the study protocol. There was also a single death in the Arm B prophylaxis period but assessed to not being related to the study drug.

Figure 3.2 presents a flow of the patients in XTEND-1, whilst a summary of the analysis populations is provided in Table 3.8.

Figure 3.2: Flow of patients in XTEND-1



Based on Figure 5 of Document B of the CS[3] which in turn cites von Drygalski et al, (2023)[37]
CS = company submission

Table 3.8: Analysis populations in XTEND-1

Analysis population	Arm A N=133	Arm B		Overall N=159
		On-demand N=26	Prophylaxis N=26	
FAS	133 (100.0)	26 (100.0)	26 (100.0)	159 (100.0)
PPS	129 (97.0)	25 (96.2)	25 (96.2)	154 (96.9)
PKAS	133 (100.0)	26 (100.0)	26 (100.0)	159 (100.0)
Sequential PK subgroup	17 (12.8)	0	0	17 (10.7)
Surgery subgroup†	10 (7.5)	0	1 (3.8)	13 (8.2)
Safety	133 (100.0)	26 (100.0)	26 (100.0)	159 (100.0)

Based on Table 10 of document B of the CS[3] which in turn cites Table 6 of the CSR.[30]
Note: Percentages are based on the number of patients in the All-Enrolled Analysis Set; patients are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each patient is counted only once in the overall column.

Analysis population	Arm A N=133	Arm B		Overall N=159
		On-demand N=26	Prophylaxis N=26	
†Patients who have undergone major surgery after the first dose of study drug. Surgery reported after the last injection of efanesoctocog alfa is not counted in the specific treatment arm and regimen but counted in the overall column. CS = company submission; CSR = clinical study report; FAS = full analysis set; PK = pharmacokinetics; PKAS = pharmacokinetics analysis set; PPS = per protocol set				

3.2.5 Demographics and baseline characteristics

Details in the CS indicated that a total of 159 patients (158 males and 1 female) were included in the study.[3]. A summary of demographic data and baseline characteristics are presented in Table 3.9.

Table 3.9: Summary of demographic and baseline characteristics, FAS

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Demographics					
Age (years)[†]					
Mean (SD)	33.9 (15.3)	42.8 (11.7)	42.8 (11.7)	44.3 (12.8)	35.4 (15.1)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12–17 years	25 (18.8)	0	0	1 (7.7)	25 (15.7)
18–64 years	104 (78.2)	25 (96.2)	25 (96.2)	12 (92.3)	129 (81.1)
≥65 years	4 (3.0)	1 (3.8)	1 (3.8)	0	5 (3.1)
Sex, n (%)					
Male	132 (99.2)	26 (100.0)	26 (100.0)	13 (100)	158 (99.4)
Female	1 (0.8)	0	0	0	1 (0.6)
Race, n (%)					
Asian	29 (21.8)	0	0	3 (23.1)	29 (18.2)
Black or African American	3 (2.3)	0	0	3 (23.1)	3 (1.9)
White	71 (53.4)	26 (100.0)	26 (100.0)	7 (53.8)	97 (61.0)
NR due to confidentiality regulations	26 (19.5)	0	0	3 (23.1)	26 (16.4)
Other	4 (3.0)	0	0	0	4 (2.5)
Region, n (%)[‡]					
Asia Pacific	33 (24.8)	0	0	4 (30.8)	33 (20.8)
Europe	67 (50.4)	14 (53.8)	14 (53.8)	5 (38.5)	81 (50.9)
North America	26 (19.5)	0	0	3 (23.1)	26 (16.4)
South America	7 (5.3)	12 (46.2)	12 (46.2)	1 (7.7)	19 (11.9)

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Weight (kg)					
Mean (SD)	78.00 (19.29)	80.80 (18.04)	80.80 (18.04)	77.31 (9.66)	78.46 (19.06)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline characteristics					
Age at diagnosis of severe haemophilia (years)					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Family inhibitor history, n (%)					
Yes	5 (3.8)	0	0	0	5 (3.1)
No	100 (75.2)	25 (96.2)	25 (96.2)	12 (92.3)	125 (78.6)
Unknown	28 (21.1)	1 (3.8)	1 (3.8)	1 (7.7)	29 (18.2)
Lowest documented historical FVIII level (%), n (%)					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of haemophilia treatment products administered throughout life[a], n (%)					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII plasma-derived	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII recombinant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII cryoprecipitate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non FVIII product	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antifibrinolytic agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Desmopressin/DDAVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fitusiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEIBA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
rFVIIa (Novoseven)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at start of first prophylaxis regimen (years)					
Number	126	25	25	11	151
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	1.0	3.0	3.0	1.0	1.0
Min, Max	0 ; 35	0 ; 62	0 ; 62	0 ; 12	0 ; 62
<6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6–<10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10–<18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior exposure days to FVIII, n (%)					
<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50–<100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100–<150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Number of bleeds in the past 12 months					
Number	122	23	23	12	145
Mean (SD)	3.2 (5.4)	35.7 (22.2)	35.7 (22.2)	9.1 (21.8)	8.3 (15.5)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of joint bleeds in the past 12 months					
Number	121	21	21	12	142
Mean (SD)	2.3 (4.5)	27.4 (18.6)	27.4 (18.6)	7.9 (19.7)	6.0 (12.1)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of spontaneous joint bleeds in the past 12 months					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of traumatic joint bleeds in the past 12 months					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-study regimen					
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B		Surgery subgroup N=13	Overall N=159
		On-demand N=26	Prophylaxis N=26		
Time on pre-study regimen					
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6–12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 11 of document B of the CS[3] which in turn cites Tables 16.2.4.1, 16.2.4.3, 16.2.4.4 and 16.2.4.5 of the CSR.[38]

Note: Percentages are based on the number of patients with non-missing data in the FAS; patients are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each patient is counted only once in the overall column.

†Age = year of informed consent – year of birth

‡Asia Pacific includes Australia, Japan, Korea, and Taiwan. Europe includes Belgium, Bulgaria, Germany, Greece, Hungary, Italy, The NL, Spain, and the UK. North America includes Canada, Mexico, and the United States. South America includes Argentina and Brazil

CS = company submission; CSR =clinical study report; FAS = full analysis set; FVIII = clotting Factor VIII, NR = not reported; rFVIII = recombinant factor VIII; SD = standard deviation; UK = United Kingdom

EAG comment: Baseline characteristics relating to demographics, anthropometry, disease characteristics and prior treatments are shown in Table 3.9 of this report. However, this includes combined data for all patients across international centres. Therefore, the EAG requested the company provide separate baseline data for the UK subgroup of patients in XTEND-1 (CQ A 23). The company responded that they had been unable to provide the requested data in time for the clarification response and added that "*…the UK-based patients in XTEND-1 are considered broadly comparable with the population of patients with severe haemophilia A within the UK. Demographically, 51% of patients in XTEND-1 were in Europe (81/159) and 16% were in North America (26/159).*[30, 37] *Given the similarities between these populations and that of the UK, the trial populations in XTEND-1 can be considered broadly representative of the severe haemophilia A population in the UK, and as such any subgroup analysis is expected to show very similar results*."[2] Since the EAG has not so far been able to review the data for the subgroup of UK patients, there is persisting uncertainty as to the match between this group and the target population in the UK. This has been highlighted as a key issue. The EAG would also have appreciated seeing a tabulation showing a comparison between the population in XTEND-1 and the UK target population.

3.2.6 Risk of bias assessment

The CS did not provide a risk of bias assessment for the XTEND-1 study[3] and declined to provide this when requested via the clarification process (CQs A 16a and 16b).[2] Given this omission, the EAG conducted its own assessment of XTEND-1 using the JBI critical appraisal checklist for quasi-experimental studies.[29] The results of the EAG's risk of bias assessment are provided in Table 3.10 below. The EAG considers that XTEND-1 is at risk of bias because of the use of non-concurrent, intra-patient comparisons potentially resulting in the observed treatment effect being confounded because of change in other aspects of care over time. In addition, it was not clear whether outcomes had been verified by an Independent Review Committee (IRC).

Table 3.10: EAG assessment of XTEND-1 using the JBI quasi-experimental studies checklist

Critical appraisal item	Judgement (rationale)
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e., there is no confusion about which variable comes first)?	Yes: it is clear that the outcomes were assessed after the start of the treatment period
2. Were the participants included in any comparisons similar?	Yes: both arms of the study included intra-patient comparisons
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Unclear: both intra-patient comparisons involved non-concurrent controls and it is possible that aspects of care other than the study interventions could have changed over time
4. Was there a control group?	Yes: but this involved patients acting as their own (non-concurrent) controls
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Yes: for both study arms, the number of bleeding episodes during the last 12 months was recorded at baseline and data on bleeding episodes were collected at 26- and 52-weeks arms during the study intervention period. It is possible that other assessments were performed during the study period however, the EAG was not provided with

Critical appraisal item	Judgement (rationale)
	access to the fully detailed CSR[30] and so could not determine this.
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	Yes: the efficacy population consisted of all included participants
7. Were the outcomes of participants included in any comparisons measured in the same way?	Yes
8. Were outcomes measured in a reliable way?	Unclear: response to treatment was evaluated by means of the Physician's Global Assessment. Response to treatment of bleeding episodes was measured with the use of the 4-point International Society on Thrombosis and Haemostasis scale, and the haemostatic response to surgery was assessed with the use of the 4-point surgical procedures scale. Joint health was assessed with the use of the HJHS. It was not reported whether outcomes were determined by IRC or by the investigator only
9. Was appropriate statistical analysis used?	Yes: the intra-patient comparison of the ABR rate during prophylaxis in group A was assessed with the use of a negative-binomial regression model. The adjusted mean change from baseline to week 52 in physical health, pain, and joint health were estimated by means of mixed effects models with repeated measures. Safety outcomes were analysed with the use of descriptive statistics
The critical appraisal is based on the Von Drygalski et al. (2023) paper.[37] ABR = annualised bleeding rate; CSR = clinical study report; EAG = External Assessment Group; HJHS = Haemophilia Joint Health Score; IRC = Independent Review Committee; JBI = Joanna Briggs Institute	

3.2.7 Efficacy results of the included studies

The following Sections detail the results for each of the outcomes defined in the DP.

3.2.7.1 Annualised bleeding rate (ABR)

3.2.7.1.1 Primary efficacy endpoint – ABR (FAS)

Section B.2.6.1.3 of the CS[3] included the following statements: "*In Arm A, [redacted] patients had ≤5 bleeding episodes per year, with 86 (64.7%) patients having no bleeding episodes during the study*." Table 3.11 presents ABR data from the XTEND-1 study.

Table 3.111: Primary efficacy endpoint – ABR (FAS)

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Total number of treated bleeding episodes	[redacted]	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Duration of efficacy period (weeks)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
ABR			
Mean (SD)	0.71 [redacted]	21.42 (7.41)	0.69 (1.35)
Median	0.00	21.13	0.00
Number of bleeds			
0	86 (64.7)	0	20 (76.9)
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Mean ABR, model based† (95% CI)	0.71 (0.52, 0.97)	–	–

Based on Table 12 of the CS[3] which in turn cites Table 13 of the CSR.[30]
Note: The efficacy period reflects the sum of all intervals of time during which patients were treated with efanesoctocog alfa according to the study arms and treatment regimens, excluding periods of pharmacokinetic evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
†Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; SD = standard deviation

3.2.7.1.2 Sensitivity analysis of the mean ABR

Section B.2.6.1.3.1 of the CS[3] suggests that the results of the sensitivity analysis (per protocol set [PPS]) were consistent with the results of the primary analysis in the FAS (Table 3.11) and states that *"The mean ABR estimated from the negative binomial model was* [redacted] *in Arm A*."[3] This is highlighted in Table 3.12.

Table 3.12: Summary of ABRs, sensitivity analysis - PPS

	Arm A N=129
Number of patients with an efficacy period	[redacted]
Total number of treated bleeding episodes	[redacted]
Total participant-years followed	[redacted]
Duration of efficacy period (weeks)	
Mean (SD)	[redacted]
Median	[redacted]
ABR	
Mean (SD)	[redacted]

	Arm A N=129
Median	[redacted]
Number of bleeds	
0	[redacted]
>0–5	[redacted]
>5–10	[redacted]
>10–20	[redacted]
>20	[redacted]
Mean ABR, model based[†] (95% CI)	[redacted]

Based on Table 13 of document B of the CS[3] which in turn cites Table 16.2.6.1.3 of the CSR.[39]
Note: Five patients (four in Arm A and one in Arm B) with important protocol deviations were not included in the PPS.
[†]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; CSR = clinical study report; PPS = per protocol set; SD = standard deviation

Furthermore, Section B.2.6.1.3.1 of the CS [3] states that "*Results of the sensitivity analysis including patients with an efficacy period of at least 26 weeks ([redacted]) were also consistent with the results of the primary analysis* (Table 3.11). *The mean ABR estimated from the negative binomial model was [redacted] in Arm A* (Table 3.13)."

Table 3.13: Summary of ABR in patients with an efficacy period ≥26 weeks, sensitivity analysis – FAS

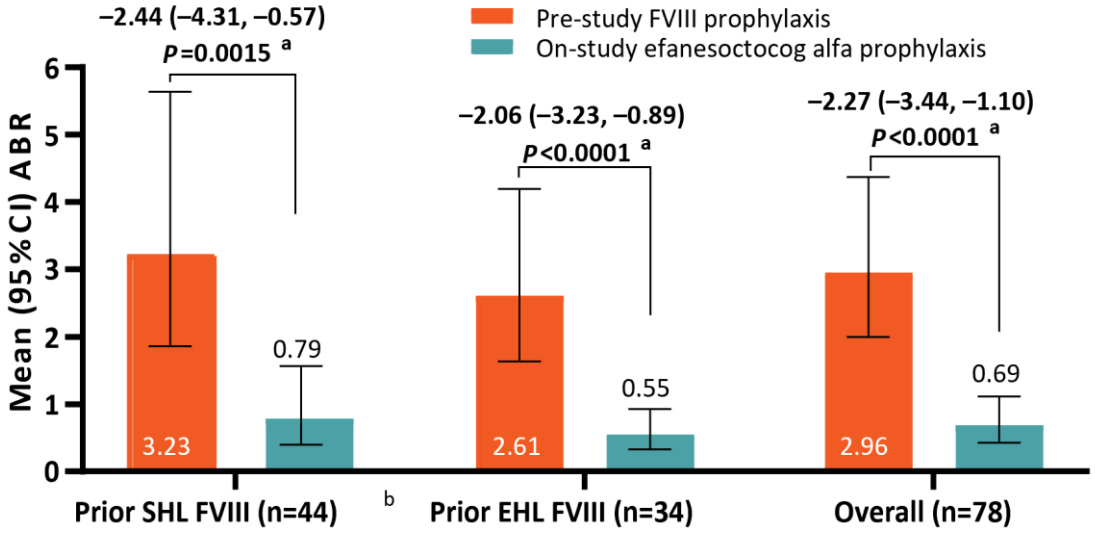
	Arm A N=128
Number of patients with an efficacy period	[redacted]
Total number of treated bleeding episodes	[redacted]
Total participant-years followed	[redacted]
Duration of efficacy period (weeks)	
Mean (SD)	[redacted]
Median	[redacted]
ABR	
Mean (SD)	[redacted]
Median	[redacted]
Number of bleeds	
0	[redacted]
>0–5	[redacted]
>5–10	[redacted]
>10–20	[redacted]
>20	[redacted]

	Arm A N=128
Mean ABR, model based† (95% CI)	[redacted]
Based on Table 14 of the CS[3] which in turn cites Table 16.2.6.1.3 of the CSR.[39] †Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable. ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; SD = standard deviation	

3.2.7.1.3 Intra-patient comparison of ABR between efanesoctocog alfa prophylaxis and pre-study prophylaxis – Arm A

Section B.2.6.1.3.4 of the CS[3] states that "*the non-inferiority of prophylaxis treatment with efanesoctocog alfa over historical prophylaxis on the key efficacy endpoint was evaluated as part of the prespecified hierarchical step-down testing procedure*." The company then stated "*non-inferiority of prophylaxis treatment with efanesoctocog alfa over historical prophylaxis for mean ABR was demonstrated in the PPS (n=77), as the upper bound of the one-sided 97.5% CI of the difference between efanesoctocog alfa prophylaxis and historical prophylaxis (estimated mean difference:* [redacted] *was below the prespecified non-inferiority margin of four bleeds per year*." Figure 3.3 and Table 3.14 summarise the results of the superiority testing of efanesoctocog alfa prophylaxis treatment over historical FVIII prophylaxis on the key efficacy endpoint in the prespecified hierarchical step-down testing procedure.

Figure 3.3: Intra-patient comparison of ABR between efanesoctocog alfa prophylaxis and pre-study prophylaxis, Arm A, FAS



Median (IQR) ABR	Pre-study FVIII prophylaxis	On-study efanesoctocog alfa prophylaxis
Prior SHL FVIII (n=44)[b]	1.05 (0.00–3.42)	0.00 (0.00–1.04)
Prior EHL FVIII (n=34)	1.10 (0.00–4.50)	0.00 (0.00–1.02)
Overall (n=78)	1.06 (0.00–3.74)	0.00 (0.00–1.04)

Based on Figure 6 of the CS[3] which in turn cites Susen et al. 2023[40]

[a]Mean difference (95% CI), P-values and mean (95% CI) were calculated using negative binomial regression model with treatment (on-study prophylaxis versus pre-study prophylaxis) as a covariate.[3, 40]

[b]Pre-study SHL includes SHL rFVIII and plasma-derived FVIII.[3, 40]

ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; EHL = extended half-life; FAS = full analysis set; FVIII = clotting Factor VIII; IQR = interquartile range; SHL = standard half-life

Table 3.14: Intra-patient comparison of ABR between efanesoctocog alfa prophylaxis and pre-study prophylaxis, Arm A, FAS

	Arm A N=133	
	Historical prophylaxis (OBS16221) N=78	Efanesoctocog alfa N=78
Number of patients with an observation or efficacy period	78	78
Total number of treated bleeding episodes	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]
Duration of observation or efficacy period (weeks)		
Mean (SD)	[redacted]	[redacted]

	Arm A N=133	
	Historical prophylaxis (OBS16221) N=78	**Efanesoctocog alfa N=78**
Median	[redacted]	[redacted]
ABR		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
>0–5	[redacted]	[redacted]
>5–10	[redacted]	[redacted]
>10–20	[redacted]	[redacted]
>20	[redacted]	[redacted]
Negative binomial regression model†		
Mean ABR (95% CI)	2.96 (2.00, 4.37)	0.69 (0.43, 1.11)
Mean difference (95% CI)	–2.27 (–3.44, –1.10)	
Rate ratio (95% CI)	0.23 (0.13, 0.42)	
p-value (superiority)‡	p<0.0001	
Wilcoxon Signed Rank test		
Median ABR (Q1, Q3)	1.06 (0.00, 3.74)	0.00 (0.00, 1.04)
Median of paired difference (95% CI)¶	[redacted]	
p-value (non-inferiority)§	[redacted]	

Based on Table 15 of document B of the CS[3] which in turn cites Table 15 of the CSR.[30]
Note: The analysis is based on the FAS and including patients in Arm A who have at least 6 months of efficacy period in the XTEND-1 study and at least 6 months of observation period on prophylaxis collected in Study OBS16221
†Estimated using a negative binomial regression model with treatment (efanesoctocog alfa prophylaxis versus historical prophylaxis) as covariate
‡P-value relates to the null hypothesis: rate ratio (efanesoctocog alfa prophylaxis/historical prophylaxis) = 1
¶ Estimated using the Hodges-Lehmann method
§P-value relates to the null hypothesis: median of paired difference (efanesoctocog alfa prophylaxis - historical prophylaxis) = 4 based on Wilcoxon Signed Rank test
ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; SD = standard deviation

3.2.7.1.4 ABR by type of bleed

Section B.2.6.1.3.5 of the CS[3] states that "*The rates of spontaneous and traumatic bleeds were low in Arm A, with a mean annualised spontaneous bleeding rate (AsBR) of 0.29 (SD: 0.73). In Arm B, the mean AsBR decreased after patients switched to prophylaxis treatment (0.45 [SD: 1.13]) compared with on-demand treatment (15.87 [SD: 9.28]). With on-demand treatment,* [redacted] *had an AsBR >5 for spontaneous bleeds, and* [redacted] *patients had an AsBR >20. After switching to prophylaxis treatment, most patients (n=22; 84.6%) had no spontaneous bleeds and no patients had an AsBR >5. For traumatic bleeds, the mean annualised traumatic bleeding rate (AtBR) was also lower with prophylaxis treatment than with on-demand*

treatment. Of note, mean ABR for spontaneous and traumatic bleeds during efanesoctocog alfa treatment in Arm B were similar to those observed in Arm A.". Table 3.15 summarises this information.

Table 3.15: Summary of ABR by type of bleed, FAS

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Total number of spontaneous bleeding episodes	[redacted]	[redacted]	[redacted]
Total number of traumatic bleeding episodes	[redacted]	[redacted]	[redacted]
Total number of unknown bleeding episodes	[redacted]	[redacted]	[redacted]
Spontaneous bleeding rate, patient-level			
Mean (SD)	0.29 (0.73)	15.87 (9.28)	0.45 (1.13)
Median	0.00	16.69	0.00
Number of bleeds			
0	107 (80.5)	1 (3.8)	22 (84.6)
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Spontaneous bleeding rate, population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Traumatic bleeding rate, patient-level			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Traumatic bleeding rate, population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Unknown type of bleeding rate, patient-level			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Unknown type of bleeding rate, population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]

Based on Table 16, CS[3]
[†]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; FAS = full analysis set; SD = standard deviation

3.2.7.1.5 ABR by location of bleed

Section B.2.6.1.3.5 of the CS[3] states that, "*In both Arm A and Arm B, joints were the most common location for bleeds. In Arm A, the mean annualised joint bleeding rate (AJBR) was 0.52 (SD: 1.09). In Arm B, the mean AJBR was lower after switching to prophylaxis treatment (0.61 [SD:1.33]) compared with on-demand treatment (17.45 [SD: 7.31]). The mean AJBR estimated from the negative binomial model was* [redacted]*. Of the 133 patients who had an efficacy period in Arm A,* [redacted] *had an AJBR of 5 or fewer episodes per year, with 96 (72.2%) patients having no joint bleeds during the study. In the on-demand group of Arm B, all patients had ≥1 bleed over the 12-month period; in contrast, 21 (80.8%) patients had no bleeds in the prophylaxis group of Arm B*". Table 3.16 summarises this information.

Table 3.16: Summary of ABR by location of bleed, FAS

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Bleeding episodes at joint			
Total number of treated bleeding episodes at joint	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	0.52 (1.09)	17.45 (7.31)	0.61 (1.33)
Median	0.00	18.42	0.00
Number of bleeds			
0	96 (72.2)	0	21 (80.8)
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Bleeding episodes at muscle			
Total number of treated bleeding episodes at muscle	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Bleeding episodes, internal			
Total number of treated bleeding episodes, internal	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Population-level, model based[†] Mean (95% CI)	[redacted]	[redacted]	[redacted]
Bleeding episodes at skin/mucosa			
Total number of treated bleeding episodes at skin/mucosa	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]

	Arm A N=133	Arm B	
		On-demand N=26	Prophylaxis N=26
Population-level, model based† Mean (95% CI)	[redacted]	[redacted]	[redacted]
Bleeding episodes at an unknown location			
Total number of treated bleeding episodes at an unknown location	[redacted]	[redacted]	[redacted]
Mean (SD), patient-level	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
Population-level, model based† Mean (95% CI)	[redacted]	[redacted]	[redacted]

Based on Table 17, CS[3]
†Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; FAS = full analysis set; NC = not calculable; SD = standard deviation

3.2.7.1.6 ABR for all bleeding episodes

Section B.2.6.1.3.5 of the CS [3] states that, "*In Arm A, the estimated mean ABR based on all bleeding episodes, i.e. treated and untreated, was low (1.11 [95% CI: 0.83, 1.48]), consistent with results for the primary endpoint using only treated bleeds"* (Table 3.17). *In Arm B, the estimated mean ABR based on all bleeding episodes was 22.21 (95% CI: 19.41, 25.42) with on-demand treatment and 0.88 (95% CI: 0.42, 1.84) when patients switched to prophylaxis treatment. These results are also consistent with the estimated ABR based on treated bleeds*". Table 3.17 summarises this information.

Table 3.17: Summary of ABR for all bleeding episodes, FAS

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Number of patients with an efficacy period	[redacted]	[redacted]	[redacted]
Total number of all bleeding episodes	[redacted]	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]	[redacted]
Duration of efficacy period (weeks)			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
ABR			
Number	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]
Number of bleeds			
0	[redacted]	[redacted]	[redacted]
>0–5	[redacted]	[redacted]	[redacted]
>5–10	[redacted]	[redacted]	[redacted]
>10–20	[redacted]	[redacted]	[redacted]
>20	[redacted]	[redacted]	[redacted]
ABR, model based†			
Mean (95% CI)	1.11 (0.83, 1.48)	22.21 (19.41, 25.42)	0.88 (0.42, 1.84)

Based on Table 18, CS[3]
Note: Summaries are based on all bleeds (treated and untreated).
†Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.
ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; FAS = full analysis set; SD = standard deviation

3.2.7.1.7 Intra-patient comparison of ABR in Arm B

Section B.2.6.1.3.5 of the CS[3] states that, "*For 26 patients in Arm B, the efficacy of efanesoctocog alfa prophylaxis was compared with on-demand efanesoctocog alfa treatment (measured by ABR). The total number of participant-years followed was* [redacted] *with on-demand treatment and* [redacted] *with prophylaxis treatment (Table 3.18 in EAG report). The bleeding rate ratio for prophylaxis vs on-demand treatment was* [redacted]*, corresponding to a clinically important reduction of* [redacted] *in ABR with prophylaxis treatment. The distribution of the ABR showed that, with on-demand treatment, the majority of patients (*[redacted]*) had an ABR >10, whereas after switching to prophylactic treatment, the majority of patients (*[redacted]*) had no bleeds. Of note, mean ABR during prophylaxis treatment in Arm B approached the ABR observed in Arm A, and patients assigned to the prophylaxis group of Arm B had a median ABR of* [redacted]*, with* [redacted] *of patients having ≤5 bleed episodes per year. In total,* [redacted] *patients had an ABR >20 with on-demand treatment, with ABR ranging up to* [redacted]*. Bleeds in these patients were predominantly spontaneous, except in* [redacted] *patients, who had mostly traumatic bleeds located in the joints*". Table 3.18 summarises this information.

Table 3.18: Intra-patient comparison of ABR between efanesoctocog alfa prophylaxis and pre-study prophylaxis, Arm B, FAS

	Arm B	
	On-demand N=26	**Prophylaxis N=26**
Number of patients with an observation or efficacy period	[redacted]	[redacted]
Total number of treated bleeding episodes	[redacted]	[redacted]
Total participant-years followed	[redacted]	[redacted]
Duration of observation or efficacy period (weeks)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
ABR		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Number of bleeds		
0	[redacted]	[redacted]
>0–5	[redacted]	[redacted]
>5–10	[redacted]	[redacted]
>10–20	[redacted]	[redacted]
>20	[redacted]	[redacted]
Negative binomial regression model†		
Mean ABR (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
p-value (superiority)‡	[redacted]	

Based on Table 19 of Document B of the CS[3] which in turn cites Table 18 of the CSR.[30]
Note: The analysis is based on the FAS and including patients in Arm A who have at least 6 months of efficacy period in the XTEND-1 study and at least 6 months of observation period on prophylaxis collected in Study OBS16221.
†Estimated using a negative binomial regression model with treatment (efanesoctocog alfa prophylaxis versus historical prophylaxis) as covariate
‡P-value relates to the null hypothesis: rate ratio (efanesoctocog alfa prophylaxis/historical prophylaxis) = 1
ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; SD = standard deviation

3.2.7.2 Change in FVIII levels

No results were reported for this outcome, which was included in the NICE scope and agreed to by the company in the DP.

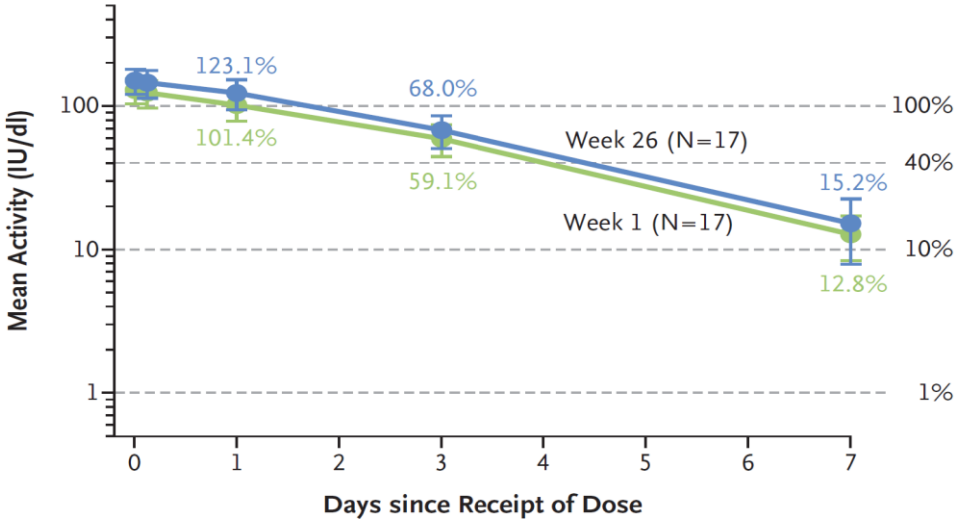
3.2.7.3 Need for further treatment with FVIII injections

No results were reported for this outcome, which was included in the NICE scope and agreed to by the company in the DP.

3.2.7.4 Durability of response to treatment

Section B.2.6.1.3.5 of the CS[3] states that, "*Factor VIII activity was well maintained over time, with levels remaining comparable at Day 7 measurements during Week 1 and Week 26. The geometric mean half-life of efanesoctocog alfa was 47.0 hours (95% CI: 42.3, 52.2), the steady state clearance 0.439 mL per hour/kg (95% CI: 0.390, 0.493), the maximum FVIII activity 151 IU/dL (95% CI: 137, 167), and the area under the activity–time curve from hour 0 to infinity 11,500 hours × IU/dL (95% CI: 10,200, 13,000). There was minimal accumulation of once-weekly efanesoctocog alfa*." This is summarised in Figure 3.4

Figure 3.4: FVIII activity over time and pharmacokinetic variables, PKAS



Pharmacokinetic Variables	Sequential-Pharmacokinetic Subgroup (N=17) *geometric mean (95% CI)*
Half-life — hr	47.0 (42.3–52.2)
Maximum activity concentration — IU/dl	151 (137–167)
AUC_{0-tau} — hr×IU/dl	11,500 (10,200–13,000)
Clearance at steady state — ml/hr/kg	0.439 (0.390–0.493)
Incremental recovery — IU/dl per IU/kg	3.00 (2.71–3.31)

Based on Figure 7 of Document B of the CS.[3].

Note: The upper part of the figure shows plasma FVIII activity levels measured by means of the activated partial-thromboplastin time–based one-stage clotting assay among 17 patients who underwent sequential blood sampling for pharmacokinetic assessment (sequential-pharmacokinetic subgroup). Error bars indicate the standard deviation of each value. The lower part of the figure shows calculated pharmacokinetic variables for baseline-corrected FVIII activity at approximately week 26 (including pharmacokinetic assessments starting at days 183, 218, and 246). Values are for the full 14-day sampling period. AUC0–tau denotes area under the activity–time curve over the administration interval.

AUC = area under curve; CI = confidence interval; CS = company submission; PKAS = pharmacokinetics analysis set

Section B.2.6.1.3.5 of the CS[3] also states that, "*In patients with evaluable FVIII activity levels 7 days after dosing, maintained FVIII activity levels of >5%, >10%, >15%, and >20% were observed in* [redacted] *respectively, with efanesoctocog alfa prophylaxis in Arm A*". This is summarised in Table 3.19.

Table 3.19: Summary of percentage of patients who achieve trough FVIII activity levels >1%, >5%, >10%, >15%, and >20% 7 days after dosing, PKAS

	Arm A N=133 Pre-dose (trough)
Number of patients with ≥1 non-missing post-baseline result	[redacted]
Number of patients with all trough samples that are within 168±5 hours from the previous dose	[redacted]
Achieving trough FVIII activity levels[†]	
>1%	[redacted]
>5%	[redacted]
>10%	[redacted]
>15%	[redacted]
>20%	[redacted]

Based on Table 20 of Document B of the CS[3] which in turn cites Table 19 of the CSR.[30]
[†]Achieving trough FVIII activity levels above x% are based on the average trough samples (i.e. nominal 168-hour time point) from each scheduled visit (Week 4, Week 13, Week 26, Week 39, Week 52/EOS/ET) using the aPTT-based one-stage clotting assay. Patients with trough samples that are outside 168±5 hours from the previous dose will be excluded from this analysis
aPTT = activated partial thromboplastin time; CS = company submission; CSR = clinical study report; EOS = end of study; ET = early termination; FVIII = clotting factor VIII; PKAS = pharmacokinetics analysis set

3.2.7.5 Haemophilia Joint Health Score

Section B.2.6.1.3.5 of the CS[3] states that, "*Six joints (left ankle, right ankle, left elbow, right elbow, left knee, right knee) were scored according to the following criteria: swelling, duration of swelling, muscle atrophy, crepitus, flexion loss, extension loss, instability, joint pain, and strength. Gait was scored based on walking and climbing stairs. The total score was the sum of scores from all six joints plus the gait score (range 0–124, highest score being the most severe disease). In Arm A, the change from baseline in HJHS was analysed as part of the hierarchical testing procedure using mixed-effect model with repeated measures (MMRM). In Arm A, patients who were on a stable pre-study prophylaxis treatment presented with a baseline mean (SD) HJHS total score of 18.1 (18.4). The estimated mean change in HJHS Total score from baseline to Week 52 was –1.54 (95% CI: –2.70, –0.37; p=0.0101) demonstrating a statistically significant improvement in functional measure of joint health. In Arm B, the mean (SD) HJHS Total score at baseline was 26.3 (13.2). The mean (SD) change from baseline to Week 52 in HJHS total score was* [redacted]*, indicating an improvement in joint health*". This is summarised in Table 3.20.

Table 3.20: Mean change in HJHS total score from baseline to Week 52, MMRM, FAS

	Arm A		Arm B	
	Prophylaxis (N=133)		On-demand->Prophylaxis (N=26)	
	Actual result	CFB	Actual result	CFB
Total Score				
Baseline				
Number	116	–	25	–
Mean (SD)	18.1 (18.4)	–	26.3 (13.2)	–
Median	[redacted]	–	[redacted]	–
Week 26				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)[†]		–1.54 (0.59)		
95% CI[†]	–	(–2.70, –0.37)	–	–
p-value	–	0.0101	–	–

Based on Table 28, CS.[3]
Note: higher HJHS scores denote poorer joint health
[†]The LS mean (SE) and 95% CI were estimated by mixed-effect model with repeated measures, with visit as fixed effect, and baseline HJHS total score as a covariate
CFB = change from baseline; CI = confidence interval; CS = company submission; FAS = full analysis set; HJHS = Haemophilia Joint Health Score; LS = least squares; MMRM = mixed-effect model of repeated measures; SD = standard deviation; SE = standard error

3.2.7.6 Complications of the disease

No results were reported for this outcome, which was included in the NICE scope and agreed to by the company in the DP.

3.2.7.7 Health-related quality of life

Outcomes were reported for the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) Physical Health score and the European Quality of Life-5 dimensions (EQ-5D). Results are summarised in the Sections below.

3.2.7.7.1 Haem-A-QoL Physical Health score

Section B.2.6.1.3.5 of the CS[3] states that, "*Quality of life data were collected in adult patients aged 17 years or older via the Haem-A-QoL questionnaire and in adolescent patients aged 12 to 16 years via the Haemo-QoL questionnaires (Appendix M). Lower scores represent better HRQoL; therefore, a negative change from baseline represents improvement during the course of the study. In Arm A, for patients aged 17 years and older, the mean (SD) Physical Health score was 37.02 (23.83) at baseline.*

The least squares mean change from baseline to Week 52 in Haem-A-QoL Physical Health score (n=98) was –6.74 (95% CI: –10.13, –3.36; p=0.0001) demonstrating a statistically significant improvement in physical health, as perceived by patients aged 17 years or above. Patients in Arm B also experienced improvement, with a mean change from baseline of [redacted]". The overall mean change from baseline at weeks 26 and 52 for patients aged at least 17 years is summarised in Table 3.21 whereas data for patients aged 13 to 16 years (including details per more specific subscales) is presented in Table 3.22.

Table 3.21: Mean change in Haem-A-QoL physical health subscale scores from baseline to Week 52 in patients ≥17 years old, MMRM, FAS

Domain	Arm A		Arm B		Overall (N=136)	
	Prophylaxis (N=110)		On-demand->Prophylaxis (N=26)			
Visit	**Actual result**	**Change from baseline**	**Actual result**	**Change from baseline**	**Actual result**	**Change from baseline**
Baseline						
Number	104	–	[redacted]	–	[redacted]	–
Mean (SD)	37.02 (23.83)	–	[redacted]	–	[redacted]	–
Median	[redacted]	–	[redacted]	–	[redacted]	–
Week 26						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52						
Number	104	98	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	29.66 (23.40)	–6.79 (18.59)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)†		–6.74 (1.71)				
95% CI†	–	(–10.13, –3.36)	–	–	–	–
p-value	–	0.0001	–	–	–	–

Based on Table 29 of Document B of the CS[3] which in turn cites Table 16.2.6.3.1 of the CSR.[39]
Note: The physical health scores are presented as the Transformed Scale Score ranging from 0–100, with lower scores indicating a better QoL. A score can be calculated when at least 50% of questions are answered (non-missing and not N/A). Assessments during major surgical/rehabilitation periods are excluded.
†The LS mean (SE) and 95% CI are estimated by MMRM, with visit as fixed effect, and baseline Haem-A-QoL physical health score as a covariate.
CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; Haem-A=QoL = Haemophilia Quality of Life Questionnaire for Adults; LS = least squares; MMRM = mixed-effect model of repeated measures; N/A = not available; QoL = quality of life; SD = standard deviation; SE = standard error

Table 3.22: Summary of Haemo-QoL total score and subscale scores and changes from baseline by visit (13–16 years old), FAS

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Total Score		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Physical Health		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Feeling		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
View of Yourself		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Family		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Friends		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1 ; Q3	[redacted]	[redacted]
Min ; Max	[redacted]	[redacted]
Support You Felt You Were Receiving		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Other People		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–

Domain	Arm A Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Sports and School		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Dealing with Haemophilia		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Treatment		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Future		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Romantic Relationships		
Baseline		
Number	[redacted]	–
Mean (SD)	[redacted]	–
Median	[redacted]	–
Q1; Q3	[redacted]	–
Min; Max	[redacted]	–
Week 26		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

Domain	Arm A	
	Prophylaxis (N=18)	
Scores	**Actual result**	**Change from baseline**
Week 52		
Number	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

Based on Table 30 of Document B of the CS[3] which in turn cites Table 16.2.6.3.4 of the CSR.[38]

Note: The total and subscale scores are presented as the Transformed Scale Score ranging from 0–100, with lower scores indicating a better QoL. A score can be calculated when at least 50% of questions are answered (non-missing and not N/A). Assessments during major surgical/rehabilitation periods are excluded. There are no participants from Arm B whose age meets the requirement for the Haemo-QoL, therefore Arm B and overall columns are not presented

CS = company submission; CSR = clinical study report; FAS = full analysis set; N/A = not applicable; QoL = quality of life; SD = standard deviation

3.2.7.7.2 EQ-5D

In Appendix N of the CS[41] it was stated that, "*In Arm A, [redacted] patients completed the EQ-5D-5L questionnaire at baseline, [redacted] at Week 26, and [redacted] at Week 52. In Arm B, [redacted] patients completed the EQ-5D-5L questionnaire at baseline, [redacted] at Week 26 and [redacted] at Week 52. The EQ 5D-5L was assessed for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Overall, the percentages of patients who reported no problems generally increased from baseline to end of study in all domains, except self-care and anxiety/depression, which remained unchanged. The mean visual analogue scale (VAS) score in Arm A was [redacted] at baseline and [redacted] at Week 52. There was a minimal change in EQ VAS as shown by mean change from baseline to Week 52 of [redacted] The small magnitude of the change in Arm A indicates that QoL remained stable over the course of the study. These results are consistent with expectations, given the short timeframe between baseline and end of study assessments for most participants, and the fact that the EQ-5D is a general instrument and not designed specifically for patients with haemophilia. In Arm B, the mean VAS score was [redacted] at baseline and [redacted] at Week 52. There was an improvement in EQ VAS as shown by mean change from baseline to Week 52 of [redacted]. In Arm A, the mean EQ-5D index score at Week 52 was 0.80 (SD: 0.18). The mean change from baseline to Week 52 in EQ-5D index score was 0.02 (SD: 0.13) suggesting that QoL measured using the EQ-5D was stable from baseline to end of study. In Arm B, the mean EQ-5D index score at Week 52 was 0.83 (SD: 0.19). The mean change from baseline to Week 52 in EQ-5D index score was 0.05 (SD: 0.17)*." This is summarised in Tables 3.23 to 3.25.

