Medicinrådet

Bilag til Medicinrådets anbefaling vedr. efanesoctocog alfa til behandling af hæmofili A

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. efanesoctocog alfa
2. Forhandlingsnotat fra Amgros vedr. efanesoctocog alfa
3. Ansøgers endelige ansøgning vedr. efanesoctocog alfa

Sobi's comments to DMC draft report of Altuvoct (efanesoctocog alfa) for the treatment of hemophilia A patients

DMC page 27: Medicinrådet vurderer, at en anvendt gennemsnitsvægt på 75 kg er noget høj ift. dansk klinisk praksis, hvor emicizumab (som ansøger alene har sammenlignet med) primært anvendes til mindre børn, som Medicinrådet vurderer i gennemsnit vejer ca. 30 kg. Derfor præsenterer Medicinrådets hovedanalyse resultaterne ved en gennemsnitsvægt på 30 mg.

Sobi's comment: As the DMC points out, emicizumab is primarily used in smaller children because of the advantages with subcutaneous administration for patients with difficult venous access in young age. However, there is no age limitation in the treatment guidelines and also adult patients are treated with emicizumab in clinical practice in Denmark. Hence, all age groups should also be included in the Altuvoct recommendation. It should also be noted that patients in need of higher FVIII levels can be found in all age groups. Below are cost comparisons for Altuvoct vs emicizumab for patients of different body weights, i.e. 30 kg and 75 kg, respectively. Cost-savings are expected for children, but notably higher cost-savings are expected with Altuvoct in patients with higher body weight. Hence, the recommendation of Altuvoct should include **all age groups.**

[redacted]

Example 1: Patient body weight **30 kg**

Altuvoct		emicizumab		Cost savings /year/patient
Amgros price DKK/IU	Annual cost /patient/year	Amgros price DKK/mg	Annual cost /patient/year	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Example 2: Patient body weight **75 kg**

Altuvoct		emicizumab		Cost savings /year/patient
Amgros price DKK/IU	Annual cost /patient/year	Amgros price DKK/mg	Annual cost /patient/year	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DMC page 22 – 2.4.3 Farmakokinetik (dalværdi)
Af EMA's EPAR [5] fremgår, at alle børn i studiet havde en vedvarende dalværdi over 3 % ved alle kontrolbesøg 7 dage efter infusion af sidste dosis. 87 % af børnene fastholdt en dalværdi over 5 %. Andelen af børn der fastholdte dalværdier over 10 % er opgivet for subgrupperne over og under 6 år. 52 % af børn mellem 6 og 12 år fastholdt dalværdier over 10 %, men det kun gjaldt for 19 % af børn under 6 år.

Sobi's comment: The most relevant data of trough levels should be assessed at **steady-state after 52 weeks** in the different age groups (see Table 7 in the SmPC), e.g. 1 to <6 years Mean (SD): **10.9** (19.7) (N=36) and 6 to <12 years Mean (SD): **16.5** (23.7) (N=36).

Table 7: Pharmacokinetic parameters at steady state of ALTUVOCT by age (one-stage clotting assay using Actin-FSL)

PK parameters Mean (SD)	Paediatric study[a]		Adult and adolescent study[a]	
	1 to < 6 years	6 to < 12 years	12 to < 18 years	Adults
	N = 37	N = 36	N = 24	N = 125
Peak, IU/dL	136 (48.9) (N = 35)	131 (36.1) (N = 35)	124 (31.2)	150 (35.0) (N = 124)
Incremental Recovery, IU/dL per IU/kg	2.22 (0.83) (N = 35)	2.10 (0.73) (N = 35)	2.25 (0.61) (N = 22)	2.64 (0.61) (N = 120)
Time to 40 IU/dL, h	68.0 (10.5)[b]	80.6 (12.3)[b]	81.5 (12.1)[c]	98.1 (20.1)[c]
Time to 20 IU/dL, h	109 (14.0)[b]	127 (14.5)[b]	130 (15.7)[c]	150 (27.7)[c]
Time to 10 IU/dL, h	150 (18.2)[b]	173 (17.1)[b]	179 (20.2)[c]	201 (35.7)[c]
Trough, IU/dL	10.9 (19.7) (N = 36)	16.5 (23.7)	9.23 (4.77) (N = 22)	18.0 (16.6) (N = 123)

DMC page 16 & Table 3 on page 14: *Ansøger har valgt udelukkende at sammenligne med emicizumab. I den kliniske analyse anvendes en ugentlig dosis på 1 mg/kg.*

Sobi's comment: The comparison was done with SmPC doses of 1,5 mg/kg Q1W.

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04.10.2024

DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.10.2024
Leverandør	Swedish Orphan Biovitrum AB (SOBI)
Lægemiddel	Altuvoct (efanesoctocog alfa)
Ansøgt indikation	Behandling og profylakse af blødning hos patienter med hæmofili A (medfødt faktor VIII-mangel). Altuvoct kan anvendes til alle aldersgrupper.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Leverandøren giver på nuværende tidspunkt en pris på Altuvoct som er synlig for alle leverandører, og dermed også den direkte konkurrent. Derfor vil leverandøren først tilbyde en væsentlig bedre pris på samme tidspunkt som konkurrenten har mulighed for det.