Table 3.23: EQ-5D VAS and change from baseline by visit, FAS

Visit	Arm A Prophylaxis (N=133)		Arm B On-demand->Prophylaxis (N=26)		Overall (N=159)	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Baseline						
Number	[redacted]	–	[redacted]	–	[redacted]	–
Mean (SD)	[redacted]	–	[redacted]	–	[redacted]	–
Median	[redacted]	–	[redacted]	–	[redacted]	–
Week 26						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 2 of Appendix N of the CS.[41]
Note: The VAS records a response from 0–100 indicating a participant's overall self-rated health state. Lower scores indicate worse health states; Assessments during major surgical/rehabilitation periods are excluded.
CS = company submission; EQ-5D = European Quality of Life-5 dimensions; FAS = full analysis set; SD = standard deviation; VAS = visual analogue scale

.

Table 3.24: Summary of EQ-5D index score and change from baseline by visit, FAS

Visit	Arm A Prophylaxis (N=133)		Arm B On-demand->Prophylaxis (N=26)		Overall (N=159)	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Baseline						
Number	[redacted]	–	[redacted]	–	[redacted]	–
Mean (SD)	[redacted]	–	[redacted]	–	[redacted]	–
Median	[redacted]	–	[redacted]	–	[redacted]	–
Week 26						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52						
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 3 of Appendix N of the CS.[41]
Note: EQ-5D index scores are calculated by applying a crosswalk link function to the individual participant responses to the EQ-5D-5L descriptive system. Higher index scores indicate better health states. Assessments during major surgical/rehabilitation periods are excluded.
CS = company submission; EQ-5D = European Quality of Life-5 dimensions; ED-5D-5L = European Quality of Life-5 dimensions 5 levels; FAS = full analysis set; SD = standard deviation

.

Table 3.25: Summary of EQ-5D-5L descriptive system by visit, FAS

Domain	Arm A	Arm B	Overall (N=159)
Visit, n (%)	Prophylaxis (N=133)	On-demand>Prophylaxis (N=26)	
Mobility			
Baseline			
Number	[redacted]	[redacted]	[redacted]
I have no problems walking	[redacted]	[redacted]	[redacted]
I have slight problems walking	[redacted]	[redacted]	[redacted]
I have moderate problems walking	[redacted]	[redacted]	[redacted]
I have severe problems walking	[redacted]	[redacted]	[redacted]
I am unable to walk	[redacted]	[redacted]	[redacted]
Week 26			
Number	[redacted]	[redacted]	[redacted]
I have no problems walking	[redacted]	[redacted]	[redacted]
I have slight problems walking	[redacted]	[redacted]	[redacted]
I have moderate problems walking	[redacted]	[redacted]	[redacted]
I have severe problems walking	[redacted]	[redacted]	[redacted]
I am unable to walk	[redacted]	[redacted]	[redacted]
Week 52			
Number	[redacted]	[redacted]	[redacted]
I have no problems walking	[redacted]	[redacted]	[redacted]
I have slight problems walking	[redacted]	[redacted]	[redacted]
I have moderate problems walking	[redacted]	[redacted]	[redacted]
I have severe problems walking	[redacted]	[redacted]	[redacted]

Domain	Arm A	Arm B	Overall (N=159)
Visit, n (%)	Prophylaxis (N=133)	On-demand>Prophylaxis (N=26)	
I am unable to walk	[redacted]	[redacted]	[redacted]
Self-care			
Baseline			
Number	[redacted]	[redacted]	[redacted]
I have no problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have slight problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have moderate problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have severe problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I am unable to wash or dress myself	[redacted]	[redacted]	[redacted]
Week 26			
Number	[redacted]	[redacted]	[redacted]
I have no problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have slight problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have moderate problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have severe problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I am unable to wash or dress myself	[redacted]	[redacted]	[redacted]
Week 52			
Number	[redacted]	[redacted]	[redacted]
I have no problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have slight problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have moderate problems washing or dressing myself	[redacted]	[redacted]	[redacted]
I have severe problems washing or dressing myself	[redacted]	[redacted]	[redacted]

Domain	Arm A	Arm B	Overall (N=159)
Visit, n (%)	Prophylaxis (N=133)	On-demand>Prophylaxis (N=26)	
I am unable to wash or dress myself	[redacted]	[redacted]	[redacted]
Usual activities			
Baseline			
Number	[redacted]	[redacted]	[redacted]
I have no problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have slight problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have moderate problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have severe problems doing my usual activities	[redacted]	[redacted]	[redacted]
I am unable to do my usual activities	[redacted]	[redacted]	[redacted]
Week 26			
Number	[redacted]	[redacted]	[redacted]
I have no problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have slight problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have moderate problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have severe problems doing my usual activities	[redacted]	[redacted]	[redacted]
I am unable to do my usual activities	[redacted]	[redacted]	[redacted]
Week 52			
Number	[redacted]	[redacted]	[redacted]
I have no problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have slight problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have moderate problems doing my usual activities	[redacted]	[redacted]	[redacted]
I have severe problems doing my usual activities	[redacted]	[redacted]	[redacted]

Domain	Arm A	Arm B	Overall (N=159)
Visit, n (%)	Prophylaxis (N=133)	On-demand>Prophylaxis (N=26)	
I am unable to do my usual activities	[redacted]	[redacted]	[redacted]
Pain/discomfort			
Baseline			
Number	[redacted]	[redacted]	[redacted]
I have no pain or discomfort	[redacted]	[redacted]	[redacted]
I have slight pain or discomfort	[redacted]	[redacted]	[redacted]
I have moderate pain or discomfort	[redacted]	[redacted]	[redacted]
I have severe pain or discomfort	[redacted]	[redacted]	[redacted]
I have extreme pain or discomfort	[redacted]	[redacted]	[redacted]
Week 26			
Number	[redacted]	[redacted]	[redacted]
I have no pain or discomfort	[redacted]	[redacted]	[redacted]
I have slight pain or discomfort	[redacted]	[redacted]	[redacted]
I have moderate pain or discomfort	[redacted]	[redacted]	[redacted]
I have severe pain or discomfort	[redacted]	[redacted]	[redacted]
I have extreme pain or discomfort	[redacted]	[redacted]	[redacted]
Week 52			
Number	[redacted]	[redacted]	[redacted]
I have no pain or discomfort	[redacted]	[redacted]	[redacted]
I have slight pain or discomfort	[redacted]	[redacted]	[redacted]
I have moderate pain or discomfort	[redacted]	[redacted]	[redacted]
I have severe pain or discomfort	[redacted]	[redacted]	[redacted]

Domain	Arm A	Arm B	Overall (N=159)
Visit, n (%)	Prophylaxis (N=133)	On-demand>Prophylaxis (N=26)	
I have extreme pain or discomfort	[redacted]	[redacted]	[redacted]
Anxiety/depression			
Baseline			
Number	[redacted]	[redacted]	[redacted]
I am not anxious or depressed	[redacted]	[redacted]	[redacted]
I am slightly anxious or depressed	[redacted]	[redacted]	[redacted]
I am moderately anxious or depressed	[redacted]	[redacted]	[redacted]
I am severely anxious or depressed	[redacted]	[redacted]	[redacted]
I am extremely anxious or depressed	[redacted]	[redacted]	[redacted]
Week 26			
Number	[redacted]	[redacted]	[redacted]
I am not anxious or depressed	[redacted]	[redacted]	[redacted]
I am slightly anxious or depressed	[redacted]	[redacted]	[redacted]
I am moderately anxious or depressed	[redacted]	[redacted]	[redacted]
I am severely anxious or depressed	[redacted]	[redacted]	[redacted]
I am extremely anxious or depressed	[redacted]	[redacted]	[redacted]
Week 52			
Number	[redacted]	[redacted]	[redacted]
I am not anxious or depressed	[redacted]	[redacted]	[redacted]
I am slightly anxious or depressed	[redacted]	[redacted]	[redacted]
I am moderately anxious or depressed	[redacted]	[redacted]	[redacted]
I am severely anxious or depressed	[redacted]	[redacted]	[redacted]

Domain	Arm A	Arm B	Overall (N=159)
Visit, n (%)	Prophylaxis (N=133)	On-demand>Prophylaxis (N=26)	
I am extremely anxious or depressed	[redacted]	[redacted]	[redacted]

Based on Table 4 of Appendix N of the CS.[41]
CS = company submission; EQ-5D-5L = European Quality of Life-5 dimensions 5 levels; FAS = full analysis set

3.2.7.8 Other outcomes reported in the CS

Other outcomes for the XTEND-1 study were reported in Document B and Appendix N of the CS, but since these were not included in the NICE Final Scope or the DP, data have not been reproduced in this report. A list of these outcomes is shown below.

- Prophylactic dose and dosing interval
- Number of injections and dose to treat bleeding episodes
- Patients' assessment of response to treatment of bleeding episodes
- Physicians' global assessment of the participant's response to efanesoctocog alfa
- Intra-patient comparison of the annualised joint bleeding rate (AjBR) in Arm B
- Target joint resolution based on spontaneous bleeds
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Patient Reported Outcomes Measurement Information System (PROMIS) pain intensity and physical function
- Haemophilia Activities List (HAL)
- Paediatric Haemophilia Activities List (pedHAL)
- Patient Global Impression of Severity (PGIS)
- Patient Global Impression of Change (PGIC)
- Treatment preference survey

3.2.7.9 Subgroup analysis for clinical effectiveness data

The following Section presents the subgroup analysis from Document B of the CS.[3] The ABR results were considered according to age group, bleeding phenotype at baseline, the number of target joints at screening and the dosing and dosing interval compliance. In addition, the subgroup of patients undergoing surgery during the study were considered separately.

3.2.7.9.1 Subgroup analysis based on ABR

A subgroup analyses of the mean ABR was performed on the FAS. The CS[3] describes the treatment effects as being consistent across subgroups defined by "*age categories, bleeding phenotype at baseline, number of target joints at screening or dosing and dosing interval compliance, confirming the primary endpoints*". The data are represented in Figure 3.5.

Figure 3.5: Forest plot of ABR and 95% CI by subgroup, FAS

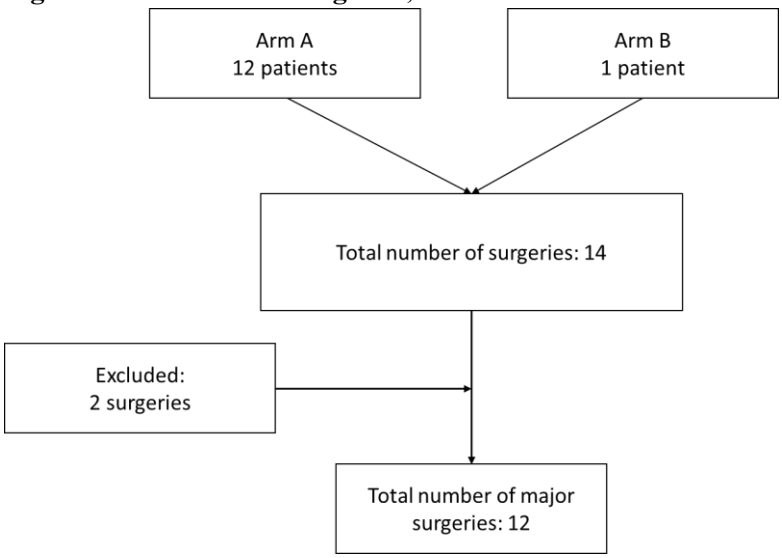
Based on Figure 8 of Document B of the CS.[3]
ABR = annualised bleeding rate; CI = confidence interval; CS = company submission; FAS = full analysis set; NC = not calculable

3.2.7.9.2 Surgery subgroup analyses

A subgroup analysis of patients who underwent a major surgery during the study period was included. This was to assess the efficacy of efanesoctocog alfa in the control and prevention of bleeding in the surgical setting.[3]

A total of 14 major surgeries were performed in 13 patients. One patient was in Arm B whilst the remaining 12 were in Arm A. "[redacted]" In two patients in Arm A major surgeries (osteosynthesis of right tibia and coronary artery bypass) the major surgery took place after the final efanesoctocog alfa dose. Therefore, two surgeries were not considered in the assessments of major surgeries (Figure 3.6).[3]

Figure 3.6: Number of surgeries, XTEND-1



Based on Figure 9 of the CS[3]
CS = company submission

It was explained that "*the investigators'/surgeons' assessment of the participant's haemostatic response to efanesoctocog alfa treatment was collected 24 hours post-surgery based on the ISTH 4-point response scale of excellent, good, fair, and poor.*" Lower average scores indicated a better investigator/surgeon of response to surgery from the treatment of efanesoctocog alfa. "*The investigators'/surgeons' assessment of the participant's haemostatic response to efanesoctocog alfa treatment was collected 24 hours post-surgery based on the ISTH 4-point response scale of excellent, good, fair, and poor.*"[3]

Investigators/surgeons rated haemostatic response as excellent for all 12 major surgeries that were included in the subgroup analyses (Table 3.26). This indicates "*that intraoperative and postoperative blood loss was deemed comparable with what would be expected for a patient without haemophilia.*"[3]

Table 3.26: Summary of investigators'/surgeons' assessment of patient's haemostatic response to efanesoctocog alfa treatment, surgery subgroup

	Surgery subgroup (N=13)
Number of major surgeries	12
Assessment of response, n (%)	
Excellent or Good	12 (100)
Excellent (=1)	12 (100)
Good (=2)	0
Fair (=3)	0
Poor/none (=4)	0
Number	12
Mean (SD)	1.0 (0.0)
Median	1.0

Based on Table 33 of the CS[3]
Note: Percentages are based on the number of major surgeries with assessments; The analysis is based on the major surgeries conducted during the treatment regimen, excluding the surgeries conducted after the last

	Surgery subgroup (N=13)
efanesoctocog alfa dose. Those excluded major surgeries are counted in the capital N in the header. CS = company submission; SD = standard deviation	

EAG comment: There was no consideration in the CS of the subgroups described in the NICE Final Scope, i.e., those defined according to the severity of haemophilia A, presence or development of FVIII inhibitors or previous treatment status.[1]

3.2.8 Adverse events

This Section reports on the safety results of XTEND-1 discussed in Section B.2.10 of the CS.[3]

3.2.8.1 Overall adverse events

In the safety analysis set (SAS), 123 (77.4%) out of 159 patients experienced a total of [redacted] treatment emergency adverse events (TEAEs) as of the cut-off date of 24 February 2022.

The company reported that: "*At least one treatment-emergent serious adverse event (TESAE) was reported in 15 (9.4%) patients overall. One (0.6%) patient from Arm B experienced a TEAE leading to death (pancreatic carcinoma metastatic), and two (1.3%) patients from Arm A experienced TEAEs leading to treatment discontinuation*".[3] An overall summary of AE data is presented in Table 3.27.

Table 3.27: Overall summary of TEAEs of XTEND-1, SAS

Category	Arm A N=133	Arm B		Surgery subgroup† N=13	Overall N=159
		O-D N=26	Prophylaxis N=26		
Total number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 TEAE	108 (81.2)	12 (46.2)	8 (30.8)	[redacted]	123 (77.4)
Patients with ≥1 treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of TESAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 TESAE	13 (9.8)	2 (7.7)	0	[redacted]	15 (9.4)
Patients with ≥1 treatment-related TESAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of TEAESIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 TEAESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to treatment discontinuation	2 (1.5)	0	0	[redacted]	2 (1.3)
Deaths	0	1 (3.8)	0	[redacted]	1 (0.6)

Based on Table 42 of the CS[3]
†Includes AEs occurring during a major surgical/rehabilitation period. But AEs which occur on the day of the major surgical/rehabilitation period starts will be included in the columns treatment arm and regimen, they will not be included in the column of surgery subgroup.
AE = adverse event; CS = company submission; O-D = on=demand; SAS = safety analysis set; TEAE = treatment-emergent adverse event; TEAESI = treatment-emergent adverse event of special interest; TESAE = treatment-emergent serious adverse event

3.2.8.2 Adverse events by system organ class and preferred term

The company outlined that *"TEAEs were most commonly reported in the following system order classes (SOC) (≥10% of patients overall); musculoskeletal and connective tissue disorders ([redacted] patients), nervous system disorders ([redacted] patients), injury, poisoning and procedural complications ([redacted] patients), infections and infestations ([redacted] patients)."* In addition: *" The most frequently reported TEAEs by preferred term (>3% of patients overall) were headache (32 [20.1%] patients), arthralgia (26 [16.4%] patients), fall (ten [6.3%] patients), back pain (nine [5.7%] patients), COVID-19 and fatigue ([redacted] patients, each), contusion, haemophilic arthropathy, and nasopharyngitis ([redacted] patients, each), and joint injury, pain in extremity and toothache ([redacted] patients, each)."*[3] The details for TEAEs by SOC and preferred term with an incidence of at least >3% are summarised in Table 3.28.

Table 3.28: Summary of TEAEs of XTEND-1 by SOC and preferred term (in >3% of patients), SAS

System organ class Preferred Term, n (%)	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Total number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least one TEAE	108 (81.2)	12 (46.2)	8 (30.8)	123 (77.4)
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatic carcinoma metastatic	0	1 (3.8)	0	1 (0.6)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Lymphadenopathy	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	26 (19.5)	5 (19.2)	1 (3.8)	32 (20.1)
Syncope	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]

System organ class Preferred Term, n (%)	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Vitreous floaters	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Excessive cerumen production	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis allergic	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]
Gastro-oesophageal reflux disease	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]	[redacted]	[redacted]
Large intestine polyp	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	25 (18.8)	1 (3.8)	0	26 (16.4)
Back pain	8 (6.0)	1 (3.8)	0	9 (5.7)
Haemophilic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]	[redacted]

System organ class Preferred Term, n (%)	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Coagulation factor VIII level increased	[redacted]	[redacted]	[redacted]	[redacted]
SARS-CoV-2 test positive	[redacted]	[redacted]	[redacted]	[redacted]
Red blood cell count increased	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Fall	10 (7.5)	0	0	10 (6.3)
Contusion	[redacted]	[redacted]	[redacted]	[redacted]
Joint injury	[redacted]	[redacted]	[redacted]	[redacted]
Limb injury	[redacted]	[redacted]	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]	[redacted]	[redacted]
Tooth fracture	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]
Social circumstances	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy of partner	[redacted]	[redacted]	[redacted]	[redacted]
Product issues[a]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 43 of the CS[3] which in turn cites Table 16.2.7.2, data on file_CSR_01-EFC16293-16.2.7_ae_data.[42]
Note from Table 43 of the CS:[3] Patients were included in each study arm and treatment regimen they participated in for the duration of time on that regimen and as such, may appear in more than one treatment regimen. Each patient was counted only once in the overall column. Events were coded using MedDRA version 24.1.[43] Patients were counted once if they reported multiple events in the same SOC or PT. Table sorted by SOC internationally agreed order and decreasing frequency of PT in the overall

System organ class Preferred Term, n (%)	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
group. AEs which occur during a major surgical/rehabilitation period were excluded, but AEs which occur on the day of the major surgical/rehabilitation period starts were included. [a]Product issue was due to device (needle) breakage (note from Table 43 of the CS).[3] AE = adverse event; COVID-19 = coronavirus disease 2019; CS = company submission; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SAS = safety analysis set; SOC = system organ class; TEAE = treatment-emergent adverse event				

3.2.8.3 Treatment-related adverse events of XTEND-1

Table 3.29 shows specific treatment-related TEAEs in safety analysis set. In total, [redacted] patients reported treatment-related AEs with [redacted] TEAEs, all in Arm A. The company reported the following: "*Treatment-related TEAEs included coagulation FVIII level increased ([redacted] patients), headache ([redacted] patients), and CD4 lymphocytes decreased, protein urine present, injection site dermatitis, malaise, and dysphoria ([redacted], each). Of the TEAEs assessed as related, [redacted] TEAE of CD4 lymphocytes decreased was assessed by the investigator as serious and resulted in discontinuation of efanesoctocog alfa."*[3]

Table 3.29: Summary of Treatment-related TEAEs of XTEND-1

System organ class Preferred Term, n (%)	Arm A	Arm B		Overall (N=159)
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	
Total number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Participants by highest relationship over all TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dysphoria	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Injection site dermatitis	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Coagulation FVIII level increased	[redacted]	[redacted]	[redacted]	[redacted]
CD4 lymphocytes decreased	[redacted]	[redacted]	[redacted]	[redacted]
Protein urine present	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 1 of the Appendix F of CS.[44]
CS = company submission; TEAE = treatment-emergent adverse event

3.2.8.4 Serious adverse events

The company outlined that: *"The majority of TEAEs were assessed by the investigator as mild in severity. Of the 159 patients included in the safety analysis set, 15 patients experienced at least one TESAE, the most common of which was haemophilic arthropathy ([redacted] from Arm A)"* Table 3.30 shows the details of patients with serious adverse events (SAEs).

Table 3.30: Summary of TESAEs by SOC and preferred term of XTEND-1

SOC Preferred Term, n (%)	Arm A	Arm B		Overall (N=159)
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	
Total number of TESAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least one TESAE	13 (9.8)	2 (7.7)	0	15 (9.4)
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatic carcinoma metastatic	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cubital tunnel syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Status epilepticus	[redacted]	[redacted]	[redacted]	[redacted]
Ulnar tunnel syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthropathy	[redacted]	[redacted]	[redacted]	[redacted]
Haemophilic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]
Mobility decreased	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]
CD4 lymphocytes decreased	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Combined tibia-fibula fracture	[redacted]	[redacted]	[redacted]	[redacted]
Traumatic haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]
Central venous catheter removal	[redacted]	[redacted]	[redacted]	[redacted]
Product issues	[redacted]	[redacted]	[redacted]	[redacted]
Device breakage	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 44 of the CS[3]
CS = company submission; SOC = system organ class; TESAE = treatment-emergent serious adverse event

3.2.8.5 Mortality

In the XTEND-1 trial, there was one reported death in a patient from Arm B. The company concluded that *"The patient had a medical history of hepatitis C virus (HCV) and died on Day 217 of metastatic pancreatic carcinoma, which was reported as a TESAE on Day 173, The TESAE was assessed by the investigator as not related to treatment."*[3]

3.2.8.6 Subgroup analysis of TEAEs

In the subgroup analysis, TEAEs based on predefined intrinsic and extrinsic factors: age, body mass index (BMI), race, human immunodeficiency virus (HIV) status, hepatitis C virus (HCV) status, geographic region, and coronavirus disease 2019 (COVID-19). The company concluded that the subgroup data *"...were generally consistent with TEAEs in the overall study population. No unique patterns or trends were identified in any subgroup."*[3] Further details are provided in Appendix F of the CS.[44]

EAG comment: Data on AEs in the comparator studies was not provided in the CS. Further details were requested by the EAG (CQs A.31 and A.32) and provided as part of the company's response to clarification and are discussed in Section 3.3.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Two Phase 3 RCTs contributing comparator data were included in the clinical effectiveness ITC: the HAVEN 3 trial assessing emicizumab[45, 46] and the A-LONG trial evaluating efmoroctocog alfa.[25, 47] Both RCTs recruited participants with severe haemophilia A without FVIII inhibitors who had received prophylactic or O-D FVIII therapy before enrolment.[2, 25, 46]

Appendix D of the CS provided a brief outline of methods as well as information on patient disposition and risk of bias for the HAVEN 3 and A-LONG trials.[16] However, some details of trial design, methods, participant eligibility, interventions and baseline and outcome data were lacking in the CS: therefore the EAG requested further details during the clarification process (CQ A 20). The information summarised in Sections 3.3.1 and 3.3.2 is based on Appendix D of the CS[16] and the company's response to the clarification letter (CL).[2]

3.3.1 The HAVEN 3 trial

3.3.1.1 Summary information for HAVEN 3

The company described HAVEN 3 as "*a Phase 3, multicentre study evaluating the use of emicizumab (bispecific monoclonal antibody bridging activated Factor IX and Factor X) as prophylaxis in adults and adolescents (aged 12 years or older) with severe haemophilia A without inhibitors.*[46]"[2]

3.3.1.2 Participant eligibility for HAVEN 3

Eligible patients were 12 years of age or older with severe congenital haemophilia A (defined as <1% endogenous FVIII activity), without current FVIII inhibitors (defined as <0.6 Bethesda units/ml), who were receiving episodic or prophylactic FVIII infusions.[2, 46]

3.3.1.3 Study design and patient disposition for HAVEN 3

The HAVEN 3 trial enrolled n=152 participants overall and included four arms: three randomised and one non-randomised. Participants in two of the randomised arms plus the non-randomised group were treated with emicizumab, all of whom received four initial loading doses of emicizumab of 3.0 milligrams per kilogram body weight per week (mg/kg/wk).[2, 16, 46]

The participants who had previously received episodic treatment with FVIII were randomly assigned in a 2:2:1 ratio to three groups as follows:

- 1.5 mg/kg subcutaneous (SC) emicizumab every week (n=36, Group A)

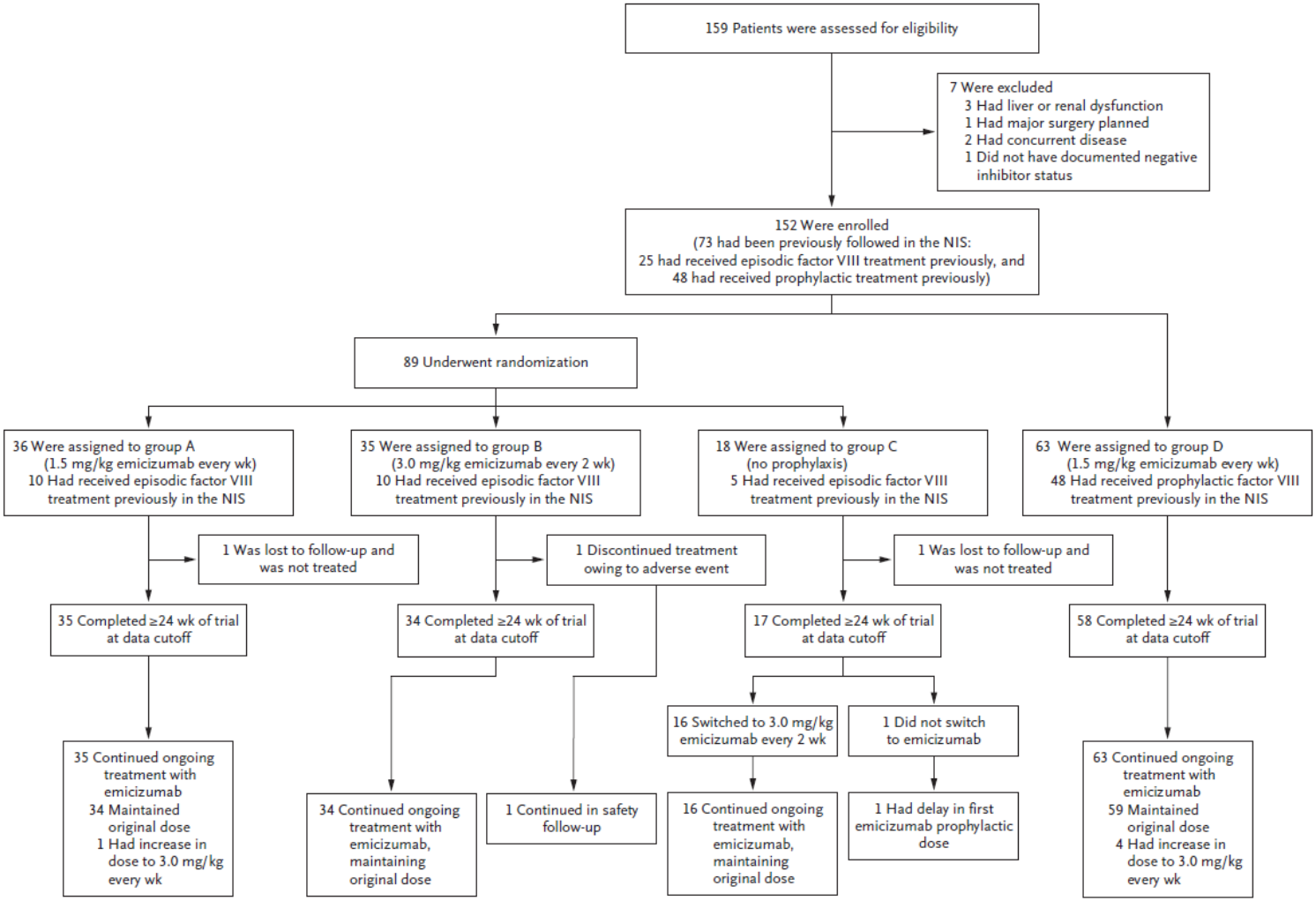
- 3.0 mg/kg SC emicizumab every two weeks (n=35, Group B)
- No prophylaxis (n=18, Group C)

Participants who were deemed to have received adequate prophylactic FVIII pre-enrolment (determined by the investigator) were allocated to the fourth, non-randomised group to receive 1.5 mg/kg SC emicizumab every week (n=63, Group D) and could continue their original FVIII prophylaxis until the second loading dose of emicizumab. At least 40 patients were required to complete at least 24 weeks of observation in a non-interventional study before they could be enrolled in Group D.[2, 16, 46]

Patients in Group C could switch to emicizumab prophylaxis given every two weeks (and remain in Group C) once they had completed at least 24 weeks of the trial while receiving no prophylaxis. All other patients could continue emicizumab therapy at or after 24 weeks. In Group A, the dose was increased to 3.0 mg/kg weekly in one patient after 24 weeks of follow-up. In Group B, one patient discontinued treatment because of AEs involving insomnia, alopecia, nightmare, lethargy, pruritus, headache, and depressed mood, all of which were considered by the investigator to be related to emicizumab. In Group C, one patient was waiting to start emicizumab prophylaxis at the time of clinical cut-off. In Group D, the dose was increased to 3.0 mg/kg weekly in one patient before 24 weeks of follow-up and in three patients after 24 weeks of follow-up. Figure 3.7 represents the patient disposition in HAVEN 3.[2, 16, 46]

The primary analysis occurred after the last randomly assigned patient and at least 40 patients from Group D had completed 24 weeks in the trial or had withdrawn, whichever occurred first.[2]

Figure 3.7: Patient disposition in HAVEN 3



Based on Figure 4 of Appendix D of the CS[16] which in turn cites Mahlangu (2018).[46]

CS = company submission; mg/kg = milligrams per kilogram (body weight); NIS = non-interventional study; wk = week

3.3.1.4 Outcome measures for HAVEN 3

The primary endpoint was the difference in the rate of treated bleeding events over a period of at least 24 weeks between randomly assigned groups of patients (Group A versus Group C and Group B versus Group C). Secondary endpoints for the randomised comparisons included all bleeding events (treated and untreated), spontaneous and joint bleeding events, and the Haem-A-QoL physical health subscale.[2]

3.3.1.5 Baseline characteristics for HAVEN 3

The company presented the following Table (copied from the supplementary material of a journal publication of HAVEN 3[46]) as part of their response to CQ A 20.[2]

Table 3.31: Demographic and clinical characteristics of participants in HAVEN 3

	Study Group*				
	Previous Episodic Treatment (randomized)			Previous Prophylactic Treatment	
Participant Characteristics	A: Emicizumab once-weekly prophylaxis (N = 36)	B: Emicizumab every-2-weeks prophylaxis (N = 35)	C: No prophylaxis (N = 18)	D: Emicizumab once-weekly prophylaxis (N = 63)	Total (N = 152)
Sex, n (%)					
Male	36 (100)	35 (100)	18 (100)	63 (100)	152 (100)
Age, yr					
Median	36.5	41.0	40.0	36.0	38.0
Range	19–77	20–65	16–57	13–68	13–77
<18 yr, no. (%)	0	0	1 (5.6)	7 (11.1)	8 (5.3)
<9 bleeding events in 24 weeks before trial entry, n (%)	9 (25.0)	5 (14.3)	4 (22.2)	53 (84.1)	71 (46.7)
Target joints†					
None, no. (%)	2 (5.6)	8 (22.9)	3 (16.7)	37 (58.7)	50 (32.9)
Yes, no. (%)	34 (94.4)	27 (77.1)	15 (83.3)	26 (41.3)	102 (67.1)
>1, no./total no. (%)	20/34 (58.8)	22/27 (81.5)	14/15 (93.3)	18/26 (69.2)	74/102 (72.5)
FVIII product used before trial entry					
Patients, n	36	34‡	18	63	151‡
Standard half-life, n (%)	31 (86.1)	31 (91.2)	15 (83.3)	53 (84.1)	130 (86.1)
Extended half-life, n (%)	4 (11.1)	2 (5.9)	2 (11.1)	10 (15.9)	18 (11.9)
Both, n (%)	1 (2.8)	1 (2.9)	1 (5.6)	0	3 (2.0)

* Participants who had received episodic treatment with FVIII before trial entry were randomly assigned in a 2:2:1 ratio to receive subcutaneous emicizumab prophylaxis (group A or B) or no emicizumab prophylaxis (group C). Participants who had previously received prophylactic treatment with FVIII were assigned to emicizumab prophylaxis in group D. (Fig. S1 in the Supplementary Appendix).

† All values are based on electronic case-report forms and not on data from the noninterventional study.

‡ In group B, one patient reported 'Other' as the product used. Therefore, percentages are based on 34 participants in group B and 151 participants in the Total column.

Based on The company's response to CQ A 20[2] which in turn cited Mahlangu (2018).[46]
CQ = clarification question; FVIII = clotting factor VIII

3.3.1.6 Efficacy data for HAVEN 3

The company did not summarise the outcome data for all bleeding events (i.e., both treated and untreated) as part of their response to the CL (CQ A 20) however, they signposted a relevant publication.[46] Table 3.32 summarises the published data for all bleeding events for randomised patients in HAVEN 3.

Table 3.32: All bleeding events (treated and untreated) for HAVEN 3

	Group A: emicizumab 1.5 mg/kg QW	Group B: emicizumab 3.0 mg/kg Q2W	Group C: no prophylaxis
No. randomised pts	36	35	18
Median (range) duration of efficacy period in weeks[a]	29.6 (17.3 to 49.6)	31.3 (7.3 to 50.6)	24.0 (14.4 to 25.0)
ABR (95% CI) for all bleeding events, model based[b]	2.5 (1.6 to 3.9)	2.6 (1.6 to 4.3)	47.6 (28.5 to 79.6)
Rate ratio (95% CI) versus control (Group C)	0.05 (0.03 to 0.10)	0.06 (0.03 to 0.10)	-
Percent difference versus control (Group C)	-95 (p<0.001)	-94 (p<0.001)	-
Median (IQR) ABR	0.6 (0.0 to 3.9)	1.6 (0.0 to 4.0)	46.9 (26.1 to 73.9)
Percent pts (95% CI) with 0 bleeding events	50 (33 to 67)	40 (24 to 58)	0 (0 to 18)
Percent pts (95% CI) with 0 to 3 bleeding events	86 (70 to 95)	86 (70 to 95)	6 (<1 to 27)

Based on Table 1 of Mahlangu et al (2018).[46]
[a]The start of the efficacy period for each participant was the first day with available data. The end of the efficacy period in Groups A and B was the day of clinical cut-off or treatment discontinuation. The end of the efficacy period in Group C was the day before the first dose of emicizumab or the day of discontinuation.[46]
[b]The ABR was calculated with the use of a negative binomial-regression model.[46]
ABR = annualised bleeding rate; CI = confidence interval; IQR = interquartile range; mg/kg = milligrams per kilogram (of body weight); no. = number; pts = patients; QW = once per week; Q2W = once every two weeks

The company provided the following summaries of efficacy data as part of their response to CQ A 20.[2] When comparing against published data for HAVEN 3, the EAG noted that the following estimates for ABR and the proportion of patients with bleeding events pertained to bleeding events treated with FVIII.[46]

"*The ABR was 1.5 (95% CI: 0.9, 2.5) with the QW emicizumab regimen (Group A) and 1.3 (95% CI: 0.8, 2.3) with the regimen of emicizumab Q2W (Group B), compared with 38.2 events (95% CI: 22.9, 63.8) with no prophylaxis (Group C). The bleeding rate was 96% lower in Group A than in Group C (rate ratio: 0.04; 95% CI: 0.02, 0.08; p<0.001), and 97% lower in Group B than in Group C (rate ratio: 0.03; 95% CI: 0.02, 0.07; p<0.001).*"[2]

"*No treated bleeding events were reported in 56% of the patients in Group A and in 60% of those in Group B, as compared with those in Group C, who all had bleeding events.*"[2]

The company also reported the following as part of their response to CQ A 20:[2] "*In an intraindividual comparison involving the 48 patients in Group D who had participated in the non-interventional study, the ABR was 1.5 (95% CI: 1.0, 2.3) with QW emicizumab therapy, compared with 4.8 events (95% CI: 3.2, 7.1) during FVIII prophylaxis.*"[2] Similar to above, the EAG noted from the published data that this

analysis related to treated bleeding events. The median (range) duration of efficacy was 33.7 (20.1 to 48.6) weeks during the emicizumab prophylaxis phase and 30.1 (5.0 to 45.1) weeks during the non-interventional study (FVIII prophylaxis) phase. The respective proportions of patients (95% confidence interval [CI]) with zero bleeding events was 54% (39% to 69%) and 40% (26% to 55%).[46]

Published data are available for additional bleeding outcomes for randomised patients in HAVEN 3: treated events of spontaneous bleeding; treated events of joint bleeding; and treated events of target-joint bleeding.[46]

3.3.1.7 HRQoL data for HAVEN 3

Mahlangu et al, (2018) reported outcome data derived from the Haem-A-QoL physical health subscale score for the randomised patients in HAVEN 3.[46] The physical functioning subscale comprises nine items, with higher scores corresponding to better HRQoL or less impairment.[48] The mean difference (adjusted for baseline scores and treatment by baseline score interaction) at Week 25 was 12.5 points (95% CI -2.0 to 27.0) for Group A versus Group C (p=0.09). The mean difference between Group B and Group C was 16.0 points (95% CI 1.2 to 30.8), described as a non-significant difference but the p-value not provided.[46]

3.3.1.8 Safety data for HAVEN 3

The CS did not include safety data for either of the comparator studies[3] and the EAG requested details of this during the clarification process. The company provided the following summary of safety data for HAVEN 3 as part of their response to CQ A 20.[2] The EAG noted that the details were closely based on published information.[46]

- "*Overall, 543 AEs were reported in 127/150 patients who received emicizumab. The most common AE was injection-site reaction, occurring in 25% of patients.*"[2]
- "*One patient discontinued treatment owing to several low-grade AEs that were considered by the investigator to be related to emicizumab. No deaths, thrombotic microangiopathy, or thrombotic events occurred.*"[2]
- "*No new FVIII inhibitors developed in participants receiving emicizumab. One patient had undergone induction of immune tolerance in 1987 and subsequently had intermittent detectable inhibitor. This patient had a detectable inhibitor titre at Week 13 (1.6 Bethesda units/mL) that spontaneously declined at Week 25.*"[2]

The company provided further tabulated details as part of their response to CQ A 32.[2] Again, it was apparent that this was based on published information[46] however, the company's summary did not show data for all groups of patients who had received emicizumab. Table 3.33 below summarises all available published safety data for HAVEN 3.

Table 3.33: AEs in participants receiving emicizumab prophylaxis in HAVEN 3

	Group A: emicizumab 1.5 mg/kg QW	Group B: emicizumab 3.0 mg/kg Q2W	Group C: no prophylaxis; switch to emicizumab 3.0 mg/kg Q2W after 24 weeks[a]	Group D: emicizumab 1.5 mg/kg QW	Total
Number of patients	36	35	16	63	150
Exposure duration, median (range) in weeks	29.3 (17.3 to 49.1)	30.1 (6.1 to 50.1)	7.1 (0.1 to 26.1)	33.1 (18.0 to 48.1)	29.0 (0.1 to 50.1)
Number of AEs	143	145	19	236	543
Most common AEs, n (%)[b]					
Injection-site reaction[c]	9 (25)	7 (20)	2 (12)	20 (32)	38 (25)
URTI	4 (11)	4 (11)	0	8 (13)	16 (11)
Nasopharyngitis	2 (6)	6 (17)	0	10 (16)	18 (12)
Arthralgia	7 (19)	6 (17)	1 (6)	14 (22)	28 (19)
Headache	3 (8)	4 (11)	1 (6)	8 (13)	16 (11)
Influenza	1 (3)	3 (9)	0	5 (8)	9 (6)
Number of SAEs[d]	1	3	0	10	14
AEs leading to discontinuation of treatment, n (%)	0	1 (3)[e]	0	0	1 (1)

Based on the company's response to CQ A 32[2] and published data.[46]
[a]Data are for the period of emicizumab prophylaxis only. At the clinical cut-off date, one participant was lost to follow-up and another was waiting to start emicizumab therapy.[46]
[b]Shows events occurring in ≥5% of all participants who received emicizumab prophylaxis.[46]
[c]The injection-site events were of Grade 1 or 2.[46]
[d]SAEs included a bleeding event (four participants), cardiac disorder (one participant), infection (three participants), musculoskeletal disorder (three participants), loosening of an orthopaedic device (one participant), psychiatric disorder (one participant) and trauma (one participant). An event of nephrolithiasis occurred in one participant after the dose was increased to 3 mg/kg/wk. None of these events were considered to be related to emicizumab treatment by the investigator.
[e]One participant in Group B discontinued treatment because of multiple low-grade AEs: insomnia (Grade 2); alopecia (Grade 1); nightmare (Grade 2); lethargy (Grade 2); pruritis (Grade 1); headache (Grade 1); depressed mood (Grade 1). These events were considered to be related to emicizumab treatment by the investigator.
AE = adverse event; CQ = clarification question; mg/kg = milligrams per kilogram (of body weight); mg/kg/wk = milligrams per kilogram (of body weight) per week; n = number; QW = once per week; Q2W = once every two weeks; SAE = serious adverse event; URTI = upper respiratory tract infection

3.3.1.9 Risk of bias assessment for HAVEN 3

Table 3.34 below shows the risk of bias assessment as presented in Appendix D of the CS for the HAVEN 3 trial.[16] The risk of bias assessment was performed using guidelines from NICE[28] however, the company did not state the source of information for the risk of bias assessment (e.g., a specific publication).

Table 3.34: Risk of bias assessment for the HAVEN 3 trial

Study Name	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the onset of the study in terms of prognostic factors, for example, severity of the disease?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
HAVEN 3	Yes: Randomisation was conducted centrally by means of an interactive voice–Web-response system and was stratified according to the number of bleeding events (<9 or ≥9) that had occurred in the preceding 24 weeks.	Yes: Interactive voice–Web-response system suggests that next allocation was not predictable.	Unclear: The patients in the three randomised arms had similar demographic and disease characteristics other than some differences in target joints and prior bleeding at baseline, but no statistical analysis was conducted.	No: The study was open-label.	No: The rates of study discontinuation were comparable between the three randomised treatment arms (3% in emicizumab QW prophylaxis versus 3% in emicizumab Q2W prophylaxis versus 6% in no prophylaxis).	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: Although ITT analysis was not explicitly mentioned, the analysis was performed within the groups patients were randomised to and missing data related to Haem-A-QoL and EmiPref assessments were considered to be missing completely at random, and no imputation was applied to the analyses.

Based on Table 12 of Appendix D of the CS.[16]
CS = company submission; EmiPref = Emicizumab Preference (survey); Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; ITT = intention-to-treat
QW = once per week; Q2W = once every two weeks

3.3.2 The A-LONG trial

3.3.2.1 Summary information for A-LONG

The company described A-LONG as "*a Phase 3, open-label, multicentre, partially randomised study evaluating the efficacy, safety, and pharmacokinetics of efmoroctocog alfa (recombinant FIII FC fusion protein [rFVIIIFc]) for prophylaxis, on-demand treatment, and perioperative management of previously treated adults and adolescents (aged ≥12 years) with severe haemophilia A.*[25]"[2]

3.3.2.2 Participant eligibility for A-LONG

The company's response to CQ A 20 included the following details on participant eligibility:[2]

"*Previously treated male patients aged 12 years or older with severe haemophilia A (defined as <1% endogenous FVIII activity or severe genotype) were eligible if previously treated prophylactically or episodically with a history of ≥12 bleeding events in the 12 months prior to the study. Exclusion criteria included a history of inhibitors, history of hypersensitivity associated with any FVIII concentrate or IV immunoglobulin, or other coagulation disorders.*"

3.3.2.3 Study design and patient disposition for A-LONG

The following details on study design were outlined in the company's response to CQ A 20.[2]

The A-LONG trial study enrolled 165 patients overall and included three treatment arms, all treated with efmoroctocog alfa:

- individualised prophylaxis comprising twice-weekly dosing of 25 IU/kg on Day 1 and 50 IU/kg on Day 4 to start with, followed by 25 to 65 IU/kg every 3 to 5 days (n=118, Arm 1).
- weekly prophylaxis at a dose of 65 IU/kg (n=24, Arm 2).
- and episodic (O-D) treatment as needed for bleeding episodes with dose ranging from 10 to 50 IU/kg, depending on bleeding severity (n=23, Arm 3).

The company additionally provided the following details:[2]

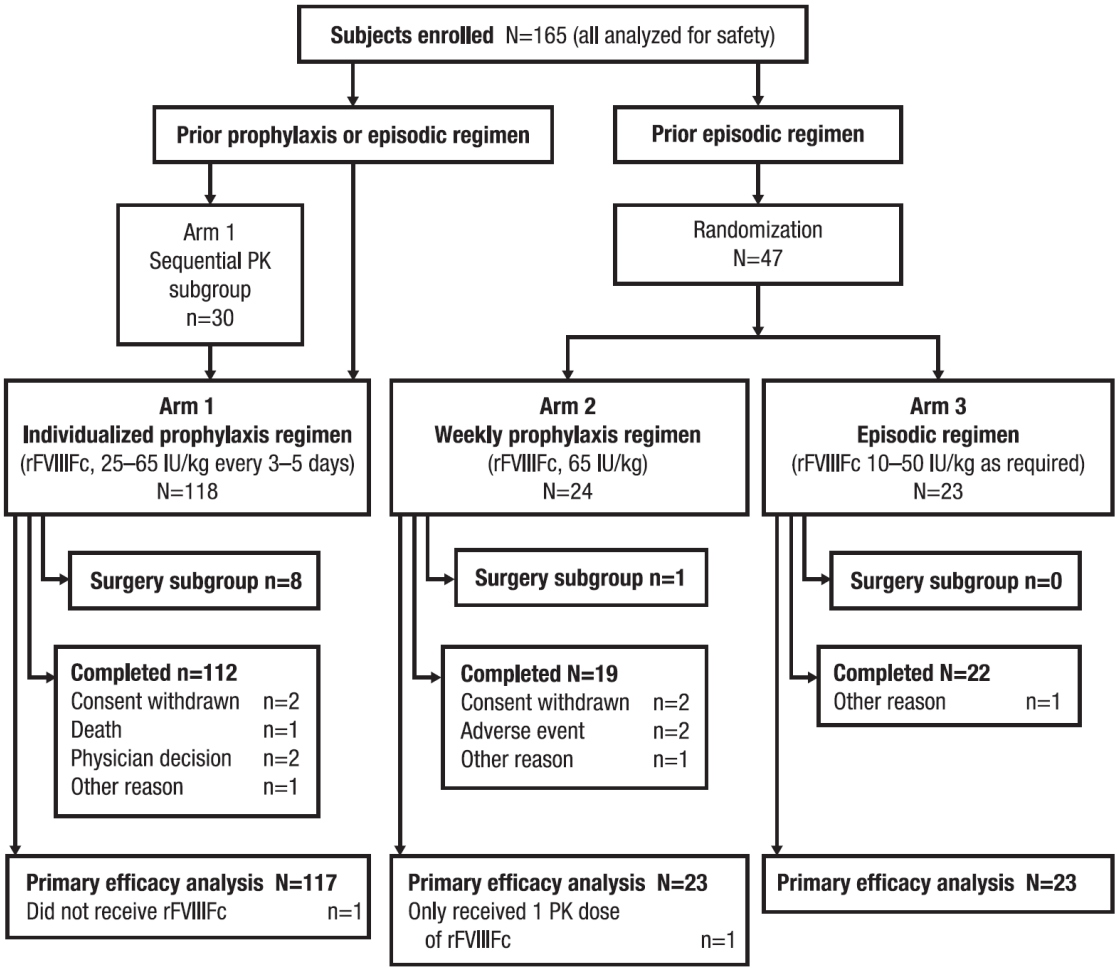
- "*In Arm 1, pharmacokinetic parameters were used to guide individual adjustments to dosing interval (down to 3 days or up to 5 days), and dose (up to 65 IU/kg) to target a steady-state trough FVIII level of 1 to 3 IU/dL or higher as needed to maintain good control of breakthrough bleeding. All patients on a prophylactic regimen prior to study entry were enrolled into Arm 1.*"[2]
- "*Patients on an episodic regimen prior to study entry had the option to enter into Arm 1 or be randomised into either Arm 2 or Arm 3. Baseline rFVIIIFc pharmacokinetic measures were evaluated in all patients.*"[2]
- "*Baseline rFVIIIFc pharmacokinetic measures were evaluated in all patients. A subgroup of patients in Arm 1* [n=28[16]] *had sequential pharmacokinetic evaluations for comparison with a commercially available rFVIII product (octocog alfa [Advate]). An injection of 50 IU/kg of rFVIIIFc was administered, and pharmacokinetic measures were assessed for 72 hours; following a washout period, an injection of 50 IU/kg of rFVIIIFc was administered, and pharmacokinetic measures were assessed for 120 hours. rFVIIIFc pharmacokinetics were reassessed 12 to 24 weeks later.*"[2]
- "*Study termination occurred after completion of the specified pharmacokinetic assessments and achievement of the prespecified rFVIIIFc exposure required to ensure acceptable inhibitor*

detection. Trough and peak levels of rFVIIIFc were checked for all patients at each visit to verify subjects maintained targeted troughs."[2]

Appendix D of the CS included the following details on patient disposition:[16]

- "*Of the 164 patients in the 3 arms combined, 4 patients (2.4%) experienced adverse events that led to discontinuation of rFVIIIFc treatment and/or withdrawal from the study: rash in 1 patient (assessed as related to rFVIIIFc treatment), femur fracture in 1 patient (assessed as unrelated to rFVIIIFc treatment), death in 1 patient (fatal outcome of polysubstance overdose and completed suicide, assessed as unrelated to rFVIIIFc treatment), and arthralgia in 1 patient (assessed as related to rFVIIIFc treatment, but patient was recorded to have discontinued the study due to withdrawal of consent). Of the 3 patients who discontinued for "other" reasons, 1 was incarcerated, 1 was traveling and could not ensure proper temperature conditions for study treatment, and 1 patient was not willing to reveal the reason for wanting to complete the early termination visit.*"[16] Figure 3.8 below represents the patient disposition in A-LONG.[16, 25]

Figure 3.8: Patient disposition in A-LONG



Based on Figure 3 of Appendix D of the CS[16] which in turn cites Mahlangu et al (2014.[25]
CS = company submission; IU/kg = international units per kilogram (body weight); PK = pharmacokinetic; rFVIIIFc = recombinant clotting factor VIII Fc fusion protein

3.3.2.4 Outcome measures for A-LONG

The company described the outcomes measures thus in their response to CQ A 20:[2]

"*The primary efficacy endpoints were ABR in Arm 1 vs Arm 3, and assessment of FVIII activity based on primary pharmacokinetic parameters. Primary safety endpoints were inhibitor development and adverse events (AE). Secondary efficacy end points included ABR in Arm 2 vs Arm 3, and the number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode.*"

3.3.2.5 Baseline characteristics for A-LONG

The company presented the following Table (copied from a journal publication of A-LONG[25]) as part of their response to CQ A 20.[2]

Table 3.35: Demographic and clinical characteristics of participants in A-LONG

Table 1. Subject demographics and baseline characteristics

	Arm 1: individualized prophylaxis (n = 118)	Arm 2: weekly prophylaxis (n = 24)	Arm 3: episodic treatment (n = 23)	Total (n = 165)
Age, y, median (min, max)	29 (12, 65)	31.5 (18, 59)	34 (13, 62)	30 (12, 65)
Weight, kg, median (min, max)	71.65 (42.0, 127.4)	75.85 (50.0, 105.0)	70.00 (48.0, 110.4)	71.60 (42.0, 127.4)
Race, n (%)				
White	79 (66.9)	12 (50.0)	16 (69.6)	107 (64.8)
Black	7 (5.9)	1 (4.2)	2 (8.7)	10 (6.1)
Asian	27 (22.9)	11 (45.8)	5 (21.7)	43 (26.1)
Other	5 (4.2)	0 (0)	0 (0)	5 (3.0)
Geographic location, n (%)				
Europe	34 (28.8)	3 (12.5)	4 (17.4)	41 (24.8)
North America	44 (37.3)	5 (20.8)	7 (30.4)	56 (33.9)
Other*	40 (33.9)	16 (66.7)	12 (52.2)	68 (41.2)
Genotype, n (%)				
Intron 22 inversion	41 (35.0)	7 (33.3)	9 (39.1)	57 (35.4)
Frameshift	24 (20.5)	4 (19.0)	6 (26.1)	34 (21.1)
Missense mutation	22 (18.8)	4 (19.0)	1 (4.3)	27 (16.8)
Nonsense mutation	19 (16.2)	6 (28.6)	1 (4.3)	26 (16.1)
Splice site change	7 (6.0)	0 (0)	4 (17.4)	11 (6.8)
Intron 1 inversion	3 (2.6)	0 (0)	1 (4.3)	4 (2.5)
Duplication	1 (0.9)	0 (0)	0 (0)	1 (0.6)
NA	0 (0)	0 (0)	1 (4.3)	1 (0.6)
VWF antigen, IU/dL, median (IQR)	118.0 (85, 151)	129.0 (86, 166)	131.0 (83, 155)	118.0 (85, 153)
Prestudy FVIII regimen, n (%)				
Prophylaxis	87 (73.7)	0 (0)	0 (0)	87 (52.7)
Episodic	31 (26.3)	24 (100)	23 (100)	78 (47.3)
Estimated bleeding events in prior 12 mo, median (IQR)†				
Prior prophylaxis	6.0 (2, 15)	—	—	6.0 (2, 15)
Prior episodic	27.0 (17, 41)	29.5 (19, 44)	24.0 (15, 36)	27.0 (18, 40)
1 or more target joint, n (%)				
Prior prophylaxis	47 (39.8)	—	—	47 (28.5)
Prior episodic	26 (22.0)	22 (91.7)	18 (78.3)	66 (40.0)
HIV-positive, n (%)	25 (21.2)	4 (16.7)	7 (30.4)	36 (21.8)
HCV-positive, n (%)	55 (46.6)	14 (58.3)	13 (56.5)	82 (49.7)

—, none; HCV, hepatitis C virus; NA, not applicable.
*Other included Australia, New Zealand, Brazil, Hong Kong, India, Japan, Russia, and South Africa.
†Calculation was based on available data.

Based on the company's response to CQ A 20[2] which in turn cited Mahlangu et al (2014).[25]
CQ = clarification question; FVIII = clotting factor VIII; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; IU/dl = international units per decilitre; kg = kilogram; max = maximum; min = minimum; NA = not applicable; VWF = von Willebrand Factor; y = years

3.3.2.6 Pharmacokinetic data for A-LONG

The company provided the following summary of pharmacokinetic data as part of their response to CQ A 20.[2]

"*Comparative pharmacokinetic data for rFVIIIFc vs rFVIII were available for 28/30 patients in the sequential pharmacokinetics subgroup. The terminal half-life of rFVIIIFc was significantly longer than that of rFVIII (geometric mean: 19.0 vs 12.4 hours, respectively; p<0.001).*"[2]

3.3.2.7 Efficacy data for A-LONG

The company provided the following summary of efficacy data as part of their response to CQ A 20[2] whilst highlighting the availability of published information.[25]

- "*ABR was significantly reduced with prophylaxis by 92% (Arm 1) and 76% (Arm 2) compared with episodic treatment, based on estimates from a negative binomial regression model (2.91, 8.92, and 37.25 for Arms 1, 2, and 3, respectively; p<0.001). The median (IQR) observed ABRs in Arms 1, 2, and 3 were 1.6 (0.0, 4.7), 3.6 (1.9, 8.4), and 33.6 (21.1, 48.7), respectively.*"[2]
- "*Among patients receiving individualised prophylaxis, over the last 3 months on the study, the median dosing interval was 3.50 days (mean, 3.87 days) and the median weekly dose was 77.70 IU/kg.*"[2]
- "*Across all arms, 757 bleeding episodes were treated with rFVIIIFc during the efficacy period. Overall, 87.3% of bleeding episodes were resolved with 1 injection, and 97.8% were controlled with ≤2 injections. The median dose per injection to treat a bleeding episode was 27.35 IU/kg.*"[2] It was not clear from the clarification response nor from the published paper[25] whether all bleeding episodes were treated.

Further details of efficacy data for A-LONG are shown in Table 3.36.

Table 3.36: Efficacy data for A-LONG

	Arm 1: individualised prophylaxis (rFVIIIFc 25 to 65 IU/kg every 3 to 5 days)	Arm 2: weekly prophylaxis (rFVIIIFc 65 IU/kg)	Arm 3: episodic treatment (rFVIIIFc 10 to 50 IU/kg as required)
Randomised pts?	No	Yes	Yes
No. pts analysed	117	23	23
ABR (95% CI), negative binomial model	2.9 (2.3 to 3.7)	8.9 (5.5 to 14.5)	37.3 (24.0 to 57.7)
Percent reduction versus control (Arm 3)[a]	92 (p<0.001)	76 (p<0.001)	-
ABR – overall, median (IQR)	1.6 (0.0 to 4.7)	3.6 (1.9 to 8.4)	33.6 (21.9 to 48.7)
ABR – spontaneous, median (IQR)	0.0 (0.0 to 2.0)	1.9 (0.0 to 4.8)	20.2 (12.2 to 36.8)
ABR – traumatic, median (IQR)	0.0 (0.0 to 1.8)	1.7 (0.0 to 3.3)	9.3 (1.7 to 11.9)
No. pts (%) with 0 bleeding events	53 (45.3)	4 (17.4)	0

Weekly dose, median (range) in IU/kg	77.9 (54.0 to 141.5)	65.6 (59.4 to 70.7)	-
Weekly dose, mean (SD) in IU/kg	85.4 (19.3)	65.8 (2.9)	-

Based on Table 2 of Mahlangu et al (2014).[25]
[a]Reduction in ABR compared with Arm 3, calculated using negative binomial model.[25]
ABR = annualised bleeding rate; CI = confidence interval; IQR = interquartile range; IU/kg = international units per kilogram (of body weight); No. = number; pts = patients; rFVIIIFc = recombinant factor VIII Fc fusion protein; SD = standard deviation

Other efficacy outcome variables available from the published paper but not reproduced here include: joint ABR (spontaneous and traumatic); muscle ABR (spontaneous and traumatic); and the dosing interval during the last 3 months of the study for patients receiving individualised prophylaxis.[25]

3.3.2.8 HRQoL data for A-LONG

The company did not present HRQoL data for A-LONG,[2, 3] nor was this available from the published paper.[25]

3.3.2.9 Safety data for A-LONG

The company provided the following summary of safety data as part of their response to CQ A 20.[2] Again, the EAG noted that the details were based closely on published data.[25]

- "*No inhibitors were detected in any patients with an evaluable inhibitor test, including 110 patients with ≥50 exposure days, for whom the inhibitor incidence was 0% (95% CI, 0, 3.3); the inhibitor incidence overall was also 0% (95% CI, 0, 2.2).*"[2]
- "*Of the 164 patients exposed to rFVIIIFc (1 patient received only rFVIII on study), 108 (65.9%) reported at least one AE (excluding the perioperative period). The types of AEs were representative of events occurring in the general haemophilia population. AEs judged by the investigator to be related to rFVIIIFc treatment occurred in 10 (6.1%) patients; of these, arthralgia and malaise were reported in more than 1 patient (2 patients each).*"[2]

The published paper included details of SAEs outside of the perioperative period.[25] Among the 164 patients analysed overall, 12 (7.3%) had at least one SAE, none of which were considered by the investigator as related to recombinant clotting factor VIII Fc fusion protein (rFVIIIFc) treatment. There were no reports of SAEs relating to vascular thrombotic events, hypersensitivity or anaphylaxis. There was one death (suicide) secondary to polysubstance overdose in a patient with prior history of depression, which the investigator considered to be unrelated to rFVIIIFc treatment. Further details of SAEs are shown in the footnote of Table 3.37 below. The published paper indicated that safety data relating to the perioperative period had been considered separately and no unique concerns were found, however specific data were not provided.[25]

Further published details on safety data for A-LONG are summarised in Table 3.37 below.

Table 3.37: Safety data[a] for A-LONG

	Arm 1: individualised prophylaxis (rFVIIIFc 25 to 65 IU/kg every 3 to 5 days)	Arm 2: weekly prophylaxis (rFVIIIFc 65 IU/kg)	Arm 3: episodic treatment (rFVIIIFc 10 to 50 IU/kg as required)
Randomised pts?	No	Yes	Yes
No. pts analysed	117	24	23
Total AEs, n	219	46	23
Pts with ≥1 AE, n (%)	80 (68.4)	18 (75.0)	10 (43.5)
Most common AEs, n (%)[b]			
Nasopharyngitis	16 (13.7)	1 (4.2)	3 (13.0)
Arthralgia	10 (8.5)	2 (8.3)	1 (4.3)
URTI	6 (5.1)	0	3 (13.0)
Headache	5 (4.3)	6 (25.0)	2 (8.7)
Influenza	5 (4.3)	0	0
Pyrexia	3 (2.6)	1 (4.2)	1 (4.3)
Pts with ≥1 SAE[c], n (%)	10 (8.5)	2 (8.3)	0

Based on Table 4 of Mahlangu et al (2014).[25]
[a]Excludes the perioperative period.[25]
[b]Shows events occurring in ≥3% of patients.[25]
[c]SAEs across the three arms included: face injury, femur fracture, back pain with associated syncope, haemarthrosis, lumbar spinal stenosis, myalgia, inguinal hernia, tooth disorder, restless leg syndrome, polysubstance overdose and completed suicide, nephrolithiasis, respiratory distress, tachycardia and hypertensive emergency. The incidence of individual SAEs was 0.6%, with all occurring in one patient each. None of the reported 17 SAEs, including one death secondary to polysubstance overdose (suicide) in a patient with prior history of depression, were considered by the investigator as related to rFVIIIFc treatment. One SAE (femur fracture) indirectly resulted in discontinuation of rFVIIIFc treatment and withdrawal from the study because the patient required surgery to treat the fracture and did not have the 12 exposure days required for enrolling in the surgery subgroup.[25]
AE = adverse event; IU/kg = international units per kilogram (of body weight); n = number; pts = patients; rFVIIIFc = recombinant factor VIII Fc fusion protein; SAE = serious adverse event; URTI = upper respiratory tract infection

3.3.2.10 Risk of bias assessment for A-LONG

Table 3.38 below shows the risk of bias assessment as presented in Appendix D of the CS for the A-LONG trial.[16] The risk of bias assessment was performed using guidelines from NICE[28] however, the company did not state the source of information for the risk of bias assessment (e.g., a specific publication).

Table 3.38: Risk of bias assessment for the A-LONG trial

Study Name	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the onset of the study in terms of prognostic factors, for example, severity of the disease?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
A-LONG	Unclear: There is no in-depth discussion about randomisation methods.[a]	Unclear: There is no in-depth discussion about randomisation methods.	Unclear: The randomised treatment groups were similar in baseline characteristics other than some differences in race, HIV, and presence of target joints at baseline, but no statistical analysis was conducted.	No: The study was open label.	Unclear: The rate of study discontinuation was higher in the weekly prophylaxis regimen group (21%) compared to episodic regimen group (4%). The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Unclear: ITT analysis was not mentioned, and efficacy analyses were performed on data from all subjects who received ≥1 dose of rFVIIIFc. Missing data were not mentioned in the study.

Based on Table 12 of Appendix D of the CS.[16]
[a]Text in Section D.3.2 of Appendix D of the CS stated that randomisation was stratified based on individual annualised bleeding episodes in the prior 12 months.[16, 25]
CS = company submission; HIV = human immunodeficiency virus; ITT = intention-to-treat; rFVIIIFc = recombinant clotting factor VIII Fc fusion protein

EAG comment:

- The CS included limited details on the two comparator studies: HAVEN 3 and A-LONG. Whilst further information became available through the clarification process, additional details would have been desirable which have been added here by the EAG. The company highlighted relevant publications which was useful, however a detailed summary of both studies should have been provided with the CS.
- Possible baseline imbalances were seen for both studies. In the HAVEN 3 trial, this related to the number of bleeding events prior to study enrolment and the number of target joints.[46] These issues were also noted by the company in their risk of bias assessment of HAVEN 3 in Appendix D of the CS.[16] The EAG noted potential imbalances in the A-LONG trial for race, geographical location, haemophilia A genotype, HIV positive status and presence of target joints.[25] The company highlighted some of these issues in their risk of bias assessment.[16] The impact of such imbalances from either study on subsequent estimation is uncertain.
- The company's risk of bias assessment as presented in Appendix D of the CS was satisfactory for both studies.[16] Risks of bias related to potential baseline imbalances across randomised groups and open-label design in both studies and additionally for A-LONG, there was lack of clarity about group allocation methods and handling of missing data as well as potential imbalance in the number of participants who dropped out of the study.[16] The impact of these risk of bias on subsequent estimation is uncertain.
- The populations for HAVEN 3 and A-LONG are narrower (age ≥12 years with severe haemophilia A and without FVIII inhibitors)[25, 46] compared to those described in the NICE Final Scope (people with haemophilia A),[1] the company's DP (people with severe haemophilia A)[3] and the SLR eligibility criteria (people with haemophilia A with or without inhibitors).[16] As part of the clarification process, the EAG asked the company to explain how the data from XTEND-1, HAVEN-3 and A-LONG can address the NICE Final Scope given the narrower populations in all three trials (CQ A 24). The company's response was as follows:[2] "*The Company is submitting within the narrower population (people with severe haemophilia A), and as such the data from the three studies (XTEND-1, HAVEN-3, and A-LONG) align to this narrower population for the appraisal. While the Company would not expect efanesoctocog alfa to be routinely used to treat patients with mild or moderate haemophilia A, efmoroctocog alfa, for example, has been approved to treat the wider population of patients by regulatory bodies (e.g. Medicines & Healthcare products Regulatory Agency and European Medicines Agency), despite the clinical evidence base being focussed on patients with severe haemophilia A only*.[12, 49]" Whilst this provides a response of sorts, it does not explain how the CS can address the clinical effectiveness and cost effectiveness of efanesoctocog alfa in the parts of the population not represented by the submission, e.g., patients aged under 12 years and/or those with mild or moderate disease.
- As outlined earlier (Section 3.2.1), there is persisting uncertainty about the comprehensiveness of the presented evidence base, and it is possible that additional comparator studies could have been available that are not considered within the CS.
- The EAG noted that no data was provided in the CS relating to AEs experienced by patients treated with comparators evaluated in the HAVEN-3 and A-LONG RCTs. The company was asked to provide the necessary data and appropriate comparative analyses (CQ A.31 and 32). The company presented an overview of AEs across HAVEN 3, A-LONG and XTEND-1 (Table 3.39) and stated that, *"A comparative analysis of XTEND-1 and HAVEN 3 is not considered appropriate due to notable differences of the durations of efficacy periods between the trials. For the base case cost effectiveness analysis, patients in Group D HAVEN 3 were followed up for a median of 29 weeks (63*

patients), compared to 52 weeks in Arm A of XTEND-1 (133 patients).”and “…an ITC of AEs was not performed as the exposure times in each study were not comparable.” [2] The EAG thanks the company for this additional information, but also notes that there is a lack of comparative analysis.

Table 3.39: Overview of AEs across HAVEN 3, A-LONG and XTEND-1

Variable	HAVEN 3			A-LONG			XTEND-1		
	Group A	Group B	Group D	Arm 1	Arm 2	Arm 3	Arm A	Arm B On-demand	Arm B Prophylaxis
Number of patients	36	35	63	117	24	23	133	26	
Duration of exposure period (weeks), median (range)	29.3 [17.3-49.1]	30.1 [6.1-50.1]	33.1 [18.0-48.1]	32.6 [8.6-56.3]	28.0 [0.0001-38.4]	27.9 [14.8-31.1]	52.1 [1.1–55.1]	50.9 [27.1–53.1]	52.1 [27.1–53.1]
No. of AEs	143	145	236	219	46	23	361	22	11
Most common AEs, N (%)									
Injection-site reaction	9 (25)	7 (20)	20 (32)	0 (0)	0 (0)	1 (4.3)	3 (2.3)	0 (0)	0 (0)
URTI	4 (11)	4 (11)	8 (13)	6 (5.1)	0 (0)	3 (13)	3 (2.3)	0 (0)	0 (0)
Nasopharyngitis	2 (6)	6 (17)	10 (16)	16 (13.7)	1 (4.2)	3 (13)	6 (4.5)	0 (0)	0 (0)
Arthralgia	7 (19)	6 (17)	14 (22)	10 (8.5)	2 (8.3)	1 (4.3)	25 (18.8)	1 (3.8)	0 (0)
Headache	3 (8)	4 (11)	8 (13)	5 (4.3)	6 (25)	2 (8.7)	26 (19.5)	5 (19.2)	1 (3.8)
Influenza	1 (3)	3 (9)	5 (8)	5 (4.3)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)
Patients with one or more SAEs				10 (8.5)	2 (8.3)	0 (0)	13 (9.8)	2 (7.7)	0 (0)
No. of SAEs	1	3	10	–	–	–	16	2	0
AE leading to discontinuation of treatment, N (%)	0 (0)	1 (3)	0 (0)	1 (0.9)	1 (4.2)	1 (4.3)	2 (1.5)	0 (0)	0 (0)

Based on Table 31 of the company's clarification response.[2]
AEs = adverse events; URTI = upper respiratory tract infection

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 ITC methodology

In the absence of head-to-head trials comparing efanesoctocog alfa with each comparator, an ITC was conducted to compare the efficacy of prophylactic treatment with the comparators, emicizumab and efmoroctocog alfa.[3] The CS stated that the analysis primarily focussed on previously treated patients, consistent with the inclusion criteria of XTEND-1.

The two Phase 3 trials that were utilised as the evidence base for the ITC were HAVEN 3 to compare with emicizumab (99, 100), and A-LONG, to compare with efmoroctocog alfa (91, 101). The company argued that XTEND-1 did not form a connected network with the emicizumab trial, therefore the anchored comparison using either Bucher's indirect comparison or network meta-analysis were not feasible for the comparison between efanesoctocog alfa and comparators. The reasoning was not completely clear and appeared to be partly because the inclusion criteria differed between arms of XTEND-1 and HAVEN 3 in that in XTEND-1, only those receiving episodic treatment could be allocated to O-D arms, while in HAVEN 3, prophylaxis was assessed in patients receiving either prophylaxis or O-D treatments before entry. It was also stated that the treatments administered as episodic regimens differed across studies, therefore O-D arms could not be considered as common comparators for anchored between-treatment comparisons.

The effects of efanesoctocog alfa versus emicizumab were compared using an unanchored matching-adjusted indirect comparison (MAIC), while the comparison of efanesoctocog alfa versus efmoroctocog alfa used propensity score matching (PSM) methods, as proposed in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 guidelines.[50, 51]

EAG comment: The difference in treatment experience or any baseline characteristics should not necessarily preclude an anchored (connected) ITC and certainly not justify an unanchored one, which would still have the same limitations in terms of baseline characteristics. On the other hand, no common comparator would imply that an unanchored ITC is the only method available. However, the EAG wonder if indeed this is the case given that all three trials had an O-D arm, albeit with different treatments, efanesoctocog in XTEND-1, FVIII (SHL) in HAVEN 3 and efmoroctocog alfa (EHL FVIII) in A-LONG, at least for the outcome bleeding rate on the assumption that the type of O-D therapy should not affect bleeding rate. However, unfortunately, between arms there was no randomisation in XTEND-1 or A-LONG (at least between O-D and individualised prophylaxis). This therefore implies the need for an unanchored comparison.

3.4.1.1 Comparison with emicizumab

The company acknowledged that, as recommended in TSD 18, both prognostic variables and effect modifiers, thus both shall be included as covariates in the model.[51] They stated that in all analyses using the MAIC method XTEND-1 patient-level data was adjusted for every baseline characteristic provided that adequate data is reported in the comparator studies.

Following the matching of baseline characteristics, the effects of efanesoctocog alfa were re-estimated using the weights obtained during the matching procedure, so that the new estimates could be interpreted as the effects of efanesoctocog alfa when administered in the population of the comparator trial.[3] The company also stated that for consistency, the new effects were estimated using the same statistical methods as adopted the comparator trial.

The company stated that the rates for comparators estimated using negative binomial model are directly reported from the model as the log of the rates and that the between-treatment comparison expressed on the log scale and exponentiated results in the estimate of incidence rate ratio (IRR).[3] They also stated that the absolute difference in rates calculated from two mean (standard deviation [SD]) values results in the comparison following normally distributed mean difference (MD) in the incidence rate.

The company stated that, although all ABRs in both trials were calculated using a negative binomial model, stratification for the history of previous bleeds (<9 or ≥9 bleeding events in the previous 24 weeks was only used for HAVEN 3 due to lack of such data in XTEND-1.[3]

The following comparisons were made:

- Arm D of HAVEN 3, emicizumab QW (prior prophylaxis) versus Arm A of XTEND-1 (prior prophylaxis)
- Arm A of HAVEN 3, emicizumab QW (prior O-D) versus Arm B of XTEND-1 (prior O-D)
- Arm B of HAVEN 3, emicizumab Q2W (prior O-D) versus Arm B of XTEND-1 (prior O-D)
- Pooled Arms A, B and D of HAVEN 3, emicizumab QW and Q2W versus pooled Arms A and B of XTEND-1

In comparisons of individual arms, ABRs for any bleed (treated and untreated), treated bleeds, spontaneous treated bleeds and joint treated bleeds were assessed. In the comparison of pooled arms, change from baseline in Haemophilia Joint Health Score (HJHS) joint score and total score were assessed.

The company also stated that, prior to matching: *"the population of XTEND-1 was trimmed to remove patients with baseline characteristics outside of the reported range for HAVEN 3. For comparisons with individual arms, this was based on age and body weight. For the comparison with the pooled arms, this was based on age and body mass index (BMI)."* (p. 91)[3] A table to show the effect of this has been reproduced in Table 3.40.

Table 3.40: Baseline characteristics

	HAVEN 3 Range of baseline variables			**XTEND-1 IPD**				
Arm	**Age (years)**	**Body weight (kg)**	**BMI (kg/m²)**	**Arm (N)**	**Age (years)**	**Body weight (kg)**	**BMI (kg/m²)**	**Patients remaining after restrictions (N)**
Arm D (prior PHX)	13–68	52.8–139	N/A	Arm A (n=133)	12–72	33.9–132.8	N/A	119
Arm A (prior O-D)	19–77	53.1–107.3	N/A	Arm B (n=26)	23.5–68.5	50–119.5	N/A	22
Arm B (prior PHX)	20–65	56.3–121.4	N/A	Arm B (n=26)	23.5–68.5	50–119.5	N/A	24
Arms A, B and D	13–77	N/A	19.2–40.6	Pooled arms (131,	12–68.5	N/A	15.0–40.8	114

	HAVEN 3 Range of baseline variables			XTEND-1 IPD				
Arm	**Age (years)**	**Body weight (kg)**	**BMI (kg/m^2)**	**Arm (N)**	**Age (years)**	**Body weight (kg)**	**BMI (kg/m^2)**	**Patients remaining after restrictions (N)**
with evaluable HJHS				HJHS assessed)				

Based on Table 34, CS.[3]
BMI = body mass index; CS = company submission; HJHS = Haemophilia Joint Health Score; IPD = individual patient data; N/A = not applicable; O-D = on-demand; PHX = prophylaxis

Matching was then performed on the basis of propensity scores estimated using a set of covariates, the company stating that: *"…in all analyses using the MAIC method XTEND-1 patient-level data was adjusted for every baseline characteristic provided that adequate data is reported in the comparator studies."* (p. 89) However, the set of baseline characteristics used for matching did vary by comparison, age being the only one that was common to all four. Body weight was common to all except with the pooled Arms A, B and D of HAVEN 3, emicizumab QW and Q2W versus pooled Arms A and B of XTEND-1, where BMI was used instead. Proportion of patients with one or more target joints was also common to all except Arm D of HAVEN 3, emicizumab QW (prior prophylaxis) versus Arm A of XTEND-1 (prior prophylaxis), where three categories of target joints were used. Also, only three covariates were used for Arm A of HAVEN 3, emicizumab QW (prior O-D) versus Arm B of XTEND-1 (prior O-D) and Arm B of HAVEN 3, emicizumab Q2W (prior O-D) versus Arm B of XTEND-1 (prior O-D).

EAG comment: The following choices were not clearly justified:

- How the various arms from HAVEN-3 were chosen given that only Arm D contained patients with the same experience i.e., prior prophylaxis. In fact, although Arms A and B were chosen for a comparison in the prior O-D population, the majority of patients had received prophylaxis previously i.e., 26/36 and 25/35 respectively.[46] However, it is also unclear whether prior experience (O-D or prophylaxis) makes much of a difference to effectiveness of prophylaxis given that the difference between Arm A (previous prophylaxis) and Arm B (previous O-D) in XTEND-1 in mean (SD) ABR seems negligible: 0.71 [redacted] and 0.69 (1.35) respectively. Indeed, the company argued in Section B.3.3.2.1 of the CS that prior treatment was not expected to be a treatment effect modifier in order to use data from Arm B of HAVEN 3, emicizumab Q2W (prior O-D) versus Arm B of XTEND-1 (prior O-D) to inform the cost effectiveness analysis (see Section 4.2.6.1).
- Why outcomes assessed varied by whether arms were pooled or not.
- Why patients were removed from XTEND-1 (population trimmed) prior to matching and how the baseline characteristics were chosen for this purpose.
- How covariates were chosen for matching given that the stated intention was to use all available data and there was no justification based on empirical evidence or expert opinion as to role in prognosis or treatment effect modification. In response to clarification, the company stated that all available baseline characteristics were used regardless of prognostic status.[2] However, it is not clear to the EAG why there was therefore variation in those characteristics between comparisons, which appeared to use the same trial data (from XTEND-1).