Amgros har derfor forhandlet to sæt pristilbud for Altuvoct (efanesoctocog alfa). Første pristilbud gælder ifm. Medicinrådsmødet den 23.10.2024 og andet pristilbud i forbindelse med indplacering i lægemiddel-rekommandationen efter det næste udbud.

Første pristilbud vil træde i kraft 1.11.2024 og er betinget af Medicinrådets anbefaling. Priserne fremgår af tabel 1.

Tabel 1: Forhandlingsresultat – 1. sæt tilbudspriser som træder i kraft 1.11.2024, hvis Medicinrådet anbefaler Altuvoct.

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Altuvoct	250 IU	1 stk.	2.235,00	[redacted]	[redacted]
Altuvoct	500 IU	1 stk.	4.470,00	[redacted]	[redacted]
Altuvoct	750 IU	1 stk.	6.705,00	[redacted]	[redacted]
Altuvoct	1.000 IU	1 stk.	8.940,00	[redacted]	[redacted]
Altuvoct	2.000 IU	1 stk.	17.880,00	[redacted]	[redacted]
Altuvoct	3.000 IU	1 stk.	26.820,00	[redacted]	[redacted]
Altuvoct	4.000 IU	1 stk.	35.760,00	[redacted]	[redacted]

Det andet pristilbud vil træde i kraft ved førstkommende udbud efter indplacering af Altuvoct i behandlingsvejledningen for Hæmofili A. Herefter er der mulighed for, at Altuvoct kommer med i rekommandationen. Priserne fremgår af tabel 2.

Tabel 2: Forhandlingsresultat – 2. sæt tilbudspriser som vil blive givet ved udbuddet

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Altuvoct	250 IU	1 stk.	2.235,00	[redacted]	[redacted]
Altuvoct	500 IU	1 stk.	4.470,00	[redacted]	[redacted]
Altuvoct	750 IU	1 stk.	6.705,00	[redacted]	[redacted]
Altuvoct	1.000 IU	1 stk.	8.940,00	[redacted]	[redacted]
Altuvoct	2.000 IU	1 stk.	17.880,00	[redacted]	[redacted]
Altuvoct	3.000 IU	1 stk.	26.820,00	[redacted]	[redacted]
Altuvoct	4.000 IU	1 stk.	35.760,00	[redacted]	[redacted]

Aftaleforhold

Amgros har indgået en aftale for Altuvoct, som gælder fra 01.11.2024 og indtil det kommende udbud.

[redacted]

Konkurrencesituationen

Konkurrencesituationen er forskellig for behandling af børn og voksne, og beskrives derfor hver for sig i det følgende.

Børn

Tabel 3 viser lægemiddeludgifter i relation til andre FVIII EHL (extended half-life)-præparater, som kan anvendes til børn < 12 år. Elocta (efmoroctocog alfa) er 1. valg til børn < 12 år, hvis der er lægefaglig indikation for at skifte til et EHL-præparat.

Priserne er vist for udvalgte varenumre, da prisen pr. mg/IU er den samme uanset pakningsstørrelse.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient – børn <12 år.

Lægemiddel	Styrke	Pakkings-størrelse	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Hemlibra (emicizumab)	150 mg/1 ml	1 stk.	45 mg SC pr. uge	[redacted]	[redacted]
Elocta (efmoroctocog alfa)	3.000 IU	1 stk.	2.400 IU IV pr. uge	[redacted]	[redacted]
Altuvoct *Første* pris	4.000 IU	1 stk.	1.500 IU IV pr uge	[redacted]	[redacted]
Altuvoct *Anden* pris	4.000 IU	1 stk.	1.500 IU IV pr uge	[redacted]	[redacted]

* Ugentlig dosis pr. patient med gennemsnitsvægt på 30 kg. **Træder i kraft 1.11.2024, hvis Medicinrådet anbefaler.
***Træder i kraft ved næste udbud, hvis Medicinrådet anbefaler.

Voksne

Tabel 4 sammenligner lægemiddeludgifter i relation til andre FVIII EHL-præparater, som kan anvendes til børn >12 år og voksne. Priserne er vist for udvalgte varenumre, da prisen pr. mg/IU er den samme uanset pakningsstørrelse. Esperoct (turoctocog alfa) er aktuelt 1. valg til min. 70% af patienterne.

Tabel 4: Sammenligning af lægemiddeludgifter pr. patient – børn >12år og voksne.

Lægemiddel	Styrke	Pakkings-størrelse	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Hemlibra (emicizumab)	150 mg/1 ml	1 stk.	105 mg SC pr. uge	[redacted]	[redacted]
Esperoct (turoctocog alfa)	3000 IU	1 stk.	5.600 IU IV pr. uge	[redacted]	[redacted]
Altuvoct *Første* pris	4000 IU	1 stk.	3500 IU IV pr uge	[redacted]	[redacted]
Altuvoct *Anden* pris	4000 IU	1 stk.	3500 IU IV pr uge	[redacted]	[redacted]

*Ugentlig dosis pr. patient med gennemsnitsvægt på 70 kg. **Træder i kraft 1.11.2024, hvis Medicinrådet anbefaler.
***Træder i kraft ved næste udbud, hvis Medicinrådet anbefaler.

Status fra andre lande

Tabel 5: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under evaluering		Link til vurdering
Sverige	Ikke ansøgt		Link til vurdering
England	Ikke anbefalet		Link til anbefaling

Konklusion

Leverandøren giver på nuværende tidspunkt en pris på behandlingen, som er synlig for alle leverandører og dermed også den direkte konkurrent. Derfor vil leverandøren først tilbyde en væsentlig bedre pris på samme tidspunkt, som konkurrenten og det er ved næste udbud.

Application for the assessment of Altuvoct (efanesoctocog alfa) for the treatment and prophylaxis of bleedings in patients with haemophilia A in Denmark

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

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Abbreviations

Abbreviation	Definition
ABR	Annualised bleeding rate
AE	Adverse event
AIC	Akaike's information criterion
AIP	Apotekets Indkøbspriser
AjBR	Annualised joint bleeding rate
AsBR	Annualised spontaneous bleeding rate
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve

Abbreviation	Definition
$AUC_{0\text{-}tau}$	Area under the plasma FVIII activity versus time curve
AUC_{inf}	Area under the activity time curve extrapolated to infinity
BE	Bleeding episodes
BIC	Bayesian information criterion
BIVV001	Efanesoctocog alfa
BU	Bethesda unit
CADTH	Canadian Agency for Drugs and Technologies in Health
CD	Cluster differentiation
CEAC	Cost-effectiveness acceptability curves
CENTRAL	Cochrane Central Registry of Controlled Trials
CHESS	Cost of Haemophilia in Europe: a Scocioeconomic Survey
CI	Confidence interval
CL	Clearance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{max}	Maximum serum concentration
C_{trough}	Trough level, pre-dose concentration of a drug
DK	Denmark
DKK	Danish Krona
DMC	Danish Medicines Council
DNAUC	Dose-normalised area under the activity-time curve
DRG	Diagnosis-related group
DSU	Decision support unit
EAHAD	European Association for Haemophilia and Allied Disorders
EC	European Commission
ED	Exposure day
EHA	European Hematology Association
EHL	Extended half-life
EMA	European Medicines Authority
EMI	Emicizumab
EP	Efficacy period
EQ-5D	EuroQol 5-dimensional quality of life-questionnaire
ESS	Effective sample size
FAS	Full analysis set
FDA	Food and Drug Administration
FII	Factor 2
FISH	Functional Independence Scale of Hemophilia
FVIII	Factor 8
FX	Factor 10
G-BA	Gemeinsamer Bundesausschuss
HAL	Hemophilia Activities List
HAS	Haute Authorité de Santé
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
Haemo-QoL	Haemophilia-specific health-related quality of life questionnaire
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HJHS	Haemophilia joint health score
HR	Hazard ratio
HRQoL	Health related quality of life

Abbreviation	Definition
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
ICH	Intracranial haemorrhage
ICTRP	International Clinical Trials Registry Platform
IPD	Individual patient data
IQR	Interquartile range
IR	Incidence rate
IRR	Incidence rate ratio
IQWiG	German Institute for Quality and Efficiency in Health Care
ISTH	International Society on Thrombosis and Haemostasis
ITC	Indirect treatment comparison
IU	International unit
IV	Intravenous
KM	Kaplan Meier
LS	Least square
MAE	Mean absolute error
MAIC	Matching-adjusted indirect comparison
MD	Mean difference
MID	Minimally important difference
MMRM	Mixed-effect model with repeated measures
MRI	Magnetic resonance imaging
MRT	Mean residence time
MSE	Mean square error
NA	Not applicable
NB	Negative binomial
NCPE	National Centre for Pharmacoeconomics
NFT	Non factor treatment
NHC	Nordic Hemophilia Council
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NIS	Non-interventional study
NR	Not reported
NRS	Numeric rating scale
OD	On demand
OM	Outcome measure
OR	Odds ratio
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Pharmakodynamic
PGA	Physician’s global assessment
PHX	Prophylaxis
PK	Pharmacokinetic
PPS	Per protocol set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
PSM	Propensity Score Matching
PT	Preferred term
QALY	Quality-adjusted life year