The lack of justification for these choices constitutes a key issue. The EAG would therefore recommend that further justification, based on empirical evidence and/or clinical expert opinion is provided as well as sensitivity analysis be conducted, which uses the pooled arms for all ABR outcomes and without any trimming.

The EAG also requested that further justification be provided for the use of a MAIC and the employment of an alternative method of population adjustment given the unreliability of all methods of population adjustment, as reported in NICE TSD 18, which the company provided in the response to CL in the form of a simulated treatment comparison (STC), at least for one outcome (any bleeding).[2, 51] The results are shown in Section 3.4.2.1.

3.4.1.2 Comparison with efmoroctocog alfa

The company stated that the PSM method allowed for estimation of both IRR and MD for incidence rate comparison between efanesoctocog alfa and efmoroctocog alfa and that the following information was "*traced*" during the PSM and reported:[3]

- The comparison of baseline characteristics between XTEND-1 and A-LONG trial
- Effective sample size
- Bar charts for distribution of weights
- Estimates of efficacy before and after adjustment as well as the results of population-adjusted indirect comparison.

They also stated that optimal full matching was performed using the MatchIt package (citing Ho et al, (2011)[52] in R Studio, which called functions from the Optmatch package (citing Hansen (2004)[53] and Hansen & Klopfer, (2006)[54]).

Although not specified in the CS, as for the comparison with emicizumab, ABRs for any bleed (treated and untreated), treated bleeds, spontaneous treated bleeds and joint treated bleeds were assessed. Also assessed were:[3] proportion of patients without any treated bleeding (odds ratio [OR]), proportion of patients without spontaneous treated bleeding (OR), proportion of patients without joint treated bleeding (OR). FVIII consumption, IU/kg/y (MD), Haem-A-QoL Total score (MD) and Haem-A-QoL Physical score (MD).

The company stated that, unlike with the comparison with emicizumab, all trial data were pooled regardless of treatment experience (prophylaxis or O-D) from both X-TEND (n=159) and A-LONG (n=117 – one patient was excluded because treatment dosing was different to that specified in the EMA and FDA labels).[16] Matching employed eight baseline characteristics (mean age, mean weight, prior prophylaxis, mean number of target joint, percentage of patients with 0 target joint, mean number of prior bleeds, percentage HIV and percentage HCV) for all outcomes and additionally Haem-A-QoL scores for Haem-A-QoL Total score (MD) and Haem-A-QoL Physical score (MD). Choice of baseline characteristics was not explicitly justified according to empirical evidence or expert opinion of prognosis or effect modification.

EAG comment: Although the company stated that MD was used as a treatment effect (efanesoctocog versus comparator estimate) for rate, which presumably means ABR, ABR treatment effect outcomes were only reported as an IRR, and MD was only used for the treatment effect on HJHS.[3] However, the EAG considers this to be of little concern given the relevance of IRR.

As stated above, the EAG considers that pooling regardless of prior treatment experience might make little difference to treatment effect. Matching on this characteristic should aid reduction in any bias, although the difference in percentage prior prophylaxis is small (see Table 3.41 below). It was not explicitly stated that all available baseline characteristics were used or how the choice was made.

As recommended by TSD 17, the EAG requested an alternative method of adjusting the IPD, which the company supplied in response to the CL, at least for one of the outcomes already estimated using matching, ABR (any treated bleeding).[2] This method used inverse probability weighting (IPW) using the same eight baseline characteristics. The results are described in Section 3.4.2.2 below. Nevertheless, as with the comparison with emicizumab, lack of justification of baseline characteristics for adjustment is a key issue.

3.4.2 ITC results

3.4.2.1 Comparison with emicizumab

For each comparison, depending on prior experience, a table showing the effect of weighting on effective sample size (ESS) and matching on baseline characteristics was presented. Given that matching achieved the same point estimates for all characteristics on which matching was based for all comparisons, only example is shown in Table 3.3 below. What did vary between comparisons was ESS (percentage of original sample):

- 76 (64%): Arm D of HAVEN 3, emicizumab QW (prior prophylaxis) versus Arm A of XTEND-1 (prior prophylaxis)
- 14 (65%): Arm A of HAVEN 3, emicizumab QW (prior O-D) versus Arm B of XTEND-1 (prior O-D)
- 19 (78%): Arm B of HAVEN 3, emicizumab Q2W (prior O-D) versus Arm B of XTEND-1 (prior O-D)
- 37 (32%) and 19 (32%) for HJHS Total score and Joint score respectively: pooled Arms A, B and D of HAVEN 3, emicizumab QW and Q2W versus pooled Arms A and B of XTEND-1.

A histogram of weights was also presented in Figures 10 to 14 of the CS, an example of which is shown in Figure 3.9. Note that all histograms seem skewed towards zero with extreme values that seem to vary as expected with percentage ESSs i.e. they varied from about 2.5 for Arm B of HAVEN 3, emicizumab Q2W (prior O-D) versus Arm B of XTEND-1 (prior O-D) to about eight for the pooled Arms A, B and D of HAVEN 3, emicizumab QW and Q2W versus pooled Arms A and B of XTEND-1.

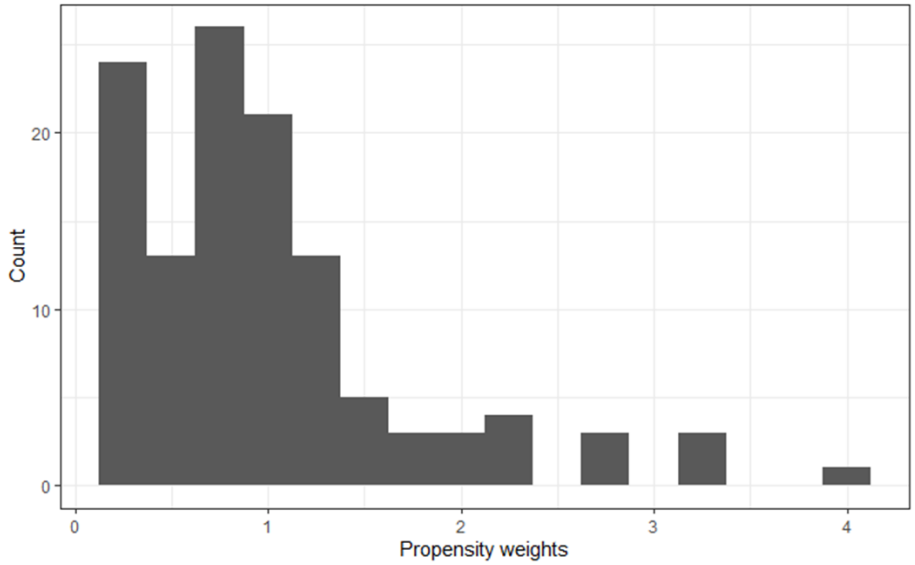
Table 3.41: Matching of baseline characteristics between XTEND-1 Arm A and HAVEN 3 Arm D (prior prophylaxis)

Variables	XTEND-1 Arm A, baseline			HAVEN 3 Arm D, baseline		XTEND-1 Arm A, after matching			
	Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS %
Mean age	34.91	14.23	119	36.4	14.4	36.4	14.4	76	64%
Mean weight	81.26	16.74		79.0	15.4	79.0	15.4		
% pts with 0 TJ	78.2%	N/A		58.7%	N/A	58.7%	N/A		
% pts with 1 TJ	5.9%			12.7%	N/A	12.7%			

Variables	XTEND-1 Arm A, baseline			HAVEN 3 Arm D, baseline		XTEND-1 Arm A, after matching			
	Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS %
% pts with 2+ TJ	16.0%			28.6%	N/A	28.6%			
% White	54.6%			74.6%	N/A	74.6%			
% Asian	21.0%			19.0%	N/A	19.0%			

Based on Table 35 of Document B of the CS.[3]
CS = company submission; ESS = effective sample size; N/A = not applicable; pts = patients; SD = standard deviation; TJ = target joint; % = percentage

Figure 3.9: Histogram of weights from MAIC adjustments comparing with HAVEN 3 Arm D



Based on Figure 10, CS.[3]
CS = company submission; MAIC = matching-adjusted indirect comparison

Table 3.42: Summary of the results for the comparison between efanesoctocog alfa versus emicizumab based on HAVEN 3

Endpoint	Results for comparison between efanesoctocog alfa *versus* emicizumab (HAVEN 3)			
	versus EMI QW (prior PHX)	*versus* EMI QW (prior O-D)	*versus* EMI Q2W (prior O-D)	*versus* EMI QW and Q2W (prior O-D and PHX)
ABR (any bleeding) (IRR)	**0.32 [0.19; 0.56]**	**0.34 [0.12; 0.95]**	**0.28 [0.10; 0.81]**	N/A
ABR (any treated bleeding) (IRR)	**0.50 [0.29; 0.86]**	0.46 [0.16; 1.37]	0.47 [0.15; 1.44]	N/A
ABR (spontaneous treated bleeding) (IRR)	0.62 [0.25; 1.50]	0.45 [0.11; 1.89]	1.35 [0.30; 6.18]	N/A
ABR (joint treated bleeding) (IRR)	**0.48 [0.24; 0.95]**	0.59 [0.18; 1.49]	0.63 [0.17; 2.29]	N/A

Endpoint	Results for comparison between efanesoctocog alfa *versus* emicizumab (HAVEN 3)			
	versus EMI QW (prior PHX)	*versus* EMI QW (prior O-D)	*versus* EMI Q2W (prior O-D)	*versus* EMI QW and Q2W (prior O-D and PHX)
HJHS Total score (MD)	N/A	N/A	N/A	**–2.37 [–4.36; –0.39]**
HJHS Joint score (MD)	N/A	N/A	N/A	**–2.06 [–3.97; –0.14]**

Based on Table 40, CS.[3]
ABR = annualised bleeding rate; CS = company submission; EMI = emicizumab; HJHS = Haemophilia Joint Health Score; O-D = on-demand; PHX = prophylaxis; QW = once weekly, Q2W = every 2 weeks; IRR = incidence rate ratio; MD = mean difference

Notes:	
	Favours Efanesoctocog alfa, significant
	Favours Efanesoctocog alfa, not significant
	Favours comparator, not significant
N/A	*No data/analysis not feasible*
bold	***Statistically significant difference***

EAG comment: As demonstrated in Table 3.42, matching was successful for all baseline characteristics in all comparisons. It might also be argued that there the weights required to balance the baseline characteristics were generally not extreme, perhaps those for the pooled Arms A, B and D of HAVEN 3, emicizumab QW and Q2W versus pooled Arms A and B of XTEND-1 being of greater concern, as reflected in the smaller percentage ESS. However, as TSD 18 states, unless the model for adjustment has been correctly specified i.e. by including all prognostic characteristics, the reliability of a MAIC in reducing bias is highly questionable. The company did, however, provide an alternative method, an STC, at least for one outcome, ABR (any bleeding) for the comparison of Arm D of HAVEN 3, emicizumab QW (prior prophylaxis) versus Arm A of XTEND-1 (prior prophylaxis). The company claimed that the results of the STC were highly consistent with those using the MAIC with IRR varying depending on the STC model. The IRRs for any bleeding were:

- Arm D of HAVEN 3, emicizumab QW (prior prophylaxis) versus Arm A of XTEND-1 (prior prophylaxis): 0.34 [0.20; 0.58],
- Arm A of HAVEN 3, emicizumab QW (prior O-D) versus Arm B of XTEND-1 (prior O-D): 0.30 [0.11; 0.83]
- Arm B of HAVEN 3, emicizumab Q2W (prior O-D) versus Arm B of XTEND-1 (prior O-D): 0.27 [0.10; 0.75]

The EAG considers that this is similar to 0.32 [0.19; 0.56] estimated using the MAIC.

The results show that efanesoctocog alfa was more effective than emicizumab at any dose in reducing the rate of any bleeding and regardless of prior treatment experience. It was also more effective in terms of HJHS (Total or Joint). With more uncertainty, it appeared to be more effective in terms of other bleeding outcomes except versus Q2W after prior O-D treatment where emicizumab might be more effective. These results should be considered in light of non-randomised (low quality evidence) and methodological issues identified in Section 3.4.1.

3.4.2.2 Comparison with efmoroctocog alfa

Tables 3.43 and 3.44 show the effect of matching on the baseline characteristics. The outcomes are shown in Table 3.45.

Table 3.43: Matching of baseline characteristics between XTEND-1 pooled arms and A-LONG for models assessing bleeding outcomes and FVIII consumption

Variables in PSM model used for ABRs, % of patients with no bleeding and FVIII consumption	Before matching					After matching					
	XTEND-1 (Arms A and B)		A-LONG (Individ. PHX)		P-value for difference	XTEND-1 (Arms A and B)		A-LONG (Individ. PHX)			P-value for difference
	Estimate mean (SD)/%	N	Estimate mean (SD)/%	N		Estimate mean (SD)/%	ESS (%)	Estimate mean (SD)/%	% balance improv.	ESS (%)	
PSM model: age + weight + prior regimen + target joint + prior bleeds + HIV + HCV (caliper: SD = 0.1, age = 20, weight = 20, target joint = 5, prior bleeds = 5)											
Mean age	35.36 (15.61)	145	33.05 (12.79)	116	0.190	29.52 (12.39)	87 (60%)	30.73 (11.75)	48	30 (26%)	0.632
Mean weight	77.42 (19.01)		73.35 (15.15)		0.056	73.53 (13.97)		73.65 (12.47)	97		0.964
Prior prophylaxis	84.1%		73.3%		**0.031**	89.7%		95.4%	47		0.338
Mean number of TJ	0.938 (1.741)		1.672 (2.072)		**0.003**	0.609 (1.417)		0.730 (1.489)	84		0.698
% pts with 0 TJ	70.3%		37.9%		**<0.001**	78.2%		75.7%	92		0.777
Mean number of prior bleeds	8.34 (15.55)		18.31 (22.37)		**<0.001**	4.40 (8.39)		5.04 (7.98)	94		0.710
% HIV	13.8%		21.6%		0.099	9.2%		6.9%	70		0.698
% HCV	34.5%		47.4%		**0.034**	33.3%		37.7%	66		0.660

Based on Table 22 of Appendix D of the CS.[16]

Statistical test: two sample t-test for continuous variables, two-sample test for equality of proportions for binary variables

Bold – statistically significant difference in baseline characteristic between studies.

Blue – percent balance improvement of baseline characteristic after PSM adjustment.

ABR = annualised bleed rate; CS = company submission; ESS = effective sample size; FVIII = clotting Factor VIII; HCV = hepatitis C virus; HIV = human immunodeficiency; PHX = prophylaxis; PSM = propensity score matching; pts = patients; SD = standard deviation; TJ = target joint; % = percentage

Table 3.44: Matching of baseline characteristics between XTEND-1 pooled arms and A-LONG for models assessing change from baseline in Haem-A-QoL scores

Variables in PSM model used for: - Haem-A-QoL Total score - Haem-A-QoL Physical domain score	Before matching					After matching					
	XTEND-1 (Arms A and B)		A-LONG (Individ. PHX)		P-value for difference	XTEND-1 (Arms A and B)		A-LONG (Individ. PHX)			P-value for difference
	Estimate mean (SD)/%	N	Estimate mean (SD)/%	N		Estimate mean (SD)/%	ESS (%)	Estimate mean (SD)/%	% balance improv.	ESS (%)	
PSM model for Haem-A-QoL Total outcome: age + weight + prior regimen + target joint + zero target joints + prior bleeds + HIV + HCV + Haem-A-QoL Total (caliper: SD = 0.05, age = 15, weight = 55, prior bleeds = 2, baseline Haem-A-QoL Total = 30)											
Mean age	39.60 (13.77)	108	34.08 (11.06)	76	**0.003**	29.58 (12.32)	20 (19%)	32.70 (9.78)	43	14 (19%)	0.414
Mean weight	80.26 (17.42)		73.65 (15.58)		**0.008**	73.22 (14.94)		74.39 (17.48)	82		0.839
% prior prophylaxis	80.6%		78.9%		0.789	95.0%		95.0%	100		1.000
Mean number of TJ	1.000 (1.761)		1.711 (2.084)		**0.016**	0.500 (1.204)		0.650 (1.276)	79		0.731
% pts with 0 TJ	67.6%		39.5%		**<0.001**	85.0%		75.0%	64		0.463
Mean no. of prior bleeds	9.90 (16.71)		18.82 (23.40)		**0.005**	2.90 (5.05)		2.90 (4.99)	100		1.000
% HIV	16.7%		25.0%		0.165	10.0%		10.0%	100		1.000
% HCV	40.7%		56.6%		**0.034**	35.0%		45.0%	37		0.557
Haem-A-QoL Total	32.40 (17.38)		30.17 (16.22)		0.375	25.55 (13.08)		24.40 (16.05)	48		0.824
PSM model for Haem-A-QoL Physical domain outcome: age + weight + prior regimen + target Joint + zero target joints + prior bleeds + HIV + HCV + Haem-A-QoL Physical domain (caliper: SD = 0.1, prior bleeds = 8, baseline Haem-A-QoL Physical domain = 45)											
Mean age	39.60 (13.77)	108	35.61 (12.35)	90	**0.033**	35.52 (12.39)	70 (65%)	35.01 (12.27)	87	28 (31%)	0.852
Mean weight	80.26 (17.42)		74.33 (15.51)		**0.012**	77.45 (14.66)		78.49 (15.07)	83		0.757

Variables in PSM model used for: - Haem-A-QoL Total score - Haem-A-QoL Physical domain score	Before matching					After matching					
	XTEND-1 (Arms A and B)		A-LONG (Individ. PHX)		P-value for difference	XTEND-1 (Arms A and B)		A-LONG (Individ. PHX)			P-value for difference
	Estimate mean (SD)/%	N	Estimate mean (SD)/%	N		Estimate mean (SD)/%	ESS (%)	Estimate mean (SD)/%	% balance improv.	ESS (%)	
% Prior prophylaxis	80.6%		76.7%		0.505	84.3%		82.9%	63		0.862
Mean number of TJ	1.000 (1.761)		1.733 (2.228)		**0.012**	1.029 (1.844)		1.035 (1.902)	99		0.989
% pts with 0 TJ	67.6%		40.0%		**<0.001**	67.1%		69.5%	91		0.820
Mean no. of Prior bleeds	9.90 (16.71)		18.83 (24.56)		**0.004**	6.94 (10.41)		6.72 (10.24)	98		0.924
% HIV	16.7%		27.8%		0.059	18.6%		16.3%	80		0.792
% HCV	40.7%		57.8%		**0.017**	42.9%		48.1%	69		0.637
Haem-A-QoL Physical	37.96 (23.84)		41.46 (24.9)		0.317	36.71 (23.11)		35.80 (21.96)	74		0.855

Based on Table 23 of Appendix D of the CS.[16]
Statistical test: two sample t-test for continuous variables, 2-sample test for equality of proportions for binary variables
Bold – statistically significant difference in baseline characteristic between studies.
Blue – percent balance improvement of baseline characteristic after PSM adjustment.
ABR = annualised bleed rate; CS = company submission; ESS = effective sample size; FVIII = clotting Factor VIII; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; HCV = hepatitis C virus; HIV = human immunodeficiency; PHX = prophylaxis; PSM = propensity score matching; pts = patients; SD = standard deviation; TJ = target joint; % = percentage

Table 3.45: Summary of the results for the comparison between efanesoctocog alfa versus efmoroctocog alfa based on A-LONG

Endpoint	Results for comparison between efanesoctocog alfa versus efmoroctocog alfa
ABR (any treated bleeding) (IRR)	**0.29 [0.17; 0.51]**
ABR (spontaneous treated bleeding) (IRR)	**0.21 [0.09; 0.49]**
ABR (joint treated bleeding) (IRR)	**0.37 [0.20; 0.71]**
Proportion of patients without any treated bleeding (OR)	**1.99 [1.20; 3.30]**
Proportion of patients without spontaneous treated bleeding (OR)	**2.06 [1.21; 3.52]**
Proportion of patients without joint treated bleeding (OR)	**1.73 [1.12; 2.67]**
Factor VIII consumption, IU/kg/y (MD)	–1,032 [–2,621; 557]
Haem-A-QoL Total score (MD)	–2.43 [–8.48; 3.62]
Haem-A-QoL Physical score (MD)	–7.01 [–14.69; 0.67]

Based on Table 41, CS.[3]
ABR = annualised bleeding rate; CS = company submission; EFMO = efmoroctocog alpha; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; IRR = incidence rate ratio; MD = mean difference; OR = odds ratio

Notes:	
	Favours Efanesoctocog alfa, significant
	Favours Efanesoctocog alfa, not significant
bold	***Statistically significant difference***

EAG comment: It appears, that on the whole, matching was reasonably successful for the nine baseline characteristics. However, there was generally a high penalty in terms of ESS, which was only n=30 and 26% of the original sample size for the A-LONG data for bleeding outcomes and FVIII consumption. However, this seems not to have been a problem for bleeding outcomes, which showed a statistically significant effect, which was in favour of efanesoctocog alfa.

The effect on balancing characteristics was generally good, the one exception being the percentage of patients with 0 target joint where there remained a fairly large discrepancy (60.3% versus 42.5% for XTEND-1 versus A-LONG respectively). The IRR point estimate did decrease from 0.29 with PSM to 0.23 with IPW, whilst remaining statistically significant (95% CI: 0.15 to 0.35).[2] The IPW estimate was also virtually identical to the naïve one (0.23 (0.15 to 0.36). Given the lack of balance of one of the baseline characteristics using the IPW method, the EAG is inclined to slightly prefer the original CS method of PSM.

The results show that efanesoctocog alfa was more effective than efmoroctocog alfa in reducing the rate of any bleeding of any kind. With greater uncertainty, this also appeared to be the case for as well as FVIII consumption and QoL. These results should be considered in light of non-randomised (low quality evidence) and methodological issues identified in Section 3.4.1.1.

3.5 Additional work on clinical effectiveness undertaken by the EAG

The EAG conducted a risk of bias assessment on the XTEND-1 study. The results of this are shown in Section 3.2.6.

3.6 Conclusions of the clinical effectiveness Section

The CS[3] and response to clarification[2] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence for FVIII replacement therapies and non-factor replacement therapies for the treatment of haemophilia A. Searches were conducted in February 2021, and updated in September 2023. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted, although additional terms for the population, and the inclusion of non-English language studies could have retrieved additional relevant records.

The clinical effectiveness SLR retrieved one intervention study (XTEND-1) and two comparator studies (HAVEN 3 and A-LONG). It is possible that additional relevant studies could have been missed. This is partly due to omission of non-English language studies from the search and study selection process. In addition, the documentation of included and excluded records suggests that studies may have been excluded from the SLR for reasons that were not pre-specified. The EAG conducted its own risk of bias assessment of the intervention study (XTEND-1) as the company declined to provide this.

The XTEND-1 study evaluated the clinical effectiveness of efanesoctocog alfa in PTPs aged 12 years or older with severe haemophilia A and no history of a positive FVIII inhibitor test result. XTEND-1 comprised two non-randomised arms: patients receiving 50 IU/kg efanesoctocog alfa IV QW on a prophylactic regimen for 52 weeks (Arm A); and patients receiving efanesoctocog alfa 50 IU/kg IV O-D for 26 weeks followed by a switch to prophylaxis (efanesoctocog alfa 50 IU/kg IV QW for another 26 weeks) (Arm B). The results suggested reduced ABR for efanesoctocog alfa given prophylactically when compared with the O-D regimen. There is persisting uncertainty as to whether XTEND-1 is representative of the UK target population given that the study population was narrower than that described in the NICE Final Scope and DP and data on the UK subgroup were not available on request. In addition, given that the population in XTEND-1 is narrower (PTPs aged ≥12 years with severe haemophilia A and without inhibitors) than those specified in the NICE Final Scope (people with haemophilia A)[1] and the company's DP (people with severe haemophilia A),[3] it is not clear whether the data from XTEND-1 can be applied in a valid way to patients younger than 12 years, those with mild or moderate disease or those with a history or current presence of FVIII inhibitors. The EAG considers that XTEND-1 is at risk of bias because of the use of non-concurrent, intra-patient comparisons potentially resulting in the observed treatment effect being confounded because of change in other aspects of care over time. In addition, it was not clear whether outcomes had been verified by an IRC.

Given the lack of randomised trials with a common comparator, an unanchored ITC had to be conducted to compare efanesoctocog alfa with emicizumab and efmoroctocog alfa. For the former, the method used to reduce confounding was a type of population adjustment, a MAIC, given the lack of IPD in the comparator trial, HAVEN 3. For the latter, IPD from A-LONG were available and so an IPD-based method (PSM) was used. A number of methodological issues were identified in these ITCs, most problematic for the MAIC, which is the less robust of the two approaches. In order to mitigate these issues, the EAG requested alternative methods, which the company implemented at least for a subset of outcomes, an STC (only for any bleeding) instead of the MAIC, and IPW (only for any treated bleeding) instead of PSM. The results of the MAIC show that efanesoctocog alfa was more effective than emicizumab at any dose in reducing the rate of any bleeding and regardless of prior treatment experience. It was also more effective in terms of HJHS (Total or Joint). With more uncertainty, it appeared to be more effective in terms of other bleeding outcomes except versus Q2W after prior O-D treatment where emicizumab might be more effective. The results of the STC seemed to support the

findings for any bleeding. The results of the PSM analysis show that efanesoctocog alfa was more effective than efmoroctocog alfa in reducing the rate of any bleeding of any kind. With greater uncertainty, this also appeared to be the case for as well as FVIII consumption and QoL. The results for any treated bleeding were also supported by the IPW analysis. Nevertheless, there remains some concerns in the methods used to estimate the effectiveness of efanesoctocog versus both comparators, but especially versus emicizumab, which were identified as a key issue.

4. COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of CEA studies. However, the search Section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness Section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness and resource identification presented in the CS.[3, 55-57] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[17, 18] The CS[3] was checked against the STA specification for company/sponsor submission of evidence.[19] The EAG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS provides details of a SLR conducted to identify relevant economic evaluations in haemophilia.[55] Searches were undertaken in September 2023.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-11/9/23	11/9/23
MEDLINE	Ovid	1946-11/9/23	11/9/23
Additional resources			
NHS EED	Internet	Not stated	18/9/23
HTA Database	Internet	Not stated	18/9/23
HTA websites			
• National Institute for Health and Care Excellence • Scottish Medicines Consortium • Institute for Clinical and Economic Review • Haute Autorité de Santé • Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen • Pharmaceutical Benefits Advisory Committee	Internet	Not stated	18/9/23

CS = company submission; NHS EED = NHS Economic Evaluation Database; HTA = Health Technology Assessment

EAG comment:

- Searches were undertaken in September 2023 to identify relevant economic evaluations in haemophilia. The CS, Appendix G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 3, 55]
- In addition to bibliographic database searches, a good range of HTA organisation websites was searched. Reference checking was conducted.
- Database searches were conducted for references published since 2013. They were not limited by language of publication.
- The database searches contained a population facet for haemophilia. This was then combined with a filter containing terms for economic evaluations. The filter was not referenced; however, it contained an extensive combination of subject heading terms and free text terms, and the EAG considered it appropriate.
- Searches were well structured, transparent and reproducible; however, searches of additional resources may have retrieved further useful references.

Appendix H of the CS provides details of a SLR conducted to identify relevant HRQoL studies in patients with haemophilia.[3, 56] Searches were undertaken in June 2022.

A summary of the sources searched is provided in Table 4.2.

Table 4.2: Data sources searched for HRQoL studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
MEDLINE	Ovid	1946-17/6/22	20/6/22
Embase	Ovid	1974-13/6/22	14/6/22
CENTRAL CDSR	Cochrane Library	To Issue 6 of 12, June 2022	14/6/22
Conference Proceedings Citation Index - Science	Web of Science	1990-date	10/6/22
EconLit	Ovid	1886-6/6/22	9/6/22
HTA Database	Internet	N/A	9/6/22
NHS EED	Internet	N/A	9/6/22
Other resources			
ScHARRHUD	Internet	N/A	9/6/22
Additional conferences			
European Hematology Association - Congress 2022 World Federation of Hemophilia - World Congress 2022	Internet	2022 2022	10/6/22
HTA Organisations			
National Institute for Health and Care Excellence Canadian Agency for Drugs and Technologies in Health	Internet	Not stated	10/6/22 13/6/22

Institute for Clinical and Economic Review			10/6/22
CENTRAL = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Review; CS = company submission; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS EED = National Health Service Economic Evaluation Database; ScHARRHUD = School of Health and Related Research Health Utilities Database			

EAG comment:

- Searches were undertaken in June 2022 to identify HRQoL studies on patients with haemophilia. The CS, Appendix H and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 3, 56]
- In CQ A6, the company was asked to update the HRQoL searches given that these were conducted in June 2022 whereas the clinical and cost effectiveness searches were last run in September 2023. The company mentioned the possibility of updating the former searches in their response, however had not provided this at the point of the EAG report submission.[2]
- A comprehensive range of bibliographic databases, HTA organisation websites and conference proceedings were searched. Reference checking was conducted.
- Database searches were conducted for references published since 2012. They were not limited by language of publication.
- The database searches contained a population facet for haemophilia. In the Embase, MEDLINE and Cochrane Library searches, this was then combined with a filter containing terms health utilities. Although the filter was not referenced it contained an extensive combination of subject heading terms and free text terms, and the EAG considered it appropriate.
- Searches were well structured, transparent and reproducible. Documentation of the search methods was particularly detailed, clear and concise.

Appendix I of the CS provides details of a SLR conducted to identify relevant cost and health care resource use (HCRU) data to populate the economic model.[3, 57] Searches were undertaken in June 2022.

A summary of the sources searched is provided in Table 4.3.

Table 4.3: Data sources searched for cost/resource use studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
MEDLINE	Ovid	2012-6/6/22	6/6/22
Embase	Ovid	1974-8/6/22	9/6/22
CENTRAL CDSR	Cochrane Library	To Issue 6 of 12, June 2022	14/6/22
Conference Proceedings Citation Index - Science	Web of Science	1990-date	10/6/22
EconLit	Ovid	1886-6/6/22	9/6/22
HTA Database	Internet	N/A	9/6/22
NHS EED	Internet	N/A	9/6/22
Other resources			
ScHARRHUD	Internet	N/A	9/6/22

Resource	Host/Source	Date Ranges	Date searched
Additional conferences			
European Hematology Association - Congress 2022 World Federation of Hemophilia - World Congress 2022	Internet	2022 2022	10/6/22
HTA Organisations			
National Institute for Health and Care Excellence Canadian Agency for Drugs and Technologies in Health Institute for Clinical and Economic Review	Internet	Not stated	10/6/22 13/6/22 10/6/22
CENTRAL = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; CS = company submission; HTA = Health Technology Assessment; NHS EED = NHS Economic Evaluation Database; ScHARRHUD = School of Health and Related Research Health Utilities Database			

EAG comment:

- Searches were undertaken in June 2022 to identify cost and HCRU studies on patients with haemophilia. The CS, Appendix I and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 3, 57]
- In CQ A6, the company was asked to update the cost and HCRU searches given that these were conducted in June 2022 whereas the clinical and cost effectiveness searches were last run in September 2023. The company mentioned the possibility of updating the former searches in their response however had not provided this at the point of the EAG report submission.[2]
- A good range of bibliographic databases, HTA organisation websites and conference proceedings were searched. Reference checking was conducted.
- Database searches were conducted for references published since 2012. They were not limited by language of publication.
- The database searches contained a population facet for haemophilia. In the Embase, MEDLINE and Cochrane Library searches, this was then combined with a filter created by the University of York Centre for Reviews and Dissemination (CRD) containing terms health care cost/resource use terms.
- Searches were well structured, transparent and reproducible. Documentation of the search methods was particularly detailed, clear and concise.

4.1.2 Inclusion/exclusion criteria

The in- and exclusion criteria used by the company are presented in Appendices G (Table 2), H (Table 2), and I (Table 2) of the CS.[55-57] The EAG considers the inclusion and exclusion criteria suitable to capture all relevant evidence.

4.1.3 Findings of the cost-effectiveness review

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagrams for the cost effectiveness studies can be found in Figure 1 (search date September 2023) of the Appendix G, for the QoL studies in Figure 1 (search date June 2022) of the Appendix H and for the costs and HCRU in Figure 1 (search date June 2022) of Appendix I.[55-57]

A total of 24 cost effectiveness studies were identified, of which two studies performed an economic assessment from a UK perspective.[58, 59]No studies were identified studying the cost effectiveness of efanesoctocog alfa. Of the 24 cost effectiveness studies, 10 were only available as an abstract, and these scored noticeably worse on Drummond's checklist for quality assessment.[60]

Furthermore, there was quite some variation regarding the health states included into the model, with for example half of the studies incorporating joint damage as a health state, whilst others for instance distinguished between joint and non-joint bleed or took development of inhibitors into account. Further details were presented in Appendix G of the CS.[55]

Furthermore, 20 studies for HRQoL inputs were included and 31 studies for the costs and HCRU. The 20 HRQoL publications consisted of 11 studies reporting utilities data in primary costing studies and nine studies reporting utilities data in cost effectiveness studies (for further details see Section 2.6.8 and Appendix H of the CS).[56]

The 31 publications for costs and HCRU consisted of 14 studies reporting costs data in primary costing studies, 11 reported costs data in cost effectiveness studies, and six studies reporting costs data in cost modelling studies (for further details see Section 2.6.9 and Appendix I of the CS).[57]

4.1.4 Conclusions of the cost effectiveness review

Searches for the cost effectiveness studies were conducted in September 2023, whereas for HRQoL inputs and for the costs and HCRU searches were conducted in June 2022, to retrieve published economic models, available economic evidence including economic evaluations, costs, and resource use, as well as relevant utility data for patients with haemophilia.[2, 3]

The CS[3] and response to clarification[2] provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data on patients with haemophilia. The economic evaluation searches were conducted in September 2023, and the HRQoL/cost searches were conducted in June 2022. Searches were transparent and reproducible, and comprehensive strategies were used. Databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted, although searches of additional resources may have identified further references for the economic evaluation SLR.

Since no CE models to address the impact of efanesoctocog alfa treatment were identified by the company, a de novo model was built, which is discussed in the remainder of this Section. Finally, the SLR did not identify any previous NICE Technology Appraisals for patients with haemophilia A, while it identified only one other appraisal submitted to another HTA body.[61]

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.4: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	As per the reference case.
Perspective on costs	NHS and PSS.	As per the reference case.

Element of HTA	Reference case	EAG comment on CS
Type of economic evaluation	Cost utility analysis with fully incremental analysis.	As per the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	As per the reference case.
Synthesis of evidence on health effects	Based on systematic review.	For the PTP population, a systematic review was done. For the PUP population no studies were available; hence, it was assumed that the results in the PUP population would be the same as in the PTP population.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	As per the reference case.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers.	For patients with higher FVIII activity levels and no bleeding in the past 6 months the age-adjusted general population utilities from the UK have been used. For other situations disutilities were applied based on EQ-5D-5L data collected in the XTEND-1 study.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population.	The CS states that the EQ-5D-5L utilities from the XTEND-1 study were mapped to EQ-5D-3L utilities. The CS does not provide information about the tariff used to value the EQ-5D-5L health states.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	As per the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	As per the reference case.

CS = company submission; EQ-5D-5L = EuroQoL-5 Dimensions 5 levels; EQ-5D-3L = EuroQoL-5 Dimensions 3 levels; EAG = External Assessment Group; FVIII = clotting factor VIII; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National

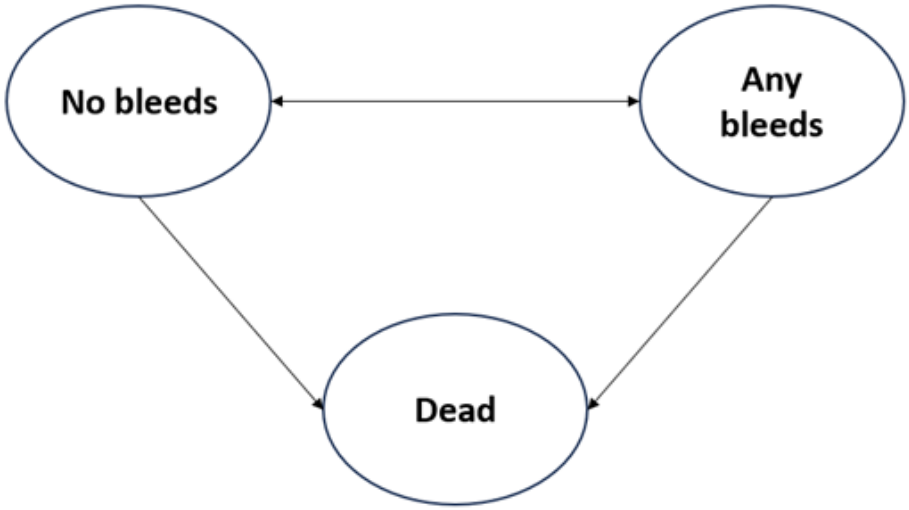
Element of HTA	Reference case	EAG comment on CS
Institute for Health and Care Excellence; PSS = Personal Social Services; PTP = previously treated patient; PUP = previously untreated patient; QALY = quality-adjusted life year; UK = United Kingdom		

4.2.2 Model structure

The company developed a Markov model in Microsoft Excel® to assess the cost effectiveness of efanesoctocog alfa for the treatment of haemophilia A in previous treated patients and previously untreated patients.

The model consists of three mutually exclusive health states and an absorbing mortality state as shown in Figure 4.1: the three mutually exclusive health states are "No bleeds", "Any bleeds", and "Dead". Patients can transition between "No bleeds" and "Any bleeds". All patients enter the model in the "No bleeds" state, and patients may move from "No bleeds" and "Any bleeds" to "Dead". In the clarification response to question B.3, the company explained the reason for not including other relevant health states such as joint damage. Joint damage would be more relevant in evaluating prophylactic therapy compared with O-D therapy. In this case joint damage has become less relevant, as the use of prophylaxis has become mainstream and with few patients fall under FVIII level 5%.

Figure 4.10: Model schematic



Based on Figure 17 of Document B of the CS[3]
CS = company submission

According to the CS, the model differentiates patients across different FVIII levels, but this differentiation is only used to assess patients' HRQoL. In the response to the CL (Question B.4.),[2] the detailed information was provided elucidating the reason ABRs were not needed to be differentiated based on the patient's FVIII level. The company further noted that such an approach would eventually result in similar results as the MAIC analysis. Therefore, in the company's base-case, the ABRs for all treatment arms remained consistent throughout the simulation and were not differentiated across FVIII level.

The severity of bleeding events was differentiated into treated (the bleeding that patient require one extra FVIII treatment) and untreated (the bleeding event is mild and does not require treatment) bleeding event. The untreated bleeding event was assumed to not incur additional medical resource use, while the treated bleeding event was linked with resource use. The model did not include a separate stage for

severe bleeding events such as intracranial bleed because according to XTEND-1 trial, 96.7% of treated bleeds were controlled by a single injection of FVIII (see CS, B.2.6.1.5.7 and response to the CL question B3).[2, 3]

Costs and utilities were applied to each health state to calculate total costs and QALYs per model cycle, which was set at 6 months. A half-cycle correction was implemented using the life table method. The input values of the model and their underlying assumptions are further elaborated in the remaining part of Section 4 of the EAG report.