Abbreviation	Definition
QOL	Quality of life
RADS	Rådet for anvendelse af dyr sygehusmedicin
RCT	Randomised Controlled Trial
RDI	Relative dose intensity
RMSE	Root mean square error
RRR	Relative risk reduction
RWE	Real world evidence
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SF-MPQ	Short-form McGill Pain Questionnaire
SHL	Standard half-life
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOC	Standard of care
STC	Simulated treatment comparisons
$t_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
TESAE	Treatment emergement serious adverse event
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TJ	Target joint
TMA	Thrombotic microangiopathy
TSD	Technical support document
VAS	Visual analogue scale
VWF	Von Willebrand Factor
WFH	World Federation of Hemophilia
WHO	World Health Organization

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Altuvoct
Generic name	Efanesoctocog alfa
Therapeutic indication as defined by EMA	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Altuvoct can be used for all age groups. According to the indication, Altuvoct can be used for all severities of haemophilia A, in all clinical settings (e.g. prophylaxis, on-demand

Overview of the pharmaceutical	
	treatment, treatment of bleeds and surgery), and for all age groups (European Medicines Agency 2024a).
Marketing authorization holder in Denmark	Swedish Orphan Biovitrum AB
ATC code	B02BD02
Combination therapy and/or co-medication	NA
(Expected) Date of EC approval	June 27th 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	NA
Orphan drug designation (include date)	Yes [redacted]
Other therapeutic indications approved by EMA	NA
Other indications that have been evaluated by the DMC (yes/no)	NA
Joint Nordic assessment (JNHB)	The current treatment practices are not similar across the Nordic countries, as Hemlibra is not recommended in Norway for the same patient population. The product is not suitable for a joint Nordic assessment since the relevant comparators differ across the markets and in Finland the application will be submitted to HILA which are not part of JNHB.
Dispensing group	BEGR/NBS
Packaging – types, sizes/number of units and concentrations	250, 500,750, 1000, 2000, 3000, 4000 IU

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Therapeutic indication relevant for the assessment	According to the indication, efanesoctocog alfa can be used for all severities of haemophilia A, in all clinical settings (e.g. prophylaxis, on-demand treatment, treatment of bleeds, surgery) and for all age groups. [redacted]
Dosage regiment and administration:	50 IU/kg once weekly
Choice of comparator	Emicizumab (1.5 mg/kg once weekly maintenance dose)
Prognosis with current treatment (comparator)	With current standard praxis (FVIII replacement therapy or non-factor therapy), patients without HIV or viral hepatitis have a near normal life expectancy although there remains a risk of premature death due to fatal bleedings. However, patients on prophylactic treatment have factor levels in the range of mild haemophilia for the majority of the time. Because of this, most patients are affected by haemarthrosis as they grow older as a result of joint and subclinical bleedings. This leads to pain and disability and has a major negative impact on health-related quality of life in patients with haemophilia. Joint damage also has implication for health care costs in terms of e.g. joint surgery.
Type of evidence for the clinical evaluation	MAIC
Most important efficacy endpoints (Difference/gain compared to comparator)	Annualised bleeding rate (ABR) (efanesoctocog alfa superior vs emicizumab in MAIC) Pharmacokinetic parameters: Area under activity-time curve (AUC), FVIII trough levels (efanesoctocog alfa superior vs emicizumab in naïve comparison) Hemophilia Joint Health Score (HJHS) (not estimable in MAIC due to lack of comparator data for the relevant population)
Most important serious adverse events for the intervention and comparator	Treatment emergent serious adverse events are few for both efanesoctocog alfa and the comparator. For efanesoctocog alfa the majority of cases were assessed as mild to moderate in severity and not related to the treatment.

Summary	
Impact on health-related quality of life	Clinical documentation: Haem-A-QoL physical health (aged ≥ 17 years), change from baseline to week 52 was -6.74 (95% CI: -10.13, -3.36). The mean (SD) change from baseline to Week 52 in EQ-5D index score was 0.02 (0.13). Mean (SD) EQ VAS change from baseline to Week 52 was 0.83 (13.18). [redacted]
Type of economic analysis that is submitted	[redacted]
Data sources used to model the clinical effects	[redacted]
Data sources used to model the health-related quality of life	[redacted]
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	[redacted]
Number of eligible patients in Denmark	[redacted]
Budget impact (in year 5)	[redacted]

Abbreviations: ABR, Annualised bleeding rate; FVIII, Factor 8; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; JHJS, Haemophilia joint health score; ICER, Incremental cost effectiveness ratio; MAIC, Matching-adjusted indirect comparison; NFT, Non-factor therapy.

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

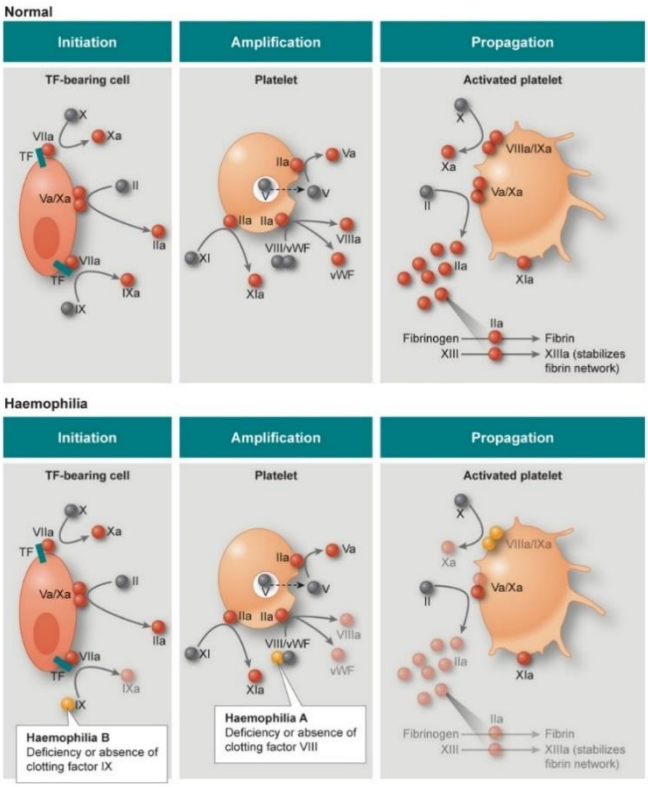
3.1.1 Aetiology

Haemophilia A is an inherited bleeding disorder associated with the partial or total deficiency of clotting factor VIII (FVIII). Haemophilia A is caused by mutations of the FVIII gene in the X chromosome, meaning that males are affected while female carriers are typically asymptomatic (De Caterina et al. 2013).

In normal haemostasis, coagulation is activated when a blood vessel is damaged resulting in the formation of a stable platelet and fibrin clot at the site of injury (De Caterina et al. 2013). Coagulation results from a pathway on specific cell surfaces, involving tissue factor (TF) and a number of different clotting factors (Figure 1) (De Caterina et al. 2013, Monroe and Hoffman 2006). Factors VIII and IX are essential for coagulation, forming a complex that activates Factor X. Activated FX (FXa) associates with activated Factor V (FVa) on the platelet surface and converts large amounts of prothrombin (Factor II; FII) to thrombin (activated Factor II; FIIa). In turn, this burst of thrombin generation helps to convert soluble fibrinogen into a solid fibrin network, which stabilises aggregations of platelets to form an impermeable clot (De Caterina et al. 2013, Monroe and Hoffman 2006).

In haemophilia A, platelet-surface thrombin generation fails because deficient FVIII leads to insufficient platelet-surface FIXa/FVIIIa complex, and thus inadequate FXa generation (Monroe and Hoffman 2006). This disruption of normal coagulation results in failed clot formation, spontaneous bleeding, or severe or excessive bleeding in response to trauma or surgery (Bolton-Maggs and Pasi 2003, Srivastava et al. 2020).

Figure 1: The process of defective clot formation in haemophilia



Note: Roman numerals refer to coagulation factors; "a" following a Roman numeral indicates activated coagulation factor

Abbreviations: TF, tissue factor; vWF, von Willebrand factor.

Sources: (De Caterina et al. 2013, Monroe and Hoffman 2006)

3.1.2 Diagnostics and assessment of severity

Testing for clotting factor levels is needed to diagnose haemophilia A and to determine the residual plasma concentration of FVIII (Srivastava et al. 2020). FVIII concentration is expressed in International Units (IU), where 1 IU is the concentration of FVIII in 1 mL of normal pooled plasma, or percentages of normal pooled plasma with normal levels ranging between 40–150%. Haemorrhage frequency and severity correlates with FVIII levels (Table 1). There are three degrees of severity in haemophilia. Whereas normal levels of FVIII are between 0.4 and 1.5 IU/mL (40–150%), patients with mild, moderate, and severe haemophilia have FVIII levels of 0.05 – 0.4 IU/mL (5–40%), 0.01-0.05 IU/mL (1–5%) and <0.01 IU/mL (<1%) respectively (Srivastava et al. 2020).

Table 1: Definitions of haemophilia severity

Severity	Definition	Symptoms
Mild	>5–40% of normal FVIII (>0.05–0.40 IU/mL)	• Spontaneous bleeding is rare, although long-term joint damage prevalent • Severe bleeding with major trauma or surgery • Bleeding after surgery, dental extractions, and accidents

Moderate	1–5% of normal FVIII (0.01–0.05 IU/mL)	• Occasional spontaneous bleeding • Prolonged or severe bleeding with trauma and surgery • Bleeding into joints and muscles after minor injury, leading to long-term joint damage • Excessive bleeding after surgery and dental extractions
Severe	<1% of normal FVIII (<0.01 IU/mL)	• Spontaneous bleeding in joints and muscles • Bleeding after injuries, accidents, and surgery • May bleed once or twice a week

Abbreviations: FVIII, Factor 8; IU, International units.
Source: (De la Corte-Rodriguez et al. 2022, Srivastava et al. 2020)