EAG comment:

Whilst the company presents this model as a 3-state model, with patients moving between the "No bleeds" and "Any bleeds" states each cycle, the implementation in Excel shows that this model would be more accurately described as a 2-state model with health states "Alive" and "Dead", where in the "Alive" state a bleeding event may occur in a proportion of the patients. By framing the model as such, it becomes clearer that no transition probabilities between "No bleeds" and "Any bleeds" need to be (and will be) estimated.

The EAG had some concerns about the 6-month cycle length as this long cycle length reduces granularity and makes it impossible to capture a second bleeding event within 6 months even though this is possible in practice. However, once it became clear from the Excel implementation that the proportion of patients with a bleed and the number of bleeds per cycle are included in the model separately, the length of the cycle was no longer a concern as it has minimal impact on the results.

4.2.3 Population

The population included in the CEA consists of patients with severe haemophilia A. While the MA also allows for the treatment of people with mild or moderate disease, the company indicated that no studies have assessed the clinical efficacy of efanesoctocog alfa in these populations. Additionally, no studies have assessed the use of efanesoctocog alfa in PUPs and thus, the company's CEA for this group is based on data from PTPs. To further support this decision, according to the company, clinical opinion supports the extrapolation of safety and efficacy data to PUPs and thus, the same efficacy data was applied for both the PUP and PTP populations of this appraisal.

The company provided the patient characteristics at baseline for the PTP population (which were based on patient-level data from the XTEND-1) as they are used in the model (see Table 4.5). In PUPs, the company assumed that patients would start treatment at 1 year old. Weight for these patients was derived from growth charts for boys up to age 18 years[62, 63] (see CS Table 47) and from then the weight was assumed to be equal to the PTP population.

Table 4.5: Patient characteristics as used in the model

Patient characteristics	PUPs	PTPs[37]
Mean age (years)	1.0	35.4
Proportion male (%)	99.4%	99.4%
Mean body weight (kg)	Derived from growth charts	78.46
Based on Table 47 of Document B of the CS.[3] CS = company submission; PTPs = previous treated patients; PUPs = previously untreated patients		

EAG comment:
No information was provided in the CS on how well the patient characteristics as observed in the XTEND-1 study match the eligible population in England and Wales. In the CL,[64] question A19, the EAG asked the company to comment on whether the trial population can be considered representative of the target population in the UK. In their response, the company indicated that 51% of patients in XTEND-1 were in Europe and 16% in North America,[28, 65] and that these populations and that of the UK are similar, concluding that thus, the trial population in XTEND-1 can be considered broadly representative of the severe haemophilia A population in the UK.

However, this does not provide any insight into whether the average age and weight as observed in XTEND-1 are reflective of people in England and Wales with severe haemophilia A. With regards to the average age of previously treated patients, National Haemophilia Database (NHD) data shows that EHL users ≥12 years are on average 35 years old, which is approximately the same as the average age in XTEND-1.[6] The same data from NHD as provided by the company indicates that for EHL users aged ≥12 years, the average weight is 79.9 kg and for SHL users 82.3 kg, so slightly higher than the weight of patients observed in XTEND-1. Thus, in Section 6 the EAG will explore two scenarios where the weight for PTP's is set to 79.9 kg and to the weighted average of EHL and SHL users, 81.3kg.

4.2.4 Interventions and comparators

The intervention considered in this analysis is efanesoctocog alfa, administered intravenously at a dose of 50 IU/kg QW.

The comparators, representing established clinical management without efanesoctocog alfa, differ depending on the population considered, i.e. PTPs and PUPs.

For both groups, emicizumab should be considered as a comparator. The company described that, since its launch in 2019, the proportion of patients receiving emicizumab has rapidly increased[5] and continues to do so, with it now being the SoC in the UK for the treatment of PUPs and PTPs.[6] The proportion of patients with severe haemophilia A receiving emicizumab has increased from [redacted]% in 2019, to [redacted]% at the end of 2022.[6] Furthermore, since Q2 2019, the use of SHLs has declined from [redacted]% to [redacted]% at the end of 2022,[6] and clinical opinion suggests that SHL use will be minimal in 5 years' time.[7]

4.2.4.1 Previously treated patients

The company anticipates that efanesoctocog alfa will be used in patients who would otherwise be offered emicizumab. The company sought advice from clinicians about reasons that patients may switch away from FVIII therapy to emicizumab:[7]

- A patient's haemostasis is inadequately controlled (i.e. they are still bleeding).
- A patient's rFVIII levels are not sufficiently controlled (i.e. poor pharmacokinetic coverage due to low peaks/troughs/AUC/SHL).
- Frequent injections resulting in poor compliance/adherence to rFVIII.

Currently, following FVIII treatment there is no other choice of treatment apart from emicizumab. Therefore, it is appropriate to compare efanesoctocog alfa to emicizumab only in this analysis.

Emicizumab can be administered at a dose of:[66]

- 1.5 mg/kg QW
- 3 mg/kg Q2W
- 6 mg/kg once per 4 weeks (Q4W).

Clinical opinion provided to the company stated that the Q2W was the most frequently used, and according to the company, this is aligned with evidence from the NHD, which shows the mean treatment frequency per week to be [redacted] in patients under 12 years old, and [redacted] in patients aged 12 years and older.[6] As such, the Q2W dose was modelled in the company base-case CEA.

4.2.4.2. Previously untreated patients

Clinical advice provided to the company stated that for newly diagnosed patients, the choice of treatment results from parental decision. All patients with severe disease/bleeding phenotype will require prophylaxis, and the majority of parents select emicizumab, as it avoids the need for general anaesthetic and central venous access.[7] Some parents will select treatment with a FVIII therapy, often because their child has presented with a severe bleed that required emergency treatment with FVIII replacement therapy. For the majority of newly diagnosed patients, an EHL would be the first choice of treatment for prophylaxis, among which, only efmoroctocog alfa is licenced for use in patients under the age of 12 years.[12] The company assumed that as patients with severe haemophilia A will present early in life, so any patients starting treatment with an EHL will be administered efmoroctocog alfa.

As such, the comparators in the PUP population of the model are:

- Emicizumab
- Efmoroctocog alfa

For long-term prophylaxis, the recommended dose of efmoroctocog alfa is 50 IU of FVIII per kg body weight at intervals of 3–5 days.[12] In the CEA, a dose of 50 IU/kg every 4 days was modelled. The dosing for emicizumab is assumed to be the same as for PTPs.

EAG comment: For a general critique regarding the comparators that were considered relevant by the company, see Section 2.3. The company referred to NHD data to justify the assumption that patient receiving emicizumab would take the drug Q2W.[6] However, the report that was referred to in the CS only contained the treatment frequencies for SHL and EHL treatments, but not for emicizumab.

4.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from the perspective of the NHS and PSS perspective, in line with the NICE reference case. The model has a time horizon such that patients are followed until the age of 100, which represents 65 years for PTPs and 99 years for PUPs. At that point, less than 0.8% of patients are still alive so this time horizon may be considered as lifetime, in line with the NICE reference case. Costs and QALYs were discounted at 3.5% as per the NICE reference case.

4.2.6 Treatment effectiveness

4.2.6.1 Annual bleeding rate and proportion of patients with bleedings

Three measures of treatment effectiveness are important to estimate the ICER, i.e. ABR for any bleed, ABR for treated bleeds, and the percentage of patients with bleeds.

As mentioned in the EAG comments to Section 4.2.2, the model is essentially a 2-state model with patients being alive or dead. Patients being alive, may experience a bleeding event or not in each cycle. This probability of a bleeding event occurring is based on data regarding the percentage of patients with bleeds. Then, using the fractions of patients with a bleeding event and the number of bleeds in that cycle (based on the ABR for any bleed), the number of QALYs are estimated. The costs are estimated using the number of treated bleeds during the cycle which is based on the ABR for treated bleeds.

Table 4.6 shows the estimates for the ABRs. For efanesoctocog alfa, the ABRs are based on those observed in Arm A (prior prophylaxis) of the XTEND-1 study.[37] The IRR for emicizumab Q2W was based on the MAIC as discussed in Section 3.4. This IRR is based on data from Arm B of HAVEN 3,[46] emicizumab Q2W (prior on demand) and Arm B of XTEND-1 (prior on demand), as the HAVEN 3 study did not have a treatment arm with patients receiving emicizumab Q2W who received prophylactic treatment prior to the clinical study (i.e. matched Arm A of XTEND-1).

Table 4.6: Summary of ABRs applied in the base-case analysis

Treatment	ABR (any bleed)	IRR for any bleed	ABR (treated bleeds)	IRR for treated bleeds	% of bleeds treated (calculated†)	Source
Efanesoctocog alfa	1.11[a]	–	0.71[a]	–	64%	XTEND-1[37]
Emicizumab Q2W	3.96	0.28[b]	1.51	0.47[b]	38%	MAIC[3]
Efmoroctocog alfa	3.83	0.29*	2.45	0.29	64%	PSM[3c]

Based on Table 49 of Document B of the CS.[3]
*Assumed to be the same as for treated bleeds.
[a]Prior prophylaxis, [b] prior on demand for both efanesoctocog alfa and emicizumab, [c] the EAG noted that this was incorrectly referred to as the MAIC in Table 49 of the CS.
† % bleeds treated = $ABR_{\text{treated bleeds}}/ABR_{\text{any bleeds}}$
ABR = annualised bleeding rate; CS = company submission; IRR = incidence rate ratio; MAIC = matching-adjusted indirect comparison; PSM = propensity score matching; Q2W = every two weeks; % = percentage

Due to differing assessment periods between trials, the proportion of patients experiencing a bleed was not assessed in the MAIC comparing efanesoctocog alfa with emicizumab. As such, the proportion of patients experiencing a bleed in each cycle was taken directly from the relevant clinical trials for efanesoctocog alfa and emicizumab.

For efanesoctocog alfa the baseline proportion of patients experiencing a bleed in one cycle was obtained from XTEND-1. In order to align with the model cycle length and the outcomes reported in HAVEN 3, the probability of experiencing a bleed was reassessed at 6 months for efanesoctocog alfa. At month 6, 44 of 133 patients (33.1%) had experienced at least one bleed with efanesoctocog alfa. The 12-month estimate was used in a sensitivity analysis (see Section 5.2.3)

The value for emicizumab was obtained directly from Arm D of HAVEN 3. The company selected the Arm D population as these patients previously received prophylaxis and were considered more generalisable to UK clinical practice. The company did not consider prior therapy (O-D or prophylaxis) a treatment effect modifier but thought it might be a prognostic factor and so the value from Arm D was preferred. The company conducted scenario analyses using values from Arm A and Arm B (Section 5.2.3). The company considered the assumption that unadjusted values can be used in the model as a conservative one. While no direct comparison of the proportion of patients experiencing a bleed was made in the MAIC analysis, after the application of MAIC weights comparing with HAVEN 3 Arm D, the proportion of patients in Arm A of XTEND-1 that experienced a bleed by month 12 was reduced from 39.25% to 36.03%.[67]

For the comparison with efmoroctocog alfa, the OR from an ITC using the PSM method for the proportion of patients with a treated bleed (OR 1.99, 95% CI 1.20-3.30) was applied to the value for

efanesoctocog alfa. Table 4.7 summarises the proportion of patients with bleedings used in the base-case analysis.

Table 4.7: Proportion of patients with bleedings used in the base-case

Treatment	Proportion of patients with bleeding events	Source
Efanesoctocog alfa	33.1%	XTEND-1 Arm A
Emicizumab	55.6%	HAVEN 3 Arm D
Efmoroctocog alfa	49.6%	ITC (Section 3.4 of this report)

Based on Table 50 of Document B of the CS.[3]
CS = company submission; ITC = indirect treatment comparison

EAG comment: For the estimation of the ABR for emicizumab, the EAG wonders why the company did not use the IRR based on a comparison of XTEND-1 Arm A and HAVEN 3 Arm D. In their submission they refer to the dosing schedule for emicizumab (Q2W) as the main reason for their choice to compare XTEND-1 Arm B and HAVEN 3 Arm B, whilst at the same time stating that "*The HAVEN 3 study demonstrated that weekly and bi-weekly doses of emicizumab have similar efficacy.*[45, 46]"

Given that for the percentage of patients with a bleeding event estimates were used from XTEND-1 Arm A and HAVEN 3 Arm D, and given the above quote from the CS, the EAG prefers to use the IRR based on these two groups for the estimation of the ABRs for emicizumab. This has the added advantage that the estimate of the IRR for any bleeds will be based on a much larger sample, thus increasing the robustness of the estimate. The impact on the estimated ABR for any bleed for emicizumab is modest, decreasing from 3.96 to 3.47. At the same time, the percentage of bleeds being treated slightly increases from 38.1% to 40.9%. In Section 6 the impact this has on the ICER will be explored.

4.2.6.2 Distribution across levels of FVIII activity

Since the company assumed that lower FVIII levels would be associated with a worse HRQoL, it was necessary to estimate per model cycle how much time patients would spend in each of the FVIII activity levels. For efanesoctocog alfa and efmoroctocog alfa, the required distribution could be found based on calculations of the time to achieve the transition from one factor activity level to the next, using available pharmacokinetic data. See Section B.3.3.3 of the CS for a complete explanation of these calculations. Note that the required pharmacokinetic data was available from the so-called one-stage assays and chromogenic substrate assays (see response to CL, Q 15 for details about these assays).[2] The first one was used for the base-case distribution whereas the latter assay was used to find an alternative distribution that was used in a scenario analysis. See Table 4.8 for the distribution for the base-case. Note that though not explained or presented in the CS, the distribution varies slightly between PUPs and PTPs.

For emicizumab, which has a different mechanism of action, a slightly adjusted method of calculating time spent in each FVIII activity level was required (see Section B.3.3.3 for all details). In addition, a conversion factor of 0.3 was used to estimate the FVIII activity level for a certain emicizumab concentration level. This conversion factor of 0.3 U/dl of FVIII activity per µg/ml of emicizumab was based on a study by Shima et al. (2016).[68] With this approach it was found that for emicizumab QW FVIII activity levels would be between 15.1% and 17.9%. As the frequency of dosing decreases, a higher variability is seen, i.e., for the less frequent dosing, FVIII activity levels have shown higher variability, i.e.,13.7–19.5% for emicizumab Q2W and 11.2–22.9% for emicizumab Q4W. Given the

assumed dosing schedule of Q2W in the model, the FVIII activity level for emicizumab in the model was set to 5-20% for all time points.

Table 4.8: FVIII distributions applied in model base-case

FVIII activity level	PUP			PTP		
	EFA	EFM	EMI	EFA	EFM	EMI
≤1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
>1-5%	0.0%	33.0%	0.0%	0.0%	24.6%	0.0%
>5-20%	27.5%	32.7%	100.0%	20.7%	35.1%	100.0%
>20-40%	24.7%	16.4%	0.0%	25.7%	17.6%	0.0%
>40-50%	8.0%	5.3%	0.0%	8.3%	5.7%	0.0%
>50%	39.8%	12.6%	0.0%	45.3%	17.1%	0.0%

Based on CS electronic model.[69]
CS = company submission; EFA = efanesoctocog alfa; EFM = efmoroctocog alfa; EMI = emicizumab; FVIII = clotting factor VIII; PUP = previously untreated patient; PTP = previously treated patient

EAG comment: The EAG looked up the study by Shima et al. (2016)[68] from which the applied conversion factor of 0.3 originates. In the supplementary appendix of that paper the pre-clinical study was described. It concerned a study in nonhuman primates, in which a 61µg (first dose) or 36µg (at 16 hours thereafter) dose of plasma emicizumab per milliliter exerted similar hemostatic activity against on-going bleeds to the estimated levels in porcine FVIII: 25U (first dose) or 7.4U (at 16 hours thereafter, trough) per deciliter. From these data, a factor for the conversion of micrograms of emicizumab per milliliter to units of equivalent FVIII hemostatic activity per deciliter was estimated to be 0.2 to 0.4 (around 0.3).

As the EAG was somewhat apprehensive about the applicability in humans of this conversion factor found in non-human primates, they asked the company if this was the only source available to show that all emicizumab patients would be in the 5-20% FVIII activity level for all timepoints (CL Q 10).[64] The company provided various references to studies that have all accepted this conversion factor, however, they did not present other sources of evidence for the conversion factor. Since then, the EAG has identified a study by Shimonishi et al. (2020), in which the stability and structure of emicizumab-induced fibrin clots were investigated and compared to FVIII-induced fibrin clots.[70] The authors stated in their conclusion:

"Moreover, our potential activity of emicizumab appeared to be similar to that predicted in pre-clinical studies (0.2-0.4 IU/dL per µg/mL).[26] Hence, emicizumab at a clinically therapeutic concentration of 50 µg/mL would be equivalent to 10-20 IU/dL FVIII."

With this second source of evidence regarding the conversion factor, the EAG considers it indeed plausible that most emicizumab patients can be classified in the 5-20% FVIII activity level.

In a follow-up question the EAG asked what the distribution of emicizumab patients across FVIII activity levels would be if the range of the conversion factor was used, rather than the mean. At the lower limit, of 0.2, 100% of patients would be in the 5-20% FVIII activity level, for all dosing schedules. At the mean, of 0.3, only in the Q4W dosing schedule would the percentage of patients in the 5-20% FVIII activity level reduce to 84%, with the other 16% being in the 20-40% level. For the upper limit of 0.4 the resulting distribution is given in Table 4.9. In a scenario analysis, the EAG will explore the

impact of using the distribution as presented for QW (see Section 4.6.9 for explanation why QW will be used rather than Q2W).

Table 4.9: FVIII distributions for emicizumab, based on conversion factor 0.4

	<1%	1-5%	5-20%	20-40%	40-50%	50%+
QW	0%	0%	0%	100%	0%	0%
Q2W	0%	0%	13%	87%	0%	0%
Q4W	0%	0%	35%	65%	0%	0%

Based on Table 39 of the company's response to CQs.[2]
CQ = clarification question; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks

4.2.7 AEs

In the model provided in the CS, none of the treatment AEs such as decreased cluster of differentiation 4 (CD4) lymphocytes, headache, or protein urine presence was included.

In response to the additional CQ from the EAG, why no AEs had been included in the cost effectiveness model, the company stated that the exclusion of AEs from the XTEND-1 model was due to the well-tolerated nature of efanesoctocog alfa in severe haemophilia A patients.[71] Among eight patients experiencing TEAEs, [redacted] TEAEs were observed, including increased coagulation FVIII levels and headaches. Serious AEs were present in 9.4% of patients, most AEs were mild to moderate and unrelated to efanesoctocog alfa. Additionally, there were only [redacted] instances of patients reporting an adverse event of special interest (AESI), both of which were pregnancies in partners of participants.

Of the 24 modelling studies identified through the SLR, only eight refer to AEs. Three studies state that AEs were not included,[72-74] whilst one indicated the AE induced costs were zero.[75] In the company's response, they quote the statement of Institute for Clinical and Economic Review (ICER) analysis based on HAVEN 3 that emicizumab and FVIII inhibitors are well-tolerated and consequently no SAEs were included. Studies that included AEs found that their inclusion had very little impact on the results.

EAG comment: Whilst in general AEs should be included in health economic models, the EAG concurs with the company that the impact of including these would have a very minimal impact of the results.

4.2.8 HRQoL

The utility values were estimated for the following health states: "No bleeds", and "Any bleeds".

4.2.8.1 HRQoL data identified in the review

A SLR was conducted, which identified 22 publications reporting on 20 HRQoL studies in haemophilia patients. Eleven of these publications presented utilities data from primary costing studies, including six studies analysing data from the CHESS and CHESS US trials, and nine studies reported utilities data in cost effectiveness studies (for further details see Appendix H of the CS).[56]. One of the studies, Benson et al. 2021, reported a general population utility value of 0.94. Despite the SLR, literature sources were not used to inform the utility values used in this model. All the utility and disutility value were obtained from XTEND-1[37] apart from the UK age-adjusted general population utility (0.91 for patients aged 35 years).[76] The EQ-5D-5L questionnaire was used in XTEND-1 at baseline, at week 26 and at week 52 and responses were mapped to the EQ-5D-3L. The mapping from EQ-5D-5L to EQ-5D-3L values was conducted using the algorithm proposed by the DSU,[77] using the 'EEPRU dataset'.[78]

4.2.8.2 Health state utility values

Studies have shown that patients without a bleed and with FVIII levels above 50% are comparable to the general population in terms of QoL.[79, 80] This assumption was confirmed by the clinical experts consulted by the company.[7] Consequently, the company applied age-adjusted general population utility values from the UK to the health state "No bleeds" in patients with FVIII activity levels above 50%.[76]

In the health state “Any bleeds”, two different disutilities, including long- and short-term bleeding-related disutilities, were considered to be relevant to patients who experienced bleeds. The rationale behind the "short-term utility loss due to bleeding" was attributed to the pain and discomfort of the bleeding, and the treatment burden that a patient experiences when using O-D FVIII treatment. The short-term disutility was assumed to apply for 7 days. For "long-term utility loss due to bleeding," the rationale was based on the anxiety of patients about potential repeated bleeding events, which may in turn limit patients’ daily activities. The long-term disutility was assumed to apply for a full cycle length (6 months). Both disutilities are applied to the age-adjusted general population utility values.

Clinical experts indicated that patients with longer bleeding-free periods experience lower anxiety.[7] Based on this, the company further assumed that long-term utility decrements would also apply for patients with lower FVIII levels, regardless of whether they had a bleeding during a cycle, as according to clinical feedback lower levels of FVIII are associated with a higher risk of bleeding events and can limit the activities patients are able to undertake. This disutility is again applied to the age-adjusted general population utility values.

To estimate the utility decrements in the “Any bleeds” health state, the company fitted four alternative TOBIT models to patient-level data from the XTEND-1 trial.[37] The results of the alternative TOBIT models are shown in Table 4.10 and are based on different combinations of independent variables including occurrence of a bleed in the past 6 months (long-term disutility), occurrence of a bleed in the past 7 days (short-term disutility), time since baseline in days, age, utility value at baseline, the proportion of time spent with <5%, and the proportion of time spent with <20% FVIII activity levels. Due to the lower Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) levels, Model 1 and Model 2 were considered to present a better fit. Model 1 was chosen for the base-case as according to the company, patients treated with efanesoctocog alfa and emicizumab were not expected to have FVIII below 5%. Notably, the CS reported that a decrement in utility due to age from Model 1 was not used because the age-adjusted general population utility values were used in the economic model. Using the disutility due to age from Model 1 would likely double count the effect of aging. In addition, the coefficient for the number of days since study initiation was also not used in the model.

Table 4.10: Utility regression models based on clinical trials data

Variable	Model 1	Model 2	Model 3	Model 4
Intercept	**0.4868**	**0.4864**	**0.4675**	**0.4491**
Baseline utility	**0.7692**	**0.7642**	**0.7747**	**0.7762**
7-day bleed disutility	**–0.0663**	**–0.0649**	**–0.0760**	**–0.0738**
6-month bleed disutility	**–0.0435**	**–0.0432**	**–0.0447**	**–0.0441**
Days since study initiation	**–0.00007**	**–0.00007**	Not used	Not used
Age	**–0.0053**	**–0.0052**	**–0.0053**	**–0.0052**
Proportion of time in <5%	Not used	–0.0782	Not used	**–0.1231**
Proportion of time in <20%	–0.0277	Not used	–0.0728	Not used

Variable	Model 1	Model 2	Model 3	Model 4
Model fit				
AIC	169.365	167.688	187.544	184.84
BIC	123.101	121.424	146.42	143.717

Based on based on Table 53 of Document B of the CS.[3]
Note: Results in **bold** are statistically significant.
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CS = company submission

Table 4.11 presents the utility and disutility values that were included in the electronic model. The proportion of patients per treatment that have <20% FVIII activity level is listed in Table 4.8. The utility of health state "Death" was defined as 0. The company included two scenario analyses, one where no disutility was assumed for patients with a lower FVIII activity level, and one where it was assumed that only patients with an FVIII activity level <5% would experience a decrease in their HRQoL.

It should be noted that the implementation of the age-adjustments in the electronic model was done such that all disutilities are also adjusted, resulting in a diminishing magnitude of disutility as patients age.

Table 4.11: Health state utility values

Health state	Utility value	Reference	Justification
Baseline utility	Age-adjusted general population utility	Section B.3.4.3.1; p128	Patients with a higher FVIII level that have not experienced a bleed in the last 6 months are comparable with the general population
Disutility for FVIII <20%	–0.0277	Section B.3.4.1; p127	Patients with lower FVIII are less able to undertake their usual activities due to the higher probability of experiencing a bleed
Long-term disutility due to bleedings	–0.0435	Section B.3.4.1; p127	Patients with recent bleeding events may have ongoing anxiety about repeated events and limit their daily activities
Short-term disutility due to bleedings	–0.0663	Section B.3.4.1; p127	Bleedings can be painful for patients and limit their ability to conduct their usual activities

Based on based on Table 54 of Document B of the CS.[3]
CS = company submission; FVIII = clotting factor VIII

4.2.8.3 Disutility values AE

No AEs were included in this CE model as also discussed in Section 4.2.7; thus, there were no disutilities related to AEs estimated in the economic analysis.

EAG comment: The main concerns of the EAG relate to two issues, i.e. a) whether applying a disutility related to mild FVIII activity levels is appropriate and b) the fact the company did not re-run the TOBIT model based on the selection of explanatory variables that have been used to estimate utilities:

a) In the CS, it was argued that patients with lower FVIII levels are less likely to undertake certain activities due to their fear of bleeding. The EAG is hesitant to accept this reasoning, especially for patients whose FVIII falls in the mild category. It is not clear to what extend patients are monitored for their FVIII activity level, to ensure that their dosing is still adequate. If there is no monitoring, patients are unlikely to be aware of their lower FVIII activity level and thus have no cause for anxiety and adjustments to the activities they do. Given the differences between the treatments, there might also be differences in the frequency of monitoring and hence differences in the impact the FVIII levels may have on HRQoL. If monitoring is not done routinely, the only conceivable way for patients to be aware of their low FVIII level is through the occurrence of a bleeding event, in which case it may be argued that the loss in QoL is already adequately accounted for by short-term and long-term utility loss due to bleeding.
   It should be noted that the regression model for the utility did indeed find a disutility for patients with mild, moderate and severe disease, independent from the occurrence of a bleeding. However, these utilities were collected in a trial setting where patients were regularly monitored for their FVIII activity level, which may not be representative for daily practice. Thus, the EAG will explore the two scenario analyses included by the company specifically for the EAG base-case.

   It should further be noted that these FVIII levels are modelled as being high immediately after administration of the treatment, after which they decrease until the next dosage. Thus, they do not reflect the (hypothetical?) concept that some patients might show more response to their treatment than others, leading to some patients spending most time at low FVIII activity levels.

b) In the CS, several regression models were provided, and Model 1 was chosen as the best option. However, a concern arises regarding the company's solution for double counting of age-related disutility. Instead of revising the regression model by for example removing the age covariate, the coefficient of age was inappropriately neglected in the calculations. One of the issues with this approach is that it assumes that the influence of age on the utility in the general population is similar to that in the XTEND-1 population. This is unlikely to be the case, because the coefficient in models 1 to 4 suggest that with each extra year of age the utility decreases by around -0.005, whereas a decrease of -0.002/-0.003 is observed in the table with general population utilities provided in the CE model. In addition, the decrease in utility increases in the general population, whereas it is assumed constant in the TOBIT models. Another concern regarding the use of Model 1 was that the covariate for days since treatment initiation was disregarded. The exclusion of any covariate can lead to a change in the coefficients of other covariates, introducing uncertainty into all disutility estimations currently used in the model. Also, not including certain covariates when applying the model of course leads to changes in the AIC/BIC, thus making the choice to use the model with the lowest AIC null and void. The EAG recommends updating all regression models for utility. This correction is crucial as it affects the estimation of utility and, consequently, is likely to impact the QALYs of all treatment groups in an unknown direction. Such update of the regression model could also explore the impact of having two separate explanatory variables, one for FVIII<5% and one for FVIII 5-20%.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs and medical costs related to the treatment of bleeding events.

Unit prices were based on the NHS reference prices and the British National Formulary (BNF).

4.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified 40 publications referring to 31 studies reporting UK relevant resource use and cost information. Out of the 31 studies, the company mentioned that 14 were primary costing studies, 11 were CEAs, and six reported costs data in cost modelling studies. An overview of the cost and HCRU SLR was presented in Appendix I of the CS.[57]

4.2.9.2 Treatment costs (with PAS)

The company estimated an annual cost of the efanesoctocog alfa treatment of [redacted] (based on an average weight of 78.5 kg) [redacted] based on an average weight of 78.5 kg. Table 4.12 presents the drug costs as these were used in the economic analysis. Note that for emicizumab the company used the list price of £80.51/mg, whilst for efmoroctocog alfa the company used the discounted price of [redacted], accounting for the commercial medicines unit (CMU) contract price.

Table 4.12: Drug costs and dosing schedules used for prophylaxis

Treatment	Dose	Price per unit	Source
Efanesoctocog alfa (list price)	50 IU/kg QW	[redacted]	Sobi
Efmoroctocog alfa (CMU contract price)	50 IU/kg Q4D	[redacted]	Sobi
Emicizumab	3 mg/kg Q2W	£80.51/mg	BNF[81]

Based on Table 55 of Document B of the CS[3]
BNF = British National Formulary; CMU = commercial medicines unit; CS = company submission; IU = international unit; kg = kilogram; PAS = Patient access scheme; QW = once weekly; Q2W = every 2 weeks; Q4D = every 4 days

EAG comment: The EAG identified one major concern, regarding the treatment frequency for emicizumab, and a smaller issue related to treatment administration costs.

a) It was unclear to the EAG why the economic analysis omitted treatment administration costs. In the clarification response to question B24, the company explained that treatment administration costs are expected to be negligible. That is because FVIII treatments or emicizumab are self-administered treatments, and although all of them may require a small start-up cost for the training of patients, this cost would be similar across treatments and would be negligible compared with the drug costs.[64] The EAG has no further comments on this point.
b) In the company's base-case analysis, all patients using emicizumab treatment were assumed to be following a biweekly (Q2W) dosing schedule based on clinical expert opinion suggesting that this is the most frequent option.[7] However, emicizumab can also be given QW or Q4W. In the clarification phase (CQ B17), the EAG asked the company to adapt the model to include the observed distribution of patients across the three dosing schedules of emicizumab (QW; Q2W; Q4W) instead of using the most frequent option for all patients. The company responded that there

is no currently available data to inform the distribution of patients across the different dosing schedules for emicizumab. Instead, the company provided scenario analyses for the QW and Q4W doses separately.[64] The company went further on commenting that "*as emicizumab QW was included in the MAIC, ABRs for the QW population have been applied in the scenarios for emicizumab QW. Emicizumab Q4W was not included in the MAIC, as patients treated with emicizumab Q4W may or may not have had an inhibitor (compared with XTEND-1 population, who had no inhibitors to therapy)".*[64] Therefore, in the scenario analysis, the impact of emicizumab on patients following a Q4W dosing schedule was assumed to be equivalent to the impact of emicizumab Q2W which was used in the company base-case. The results of these two scenarios in Appendix A of the clarification response showed that using emicizumab QW led to a small increase in QALYs and a small decrease in costs, whilst there was no difference in outcomes for emicizumab Q4W compared to emicizumab Q2W.[64] Regarding this matter, the CS also mentioned that using the Q2W for emicizumab treatment in the company base-case, "*aligns with the National Haemophilia Database (NHD), which shows the mean treatment frequency per week was* [redacted] *in patients under 12 years old, and* [redacted] *in patients aged 12 years and older*."[3, 6] Firstly, the EAG was unable to validate the mean frequencies presented by the company in the NHD report.[6] In this report, only weekly treatment frequencies for EHL- and SHL-rFVIII treatments were documented (Table 3 of the report).[6] Secondly, as also mentioned in the CS, and confirmed by clinical experts, younger patients are likely to be using higher doses and also more frequent dosing schedules.[7] This expectation of clinicians aligns with the dosing schedule assumed in the base-case of the emicizumab appraisal submitted to CADTH, which employed a QW dosage for the maintenance phase of the treatment based on the same reasoning.[61] Therefore, in the absence of appropriate evidence on the distribution of patients across the three dosing schedules of emicizumab (QW; Q2W; Q4W) treatment, the EAG suggests using the QW dosing schedule in the base-case analysis. This argumentation further reinforces the EAG preferred option to estimate the percentage of patients with a bleeding event discussed in Section 4.2.6. In this Section, the EAG explained that estimates from XTEND-1 Arm A and HAVEN 3 Arm D were deemed more appropriate to define IRR used for the estimation of the ABRs for emicizumab treatment, hence the estimates from the QW dosing schedule.

4.2.9.3 Wastage and relative dose intensity

The CS noted that to obtain the most efficient use of FVIII therapies and emicizumab, the number of doses that are used for prophylaxis would be rounded up or down by clinicians. Therefore, the company did not consider drug wastage for prophylactic treatments in the model computations. Relative dose intensity (RDI) was also not part of the base-case analysis as the company assumed 100% RDI for all treatments.

Patients in the PTPs population that were using emicizumab treatment prophylactically were assumed to be administered FVIII treatment (octocog alfa) to treat acute bleeding events. As such, patient would have a small supply of octocog alfa in case such bleeding occurs. The CS stated that wastage costs were estimated using the proportion of patients that did not experience a treated bleed in Arm D of the HAVEN 3 trial (55.6%). For this proportion of patients, the company assumed that they would incur the cost of 6,000 IU of octocog alfa, every 4 cycles (i.e. every 2 years).

EAG comment: The main concerns of the EAG regarding wastage costs relate to a) the company's approach to omit wastage costs for prophylactic FVIII therapies and emicizumab treatment; and b) the

company's approach to implement wastage costs for octocog alfa for patients receiving prophylaxis with emicizumab.

a) Regarding the company's assumption that no wastage occurs for prophylactic FVIII therapies and emicizumab, the EAG is unclear what the source is for the company's statement that "for prophylaxis, clinicians will round doses up or down to obtain the most efficient use of FVIII therapies and with emicizumab".[3] The EAG was unable to identify such statements in the minutes with the clinical experts[82] and is concerned that this assumption may have been defined arbitrarily, hence not reflecting current practice in the UK. To further endorse this concern, the EAG noted that in the emicizumab appraisal submitted to CADTH, the company also estimated treatment acquisition costs for both emicizumab and FVIII treatments using the exact doses per milligram required. However, according to clinical experts consulted by CADTH, patients on both emicizumab and FVIII treatments would typically have their dose rounded up to the nearest whole vial, with the drug dispensed accordingly to minimise wastage.[61] For this reason, CADTH considered that the company's' approach underestimated the treatment-acquisition costs of emicizumab and FVIII treatments and adjusted their costs accordingly allowing dispensed drugs to be rounded up to the nearest vial to better reflect clinical practice.[61] While the company in the current appraisal included a scenario analysis in which wastage costs could be included for emicizumab treatment, they did not provide similar scenarios for efanesoctocog alfa and efmoroctocog alfa. The EAG consulted a clinical expert from the UK on this matter but did not receive a timely response. Furthermore, as the electronic model of the company did not include the functionality to account for wastage costs of efanesoctocog alfa and efmoroctocog alfa treatments, requiring a model restructure if these costs were to be implemented, the EAG was unable to assess the impact of this issue within the available timeframe. Nonetheless, the EAG anticipates that considering the current difference in treatment acquisition costs between emicizumab and efanesoctocog alfa, including these additional wastage costs would likely increase the incremental costs between the two treatments deeming emicizumab an incrementally more expensive treatment option. This expectation is confirmed when looking at the individual impact of including wastage costs for emicizumab versus FVIII treatments in the CADTH appraisal.[61] The direction of the impact when including wastage on the comparison of efanesoctocog alfa and efmoroctocog alfa would be hard to anticipate, but the EAG does not expect it to be significant.
b) Regarding the wastage costs for octocog alfa, the rFVIII treatment used when bleeding events occur for patients using emicizumab treatment, the CS stated that: *"With regard to emicizumab treatment, patients are often administered FVIII in the event of an acute bleed. Any remaining FVIII may be wasted if no further bleeding occurs before its expiry date. Additional costs of such doses was included for the proportion of patients that do not experience a treated bleed (56%, HAVEN 3 Arm D)"*.[3] Firstly, it is not specified on what basis the company assumed that wastage costs in this case would be reflected with the cost of 6,000 IU of octocog alfa, every 4 cycles. Secondly, the EAG thinks that the quoted statements of the company are contradictory. That is because the company argues to be accounting for wastage costs of "*remaining FVIII if no <u>further</u> bleeding occurs before its expiry date",* while they used the percentage of patients who did <u>not</u> experience a treated bleed (56%) to calculate these costs. Considering the first part of the quote above (mainly the word "further"), it would be expected that wastage would be considered for the proportion of the treated bleeds as defined in Table 4.14 below (38.1%). Although it is not clearly specified, the EAG assumes that the company aimed to account for wastage for patients on emicizumab treatment that store FVIII treatment at home to prevent a bleeding event, but do not eventually use before its expiry date. However, in any case, it remains unclear to the EAG from where these inputs and

assumptions originated (including the 6,000 IU of octocog alfa, every 4 cycles), and if all patients on emicizumab treatment may keep octocog alfa to ensure immediate accessibility. Additionally, the EAG questions the approach of including these wastage costs in the electronic model. By assuming that each cycle 56% of the patients wastes 1/4th of the supply of octocog alfa (thus spreading the waste from once per four cycles over all four cycles), it is implicitly assumed that each cycle the same patients do not have a bleed. If the percentage of patients with a bleed would be 50% per cycle, and each cycle the other 50% of the patients has a bleeding, then there would be no wastage, as each patient has one bleed per year. If we assume that the distribution of the 56% of patients is not at all correlated, so purely random, then simulation shows that each cycle about 4.5% of patients has just had the 4th (or 8th, 12th etc) cycle without a bleed and thus wastage of the octocog alfa.

Overall, the EAG considers this approach very uncertain, lacking face validity, and therefore assessed the impact of omitting these costs on the cost effectiveness outcomes in the exploratory scenario analyses.

4.2.9.4 Bleeding events

To define health state costs for the "Any bleeds" health state, the company estimated the costs related to bleeding events. Drug costs and dosing schedules for bleeding events related to efanesoctocog alfa, efmoroctocog alfa and emicizumab treatments are presented in Table 4.13. Note that octocog alfa was assumed to be used as a FVIII treatment in case of acute bleeding events for patients using prophylactic treatment with emicizumab.

Table 4.13: Drug costs and dosing schedules used for the management of bleeding events

Treatment	Dose	Price per unit	Source
Efanesoctocog alfa (PAS price)	25 IU/kg	[redacted]	Sobi
Efmoroctocog alfa (CMU contract price)	50 IU/kg	[redacted]	Sobi
Octocog alfa	50 IU/kg	£0.71/IU	BNF[83]

Based on Table 55 of Document B of the CS[3]
BNF = British National Formulary; CMU = commercial medicines unit; CS = company submission; IU = international unit; kg = kilogram; PAS = Patient Access Scheme

It was further assumed that not all bleeding events would be treated. The proportion of bleedings treated was based on the ABR for treated bleeds divided by the ABR for any bleeds, where these ABRs were based on an MAIC/ITC analysis using data from the clinical trials. Table 4.14 presents the proportion of bleeds being treated per treatment arm as used in the economic model. For further details on the MAIC/ITC analysis we refer to Section 4.2.6.