3.1.3 Symptoms and long-term complications of haemophilia A

Bleedings

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 (Srivastava et al. 2020). Common signs of haemophilia include (Srivastava et al. 2020):

- Bleeding into the joints causing swelling and pain
- Bleeding into the skin or muscle and soft tissue causing a build-up of blood in the area
- Bleeding of the mouth and gums, and bleeding that is hard to stop after losing a tooth
- Bleeding after circumcision
- Bleeding after having vaccinations
- Bleeding in the head of an infant after a difficult delivery
- Blood in the urine or stool
- Frequent and hard-to-stop nosebleeds

Life-threatening bleeding in haemophilia:

- Intracranial
- Internal

Intracranial haemorrhage (ICH) is a severe and life-threatening complication in PwHA. 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 (Zwagemaker et al. 2021).

Joint bleedings, synovitis and arthropathy

Bleeding frequency and location vary according to age, with the knees and elbows most commonly affected in PwHA aged >30 years, whereas adolescents and young adults usually present with bleeding affecting the ankles (Srivastava et al. 2020).

In people with severe disease, 90% of bleeding episodes involve the musculoskeletal system, primarily involving spontaneous joint bleeds (haemarthroses) that occur without any clearly identified cause and usually affecting one joint at a time (Rodriguez-Merchan 2010). Pain onset and local discomfort are the most common signs that bleeding has started (acute joint bleeds), and acute symptoms usually resolve with FVIII replacement treatment and rehabilitation (Srivastava et al. 2020). However, joint bleeds are often subclinical, going unnoticed on physical examination, particularly among PwHA receiving

prophylactic therapy. Subclinical joint bleeds can only be detected with ultrasound or magnetic resonance imaging scans (Mancuso et al. 2023).

Synovitis is a swelling in the synovial membrane that lines joints with cavities, known as synovial joints. The condition is usually painful, especially when the joint is moved. Synovitis is common in haemophilia and is caused by joint bleedings and the deposition of iron, which triggers an inflammatory response and bone rearrangement resulting in cartilage damage. Synovitis also increases the risk of additional bleeds. A single joint bleed can thus initiate a vicious circle resulting in arthropathy (Table 2) (Gooding et al. 2021, Mancuso et al. 2023). In the Nordics, a clinical expert reported that there are cases of patients with mild haemophilia facing joint surgery due to a single bleeding episode (Sobi 2024a).

Table 2: The natural history of chronic arthropathy

Stage of joint damage	Manifestations
Synovitis	Localised pain, swelling, inflammation Can be asymptomatic
Acute joint bleeds	Localised pain, swelling, inflammation Transient functional impairment (reversible)
Subacute joint bleeds	Damage to joint and surrounding tissues that persist between bleeding episodes Decreased mobility, swelling, muscle shortening, pain
Chronic arthropathy	Progressive, irreversible, joint damage Limited joint mobility, loss of muscle function, stiffness, chronic pain, disability

Synovitis and osteochondral changes are common in patients with severe haemophilia A, but also occur in moderate to mild haemophilia A. In the DYNAMO study of people with moderate (n=19) or mild (n=32) haemophilia A, the median annual joint bleeding rate was 0.0 (IQR: 0.0–0.2), yet MRI showed that 71% had soft-tissue changes in their ankles and 35% had osteochondral changes (Zwagemaker et al. 2021). In a study of 85 PwHA aged 42 years (median) with a mild bleeding phenotype, 36.5% had arthropathy; those with FVIII activity <17% were most susceptible, and the risk increased by 7.9% for each additional year of age and decreased by 7.7% for each 1 IU/dL increase in FVIII level (De la Corte-Rodriguez et al. 2022). In a Swedish registry based cohort study of 315 people with mild haemophilia (75.9% haemophilia A), patients had a ninefold and 16-fold increased incidence of arthropathy-related hospital admission and arthropathy diagnosis respectively, compared to matched controls in the general population (Osooli et al. 2017).

The only therapeutic options for haemophilic arthropathy are orthopaedic surgery and conservative treatment with the aim of preservation of function and pain relief to postpone orthopaedic surgery as long as possible. However, most people with severe haemophilia undergo joint surgery during their lifetime (Tagariello et al. 2009, Trossaert et al. 2024). Surgery commonly involves knee replacement followed by hip replacement (Lobet et al. 2014).

Pain, anxiety and quality of life

While surgery is an ultimate consequence of arthropathy diagnosis, many people suffer reduced mobility, joint pain and days lost from school or work due to frequent hospital admissions for arthropathy prior to that surgery. Such consequences have been shown to have substantial impacts on the health-related quality of life of people with haemophilia (Osooli et al. 2017). Pain, depression, and anxiety medications are more commonly used in people with haemophilia A than in matched controls. The MIND study was a retrospective analysis of registry data from Nordic countries including 3,246 people with haemophilia (>70% haemophilia A) over an 11-year period, with ≥1 observation year during 2007–2017. The age-adjusted ORs were higher in people with haemophilia than matched controls for most pain medications and several prescription drugs for depression/anxiety. Non-opioid pain medication use was higher in all haemophilia subgroups versus matched controls in Denmark, Norway, and Sweden, with ORs of 1.40 to 5.64. Even after adjusting for inhibitors and joint complications, there was a higher likelihood of use and higher volume of use of pain medications in people with haemophilia versus matched controls (Steen Carlsson et al. 2023).

Pain is a strong contributor to the reduced quality of life in PwHA. PwHA who report a higher frequency of joint pain and/or a history of joint surgery have significantly lower quality of life EQ-5D-3L values. In a cross-sectional survey of 184 PwHA, the mean (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. PwHA with ≥2 target joints versus no target joints had lower EQ-5D-3L utility values (0.43 vs 0.85; $p<0.001$). For PwHA reporting joint pain every day (n=80) the mean (SD) EQ-5D-3L utility values were 0.49 (0.30), compared with 0.93 (0.15) in those (n=51) with no joint pain (Carroll et al. 2019).

Anxiety is common in PwHA and caregivers, partly related to treatment administration and risk for bleedings, but also around joint health. Anxiety around joints tends to progress from an abstract concern to a real, tangible anxiety as patients grow older (Skinner et al. 2020).

Limitations in daily living

PwHA or caregivers rarely have their minds free of haemophilia – dimensions such as bleeding risk, treatment efficacy, and injection schedule add to the mental burden of disease, even if they are receiving prophylaxis (Krumb and Hermans 2021). They often feel limited, and typically avoid situations and activities that they associate with risk. The majority of PwHA (78%) refrain from activities due to their haemophilia, such as sport and travel (Skinner et al. 2020). In the Nordics, the greatest burden that PwHA

experience today is living with the fear of bleedings and limiting their way of living because of that (Sobi 2024a).

Infections

Until the mid-1980s there was a high rate of hepatitis B and C (HBV/HCV) and HIV transmission in patients with haemophilia due to virus contamination of plasma-derived coagulation factor concentrates. Because of this, infections remain common causes of death in older patients that initiated treatment before virus inactivation of cryoprecipitate was introduced in 1986. Since then, no HBV/HCV/HIV transmission has occurred in the Nordics (Nordic Hemophilia Council 2022). Today, most patients use recombinant factor concentrates, which do not have the same issue of risk for contamination.

3.1.4 Life expectancy

Haemophilia is a life-threatening condition representing a substantial burden to health, which has been reported in a multitude of studies historically. Over the past fifty years, developments in the treatment of bleeding disorders has brought the life expectancy in people with haemophilia A and without HIV and/or viral hepatitis closer to that of the general population (Hay et al. 2021). However, despite availability to treatment, in a Swedish registry study, the hazard ratio for all-cause mortality was 2.2 (95% CI: 1.8, 2.7) in the total population of PwHA or PwHB, and in the severe haemophilia subgroup 8.2 (95% CI: 3.2, 20.8) when patients with HIV and/or viral hepatitis were excluded (Lovdahl et al. 2013).

In a systematic review including studies published between 2010 and 2020, in PwHA, the most frequent causes of death were HIV/HCV/HBV and hepatic disease (32.4%), haemorrhage (21.4%), other (19.4%), and malignancy (9.9%) (Hay et al. 2021). Haemorrhage is the cause of death in approximately 20% of PwHA, and ICH accounts for approximately 70% of haemorrhage related deaths in PwHA (Hay et al. 2021).

3.2 Patient population

To estimate the Danish prevalence of people with haemophilia A, a prevalence of 0.72 per 10 000 inhabitants from the literature was used and combined with population size data from Statistics Denmark (Tomeo et al. 2021, Statistics Denmark 2024a). Estimations are shown in Table 3. These estimations are roughly aligned with registry data. In Denmark, the treatment of haemophilia A is handled by the two haemophilia centres in Aarhus and Copenhagen. In 2016, the centres had registered a total of 388 patients with haemophilia A, of whom 132 were on prophylactic (preventive) treatment and 256 received treatment on-demand (as needed) (RADS 2016). Patients on prophylactic treatment can be assumed to have a moderate to severe phenotype, whereas patients receiving treatment on demand can be assumed to have a milder phenotype (Nordic Hemophilia Council 2022). Globally, the incidence of haemophilia A is 24.6 out of 100,000 male births (World Federation of Hemophilia. 2021). Assuming similar incidence rates, and the birth rate for boys in Denmark in 2022 (30,128) (Statistics Denmark 2024b), this corresponds to an incidence of approximately 7 patients in Denmark.

The incidence and prevalence in the past 5 years are shown in Table 3. We assumed that the incidence of 7 as described previously was constant for all years. To estimate the prevalence in Denmark we applied the incidence to the patient number of 388 reported by RADS (RADS 2016), for each year following 2016 up until the year of minus one. In lack of absolute global prevalence estimates, we report the annual birth rates per 100 000 among males for the general patient population and for those with severe form.