Table 4.14: Proportion of bleeds that were treated

Treatment	Proportion of bleeds treated
Efanesoctocog alfa	64.0%
Efmoroctocog alfa	64.0%
Emicizumab	38.1%

Based on Table 56 of Document B of the CS[3]
CS = company submission

Based on clinical input, the CS stated that when a patient experiences a bleed while being on a prophylactic FVIII treatment, restoring FVIII (with additional FVIII doses) to normal levels is sufficient

to resolve the most commonly occurring acute bleeding events.[7] When a patient experiences a bleed while being on emicizumab treatment, factor FVIII levels need to be raised using a FVIII factor replacement therapy which is usually the same rFVIII treatment that patients were using prior to switching to emicizumab and this was defined to be octocog alfa in this appraisal.[7] Regarding the number of doses, the company assumed that acute bleeding events are usually resolved with two doses of 2000 IU of rFVIII, equating to two doses of approximately 25 IU/kg each. This dosing assumption is also in alignment with the specification in the octocog alfa SmPC.[26] However, for efanesoctocog alfa the company assumed that one dose of 25 IU/kg would suffice to resolve acute bleeds, referring to input from the consultation with clinical experts.[7]

Bleeding events were also assumed to incur management costs. Management procedures were thought to include Accident & Emergency (A&E) visits, specialist visits, and nurse visits. The number of A&E and specialist visits required to treat a bleeding event were estimated based on the study by Shrestha et al. 2017[84] and are shown in Table 4.15. The CS noted that because Shrestha et al. (2017) reported the need for more than one specialist visits to treat a bleeding event, it was assumed that an additional nurse visit would not be necessary. It was further reported that clinicians validated these input parameters mentioning that patients would usually have a consultation with the haematologist, either face-to-face or via phone call, avoiding A&E whenever possible.[7]

Costs of emergency visits, specialist, and nurse visits were extracted from the National Cost Collection for the year 2020–2021 and are shown in Table 4.15.[85] The cost per emergency visit cost was based on the total average cost for A&E from Healthcare Resource Groups (HRG) data. The original CS stated that the cost of a specialist visit was based on the average Outpatient Attendances Data for Clinical Haematology (£193.24; service code 303), while the nurse visit cost was based on Specialist Nursing, Haemophilia Nursing Service, Adult, face to face (currency code N17AF) cost. In the clarification phase, the EAG noticed that there was a mismatch in the value reported in the CS for the cost of the specialist visit and the respective cost used in the economic model (£193.24 in the CS versus £538.9 in the economic model). In the clarification response B25, the company clarified that the appropriate cost for specialist visit should be £531.53 based on the weighted average cost of consultant-led Outpatient Attendances for Haemophilia services (service code 309) and provided updated company's base-case results.[64] Finally, the CS explained that the cost of blood tests was not included in the model as it was not expected to be different between treatments.

Table 4.15: Health care resource use for the management of bleeding events

Procedure	Number of visits per event	Cost per event	Source
A&E visit	0.06	£296.87	2021/22 NHS [85]
Specialist visit	1.11	£531.53*	2021/22 NHS [85]
Nurse visit	0	£45.11	2021/22 NHS [85]

Based on Table 58 of Document B of the CS[3]
*In the original CS this was cost was £193.24. Following the clarification phase, the cost was assumed to be £531.53.[64]
A&E= accident and emergency; CS = company submission; NHS = National Health Service

EAG comment: The main issues for the EAG concern a) the dose of efanesoctocog alfa used to treat an acute bleeding, b) the assumption that all contact with a HCP in case of a bleeding will be with a specialist, c)the assumed resource use for all treated bleedings and d)issues about the unit costs applied.

a) Considering the dosing schedule used to treat acute bleeding events, the company assumed that one dose of 25 IU/kg would suffice to resolve the same type of bleed for patients using efanesoctocog alfa treatment, whereas for patients using efmoroctocog alfa or emicizumab treatments two doses of 25 IU/kg would be needed. To justify this assumption the company stated that "*clinicians also felt that the high sustained pharmacokinetic profile of efanesoctocog alfa would allow for 1x 25 IU/kg dose to resolve the same type of bleed*[3, 7] The EAG does not think this assumption is sufficiently substantiated. The EAG's concern is strengthened by the company's response to CQ B8b on this matter reporting that "*bleeding events in the XTEND-1 trial were treated with a single dose of efanesoctocog alfa 50 IU/kg"*.[64] The company went further on with their response mentioning that " *for minor/moderate bleeding episodes occurring within 2 to 3 days after a recent prophylactic dose, an initial 30 IU/kg dose could instead be used. If the bleeding episode did not resolve, additional doses of 30 or 50 IU/kg could be administered every 2 or 3 days, as needed. In total, across the 2 treatment arms, 362 bleeds were treated with efanesoctocog alfa, with 74% (268 of 362) occurring in Arm B during the on-demand treatment phase. Analysis per bleeding episode showed that overall, 99.7% were controlled with ≤2 injections of efanesoctocog alfa, with 96.7% controlled by only one injection. No bleeding episode required more than three injections".*[64] From the listings provided as part of the CSR,[39] we found that in Arm A 20/86 bleeding episodes was treated by one dose <40 IU/kg, with the other 66 episodes being treated by dosages around 50 IU/kg. Thus, based on this trial data and response from the company, the EAG is convinced that the base-case analysis should also use one dose of 50 IU/kg to treat bleeding events for patients in the efanesoctocog alfa arm and therefore, this parameter was adjusted in the EAG's base-case preferred assumptions.

b) The CS noted that because Shrestha et al. (2017)[84] reported the need for more than one specialist visits to treat a bleeding event, it was assumed that an additional nurse visit would not be necessary. The company continued mentioning that "*the number of HCP contacts was obtained from US data, and clinicians confirmed that this data appeared reasonable, as typically patients would have a consultation with the haematologist, either face-to-face or via phone call, and avoid A&E, where possible* [7]." From these statements, it is unclear to the EAG why the nurse visit is assumed to be substituted by the '*more than one specialist visit'*, when it is very likely as stated in the CS and confirmed by clinical experts, that contacts via phone may also be used to manage bleeding events and these calls can potentially also be resolved by (specialist) nurses. This assumption is not justified in the company's report based on the feedback from clinical experts nor from another source and lacks face validity.

c) Furthermore, the EAG has also concerns around the appropriateness of the costing inputs that were used in the company base-case. Firstly, in CQ B3, the company was asked to comment on the fact that using the bleed and no bleed health states may miss granularity in terms of bleeding levels and locations, as severe levels of bleeding, or intra-cranial or joint bleeding might be expected to require different treatment paths.[64] The company replied that "*the majority of bleeds observed in XTEND-1 were joint or muscle bleeds, and 96.7% were controlled by a single injection of efanesoctocog alfa. No intracranial bleeds were observed. The Company expect that the majority of bleeds for patients treated prophylactically with efanesoctocog alfa to be controlled using efanesoctocog alfa alone, in line with current therapies. The model does account for some differences in resource use by bleed severity via the modelling of treated and untreated bleeds, as untreated bleeds are likely to be those*

of lower severity, for example a cut while shaving. More severe bleeds, such as bleeds following joint impact during exercise, will require treatment, but typically can be controlled with FVIII alone (a treated bleed). While more complicated bleeds can require additional treatment, beyond that included in the model, this is typically associated with events such as surgery, or major trauma, the rate of which is not expected to differ between treatment arms. As such, the cost of such complications is expected to be equal between arms and has not been included in the model".[64] Based on the company's response the EAG agrees with the company that the majority of the bleeding events are likely mild to moderate, which is also confirmed in the study by Benson et al. 2021[58] which incorporates granularity in bleeding events showing that minor/moderate bleeding events accounted for about 99% of the cases and major bleeding events for only 1%. However, in their cost-effectiveness analysis on haemophilia A patients in the UK, Benson et al. (2021)[58] assumed a cost of £566.47 per severe bleeding event, whilst assigned a zero cost to additional resource use for mild to moderate bleeds. Benson et al. 2021[58] used interviews with clinical experts to inform the resource use inputs and they originated costs from the 2017/18 NHS.[58, 85] As shown in Table 4.16 below, the cost per bleeding event used in the current appraisal was set at £610.45 irrespective of severity. Considering also that multiple of these bleeds can be resolved by phone contact as explained in the previous comment, the EAG thinks that these costs are overestimating bleeding costs and do not reflect UK clinical practice.

d) The EAG noted that the company used the 2020/21 NHS[85] source to inform the cost inputs for the management of bleeding events. Given the availability of the 2021/22 NHS[85] the EAG looked at the differences in the cost items. It was noticed that while for the emergency visit and the specialist visit, the costs were similar, the cost for Haemophilia Nursing Service (code N17AF) changed substantially from £45.11 to £523.55 and deviations in this service code were significant for all relevant costs (codes for face to face or phone contacts for adults and children; codes N17AF, N17AN, N17CF, N17CN). The EAG is unsure about the cause of this significant fluctuation in the haemophilia nursing codes but speculates that it might be attributable to the introduction of these new codes and the impact of the COVID-19 pandemic which required a whole new restructure of non-face to face contact system. For all the above reasons, the EAG thinks the company did not appropriately inform the cost and HCRU inputs in the economic model. Therefore, to reflect uncertainty, the EAG ran scenario analyses in which the current number of specialist visits were spread among specialists and nurse visits (to account for contacts resolved via phone), and also a scenario analysis in which all resource use due to the management of bleeding events were omitted from the computations.

4.2.9.5 Health state costs

For the health-state "No bleeds", there were no resource use assumed. For the "Any bleeds" state, as summarised in the previous Section the costs per treatment of bleeding events were specified using additional medical treatment costs and costs related to management procedures.

Table 4.16: Health state costs

Health state	Costs	Reference	Justification
No bleeds	0	Section B.3.5.2 in CS	The CS noted that the cost of blood tests was not included in the model as it was not expected to be different between treatments.
Any bleeds	£610.45*	Section B.3.5.1 in CS Section B.3.5.2 in CS	The costs per bleeding event were specified using additional medical

Health state	Costs	Reference	Justification
			treatment costs and costs related to management procedures.
*Based on the calculations in the electronic model or the total costs that can be produced based on the resource use and costs presented in Table 58 of Document B of the CS.[3] CS = company submission			

4.2.9.6 Adverse event costs

No AEs were included in this CE model as also discussed in Section 4.2.7; thus, there were no costs related to AEs estimated in the economic analysis.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Main results original CS

Table 5.1 shows the company's deterministic base-case results from the original submission. For the PUP population, the total discounted costs associated with efmoroctocog alfa treatment were estimated at [redacted], the total costs associated with efanesoctocog alfa were estimated at [redacted], and the total costs associated with emicizumab were estimated at [redacted], indicating that treatment with efanesoctocog alfa increased total costs by [redacted] compared to efmoroctocog alfa, whilst emicizumab increased total costs by [redacted] compared to efmoroctocog alfa. Total QALYs associated with efmoroctocog alfa were estimated at [redacted], total QALYs associated with efanesoctocog alfa were estimated at [redacted], and total QALYs associated with emicizumab were estimated at [redacted] leading to an incremental number of [redacted] QALYs gained for patients treated with efanesoctocog alfa as compared to efmoroctocog alfa and an incremental number of [redacted] QALYs as compared to emicizumab. These produced an ICER for efanesoctocog alfa versus efmoroctocog alfa of £18,211 per QALY gained, whilst efanesoctocog alfa was estimated to be more effective and less costly than emicizumab (i.e. efanesoctocog alfa was a dominant treatment).

For the PTP population, the total discounted costs associated with efanesoctocog alfa were estimated at [redacted] and the total costs associated with emicizumab were estimated at [redacted], indicating that emicizumab increased total costs by [redacted] compared to efanesoctocog alfa. Total QALYs associated with efanesoctocog alfa were estimated at [redacted] and total QALYs associated with emicizumab treatment were estimated at [redacted] leading to an incremental number of [redacted] QALYs gained for patients treated with efanesoctocog alfa. These indicate that efanesoctocog alfa would be a less expensive and more effective treatment option, dominating emicizumab treatment option in the PTP population.

Table 5.1: Company's base-case deterministic cost effectiveness results in the original submission (note: incremental compared to first row)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
PUPs							
Efmoroctocog alfa	[redacted]	27.054	[redacted]	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	[redacted]	[redacted]	0.000	[redacted]	£18,211
Emicizumab	[redacted]	27.054	[redacted]	[redacted]	0.000	[redacted]	Dominated
PTPs							
Efanesoctocog alfa	[redacted]	22.369	[redacted]	–	–	–	–
Emicizumab	[redacted]	22.369	[redacted]	[redacted]	0.000	[redacted]	Dominated

Based on: Table 63 and Table 65 Document B of the CS[3]
CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; PUPs = previously untreated patients; PTPs = previously treated patients; QALYs = quality-adjusted life years

5.1.2 Main results based on model after the request for clarification

Following the clarification phase, the company provided their updated base-case results, correcting the mismatch in the value for the cost of specialist visit reported in the CS compared with the respective cost used in the economic model (see Section 4.2.9 for further details).

Table 5.2 shows the company's updated deterministic base-case results. The updated deterministic results are quite similar to the company's base-case results in the original submission (shown in Table 5.1) presenting some relatively small changes in the total costs of treatments. Specifically, for the PUP population, the updated cost results led to an ICER for efanesoctocog alfa versus efmoroctocog alfa of £18,899 per QALY gained, whilst emicizumab treatment increased total costs by [redacted] compared to efmoroctocog alfa which was the least costly treatment option. For the PTP population, emicizumab treatment increased total costs by [redacted] compared to efanesoctocog alfa.

Table 5.2: Company's updated base-case cost effectiveness results (note: incremental compared to first row)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
PUPs							
Efmoroctocog alfa	[redacted]	27.054	[redacted]	–	–	–	–
Efanesoctocog alfa	[redacted]	27.054	[redacted]	[redacted]	0.000	[redacted]	£18,899
Emicizumab	[redacted]	27.054	[redacted]	[redacted]	0.000	[redacted]	Dominated
PTPs							
Efanesoctocog alfa	[redacted]	22.369	[redacted]	–	–	–	–
Emicizumab	[redacted]	22.369	[redacted]	[redacted]	0.000	[redacted]	Dominated

Based on: Tables 41 and 43 from the company's response to CQs.[2]
CQ = clarification question; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; PUPs = previously untreated patients; PTPs = previously treated patients; QALYs = quality-adjusted life years

5.2 Company's sensitivity analyses

In this Section, only the results of the revised company analyses will be presented. The company performed a probabilistic sensitivity analysis (PSA), a deterministic sensitivity analyses (DSA) and a scenario analyses. The updated PSA, DSA and scenario analyses presented in this Section were extracted from the model submitted by the company following the clarification phase and reported by the EAG using this updated model version.

5.2.1 Probabilistic sensitivity analysis

After the change in the cost of a specialist visit during the clarification phase, the PSA results from the base-case analysis are presented in Table 5.3 below. The cost effectiveness acceptability curves (CEAC) in Figure 5.4 shows that for PUPs, the probability of efanesoctocog alfa to be cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], respectively, when compared with compared with efmoroctocog alfa, whilst it was [redacted] of simulations.

Table 5.3: Company's base-case probabilistic cost effectiveness results after the CL (note: incremental compared to first row)

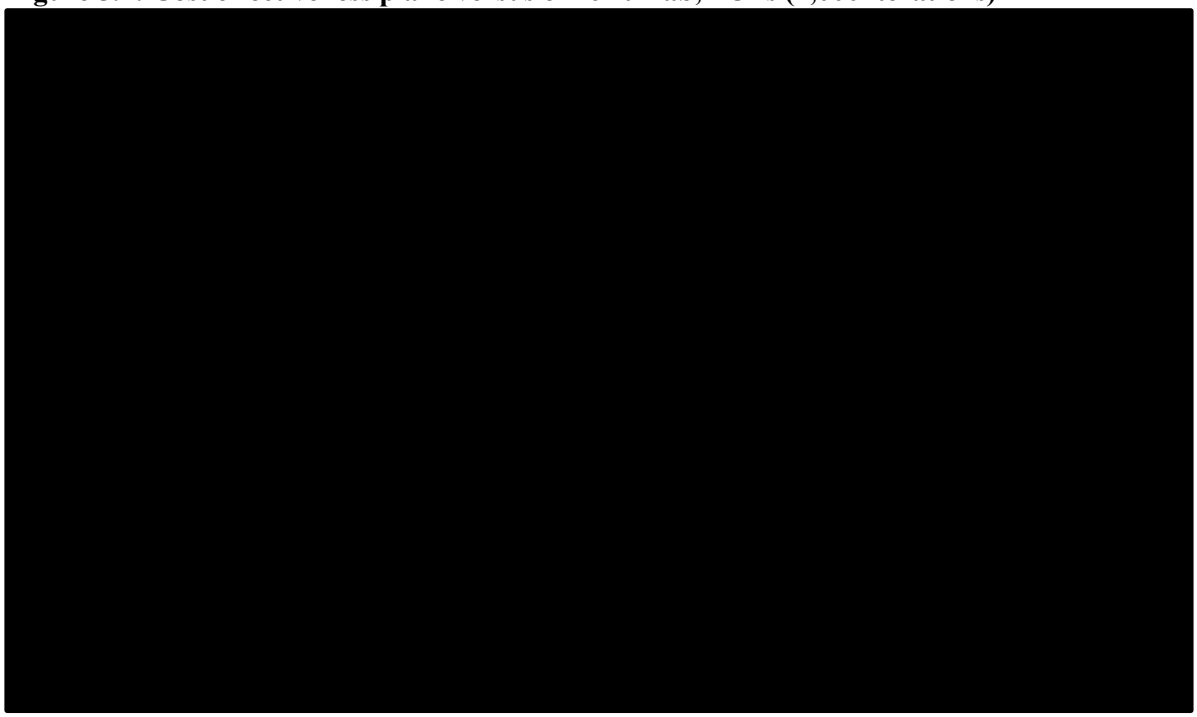
Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
PUPs					
Efmoroctocog alfa	[redacted]	[redacted]	–	–	–
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£20,475
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
PTPs					
Efanesoctocog alfa	[redacted]	[redacted]	–	–	–
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Based on the electronic model after the clarification phase.[69]
CL = clarification letter; ICER = incremental cost-effectiveness ratio; Incr. = incremental; PUPs = previously untreated patients; PTPs = previously treated patients; QALYs = quality-adjusted life years

Figure 5.1: Cost effectiveness plane versus efmoroctocog alfa, PUPs (1,000 iterations)

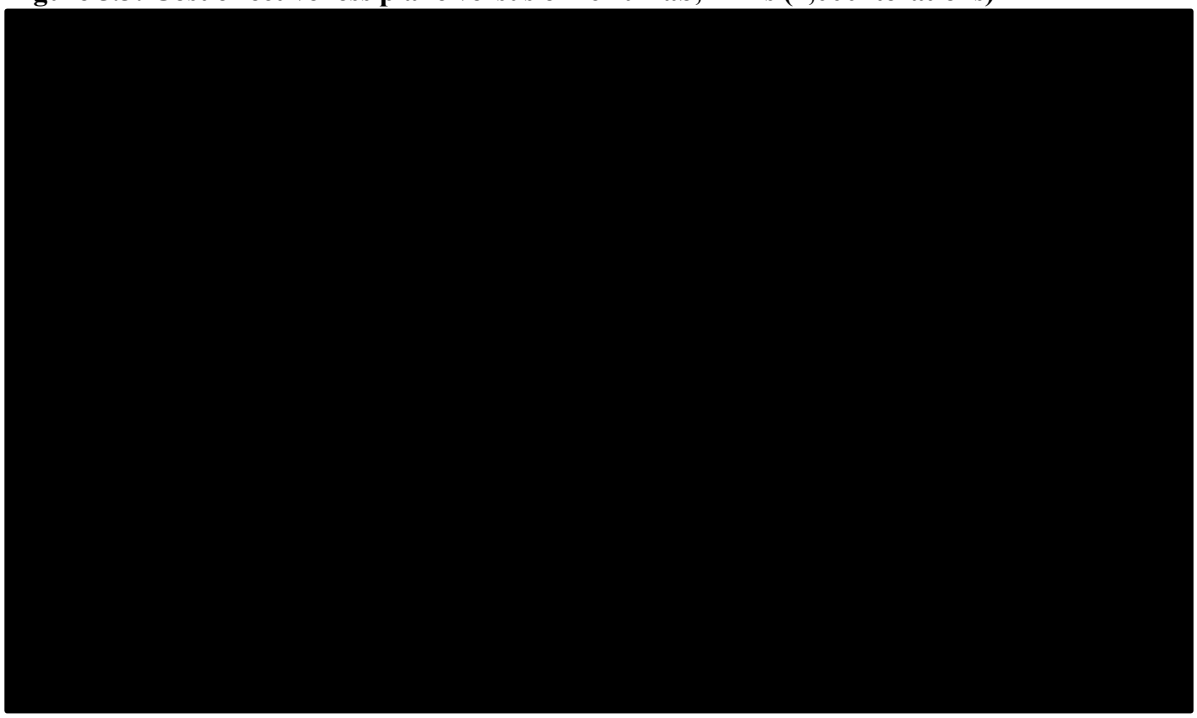
Based on the model submitted following the clarification phase.[69]
PUPs = previously untreated patients; QALYs = quality-adjusted life years

Figure 5.2: Cost effectiveness plane versus emicizumab, PUPs (1,000 iterations)



Based on the model submitted following the clarification phase.[69]
PUPs = previously untreated patients; QALYs = quality-adjusted life years

Figure 5.3: Cost effectiveness plane versus emicizumab, PTPs (1,000 iterations)



Based on the model submitted following the clarification phase.[69]
PTPs = previously treated patients; QALYs = quality-adjusted life years

Figure 5.4: CEAC, PUPs (1,000 iterations)

Based on the model submitted following the clarification phase.[69]
CEAC = cost effectiveness acceptability curve; PUPs = previously untreated patients; WTP = willingness-to-pay threshold

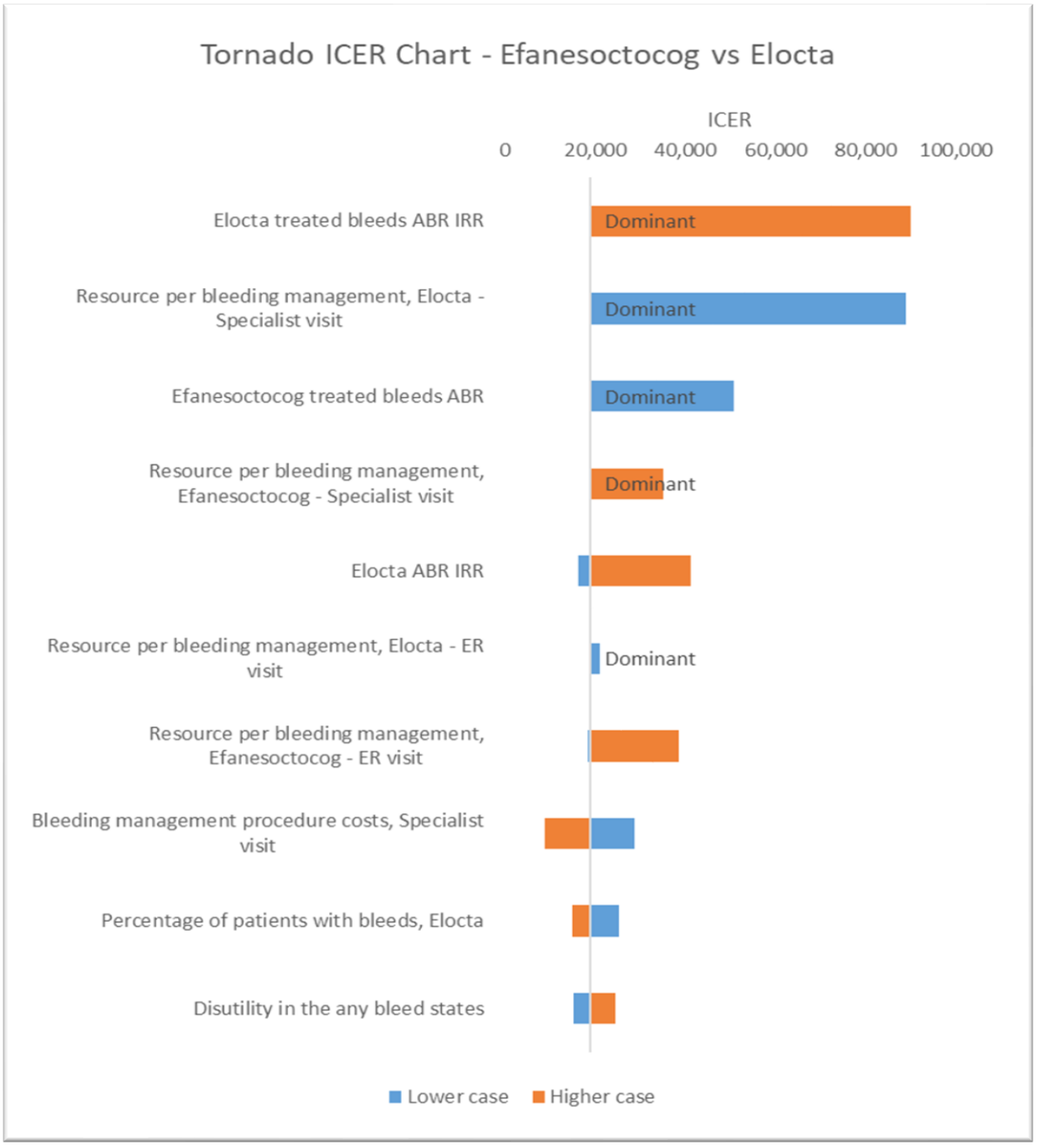
Figure 5.5: CEAC, PTPs (1,000 iterations)

Based on the model submitted following the clarification phase.[69]
CEAC = cost effectiveness acceptability curve; PTPs = previously treated patients; WTP = willingness-to-pay threshold

5.2.2 Deterministic sensitivity analysis

The results of the company's DSA for the PUP population are displayed in Figure 5.6, showing the impact of the 10 most influential parameters for the ICER of efanesoctocog alfa versus efmoroctocog alfa. Parameters relating to the ABRs for all bleeds and for treated bleeds, as well as the resource use associated with bleeding management procedures had the largest impact on the ICER. The CS further noted that the resource use associated with bleeding events was varied independently for each comparator, which is likely to overestimate the uncertainty around these parameters, as in reality, these parameters will likely be correlated.

Figure 5.6: Tornado plot showing the top 10 most influential parameters with an impact on ICER of efanesoctocog alfa versus efmoroctocog alfa, PUPs



Based on the model submitted following the clarification phase.[69]

ABR = annualised bleeding rate; ER = Emergency Room; ICER = incremental cost-effectiveness ratio; IRR = incidence rate ratio; PUPs = previously untreated patients; Q2W = every 2 weeks

Similarly, to the company's base-case analysis, efanesoctocog alfa was found to be dominant when compared to emicizumab in both PUPs and PTPs when using the upper and lower value of all parameters used in the company's DSA analyses. For this reason, tornado plots representing ICER changes were not produced for the comparisons of efanesoctocog alfa versus emicizumab in both PUPs and PTPs. However, to represent uncertainty for these comparisons the company presented tornado plots showing the parameters that had the largest impact on incremental QALYs and costs in PUPs and PTPs. As shown in Figure 5.7 and Figure 5.9 the proportion of patients experiencing a bleed in each cycle was a driver of QALYs, as well as the disutilities assigned to bleeding events, and the ABR for emicizumab treatment. Figure 5.8 and Figure 5.10 show that the number of bleeds and associated resource use the most influential parameters for the incremental costs in both PUP and PTP populations.

Figure 5.7: Tornado plot showing the top 10 most influential parameters with an impact on incremental QALYs of efanesoctocog alfa versus emicizumab, PUPs

Based on the model submitted following the clarification phase.[69]
ABR = annualised bleeding rate; IRR = incidence rate ratio; PUPs = previously untreated patients; QALYs = quality-adjusted life years; Q2W = every 2 weeks

Figure 5.8: Tornado plot showing the top 10 most influential parameters with an impact on incremental costs of efanesoctocog alfa versus emicizumab, PUPs

Based on the model submitted following the clarification phase.[69]
ABR = annualised bleeding rate; IRR = incidence rate ratio; PUPs = previously untreated patients; Q2W = every 2 weeks

Figure 5.9: Tornado plot showing the top 10 most influential parameters with an impact on incremental QALYs of efanesoctocog alfa versus emicizumab, PTPs

Based on the model submitted following the clarification phase.[69]

ABR = annualised bleeding rate; IRR = incidence rate ratio; PTPs = previously treated patients; QALYs = quality-adjusted life years; Q2W = every 2 weeks

Figure 5.10: Tornado plot showing the top 10 most influential parameters with an impact on incremental costs of efanesoctocog alfa versus emicizumab, PTPs

Based on the model submitted following the clarification phase.[69]
ABR = annualised bleeding rate; ER = Emergency Room; IRR = incidence rate ratio; PTPs = previously treated patients; Q2W = every 2 weeks

5.2.3 Scenario analyses

Company scenario analyses results are presented in Table 5.4 and Table 5.5. The rationale for each scenario is outlined in Table 69 of the CS and summarised in the column describing the scenarios of Table 5.4 and Table 5.5. In all scenarios presented by the company, efanesoctocog alfa remained the most effective treatment option while it dominated emicizumab treatment in both PUPs and PTPs. The scenarios leading to the highest increase on the ICER were those that adjusted the disutility according to lower FVIII levels, and those that adjusted the proportion of patients experiencing a bleed. Efanesoctocog alfa compared to efmoroctocog alfa, remained cost-effective at a willingness-to-pay (WTP) threshold of £30,000 per QALY in all but three of the scenarios. The first was the scenario in which discounting in costs and outcomes was omitted as the incremental cost associated with efanesoctocog alfa increased. The second was the scenario in which ABR levels were derived from HAVEN 3 Arm B. In this scenario the lower bleed rates led to fewer incremental QALYs and to higher incremental cost due to less savings from the bleeding events being avoided. The third was the scenario that excluded the disutility for FVIII levels <20% (20 IU/dl). The ICER in this scenario increased because the benefits of sustained FVIII levels are estimated to be a driver of QALYs for efanesoctocog alfa.

Table 5.4: Company scenario analyses after the CL, PUPs

Scenario	Versus efmoroctocog alfa			Versus emicizumab		
	Incr. costs	Incr. QALYs	ICER/ QALY	Incr. costs	Incr. QALYs	ICER/ QALY
Base-case	[redacted]	[redacted]	£18,899	[redacted]	[redacted]	Dominant
6% discount rate for costs and outcomes	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
No discount for costs and outcomes	[redacted]	[redacted]	£54,927	[redacted]	[redacted]	Dominant
All bleeds assumed to be treated	[redacted]	[redacted]	£20,076	[redacted]	[redacted]	Dominant
Baselines rates for any bleeds (2.6) and treated bleed (1.3) of the emicizumab arm informed from Arm B of Haven 3 and ABRs for comparators calculated relative to this baseline	[redacted]	[redacted]	£37,622	[redacted]	[redacted]	Dominant
Baseline ABRs for any bleeds ([redacted]) and treated bleeds (0.61) informed from Arm B of XTEND-1 during the prophylaxis period	[redacted]	[redacted]	£21,295	[redacted]	[redacted]	Dominant
Baseline rates for any bleeds (3.3) and treated bleeds (1.6) for the emicizumab arm informed from Arm D of Haven 3 and ABRs for comparators calculated relative to this baseline	[redacted]	[redacted]	£12,182	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in each cycle for efanesoctocog alfa informed from 12-month XTEND-1 data	[redacted]	[redacted]	£18,899	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in the emicizumab arm informed from Arm A of the HAVEN 3	[redacted]	[redacted]	£18,899	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in the emicizumab arm	[redacted]	[redacted]	£18,899	[redacted]	[redacted]	Dominant

Scenario	Versus efmoroctocog alfa			Versus emicizumab		
	Incr. costs	Incr. QALYs	ICER/ QALY	Incr. costs	Incr. QALYs	ICER/ QALY
informed from Arm B of the HAVEN 3						
Chromogenic assay for assessing FVIII levels for efanesoctocog alfa and efmoroctocog alfa	[redacted]	[redacted]	£14,344	[redacted]	[redacted]	Dominant
No disutility associated with FVIII levels below 20%	[redacted]	[redacted]	£37,718	[redacted]	[redacted]	Dominant
Utility values estimated from Model 2	[redacted]	[redacted]	£11,051	[redacted]	[redacted]	Dominant
Drug wastage was included for emicizumab using the method of moments	[redacted]	[redacted]	£18,899	[redacted]	[redacted]	Dominant

Based on Table 47 from the company's response to CQs.[2]
ABR = annualised bleeding rate; CL = clarification letter; EAG = External Assessment Group; FVIII = clotting factor VIII; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year; PUPs = previously untreated patients; % = percentage

Table 5.5: Company scenario analyses after the CL, PTPs

Scenario	Versus emicizumab		
	Incr. costs	Incr. QALYs	ICER/QALY
Base-case	[redacted]	[redacted]	Dominant
6% for costs and outcomes	[redacted]	[redacted]	Dominant
No discount for costs and outcomes	[redacted]	[redacted]	Dominant
All bleeds assumed to be treated	[redacted]	[redacted]	Dominant
Baselines rates for any bleeds (2.6) and treated bleed (1.3) of the emicizumab arm informed from Arm B of Haven 3 and ABRs for comparators calculated relative to this baseline	[redacted]	[redacted]	Dominant
Baseline ABRs for any bleeds ([redacted]) and treated bleeds (0.61) informed from Arm B of XTEND-1 during the prophylaxis period	[redacted]	[redacted]	Dominant
Baseline rates for any bleeds (3.3) and treated bleeds (1.6) for the emicizumab arm informed from Arm D of Haven 3 and ABRs for comparators calculated relative to this baseline	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in each cycle for efanesoctocog alfa informed from 12-month XTEND-1 data	[redacted]	[redacted]	Dominant

Scenario	Versus emicizumab		
	Incr. costs	Incr. QALYs	ICER/QALY
% of patients experiencing a bleed in the emicizumab arm informed from Arm A of the HAVEN 3	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in the emicizumab arm informed from Arm B of the HAVEN 3	[redacted]	[redacted]	Dominant
Chromogenic assay for assessing FVIII levels for efanesoctocog alfa and efmoroctocog alfa	[redacted]	[redacted]	Dominant
No disutility associated with FVIII levels below 20%	[redacted]	[redacted]	Dominant
Utility values estimated from Model 2	[redacted]	[redacted]	Dominant
Drug wastage was included for emicizumab using the method of moments	[redacted]	[redacted]	Dominant

Based on Table 48 from the company's response to CQs.[2]
ABR = annualised bleeding rate; CL = clarification letter; EAG = External Assessment Group; FVIII = clotting factor VIII; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year; PTPs = previously treated patients; % = percentage

5.3 Model validation and face validity check

Validation efforts conducted on the economic model were shortly discussed in the validation Section of the CS (Section B.3.13).[3] Model developers and independent health economists were commissioned to check the quality of the economic model focussing on cell-by-cell checks and logical checks. The company further indicated in Section B.3.13 of the CS that the validation process was assessed using the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool with results of this assessment mentioned to be presented in Appendix Q of the CS.[86]

The company stated that expert opinion was solicited to validate key model inputs and assumptions from a clinical perspective. According to the CS, clinical opinion was requested to validate the current pathway of care for patients with severe haemophilia A, the clinical input data used in the model, the impact of factor levels on HRQoL, the durability of the treatment effect and the resource use. The CS states that overall, the validation process did not identify issues with the structural or computational accuracy of the model.

EAG comment: From the information provided through the AdViSHE tool, it is clear that the company has made great efforts to ensure the model validity. Unfortunately, at several points the EAG did encounter issues with the validity of the model inputs; these issues have been raised across the different EAG comments in Section 4. In addition, an important error was found in the electronic model, in the calculation of QALYs for the emicizumab group (see Section 6.1) and at many points the CS was not transparent e.g. regarding the TOBIT models, for which only point estimates were presented, and little detail was provided regarding the sample size for the EQ-5D data.

On the other hand, the EAG was delighted with the cross-validation testing that was done.

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 Explanation of the EAG adjustments

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case includes several changes to the original cost effectiveness model provided by the company base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and they can be subdivided into three categories (derived from Kaltenthaler et al. 2016)[87]:

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong).
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to).
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

6.1.1.1 Fixing errors

Errors that were found in the original model during clarification were corrected by the company in a revised electronic model.

In the revised model, a few other issues were identified:

- The calculation of the QALYs with no bleeding in the emicizumab arm were not correct, as they used the distribution across FVIII levels from the efanesoctocog alfa instead of those from emicizumab. On worksheet 'Trace Hemlibra', in cells AT17:AT216, where it now states MMULT(Trace_Efanesoctocog!Z216:AD216,Utilities!$E$11:$E$15) it should instead state MMULT(AA216:AE216,Utilities!$E$11:$E$15).
- In the PSA settings for the disutility for patients with FVIII level <20%, the values for <1%, 1-5%, and 5-20% are independently drawn, leading to PSA iterations where a smaller disutility is used for the <1% level than for the 5-20% level. Thus, on worksheet 'DSA-PSA inputs' in cells R106 and R107, the formula has been replaced by =R105
- Similarly, for resource use after a bleeding, i.e. visit A&E, specialist visit and nurse visit, random draws are made during the PSA for each treatment arm separately. As there is no reason to assume that resource use for a bleeding depends on the treatment arm, we have made sure that the same random value is used for all three treatment arms, to avoid random noise in the PSA. Thus, on worksheet 'DSA-PSA inputs' in cells P76 and P79 we have replaced the formula by =P73, and the same for P77/P80 (=P74) and P78/P81 (=P75).
- In the PSA, the EAG found that the coefficients from the utility model were varied independently, rather than according to their estimated variance-covariance matrix. However, as no output from the TOBIT models was provided with the company submission, the EAG could not correct for this. This error of course only impacts the PSA results, and not the various point estimates provided in this Section.

6.1.1.2 Fixing violations

No violations were identified.

6.1.1.3 Matters of judgement

The EAG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

- The company base-case estimated the ABR for emicizumab using data from the comparison of the XTEND-1 Arm B and HAVEN 3 Arm B. The main reason behind this choice was the dosing schedule for emicizumab (Q2W). The CS further commented that weekly and bi-weekly doses of emicizumab have shown similar efficacy in the HAVEN 3 trial.[45, 46] Considering that the percentage of patients with a bleeding event were estimated from XTEND-1 Arm A and HAVEN 3 Arm D, that weekly and bi-weekly doses of emicizumab have shown similar efficacy, and that the IRR for any bleeds from XTEND-1 Arm A and HAVEN 3 Arm D are based on a much larger sample increasing the robustness of the estimates, the EAG thinks the IRR based on these two groups are more appropriate for the estimation of the ABRs for emicizumab.
- The company base-case assumed that all patients on emicizumab treatment would follow a biweekly (Q2W) dosing schedule based on clinical expert opinion suggesting that this is the most frequent option.[7] In the absence of appropriate evidence on the distribution of patients across the three dosing schedules of emicizumab (QW; Q2W; Q4W) treatment, the EAG finds the QW dosing schedule to be more appropriate for the base-case analysis. Further reasoning is provided in EAG comments in Section 4.2.9. This argumentation further reinforces the EAG preferred option to use data from XTEND-1 Arm A and HAVEN 3 Arm D (where the dosing schedule was QW) to define the IRRs that were used for the estimation of the ABRs for emicizumab treatment (previous point).
- Considering the dosing schedule used to treat acute bleeding events, the company assumed that one dose of 25 IU/kg would suffice to resolve the same type of bleed for patients using efanesoctocog alfa treatment, whereas for patients using efmoroctocog alfa or emicizumab treatments two doses of 25 IU/kg would be needed. To justify this assumption the company stated that "clinicians also felt that the high sustained pharmacokinetic profile of efanesoctocog alfa would allow for 1 x 25 IU/kg dose to resolve the same type of bleed".[3, 7] The EAG does not think this assumption is sufficiently substantiated and based on the trial data presented by the company during the clarification phase (see Section 4.2.9 for further details), the EAG is convinced that the base-case analysis should use one dose of 50 IU/kg to treat bleeding events for patients in the efanesoctocog alfa arm similar to the efmoroctocog alfa and emicizumab treatment.

The overview of these changes and the bookmarks for the justification of the EAG changes are presented in Table 6.1.

Table 6.1: Company and EAG base-case preferred assumptions

Base-case preferred assumptions	Company	EAG	Justification for change
Data to inform ABR for emicizumab	ABRs and % bleeds that are treated for emicizumab informed from XTEND-1 Arm B and HAVEN 3 Arm B	ABRs and % bleeds that are treated for emicizumab informed from XTEND-1 Arm A and HAVEN 3 Arm D	Section 4.2.6

Base-case preferred assumptions	Company	EAG	Justification for change
Emicizumab dosing	Q2W	Q1W	Section 4.2.9
Dosage to treat bleeding events for efanesoctocog alfa	one dose of 25 IU/kg	one dose of 50 IU/kg	Section 4.2.9
ABR = annualised bleeding rates; EAG = External Assessment Group; IU = international units; kg = kilogram; Q2W = once every two weeks; % = percentage			

6.1.2 Additional scenarios conducted by the EAG

After the proposed changes for the EAG base-case analysis were implemented in the company's model, the EAG performed the following exploratory scenario analyses to investigate the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Scenario 1: Alternative weight values (Section 4.2.3)

The EAG explored the impact of using alternative weight values. Specifically, data from NHD presented by the company showed that for EHL users aged ≥12 years, the average weight is 79.9 kg and for SHL users 82.3 kg, so slightly higher than the weight of patients observed in XTEND-1. Thus, the EAG will explore a scenario where the weight for PTP's is set to 79.9 kg and to the weighted average of EHL and SHL users, 81.3kg.

6.1.2.2 Scenario 2: Distribution of emicizumab patients according to conversion factor of 0.4 (Section 4.2.6.2)

The EAG's asked the company to provide the distribution of emicizumab patients across FVIII activity levels for the range of the conversion factor rather than the mean. At the lower limit, of 0.2, 100% of patients would be in the 5-20% FVIII activity level, for all dosing schedules. At the mean of 0.3, only in the Q4W dosing schedule would the fraction in 5-20% reduce to 84%, with the other 16% in the 20-40% level. For the upper limit of 0.4 the resulting distribution is given in Table 4.9. In a scenario analysis, the EAG will explore the impact of using the distribution as presented for QW.

6.1.2.3 Scenario 3: Disutility related to lower FVIII (Section 4.2.8)

The model incorporated disutility related to the time spent in FVIII levels <20%. The reasoning stemmed from the expectation that patients with lower FVIII levels are less capable of undertaking certain activities due to the fear a bleeding event. The EAG thinks this argument is not convincing as most patients will not be aware of their FVIII level unless they have frequent bleeding (in which case disutilities for bleeding are applied). Given that the levels of >5% are usually classified as mild in haemophilia A, it seems reasonable to assume that any anxiety-related disutility does not apply to the 5-20% activity level. In addition, the regression model used by the company included number of days from treatment initiation, whilst this is not used in the CE model. Therefore, in an exploratory scenario analysis, the EAG will explore the impact of applying regression model 4 (Table 4.10) for the QALY estimation.

6.1.2.4 Scenario 4: Wastage costs for octocog alfa (Section 4.2.9)

The company implemented wastage costs for octocog alfa, used to treat bleeding events for patients on emicizumab. The approach was not sufficiently justified and according to the EAG, the sources used to

inform inputs and assumptions for this approach (including the 6,000 IU of octocog alfa, every 4 cycles) were also not clearly specified. Additionally, the EAG was not convinced the implementation in the electronic model was correct. Therefore, the EAG considers this approach lacks face validity, and assessed the impact of omitting these costs on the cost effectiveness outcomes and the impact of assuming the wastage costs would apply for half of the population defined by the company.

6.1.2.5 Scenario 5: Resource use and costs inputs for the treatment of bleeding events (Section 4.2.9)

The EAG has several concerns around the appropriateness of the costing inputs that were used in the company base-case. Firstly, the CS noted that because Shrestha et al. (2017)[84] reported the need for more than one specialist visits to treat a bleeding event, it was assumed that an additional nurse visit would not be necessary. The EAG found this assumption not justifiable based on the company's feedback from clinical experts and the fact no other source was provided. Secondly, the cost per bleeding event used in the company's base-case was set at £610.45 irrespective of bleed severity. In the clarification phase, the company explained that most bleeds observed in XTEND-1 were joint or muscle bleeds, and 96.7% were controlled by a single injection of efanesoctocog alfa. The EAG noted that Benson et al. (2021)[58] assumed a cost of £566.47 per severe bleeding event, whilst assigned a zero cost to additional resource use for mild to moderate bleeds. These combined with the fact that multiple of the bleeds can be resolved by phone contact, as explained by the company's clinical expert opinion, the EAG thinks that the company's cost per bleeding event is likely overrepresenting costs in UK clinical practice. Therefore, the EAG ran scenario analysis in which the number of specialist visits were spread among specialists and nurse visits (to account for contacts resolved via phone), and a scenario analysis in which all resource use due to the management of bleeding events were omitted from the computations.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG base-case was defined using the base-case of the company following the clarification phase as starting point. Table 6.2 shows the deterministic cost effectiveness results of the EAG preferred base-case analysis. All results are discounted.

Following the EAG adjustments, treatment with efanesoctocog alfa increased total costs by [redacted] compared to efmoroctocog alfa, whilst emicizumab increased total costs by [redacted] compared to efanesoctocog alfa. At the same time, [redacted] QALYs were gained for patients treated with efanesoctocog alfa as compared to efmoroctocog alfa and [redacted] QALYs as compared to emicizumab. These produced an ICER for efanesoctocog alfa versus efmoroctocog alfa of £43,798 per QALY gained, whilst efanesoctocog alfa was estimated to be more effective and less costly than emicizumab (i.e. efanesoctocog alfa was a dominant treatment).

For the PTP population, emicizumab increased total costs by [redacted] compared to efanesoctocog alfa whilst reducing the number of QALYs by [redacted]. This indicates that efanesoctocog alfa would be a less expensive and more effective treatment option, dominating emicizumab treatment option in the PTP population.

These results indicate that the ICER of efanesoctocog alfa versus efmoroctocog alfa when using the EAG's preferred assumptions increase substantially (more than two times) as opposed to the company's base-case analysis. For the comparison efanesoctocog alfa with emicizumab, although the absolute difference in costs and QALYs was reduced when using the EAG's preferred assumptions, for both

populations, efanesoctocog alfa would remain a less expensive and more effective treatment option, dominating emicizumab.

Table 6.2: EAG preferred base-case deterministic cost effectiveness results – full incremental

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
PUPs							
Efmoroctocog alfa	[redacted]	27.05	[redacted]	-			
Efanesoctocog alfa	[redacted]	27.05	[redacted]	[redacted]	0.00	[redacted]	£43,798
Emicizumab	[redacted]	27.05	[redacted]	[redacted]	0.00	[redacted]	Dominated
PTPs							
Efanesoctocog alfa	[redacted]	22.37	[redacted]	-			
Emicizumab	[redacted]	22.37	[redacted]	[redacted]	0.00	[redacted]	Dominated

EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; PUPs = previously untreated patients; PTPs = previously treated patients; QALYs = quality-adjusted life years

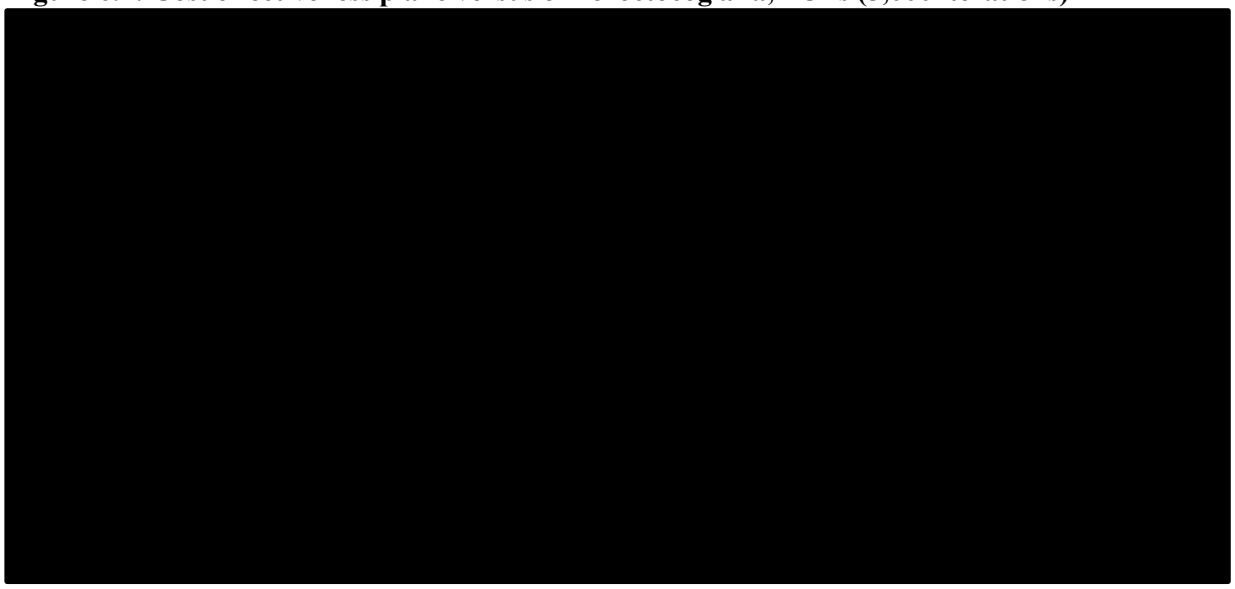
Table 6.3 shows the probabilistic cost effectiveness results of the EAG preferred base-case analysis. All results are discounted. The probabilistic results are aligned with the deterministic EAG base-case results. Figures 6.1 to 6.3 show the distribution of all PSA outcomes over the cost effectiveness plane. These show clearly that all PSA iterations in the comparison of efanesoctocog alfa versus emicizumab show an increase in QALYs whilst saving costs; hence, the CEACs for these comparisons show a flat line at 100% probability of being acceptable. Based on the CEAC in Figure 6.4, the results show that for PUPs, the probability of efanesoctocog alfa being cost-effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], respectively, when compared with compared with efmoroctocog alfa, whilst it was [redacted] of simulations.

Table 6.3: EAG preferred base-case probabilistic cost effectiveness results

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
PUPs					
Efmoroctocog alfa	[redacted]	[redacted]	–	–	–
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£44,387
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
PTPs					
Efanesoctocog alfa	[redacted]	[redacted]	–	–	–
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

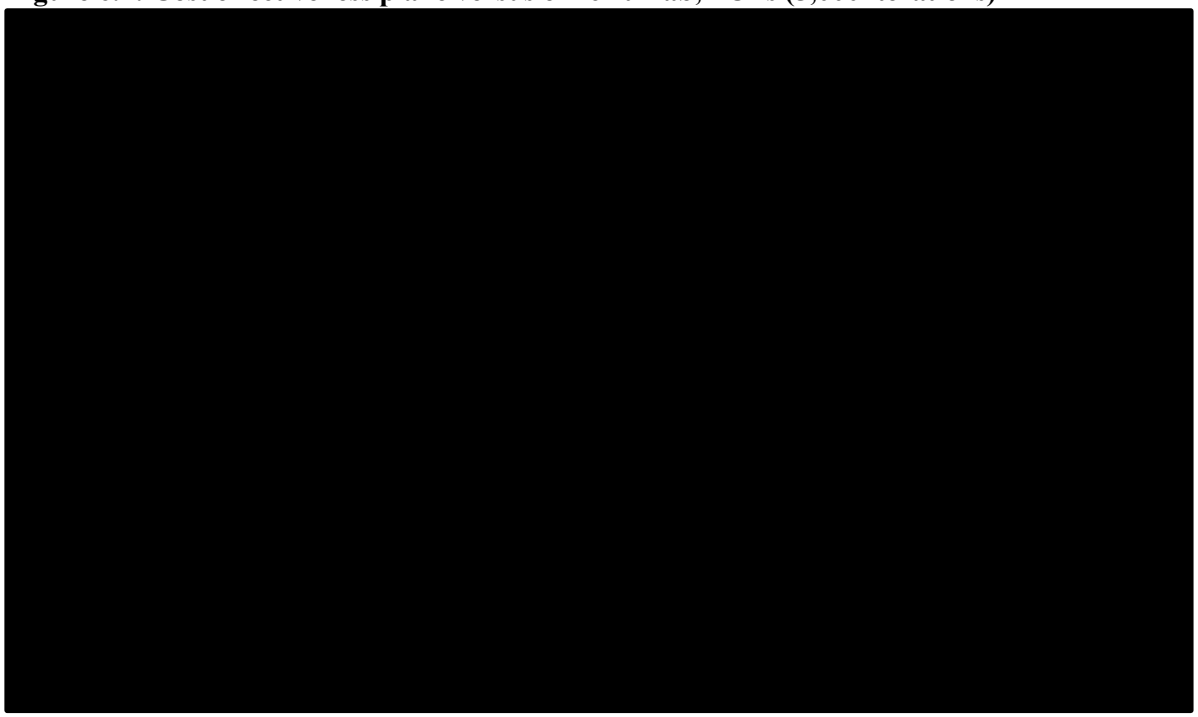
Based on the electronic model after the clarification phase
EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; PUPs = previously untreated patients; PTPs = previously treated patients; QALYs = quality-adjusted life years

Figure 6.1: Cost effectiveness plane versus efmoroctocog alfa, PUPs (5,000 iterations)



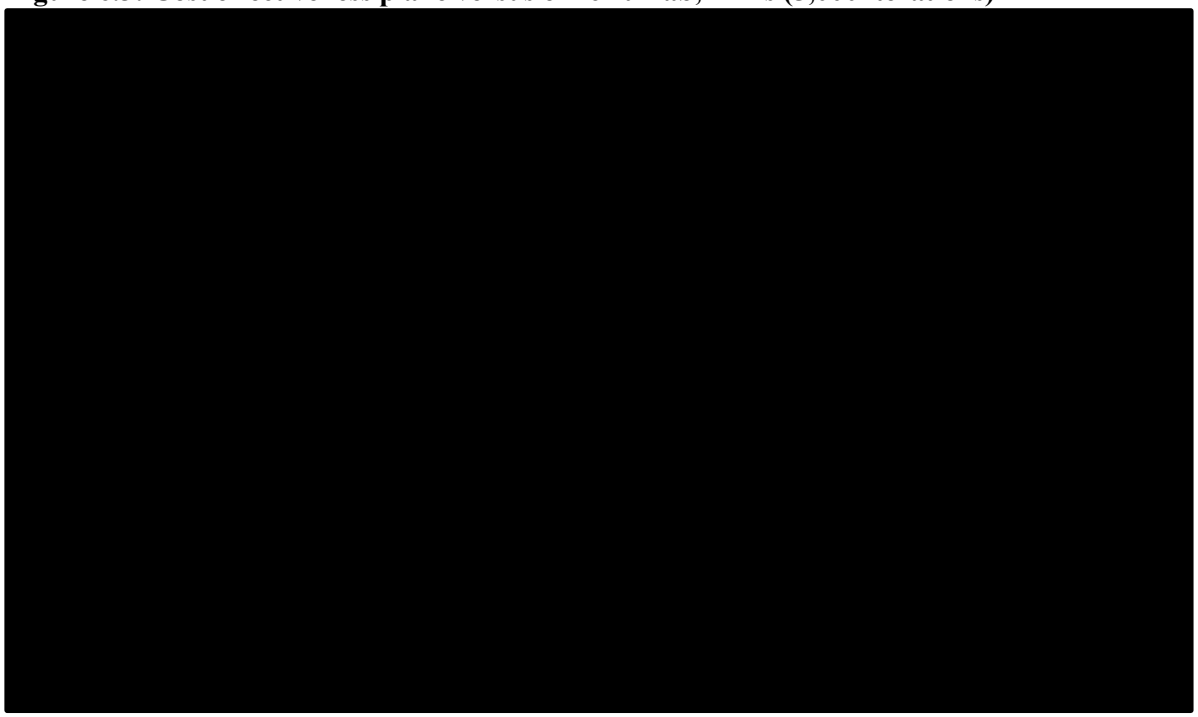
Based on the model submitted following the clarification phase
PUPs = previously untreated patients; QALYs = quality-adjusted life years

Figure 6.2: Cost effectiveness plane versus emicizumab, PUPs (5,000 iterations)



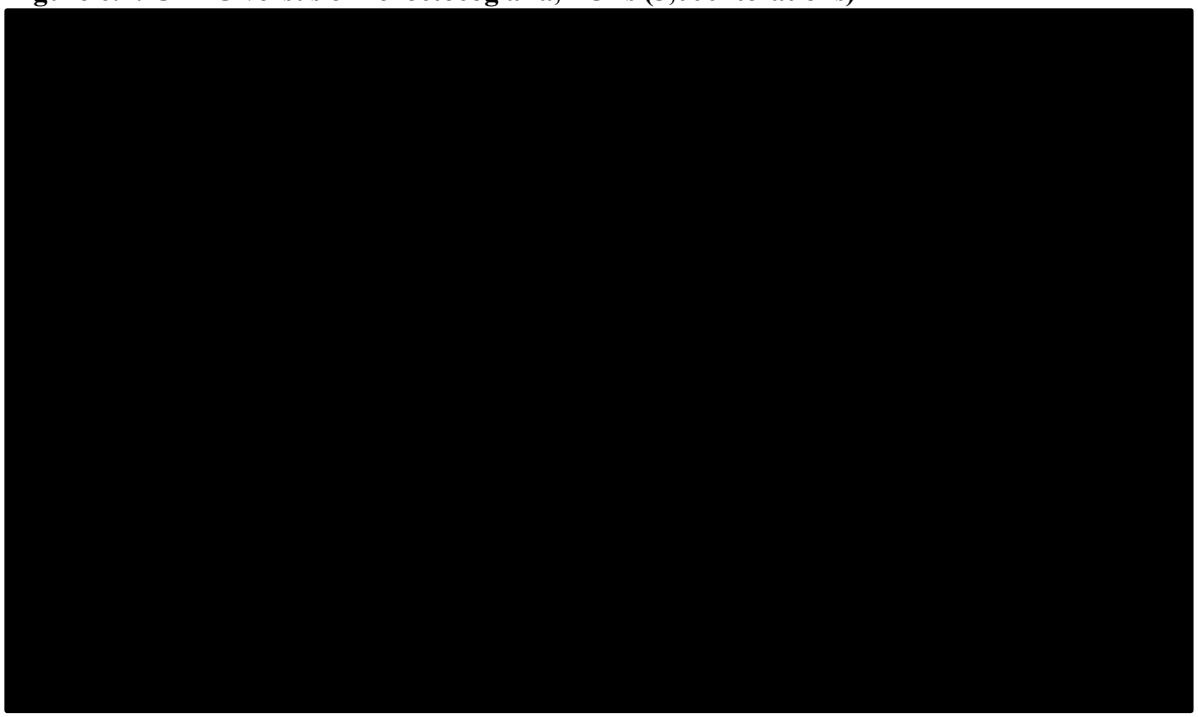
Based on the model submitted following the clarification phase
PUPs = previously untreated patients; QALYs = quality-adjusted life years

Figure 6.3: Cost effectiveness plane versus emicizumab, PTPs (5,000 iterations)



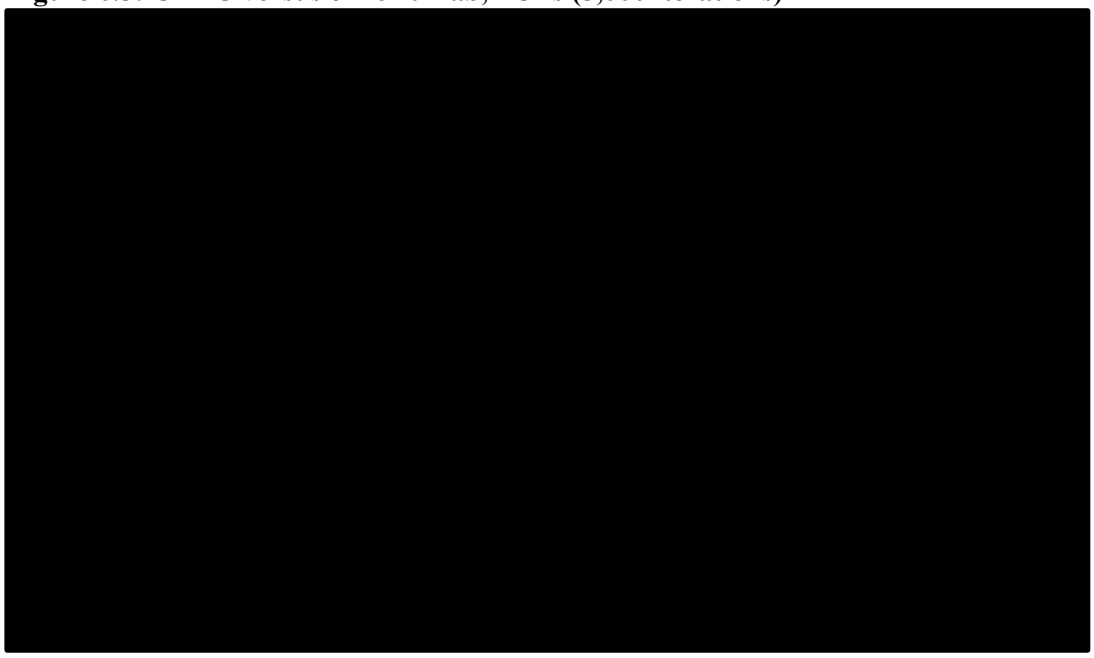
Based on the model submitted following the clarification phase
PTPs = previously treated patients; QALYs = quality-adjusted life years

Figure 6.4: CEAC versus efmoroctocog alfa, PUPs (5,000 iterations)



Based on the model submitted following the clarification phase
CEAC cost effectiveness acceptability curve; PUPs = previously untreated patients; WTP = willingness-to-pay

Figure 6.5: CEAC versus emicizumab, PUPs (5,000 iterations)



Based on the model submitted following the clarification phase
CEAC cost effectiveness acceptability curve; PUPs = previously untreated patients; WTP = willingness-to-pay

Figure 6.6: CEAC versus emicizumab, PTPs (5,000 iterations)

Based on the model submitted following the clarification phase
CEAC cost effectiveness acceptability curve; PTPs = previously treated patients; WTP = willingness-to-pay

In Table 6.5 and Table 6.6 it is shown how the EAG base-case compares to the CS base-case, and how the individual adjustments that were made by the EAG impact the results of the two subpopulations (i.e., PTPs and PUPs patient population). It is clear that the correction of the programming error leads to a decrease in the number of QALYs yielded by treatment with emicizumab. Of the two changes made in the EAG base-case, the change in the dosage of efanesoctocog to treat bleeding events has the largest impact, especially in the comparison against efmoroctocog, where the ICER more than doubles.

Table 6.4: Deterministic EAG base-case versus company base-case, PUPs, full incremental

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Efmoroctocog alfa	[redacted]	[redacted]	–		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£18,211
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CS base-case following the clarification phase					
Efmoroctocog alfa	[redacted]	[redacted]	–		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£18,899
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base-case					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£43,798
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CS and Only correction error					
Efmoroctocog alfa	[redacted]	[redacted]	–		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£18,899
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Correction error and ABRs from XTEND-1 Arm A and HAVEN 3 Arm D					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£18,899
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Correction error and one dose of 50 IU/kg to treat bleeding events with efanesoctocog alfa					
Efmoroctocog alfa	[redacted]	[redacted]			
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£43,798
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ABR = annualised bleeding rate; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; IU/kg = International units per kilogram (body weight); PUPs = previously untreated patients; QALYs = quality-adjusted life years

Table 6.5: Deterministic EAG base-case versus company base-case, PTPs, full incremental

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CS base-case following the clarification phase					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base-case					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CS and Only correction error					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Correction error and ABRs from XTEND-1 Arm A and HAVEN 3 Arm D					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Correction error and one dose of 25 IU/kg to treat bleeding events with efanesoctocog alfa					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ABR = annualised bleeding rate; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; IU/kg = International units per kilogram (body weight); PTPs = previously treated patients; QALYs = quality-adjusted life years

6.3 Exploratory scenario analyses conducted by the EAG

6.3.1 EAG defined scenario analyses

The exploratory scenario analyses are presented in Table 6.6 and Table 6.7, respectively, for PUPs patients and PTPs patients. These results are all conditional on the EAG base-case.

Table 6.6: EAG scenario analyses (conditional on EAG base-case), PUPs, full incremental

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£43,798
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Alternative weight values: 79.9 kg (average EHL patients)					
Efmoroctocog alfa	[redacted]	[redacted]			
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£44,861
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Alternative weight values: 81.3 kg (weighted average EHL and SHL patients)					
Efmoroctocog alfa	[redacted]	[redacted]			
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£45,924
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Distribution of emicizumab patients according to conversion factor of 0.4					
Efmoroctocog alfa	[redacted]	[redacted]			
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£43,798
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Use model 4 for utilities					
Efmoroctocog alfa	[redacted]	[redacted]			
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£25,523
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Wastage costs for octocog alfa omitted					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£43,798
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Wastage costs for octocog alfa assumed for half of the population					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£43,798
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Specialist visits were spread among specialists and nurse visits					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£66,557
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Set costs of management per bleeding event to zero					
Efmoroctocog alfa	[redacted]	[redacted]	-		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	£95,046
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

EAG = External Assessment Group; EHL = extended half-life; FVIII = clotting factor VIII; ICER = incremental cost-effectiveness ratio; PUPs = previously untreated patients; QALYs = quality-adjusted life years; SHL = standard half-life

Table 6.7: EAG scenario analyses (conditional on EAG base-case), PTPs, full incremental

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Alternative weight values: 79.9 kg (average EHL patients)					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Alternative weight values: 81.3 kg (weighted average EHL and SHL patients)					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Distribution of emicizumab patients according to conversion factor of 0.4					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Use model 4 for utilities					
Efanesoctocog alfa	[redacted]	[redacted]	–		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Wastage costs for octocog alfa omitted					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Wastage costs for octocog alfa assumed for half of the population					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Specialist visits were spread among specialists and nurse visits					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Set costs of management per bleeding event to zero					
Efanesoctocog alfa	[redacted]	[redacted]	-		
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

EAG = External Assessment Group; EHL = extended half-life; FVIII = clotting factor VIII; ICER = incremental cost-effectiveness ratio; PTPs = previously treated patients; QALYs = quality-adjusted life years; SHL = standard half-life

6.3.2 Company defined scenario analyses for EAG base-case

Tables 6.8 and 6.9 show the results of the various scenarios as defined by the company. For the comparison of efanesoctocog alfa versus emicizumab, both for PUPs and PTPs, we notice that only the discount rate scenarios and scenarios that remove the disutility for patients with an FVIII activity level between 5% and 20% show a large impact on the outcomes. The discount rate scenarios influence the

absolute value of the incremental costs and the incremental QALYs both in the same direction, whereas the utility scenarios only decrease the QALY gains.

For both PUPs and PTPs, we also observe some influence of the choice of assay for assessing FVIII levels for efanesoctocog alfa and efmoroctocog alfa, as this influences the time in lower FVIII levels associated with a disutility.

For the PUPs, in the comparison of efanesoctocog alfa versus efmoroctocog alfa, we furthermore notice an impact on the ICER of the choice of base line bleeding rates (now from the emicizumab arm informed by Arm B of Haven 3) and ABRs for comparators calculated relative to this baseline. Though the impact on incremental costs and incremental QALYs is modest, as they work in opposite directions the combined impact on the ICER is large.

Table 6.8: Company defined scenario analyses using EAG base-case, PUPs

Scenario	Versus efmoroctocog alfa			Versus emicizumab		
	Incr. costs	Incr. QALYs	ICER/ QALY	Incr. costs	Incr. QALYs	ICER/ QALY
Base-case	[redacted]	[redacted]	**£43,798**	[redacted]	[redacted]	**Dominant**
6% for costs and outcomes	[redacted]	[redacted]	£21,026	[redacted]	[redacted]	Dominant
No discount for costs and outcomes	[redacted]	[redacted]	£80,825	[redacted]	[redacted]	Dominant
All bleeds assumed to be treated	[redacted]	[redacted]	£46,525	[redacted]	[redacted]	Dominant
Baselines rates for any bleeds (2.6) and treated bleed (1.3) of the emicizumab arm informed from Arm B of Haven 3 and ABRs for comparators calculated relative to this baseline	[redacted]	[redacted]	£60,320	[redacted]	[redacted]	Dominant
Baseline ABRs for any bleeds ([redacted]) and treated bleeds (0.61) informed from Arm B of XTEND-1 during the prophylaxis period	[redacted]	[redacted]	£46,700	[redacted]	[redacted]	Dominant
Baseline rates for any bleeds (3.3) and treated bleeds (1.6) for the emicizumab arm informed from Arm D of Haven 3 and ABRs for comparators calculated relative to this baseline	[redacted]	[redacted]	£39,292	[redacted]	[redacted]	Dominant

Scenario	Versus efmoroctocog alfa			Versus emicizumab		
	Incr. costs	Incr. QALYs	ICER/ QALY	Incr. costs	Incr. QALYs	ICER/ QALY
% of patients experiencing a bleed in each cycle for efanesoctocog alfa informed from 12-month XTEND-1 data	[redacted]	[redacted]	£55,833	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in the emicizumab arm informed from Arm A of the HAVEN 3	[redacted]	[redacted]	£43,798	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in the emicizumab arm informed from Arm B of the HAVEN 3	[redacted]	[redacted]	£43,798	[redacted]	[redacted]	Dominant
Chromogenic assay for assessing FVIII levels for efanesoctocog alfa and efmoroctocog alfa	[redacted]	[redacted]	£33,241	[redacted]	[redacted]	Dominant
No disutility associated with FVIII levels below 20%	[redacted]	[redacted]	£87,411	[redacted]	[redacted]	Dominant
Utility values estimated from Model 2	[redacted]	[redacted]	£25,609	[redacted]	[redacted]	Dominant
Drug wastage was included for emicizumab using the method of moments	[redacted]	[redacted]	£43,798	[redacted]	[redacted]	Dominant

Based on the model submitted following the clarification phase, the EAG run these scenarios.[69]

ABR = annualised bleeding rate; EAG = External Assessment Group; FVIII = clotting factor VIII; ICER = incremental cost-effectiveness ratio; Incr. = incremental; PUPs = previously untreated patients; QALYs = quality-adjusted life years; % = percentage

Table 6.9: Company defined scenario analyses using EAG base-case, PTPs

Scenario	Versus emicizumab		
	Incr. costs	Incr. QALYs	ICER/QALY
Base-case	[redacted]	[redacted]	Dominant
6% for costs and outcomes	[redacted]	[redacted]	Dominant
No discount for costs and outcomes	[redacted]	[redacted]	Dominant
All bleeds assumed to be treated	[redacted]	[redacted]	Dominant
Baselines rates for any bleeds (2.6) and treated bleed (1.3) of the emicizumab arm informed from Arm B of	[redacted]	[redacted]	Dominant

Scenario	Versus emicizumab		
	Incr. costs	Incr. QALYs	ICER/QALY
Haven 3 and ABRs for comparators calculated relative to this baseline			
Baseline ABRs for any bleeds ([redacted]) and treated bleeds (0.61) informed from Arm B of XTEND-1 during the prophylaxis period	[redacted]	[redacted]	Dominant
Baseline rates for any bleeds (3.3) and treated bleeds (1.6) for the emicizumab arm informed from Arm D of Haven 3 and ABRs for comparators calculated relative to this baseline	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in each cycle for efanesoctocog alfa informed from 12-month XTEND-1 data	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in the emicizumab arm informed from Arm A of the HAVEN 3	[redacted]	[redacted]	Dominant
% of patients experiencing a bleed in the emicizumab arm informed from Arm B of the HAVEN 3	[redacted]	[redacted]	Dominant
Chromogenic assay for assessing FVIII levels for efanesoctocog alfa and efmoroctocog alfa	[redacted]	[redacted]	Dominant
No disutility associated with FVIII levels below 20%	[redacted]	[redacted]	Dominant
Utility values estimated from Model 2	[redacted]	[redacted]	Dominant
Drug wastage was included for emicizumab using the method of moments	[redacted]	[redacted]	Dominant
Based on the model submitted following the clarification phase, the EAG run these scenarios.[69] ABR = annualised bleeding rate; EAG = External Assessment Group; FVIII = clotting factor VIII; ICER = incremental cost-effectiveness ratio; Incr. = incremental; PTPs = previously treated patients; QALYs = quality-adjusted life years; % = percentage			

6.4 Conclusions of the cost effectiveness Section

The model provided by the company follows a very simple structure, basically calculating each cycle for how many patients will have bleeding, how many bleedings occur and how many are treated. The probabilities and proportions remain the same over time, with the only thing changing over time is patients dying, according to UK mortality data for the general population.

The estimation of these probabilities and proportions are based on indirect estimation methods, as none of the included treatments has been compared to others in a head-to-head trial. Thus, the company had to rely on an unanchored MAIC to compare efanesoctocog alfa and emicizumab and on an ITC with PSM for the comparison of efanesoctocog alfa and efmoroctocog alfa. It is clear that both these methods, but especially the MAIC, lead to results much more uncertain than if they had been based on data from a direct comparison. As such, uncertainty beyond the explored parametric uncertainty remains in all CEA analyses.

The EAG did not agree with the company's choice to estimate the ABR for emicizumab using data from the comparison of the XTEND-1 Arm B and HAVEN 3 Arm B. The main reason behind this choice was the dosing schedule for emicizumab (Q2W). As the CS commented themselves that weekly and bi-weekly doses of emicizumab had similar efficacy in the HAVEN 3 trial,[45, 46] the EAG prefers to

use the outcomes based on XTEND-1 Arm A and HAVEN 3 Arm D, which involved patients with previous prophylactic treatment and a dosing schedule of QW for emicizumab. The added benefit of this choice is that the percentage of patients with a bleeding event were also estimated from this comparison and hat the estimated IRRs are now based on a much larger sample increasing the robustness of the estimates.

Whilst the probabilities and proportions used to fill the Markov trace made no distinction in level of FVIII activity, the company still estimated the distribution of patients over these levels over time, as they expected that QoL would be related to these activity levels.

For emicizumab, which has a different mechanism of action, a slightly adjusted method of calculating time spent in each FVIII activity level was required, using a conversion factor of 0.3 to estimate the FVIII activity level for a certain emicizumab concentration level. The source for this conversion factor was a pre-clinical study in non-human primates, causing some apprehensiveness with the EAG about the applicability in humans of this conversion factor. However, the EAG identified a study in which the stability and structure of emicizumab-induced fibrin clots were investigated and compared to FVIII-induced fibrin clots,[70] which concludes that potential activity of emicizumab observed appears to be similar to that predicted in pre-clinical studies (0.2-0.4 IU/dl per μg/mL).

Thus, the EAG considers it indeed plausible that most emicizumab patients can be classified in the 5-20% FVIII activity level. In a scenario though, the EAG explored what the impact would be if the upper limit of the range for the conversion factor is used, in which case all patients are classified in the 20-40% FVIII activity level.

The company modelled the utilities by using the age-adjusted utilities for the general UK population as the starting point, for patients with no bleeding in a cycle and an FVIII level above 20%. Based on a TOBIT regression analysis, using EQ-5D data collected in the XTEND-1 study, the company estimated disutilities for the short-term impact of a bleeding (over a period of 7 days), a long-term disutility for 6 months as a result of the bleeding, and a disutility for patients with an FVIII activity level below 20%.

The company selected the best fitting TOBIT model (note that no outputs for this modelling were provided), but then excluded the covariates age and days from study initiation in the estimation of utility, whilst using the other coefficients for the estimation of the disutilities. This creates substantial uncertainty about the validity of the disutilities applied in the model.

The disutility for patients with an FVIII activity level below 20% was argued by the company to reflect the expectation that patients with lower FVIII levels are less capable of undertaking certain activities due to the fear a bleeding event. The EAG thinks this argument is not convincing as most patients will not be aware of their FVIII level. Therefore, in an exploratory scenario analysis, the EAG explored the impact of omitting this utility loss for patients in the 5-20% activity level by applying regression model 4.

It should be noted that these FVIII levels are modelled as being high immediately after administration of the treatment, after which they decrease until the next dosage. Thus, they do not reflect the (hypothetical?) concept that some patients might show more response to their treatment than others, leading to some patients spending most time at low FVIII activity levels.

With regard to the cost-side of the CEA, some additional issues were identified. The first relates to the treatment of acute bleeding with FVIII. The company assumed that one dose of 25 IU/kg would suffice for patients using efanesoctocog alfa treatment, whereas for patients using efmoroctocog alfa or

emicizumab treatments two doses of 25 IU/kg would be needed. To justify this assumption the company referred to expert opinion whereas the data from XTEND-1 clearly shows that the large majority of patients received 50 IU/kg to treat a bleeding event, and the others around 30 IU/kg. No data other than expert opinion was provided to support the claim that in clinical practice only 25 IU/kg would be used and would be sufficient. Thus, the EAG presented a preferred base-case in which one dose of 50 IU/kg are used to treat bleeding events for patients in the efanesoctocog alfa arm, similar to the efmoroctocog alfa and emicizumab treatment.

Another costing issue relates to the use of octocog alfa to treat bleeding events for patients on emicizumab. The company stated, in a confusing way and without providing any sources, that in the group of patients not bleeding every 2 years a non-used supply of octocog alfa is wasted. Given the lack of justification and the incorrect approach to implementing this in the electronic model, the EAG and assessed the impact of omitting these costs on the cost effectiveness outcomes.

Finally, the EAG has several concerns around the costing inputs used for the non-medical treatment costs of a bleeding event. The EAG found it unlikely that for each bleeding, without regard for the severity 1.1 outpatient specialist visits take place and no nurse visits or telephone consultations. In the clarification phase, the company explained that most bleeds observed in XTEND-1 were joint or muscle bleeds, and 96.7% were controlled by a single injection of efanesoctocog alfa, which seems to suggest they were relatively mild. The EAG thinks that the company's cost per bleeding event is likely overrepresenting costs in UK clinical practice. Therefore, the EAG ran scenario analyses in which the number of specialist visits were spread among specialists and nurse visits (to account for contacts resolved via phone), and a scenario analysis in which all resource use due to the management of bleeding events were omitted from the computations.

Besides all the issues mentioned above, the EAG identified an error in the model in the calculation of the QALYs with no bleeding in the emicizumab arm. Correction of this error led to a substantial increase in the number of QALYs gained with efanesoctocog alfa compared to emicizumab.

The changes made to the company base-case lead to results indicating that the ICER of efanesoctocog alfa versus efmoroctocog alfa when using the EAG's preferred assumptions increases substantially (more than two times) as opposed to the company's base-case analysis. For the comparison efanesoctocog alfa with emicizumab, although the absolute difference in costs and QALYs was reduced when using the EAG's preferred assumptions, for both populations, efanesoctocog alfa would remain a less expensive and more effective treatment option, dominating emicizumab.

For the comparison of efanesoctocog alfa versus emicizumab, both for PUPs and PTPs, the EAG notice that only scenarios that remove the disutility for patients with an FVIII activity level between 5 and 20% (by using utility model 4), or where emicizumab patients are classified as FVIII level 20-40%, show a large impact on the outcomes.

For the PUPs, in the comparison of efanesoctocog alfa versus efmoroctocog alfa, the EAG notice an impact on the ICER of the choice of baseline bleeding rates (now from the emicizumab arm informed by Arm B of Haven 3) and ABRs for comparators calculated relative to this baseline. Though the impact on incremental costs and incremental QALYs is modest, as they work in opposite directions the ICER increases substantially. In contrast, the ICER substantially decrease when the disutility for patients with an FVIII activity level between 5 and 20% is omitted by using utility model 4.

All the changes in the costing of the bleeding events have very limited impact. It should be kept in mind though, that results are based on the list price for emicizumab, so it is unclear if efanesoctocog alfa

remains cost saving in the base-cases and various scenarios when compared to emicizumab, but in all explored situations efanesoctocog alfa yielded additional QALYs.

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Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5:00pm on Wednesday 24 January 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Incorrect PAS discount reported

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.9.2 of the EAG report (page 152) states the incorrect PAS discount for efanesoctocog alfa of [redacted]	The PAS discount should be updated to [redacted]	The stated PAS discount was incorrect.	This has been changed as suggested.

Issue 2 Table labelling

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 5.4 and Table 5.5 in Section 5.2.3 are titled "Company scenario analyses after the CL updated by the EAG, PUPs" and "Company scenario analyses after the CL updated by the EAG, PTPs", respectively	Remove the wording "updated by the EAG"	These tables are identical to those presented in the clarification letter (Table 47 and Table 48). The current wording may lead readers to assume that these are results that include the EAGs error corrections.	This has been changed as suggested. In addition, the EAG has added a reference to Table 47 and Table 48 of the clarification letter in Table 5.4 and Table 5.5, respectively.

Location of typographical error	Description of typographical error and proposed amendment	Justification for amendment	EAG response
EAG report, page 14, Table 1.1 (row 4) EAG report, page 17, Table 1.4 (row 2)	Please amend to say: "*This is partly due to omission of **non-English** language studies*"	To align with the EAGs critique in Section 3.1.2.	The EAG has made the suggested correction to Tables 1.1 and 1.4. In addition, the EAG has made the same correction to Section 3.6, 2nd paragraph.
EAG report, page 40, Table 1.10 (row 5)	Please amend the incremental cost vs emicizumab in the CS original base-case to: **£8,207,273**	Amended for consistency with the CS	The EAG has made the suggested correction to Table 1.10.
EAG report, page 40, Table 3.1 (row 7)	Please amend the date range for DARE from '*To January 2021*' to: ***Q1 2016***	Date range amended for accuracy	Amended as requested.
EAG report, page 40, Table 3.1 (row 8)	Please amend the date range for the HTA database from '*To January 2021'* to: ***Q4 2016***	Date range amended for accuracy	Amended as requested.
EAG report, page 99, Table 3.28	Please move the whole row for the preferred term 'Pain in extremity' from the '*Injury, poisoning and procedural complications'* SOC to ***Musculoskeletal and connective tissue disorders*** SOC	Table row moved to the correct SOC for accuracy	The row has been moved as suggested.

Location of typographical error	Description of typographical error and proposed amendment	Justification for amendment	EAG response
EAG report, page 99, Table 3.28	We noted that some TEAEs of XTEND-1 by SOC and preferred term in **>3%** of patients are missing from the table, e.g. the following SOC: immune system disorders (overall: 3.1%), metabolism and nutrition disorders (overall: 3.1%), psychiatric disorders (overall: 4.4%), eye disorders (overall: 3.8%), respiratory, thoracic and mediastinal disorders (overall: 3.8%), and skin and subcutaneous tissue disorders (overall: 8.2%). As well as contusion (PT, overall: 3.8%) in the injury, poisoning and procedural complications SOC.	Flagged for accuracy; however, please clarify if a different approach was taken.	The details from Table 43 of the CS have now been shown in full in Table 3.28 of the EAG report.
EAG report, page 126, Table 3.42	All results presented in dark green cells are statistically significant and should be **bolded** (rows 3,4, 6–8)	Formatting updated to indicate statistical significance in line with the table key	Not a factual inaccuracy however, bold text has been added as suggested in the interests of being consistent with the source material and table key.
EAG report, page 129, Table 3.43	All statistically significant p-values should be **bolded** (the following values	Formatting updated to indicate statistical	Not a factual inaccuracy however, bold text has been added in the

Location of typographical error	Description of typographical error and proposed amendment	Justification for amendment	EAG response
	in column 6: 0.056, 0.031, 0.003, <0.001, <0.001, 0.034)	significance in line with the table key	interests of being consistent with the source material and table key. Please note that bold text has not been applied to the p-value 0.056 in column 6 as this value does not suggest statistical significance.
EAG report, page 129, Table 3.43	Please amend the source information from 'Table 22, CS' to ***'Table 22, Appendix D of CS'***	Source information updated for accuracy	This has been changed as suggested and the reference has been updated.
EAG report, page 130-131, Table 3.44	All statistically significant p-values should be **bolded** (the following values in column 6: 0.003, 0.008, 0.016, <0.001, 0.005, 0.034, 0.033, 0.012, 0.012, <0.001, 0.004, 0.017)	Formatting updated to indicate statistical significance in line with the table key	Not a factual inaccuracy however, bold text has been added in the interests of being consistent with the source material and table key.
EAG report, page 130–131, Table 3.44	Please amend the source information from 'Table 23, CS' to ***'Table 23, Appendix D of CS'***	Source information updated for accuracy	This has been changed as suggested and the

Location of typographical error	Description of typographical error and proposed amendment	Justification for amendment	EAG response
			reference has been updated.
EAG report, page 132, Table 3.45	All results presented in dark green cells are statistically significant and should be **bolded** (rows 2–7)	Formatting updated to indicate statistical significance in line with the table key	Not a factual inaccuracy however, bold text has been added in the interests of being consistent with the source material and table key.
EAG report, page 148	Please amend the age used for general population utility to **35**	For consistency with the CS	This has been changed as suggested.
EAG report Section 6.1.1.3, page 174, bullet 3	Please amend the quote from the CS to state: "clinicians also felt that the high sustained pharmacokinetic profile of efanesoctocog alfa would allow for 1 x 25 IU/kg dose to resolve the same type of bleed"	For consistency with the company submission	This has been changed as suggested.
EAG report, page 180, Table 6.4 (row 5)	Please amend the incremental cost vs emicizumab in the CS original base-case to: **£8,207,273**	Amended for consistency with the CS	The EAG has made the suggested correction to Table 6.4.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, all sections	At the request of NICE, marking in the submission has been updated so that all ICERs are unredacted, however total QALYs are now redacted. This change should be reflected in the EAG report.		The mark-up has been amended as suggested.

<table>
<tr><td>Table 2.1, Page 25, row 2</td><td>The anticipated license should be marked as CiC.</td><td>The anticipated license for efanesoctocog alfa is [redacted]</td><td>The mark-up has been added as suggested.</td></tr>
<tr><td>Section 2.1, Page 33</td><td>The anticipated license should be marked as CiC.</td><td>the company’s anticipated license for efanesoctocog alfa: “[redacted]”</td><td>The mark-up has been added as suggested.</td></tr>
<tr><td>Table 3.16 of the EAG report, Page 70, row 7</td><td>The proportion of patients in Arm B without a bleed in the ‘On-demand’ phase is marked as CiC, however this does not need to</td><td><table><tr><td colspan="4">Number of bleeds</td></tr><tr><td>0</td><td>96 (72.2)</td><td>0</td><td>21 (80.8)</td></tr></table></td><td>The mark-up has been removed.</td></tr>
</table>

	be redacted.		

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert perspectives

Information that is depersonalised data [DPD] has been highlighted in pink.

Name: Charles Hay

Name of organisation: Manchester Royal Infirmary

Job title or position: Professor of Haemostasis and Thrombosis, Consultant Haematologist Director of the UK National Haemophilia Database (NHD)

Clinical expert perspectives:

I think that uptake of this drug, which I do think is a significant advance, is likely to be much less in Manchester than in some other centres because 90% of our patients with severe haemophilia A use emicizumab and almost all seem happy with the drug. However, we are at one end of the bell curve and overall uptake of EMI is 55%, with some centres having switched only 20% of their severe Haemophilia A patients to Emi. I would anticipate that if EFFA is approved as an alternative to standard factor VIII prophylaxis, that uptake of EFFA in those centes using less EMI would be significant. I would expect clinical outcomes with EFFA to be almost as good as Emi and better that prophylaxis using current extended half-life factor VIII preparations. If Effa is only approved for those currently using EMI, then uptake will be very limited and that would be a great pity. Some have estimated that 20% of Emi patients would switch. This is speculation and I would expect far fewer of the Manchester Cohort to switch than that.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5:00pm** on **Friday 8 March 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating haemophilia A and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Alice Taylor
2. Name of organisation	Great Ormond Street Hospital for Children NHS Foundation Trust
3. Job title or position	Consultant Paediatric Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with haemophilia A? ☐ A specialist in the clinical evidence base for haemophilia A or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for haemophilia A? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To normalise lifestyle for those affected and to prevent both early mortality- eg from spontaneous intracranial bleeding- and avoidable morbidity- eg joint damage from bleeding.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Annualised bleed rate of zero. Normal musculoskeletal health.
10. In your view, is there an unmet need for patients and healthcare professionals in haemophilia A?	Yes
11. How is haemophilia A currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	• Yes- please see guidelines of UK Haemophilia Centres Doctors' Organisation, 'Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B' Rayment et al, 2020. • Pathway of care is extremely well- defined in the UK, with recommendations that all children with severe haemophilia should receive primary prophylaxis- ie to start in early childhood. • There is ongoing debate about the merits of factor vs non-factor therapy. The advantage of this novel treatment is that it is factor VIII based. It is therefore easier to extrapolate from pre-existing data on joint health in children on prophylaxis. • The technology would have enormous implications for children, in whom venous access remains an extraordinary challenge. The previous standard of care was to insert Port-a-caths to allow regular venous access and treatment. A once-weekly factor VIII may avoid the necessity of this surgery, and allow ongoing peripheral treatment (ie through veins in the arms). • This therapy could be extremely helpful for patients with mild and moderate haemophilia- so that a single dose of factor could cover a procedure and reduce need for hospital attendance, optimise early discharge and possibly reduce risk of inhibitor (or anti-FVIII antibody) development.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	• The current UK standard of care is to initiate primary prophylaxis in early childhood as above. We can either offer standard half-life factor VIII products- which need to be administered every 48 hours- or extended half-life factor VIII products- which are licensed for use every 72 hours. The alternative is a subcutaneous bypassing product which we lack longer-term data on in children. We find we frequently need to use extended half-life

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	products every 48 hours in small children, with relatively high metabolic rates, in order to maintain a measurable level at 48 hours. Being able to offer a once-weekly factor VIII alternative will be game-changing for very small children in whom peripheral venous access is a struggle. • The technology should only be used in a UK Haemophilia Centre or Comprehensive Care Centre. • Beyond establishing appropriate laboratory assays, no additional further investment is required. • Again- there is much scope for patients with mild and moderate haemophilia A too for reasons mentioned above.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• Yes, quality of life should certainly be improved, if not length of life. - in those patients in whom factor VIII is appropriate, and in whom venous access is challenging or achieving high factor VIII levels with standard half-life products difficult. • Advantage of a once-weekly factor VIII over emicizumab is that it allows tailoring of treatment to allow higher levels to support physical activity. • This treatment will balance maintaining IV access skills in parents and children- with consequently more independence and less contact with emergency or out-of-hours care: since parents will be better able to treat breakthrough bleeds compared to non-factor therapies. • Yes- without a doubt. As a paediatric treater, I would argue that the paediatric patients have most to gain, since the burden of care will be greatly reduced. This will set good healthcare-related patterns from an early age, so compliance is enhanced from the very beginning. The reduction of treatment burden will have implications for the entire family.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• More effective for children as above. • Patients with more challenging vascular access. • Disabled patients with less manual dexterity or impaired fine motor coordination.

	• Elderly patients with less manual dexterity or impaired fine motor coordination. • Treatment for patients with a previous inhibitor who have now become tolerant of factor VIII. Switching to a non-factor therapy is not an option due to risk of inhibitor recurrence.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	• Being able to receive a treatment once weekly rather than once-every-two-days will have an enormous impact on ease of care. This means less time required for factor preparation, less time for access, better factor VIII levels and hence more protection in the event of bleeding or injury that could lead to bleeding. • Once weekly intravenous treatment will be far more acceptable to patients than treatment every alternate day. • There will no additional monitoring required.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• The technology should be made available for all patients with severe haemophilia A. It should be a treatment option alongside current standard of care (ie standard or extended half-life factor VIII products and bypassing bispecific antibodies). • I would also argue that most patients with moderate haemophilia should be on prophylaxis anyway to improve joint health. • Mild haemophilia A patients would benefit for procedure cover. • As with any switch in therapy, baseline blood tests will be performed before and after changing, examining factor VIII levels.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	• Yes: it is difficult to fully capture what the reduction of burden of treatment will mean for families of boys with haemophilia. • Although the QALY calculation may reflect the impact on family life, small children can obviously not articulate for themselves and it is important we advocate for them. • The substantial improvement in health-related benefits will include the following:

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	• I) Reduction of needle phobia: this has significant implications for time and effort involved in treatment. Once weekly treatment allows maintenance of venous access skills in both parents and child and allows independence from health care settings for delivery of emergency treatment. • II) Reduction of healthcare environment/ hospital phobia. • III) Reduction of phobia of healthcare professionals. • IV) Reduction of school absence due to bleeds or difficulties with treatment and therefore optimisation of academic and developmental potential. • V) Reduction of fear and resentment of haemophilia encouraging understanding and a healthy mindset toward the future care. • VI) Improvement in quality of life for the entire family, including potential reduction in the psychological burden or guilt faced by carrier mothers.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	• Yes: a once-weekly treatment for haemophilia would have once been considered a holy grail. There will be an enormous reduction of care burden associated. • High trough factor VIII levels at one week should offer far better bleed protection than ever previously achieved. This has never been possible with standard half life products for children, who will typically demonstrate very fast clearance (or short half-life of factor VIII). • Yes- this is a step-change in the management of the condition, since represents a longer-lasting treatment that will have a very meaningfully impact of the lives of affected patients. • The paediatric population are likely to particularly benefit, since this treatment may mean that indwelling venous access devices- with consequent risk of surgery or infection- are no longer required. This in turn has impact on hospital admissions, surgical waiting lists and need to medical complications to be treated. • Flexibility of dosing- ie excellent trough levels can allow dosing to be around lifestyle events that are important to the patient- such as sporting fixtures.

	• Likely to increase compliance since less burdensome and fraught. • Ability to engender a less disease-focused mindset since
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	• No known impact of adverse effects of this new treatment.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• Current UK practice is to treat alternate day (standard half-life) or every 3 days (extended half-life) with factor VIII to offer effective prophylaxis. • As above: it would be a paradigm shift in current practice if we could move to effective once-weekly prophylaxis with factor VIII. This would have an enormous impact on the UK population with direct extrapolation of the results. • Primary outcomes measured in the Phase 3 trial of use of the technology in >12 year olds were based on annualised bleeding rate, as a typical assessment of haemophilia treatments. This was classified as any occurrence of haemorrhage that required administration of BIVV001 (from first injection to no more than 72 hours after last injection to treat bleeding episode). • Other important outcomes include: • Reported outcomes in pain intensity and changes in baseline. • Haemophilia Joint Health Scores and changes in baseline. • Maintenance of trough factor VIII levels of >3-5IU/dl at one week. • Number of injections required to treat a bleeding episode. • Total dose of BIVV001 required to treat a bleeding episode. • Total annualised requirement of BIVV001 to treat an individual. • Target joint resolution. • Number of injections/ dose required for perioperative haemostasis in major and minor surgery.

	• Blood loss and blood product requirement in major and minor surgery covered with BIVV001. • Number of patients with factor VIII -neutralising antibodies (inhibitors) on BIVV001. • Number of patents with treatment-emergenct adverse events. • Number of participants with thrombotic and embolic events. • Pharmacokinetics of BIVV001 use: assessment of maximum factor VII activity, elimination half-life, clearance, accumulation, recovery to circulation. • A critical surrogate outcome (included as a secondary outcome measure in the Phase 3 trial) should also include haemophilia- specific health-related quality of life assessment (including physical health, mental health, adaptation to a chronic condition). From the paediatric angle, it is essential that haemophilia and its management is normalised. Reducing burden of care will encourage compliance, and therefore will have enormous impact on long-term clinical outcomes. • There are no adverse events not apparent in the clinical trials that have subsequently come to light that I am aware of.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	• Konkle et al, BIV001 fusion protein as factor VIII replacement therapy for haemophilia A, New England Journal of Medicine, 383:1018, September 10 2020. • Lissitchkov T, Willemze A, Katragadda S, Rice K, Poloskey S, Benson C. Efanesoctocog alfa for hemophilia A: results from a phase 1 repeat-dose study. Blood Adv. 2022 Feb 22;6(4):1089-1094. doi: 10.1182/bloodadvances.2021006119. Erratum in: Blood Adv. 2022 Jun 28;6(12):3625. PMID: 34794179; PMCID: PMC8864644.
22. How do data on real-world experience compare with the trial data?	We are currently limited with real-world evidence since the technology has only been available on a clinical trial basis.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into	• Yes: • i) Those who are disabled as a result of haemophiliac arthropathy, with consequent more difficulty in administering regular intravenous treatment,

account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	may receive most benefit from a once-weekly as opposed to a more-frequent treatment. • Ii) Children in single- parent households, or who move between parents, are likely to benefit from the increased flexibility once-weekly dosing offers.
24. Is factor VIII replacement therapy, other than efmoroctocog alfa, used as prophylactic or on-demand therapy in people with haemophilia A (including previously treated and untreated populations)?	• Yes- please see previously mentioned UK standards of care. • UKHCDO 2022-3 annual report outlines that of patients with severe haemophilia A without inhibitors: • 483 received standard half-life factor VIII.

• If so, what proportion of people have standard half-life FVIII therapy in NHS practice? • How would you expect this proportion to change over time?	• 347 received enhanced half-life factor VIII. • 1261 received emicizumab/ non-factor therapy. • Therefore 23% of patients with severe haemophilia A in the UK without inhibitors received standard half-life therapy. • I would expect the proportion of people on standard half-life factor VIII in NHS practice to continue to decrease (following the gradual introduction of the enhanced half-life products from 2016 onwards, and introduction of emicizuamb/ non-factor based therapy for patients with severe haemophilia A without inhibitors from 2019 onward). • Please also see THUNDER trial regarding poor joint health outcomes in patients with moderate haemophilia A- we would also wish to see these patients considered.
25. What proportion of people have severe haemophilia A in the NHS compared to mild or moderate?	• 9316 patients with haemophilia A registered in the UK 2022-3. • Severe: 2230 (24%), Moderate 873 (9%), Mild 6110 (66%) registrations of haemophilia A in UK 2022-3. Therefore approximately one-quarter of people with haemophilia A have severe haemophilia A, compared to three-quarters with moderate or mild.
26. What is the dosing frequency for emicizumab in the NHS (weekly vs. biweekly)? • Would you expect different outcomes by emicizumab dosing frequency?	• Emicizumab dosing is either weekly or every two weeks according to weight/ dosing pragmatism. • No, we do not expect different outcomes according to emicizumab dosing frequency. • We are concerned that a disadvantage to emicizumab is that the potential for inhibitor development is just being moved later in a child's life- which could be very problematic.
27. Would you expect data from the XTEND-1 trial (people with previously treated severe haemophilia A) to be generalizable to the following populations: • people with previously untreated haemophilia A? • the NHS population with haemophilia A?	• Yes: previously untreated patients/ children have even more to gain for the reasons of vascular access mentioned above. • Likely to be fewer subclinical bleeds with better trough levels. • Setting a template for good health in childhood will encourage better health in adulthood.

28. Who would receive on-demand therapy compared with prophylaxis in the NHS? • Would you expect different outcomes by prior treatment (on-demand or prophylaxis)? • What patient characteristics would affect a treatment response to FVIII therapy?	• Primary prophylaxis should be offered to all children and on-demand therapy is increasingly outmoded as a therapy choice. • There is clear data to support the advantages of regular prophylaxis vs on-demand therapy: the pathophysiology of haemophilia means bleeding should be prevented in the first place to stop the vicious cycle of haemarthrosis establishing synovitis, synovial hypertrophy and subsequent arthopathy. • The standard of care is rapidly becoming prophylaxis for all patients with severe haemophilia A, all patients with moderate haemophilia A and some patients with mild haemophilia A who bleed. • Characteristics affecting a treatment response include dose according to body weight and anti-factor VIII antibodies/ inhibitors, since these will have a clearly detrimental impact on the response to factor VIII therapy. In young children, a very important characteristic is their increased metabolism/ short half-life so that larger doses are demanded per kg of body weight to maintain an adequate trough factor VIII level at 48 hours. This is all-important in prevention of breakthrough bleeding. • Being able to use a product with a reliable trough level at one week post treatment will allow far improved safety with physical activity, so that there will be less scope for both spontaneous bleeds and bleeding with injury.
29. How often are FVIII levels monitored in standard NHS practice? • If people are aware that their FVIII level is reduced (<20%), would they be less capable of undertaking certain activities due to the fear of a bleeding event? • What level of FVIII activity would impact quality of life?	• Absolutely- the psychology of haemophilia is a very important and under-researched area of care. Knowledge of being prone to bleeds when factor levels are lower may make some people with haemophilia unduly cautious and avoidant of even minimal levels of physical activity. In turn, this can lead to poor physical conditioning, decreased muscle tone and bone strength, propensity to obesity and cardiovascular ill-health and increased risk of all other associated diseases, from diabetes to osteoarthritis.

	• We do not have data to stipulate clearly what level of factor VIII activity would impact quality of life, since this is highly individualised. Looking at people with mild haemophilia, we would not expect to see spontaneous bleeds with factor VIII levels of more than 10IU/dL. This should certainly offer improved bleed control if such levels become the new accepted trough levels in well-treated severe haemophilia A with the new technology. • Please see the Delphi panel consensus on preservation of joint health in people with moderate and severe haemophilia A in support of this (Laffan et al 2023, Haemophilia)- suggesting that prophyalxis should target a trough of 15IU/dL, and longer periods of factor VIII levels of 20-30IU/dl will offer better bleed prevention.
30. The company assumes that people having efmoroctocog alfa or emicizumab who experience a bleeding event would be treated with 2 doses of 25 IU/kg. • What dose would be used in NHS practice to treat a bleeding event in people having: o efmoroctocog alfa? o emicizumab? o efanestocog alfa?	Dosing of a bleed event is highly individualised according to the person (a small child will reuqire far more factor per kg of body weight compared to an adult), nature of the bleed (ie severe or mild), the timing of most recent therapy (ie whether tratment due or recently given) and ability to give subsequent doses (for example, a patient autonomous in peripheral venepuncture versus a small child whom we wish to support away from hospital over a weekend- for example). In our experience, most children who have a significant breakthrough bleed will require 50IU/kg of factor VIII on top of emicizumab dosing.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Efanestocog alfa represents a potential paradigm shift in the management of severe haemophilia A. Once-weekly dosing of factor VIII should allow far greater freedom and independence from a chronic condition or disease-focused lifestyle, allowing for far improved general health of affected individuals. For children, it is likely the reduced treatment burden will enhance compliance and freedom of the entire family from a disease-focused mindset. There should be a reduction of hospitalisation related to venous access and bleeds, and establishment of a far healthier psychological mindset about physical capabilities with haemophilia, leading to improved all-round general health.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

Information on completing this form

In part 1 we are asking you about living with haemophilia A or caring for a patient with haemophilia A. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5:00pm** on **Friday 8 March 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with haemophilia A

Table 1 About you, haemophilia A, current treatments and equality

1. Your name	Clive Smith
2. Are you (please tick all that apply)	☒ A patient with haemophilia A? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with haemophilia A? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Haemophilia Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I have 2 brothers who also have severe haemophilia A. I am the chair of the Haemophilia Society and know many people in the UK, Europe and internationally with haemophilia. ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with haemophilia A? **If you are a carer (for someone with haemophilia A) please share your experience of caring for them**	I was diagnosed with severe haemophilia A at around 2 weeks old. My twin brother and I were both tested as a result of my older brother being diagnosed some 4 years earlier. During the early years, my life was governed by my haemophilia. I would have internal bleeds on an almost weekly basis resulting in travelling to Gt Ormond St Hospital for treatment. My 2 brothers had a similar experience, meaning that hospital wasn't a second home; it was home. Age 4/5 my parents were able to administer treatment at home which reduced hospital visits dramatically. However, it was a very challenging time due to the contaminated blood scandal. We were worried about administering treatment. Several years of my life were dominated by going to school on either crutches or in a wheelchair. It would not be unusual for all 3 of us to attend school unable to walk. My mother would have to decide who was most deserving of the wheelchair. Age 10, my siblings and I began treating prophylactically, three times a week. The philosophy around treatment had changed from being reactive to proactive and the difference it made to my life was huge. My annual bleed rate reduced from around 50 a year to only handful. For the first time I was able to spend time in the playground with friends and play a little sport. However, the damage to 3 of my joints was already done. I have no memory of ever being able to touch my left shoulder with my left hand. My left arm does not straighten properly. Carrying any sort of weight for even a short period of time becomes challenging – carrying a shopping bag for example. I have severe arthritis in both my ankles and my left leg is smaller than my right leg (in terms of muscle mass) due to the amount of time I spent not bearing weight on it. I live with daily background pain in my joints, which I would score at 2/3 on a good day. More recently I have moved from a standard half-life (SHL) product to an extended half-life (EHL) product. I had agreed with my consultant to make this change in

	January 2020. Having used up my existing product, I moved onto the EHL in around March/April of 2020. I initially reduced the frequency of administration from 3 to 2. However, once lockdown lifted and I found myself being more active generally, I increased my dose back to 3 times a week.
7a. What do you think of the current treatments and care available for haemophilia A on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	In terms of treatments, I think there is a good range of treatments available to treat haemophilia A. However, the products available continue to have a heavy burden of treatment and still restrict life choices for many people with haemophilia. Outcomes remain mixed with joint damage still common in people with haemophilia, life threatening bleeds remain a risk and we are a long way from people living a haemophilia-free life with a haemophilia-free mind-set. In terms of care, I think there are several areas which are woefully lacking. The 2019 Peer Review of HTCs highlighted physiotherapy and mental health support as 2 areas requiring significant investment. 2/3 of centres do not have adequate support in these areas. For there to be insufficient mental health support at the same time as there is an ongoing public inquiry into the contaminated blood scandal is appalling. In terms of the lack of physiotherapy, I also find this very troubling. We cannot think that simply treating patients with good treatments and reducing ABRs to zero is the goal. As I heard one health care professional say recently, we must treat the whole of the patient, not just the hole in the patient. Joint health is arguably the biggest single challenge for people with haemophilia. Every person with haemophilia should have a PK Study and know and understand individual levels. They should be aware of risk factors and be educated on how they can best look after their joints. In terms of other people's view on treatment, I think my opinion would accord with many others who are well informed about options. In terms of care, I fear that many people with haemophilia are not fully aware of what they are entitled to and are simply grateful for what they get.
8. If there are disadvantages for patients of current NHS treatments for haemophilia A (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The disadvantages of treatment with factor replacement products revolve mainly around the frequency of administration and how long the treatments are effective at increasing Factor VIII activity levels. Most people continue to need to treat intravenously every 2-3 three days. Their levels will drop between treatments

	increasingly the risk of bleeds and restricting what social and work activities they can undertake. There is one treatment available as subcutaneous administration, Emicizumab. Emicizumab creates challenges when it comes to having internal bleeds and surgery. Emicizumab provides a low but steady level of protection which allows for low intensity day to day life to continue as normal but still restricts people in terms of sport and work activities. Whilst many people remain trouble free for substantial periods, when issues occur, they are often more complicated to treat than when someone is being treated with factor replacement therapy. People on Emicizumab also need treatment on demand with factor products for bleeds and for surgery.
9a. If there are advantages of Efanesoctocog alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Efanesoctocog alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	From a patient perspective, the 2 significant benefits of Efanesoctocog alfa are frequency of administration and the period of time over which factor activity levels are increased. More broadly, I believe there are two further benefits: Firstly, Efanesoctocog alfa represents the first *truly* extended half-life product for people with severe haemophilia A. As I set out above, although I have moved from an SHL to an EHL, I am still administering 3 times a week. Secondly, it brings haemophilia A treatment into greater alignment with that for haemophilia B. Whilst there are many unmet needs in treatment for severe haemophilia B, treatment for severe haemophilia B with EHLs is far superior and I have spoken to several people with severe haemophilia B who feel incredibly well protected by their treatment regime. As well as the factors mentioned above, Efanesoctocog alfa provides an opportunity for people with severe haemophilia A to have greater protection from micro-bleeds. The insidious nature of these bleeds should not be underestimated. Many people with severe haemophilia A have low ABRs and are able to control their condition well with current treatment. However, for the first time in the UK we have an ageing population with severe haemophilia and we should aspire to providing the best protection possible for joints.

	I believe the most important advantage is the length of time Factor VIII levels are increased. Current factor treatments allow factor levels to briefly peak in the normal range before dropping back to less than 5% of normal before the next dose is given. Emicizumab provides bleed protection that is thought to be broadly equivalent to being in the low/mild haemophilia range (sometimes this is suggested to be around 15%. Efanesoctocog alfa on the other hand has a longer half-life in the body and so has the peaks that current factor products have but will have troughs that are still in the high mild range of 20-40%, even on weekly dosing. I believe Efanesoctocog alfa addresses both of the disadvantages I have set out in question 8 and more.
10. If there are disadvantages of Efanesoctocog alfa over current treatments on the NHS please describe these. For example, are there any risks with Efanesoctocog alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Some people have an aversion to pegylated products and Efanesoctocog alfa provides an alternative method of extending Factor VIII levels. Some people may prefer a subcutaneous treatment if they have venous access issues. It may also be preferred in children with needle-phobia or in older people in care who struggle to administer their own treatment.
11. Are there any groups of patients who might benefit more from Efanesoctocog alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	For people who have difficulty with mobility issues due to their haemophilia, Efanesoctocog alfa presents an opportunity to effectively hit “pause” on the damage done to joints. Joints can never be improved, but they can be protected from further damage. It may also assist in the amount of background pain that people live with. Many people with severe haemophilia describe how they tend to get aches and niggles shortly before they are due to infuse again. This is certainly something I have experienced and was part of the rationale for increasing my frequency of treatment with an EHL. Those with very little or no joint damage also stand to benefit by being protected from micro-bleeds. Further, many people with severe haemophilia who have no experience of a bleed can leave it too long to seek medical attention. As a result, damage is done or more damage is done than necessary. Efanesoctocog alfa has

	the potential to protect from many more bleeds and reduce the incidence of bleeds being more serious than they need to be.
12. Are there any potential equality issues that should be taken into account when considering haemophilia A and Efanesoctocog alfa? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	None that are immediately apparent.
13. How often do you or the person you care for have your FVIII levels checked? • If you know yourA levels are low, do you act differently to reduce the risk of bleeding? • What level of FVIII activity levels would impact your quality of life?	Twice a year. If I know my levels are low, I tailor my behaviour accordingly. I restrict my behaviour and activity accordingly. It can be very limiting at times. Less than 5% factor levels would impact my life substantially. However, I would tailor my activity well before this.
14. Are there any other issues that you would like the committee to consider?	No, thank you.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Treatment for severe haemophilia A is currently good
- Treatment for severe haemophilia could be very good/excellent with Efanesoctocog alfa as a new treatment option
- People with severe haemophilia A need better protection in day to day living to help them age well
- People with severe haemophilia A need protecting from micro-bleeds
- People with severe haemophilia A have the potential to live better, safer lives with access to Efanesoctocog alfa

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with haemophilia A or caring for a patient with haemophilia A. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5:00pm** on **Friday 8 March 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with haemophilia A

Table 1 About you, haemophilia A, current treatments and equality

1. Your name	Edward Rippingale-Combes
2. Are you (please tick all that apply)	☒ A patient with haemophilia A? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with haemophilia A? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Haemophillia Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with haemophilia A? **If you are a carer (for someone with haemophilia A) please share your experience of caring for them**	I have lived with Severe Haemophilia A for over 40 years, and have been on prophylaxis treatment for nearly 30 years, and have been self-injecting since I was about 12 (over 30 years). I have been on almost all types of haemophilia treatments at one time or another – from cryo treatment, early pooled and fractionated fviii (and was impacted by the viral contamination), recombinant fviii to extended half-life recombinant products. I have been on Efanesoctocog since summer 2020, so nearly 4 years. I have experienced treatments go from being a burdensome large volume infusion over a long period of time very regularly, to a less-burdensome small volume once a week (Efanesoctocog alfa). The difference this has made to my vein health and ability to access my veins with a needle is quite significant. I have experienced numerous bleeds over the years – both spontaneous and traumatic and have haemophilia related joint damage in most major joints. IU have had ankle fusions to both ankles as a result of this
7a. What do you think of the current treatments and care available for haemophilia A on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Current treatments are based on preventative or on-demand treatment and usually are an intravenous injection of recombinant fviii every 48hours (prophylaxis), or in mild/moderate Haem A cases a DDAVP injection to stimulate fviii naturally in the body. A monoclonal anti-body is also available for severe haemophiliacs for prophylactic management but bleed management still requires an intravenous injection of clotting factors. I think the current standards of treatment are good and give a choice to the patient and carers about how to manage the individuals hameophillia. I think a lot more thought about treatment is given to lessening the burden of treatment.
8. If there are disadvantages for patients of current NHS treatments for haemophilia A (for example, how	I think treatments are much safer than in the past but there is a gap in choice for those that don't want a mono-clonal anti-body. The extended half life or standard half life products are good but do carry quite the burden and have limitations. For

they are given or taken, side effects of treatment, and any others) please describe these	example regular injections leave visible marks and bruising on the arms (or injection site) which cause embarrassment, and skin irritation is relatively frequent (or has been for me). In my experience, the regular accessing of veins leaves little time for the veins to fully heal between injections which causes extra discomfort, pain and bruising and a higher amount of 'vein collapse' at the point of accessing the veins which causes feelings of anxiety and stress. Also, the volume of product required to be stored at home (in a refrigerator) or carried when travelling (refrigerated) can be prohibitive and make travelling or working away from home more problematic and limiting. An injection every 48hours is quite burdensome as a prophylactic regime and is quite interruptive to daily life.
9a. If there are advantages of Efanesoctocog alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Efanesoctocog alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I have found efanesoctocog to be advantageous to me because of the longer period of time between injection gives more time for the vein to heal, as a result I very very rarely have a vein collapse and the vein has time to heal so pain at each injection seems to be less to me. I also don't have a persistent discolouration/bruise in the area from repeated vein accessing which has lessened social anxiety when wearing short sleeved shirts and T shirts. Also, the extended frequency of injection has meant that I can inject on the same day each week, which fits in much better with my working and family life. I also find it much easier to remember my injections due to the fixed day rather than the variable days when on standard of extended half-life products. Travelling has also become much easier – I can now easily take a couple of weeks' worth of injections plus extra emergency doses in a small cool bag measuring about 20cm wide and 10cm deep, which means that I have been able to go away for longer and have less factor to carry – which makes a huge difference. I also have found it easier to travel with work, or to stay at friends and families houses as I can now time my injections to avoid having to inject in front of other people, which has lessened by anxiety about travelling and socialising. I also have found that I worry less about spontaneous bleeds into joints, and I worry less about minor slips and trips that would normally have caused a big problem because I have now learnt after being on Efanesoctocog for nearly 4 years that

	bleeds don't escalate as fast or as severely as on previous treatments. I am almost free of major bleeds now and the worry of injury, or spontaneous bleeds from the most innocuous of events/injuries during the normal course of being a human (e.g. cooking, walking up and down stairs, or just lifting rubbish sack into the bin!) is now not as completely occupying my mind in the same way it did before. I feel I now have to pre-plan less which has helped to ease my anxiety around my haemophilia.
10. If there are disadvantages of Efanesoctocog alfa over current treatments on the NHS please describe these. For example, are there any risks with Efanesoctocog alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have not come across any disadvantages, beyond the need to keep it refrigerated, which needs some pre-planning if travelling, or when storing at home. I haven't heard of any side effects, one thing I have anecdotally noted (and this would need pharmaceutical/medical experts to comment from trial data) is that when I do have a bleed it takes slightly longer (i.e. it is slower) to resolve than my recollections of bleeds when on standard half life products, BUT a big caveat to that is that the bleeds have been much less severe in the first place when compared to bleeds when on standard treatment. e.g. a traumatic bleed of my forearm took about 48 hours to feel like it was well on the way to resolving, whereas previously on a standard half life product I would have expected that to feel like it was resolving in half that time. This is just my anecdotal experience though, and I have not actually measured this (I don't know how I would). I don't feel efanesoctocog is any more risky than other recombinant treatments I have had, and I feel it is less risky than fractionated treatments, and for me it feels more acceptable compared to a mono-clonal antibody.
11. Are there any groups of patients who might benefit more from Efanesoctocog alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I feel that efanesoctocog, although of benefit to all severe haemophiliacs, would particularly benefit adolescent and working age patients due to the way it more easily fits in with life, and allows greater FVIII levels for less injections which would facility easier travelling, participating in sport, and more active jobs – all of which would help preserve joints for longer. Having said that I also believe it would be beneficial for older haemophiliacs – especially those with perhaps joint damage in their upper limbs that makes more regular injections more awkward and demanding. It may be also easier to overcome the psychological barrier of injecting yourself every other day which may increase individual compliance and acceptability

12. Are there any potential equality issues that should be taken into account when considering haemophilia A and Efanesoctocog alfa? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I don't really know to be honest, I cant think that any group would be particularly disadvantaged by using Efanesoctocog compared to not using it? I think any of the mentioned groups would be able to benefit and should have equal access.
13. How often do you or the person you care for have your FVIII levels checked? • If you know yourA levels are low, do you act differently to reduce the risk of bleeding? • What level of FVIII activity levels would impact your quality of life?	They are checked every 4-6 months at the haemophilia centre at my regular reviews. I don't check them myself at home. If I knew I had not had an injection, or had been forced to delay one due to travel or work, or if I was towards the end of a period before my next injection, I definitely behave differently – I have always been like this – on standard half life products this would be a mind set every other day, but on Efanesoctocog this is normally only on the Saturday/Sunday before my injection on a Monday morning, it now isn't so much of an active thought in-between injections as it used to be. I know from prior experience that levels in the single figures significantly impacts me with day to day tasks and activities, but once I achieve above about 15 niggles like bleeds in my fingers from typing are much more lessened. For example, typing this document would be likely to give me a finger bleed if my levels were in low single figures, but in low double figures it would not.

14. Are there any other issues that you would like the committee to consider?	I don't know if this would fall within the scope of NICE but I think that recommendations that the product be packaged in such a way as to minimise plastic waste and to maximise recycling of the packaging of the box and ancillaries packaging that are supplied with the treatment. I appreciate that clinical waste (used needles and syringes) cant be recycled but packaging for these items could be. I also think that patients that are treated with Efanesoctocog should also still be able to access a standard half-life product for emergency/major bleed treatment – i.e. manage the prophylaxis side of the treatment with Efanesoctocog and then bleed treatment with standard half-life treatments.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Efanesoctocog increases quality of life – less bleeds, more freedom
- Efanesoctocog decreases treatment burden – less injections, less vein complications
- Efanesoctocog increases confidence in being active knowing that levels are maintained higher, for longer
- Efanesoctocog has helped me to better manage my anxieties around treatment and pre-planning my day-to-day haemophiliac life
- Efanesoctocog has allowed me more freedom to travel, including overseas, for work and pleasure

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