Table 3 Incidence and prevalence in the past 5 years

Year	[Current year minus 5]	[Current year minus 4]	[Current year minus 3]	[Current year minus 2]	[Current year minus 1]
Incidence in Denmark	7	7	7	7	7
Prevalence in Denmark	409	416	423	430	437
Global prevalence *	Estimated for all HA is 17.1/100.000 males; severe form 6.0/100.000 males (World Federation of Hemophilia. 2021) Based on world population size of 7.9 billions, whereof 4 billion males, expected number of patients with haemophilia worldwide is approximately 831,000, of which approximately 282,000 are severe				

* For small patient groups, also describe the worldwide prevalence.

Efanesoctocog alfa is indicated for treatment and prophylaxis of bleeding in patients of all age groups with haemophilia A (congenital factor VIII deficiency). According to the indication, efanesoctocog alfa can be used for all severities of haemophilia A, in all clinical settings (e.g. prophylaxis, on-demand treatment, treatment of bleeds, surgery) and for all age groups (European Medicines Agency 2024a). [redacted]

[redacted]

According to the DMC treatment guidelines from 2023, [redacted]

[redacted]

Expected number of patients year 1 – 5 are presented in Table 4. To estimate the growth of the eligible patient population the ratio of births with severe haemophilia to all

severities (6/17,1 = 0,35; based on global prevalence numbers) was used and applied this ratio to the annual estimated Danish incidence of 7 and to the starting estimate of 437 from Table 3.

Table 4 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	156	158	161	163	166

3.3 Current treatment options

Internationally, prophylactic treatment with FVIII concentrates is the standard of care for haemophilia A as emphasised by the World Federation of Hemophilia guidelines from 2020 (Srivastava et al. 2020). This is the case also in the Nordics (Nordic Hemophilia Council 2022, Medicinrådet 2023). In Denmark, the recommendation for the NFT emicizumab has been extended to include severe haemophilia without inhibitors, and emicizumab is therefore now also part of the standard of care for a subset of PwHA (see below) (Medicinrådet 2023).

Standard half-life (SHL) FVIII concentrates have half-lives of 10–14 hours, typically requiring infusions every other day (Holmstrom et al. 2021). The need for better bleed protection led to the development of recombinant FVIIIs that remained in the circulation longer. The first extended half-life (EHL) FVIII product has been available since 2016. Currently licensed EHL FVIII products were made by either fusing FVIII with the Fc antibody domain, or by PEGylation of FVIII. The Fc fusion FVIII efmoroctocog alpha (Elocta) has a half-life of 19.0 hours, and the PEGylated FVIIIs, damoctocog alfa pegol (Jivi), rurioctocog alfa pegol (Adynovi), and turcotocog alfa pegol (Esperoct), have a half-life of 18.7 hours, 14.3 hours, 19.0 hours, respectively. Current EHL FVIIIs show a 1.4- to 1.6-fold improvement in half-life compared with SHL FVIIIs, and EHL products require infusions typically every 3 to 7 days, thus easing the administration burden on PwHA (Marchesini et al. 2021).

FVIII interacts with von Willebrand factor (VWF) and platelets to generate a normal haemostatic response. VWF acts as a chaperone for FVIII and, under normal conditions, >95% of FVIII circulating in plasma is bound to VWF in a high-affinity non-covalent association, and during clotting, thrombin cleavage releases activated FVIII from VWF (Terraube et al. 2010). However, the FVIII-VWF interaction imposes a biological limit on the half-life of endogenous FVIII and replacement FVIII products, as the complex is subject to the VWF clearance pathway with a half-life of about 16 hours (VWF half-life ceiling) (Pipe et al. 2016).

Emicizumab (Hemlibra) is a humanized monoclonal bispecific anti-FIXa/FX antibody that promotes thrombin formation by mimicking FVIIIa activity (European Medicines Agency 2023). Emicizumab was approved in Europe in 2018, and is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) in all age groups:

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

Administered subcutaneously, emicizumab reaches a steady state with a long plasma half-life that allows dosing intervals of every week, every two weeks, or monthly.

Treatment guidelines used in the Nordic setting are the Nordic Hemophilia Council (NHC) guidelines (Nordic Hemophilia Council 2022) and the international guidelines issued by the World Federation of Hemophilia (WFH) (Srivastava et al. 2020). In Denmark, recommendations for choice of treatment are issued by the Medicines Council (Medicinrådet 2023).

The latest treatment guidelines from the DMC were updated in January 2023. According to these guidelines, one of the SHLs or EHLs recommended for the age group in question should be used for prophylactic treatment of haemophilia A, with a preference for products with lower costs. Switching to cheaper products is recommended, but not more frequently than every three years, in order to minimize the risk of compliance issues. Switching from a SHL to an EHL FVIII product or emicizumab is recommended in certain cases (Medicinrådet 2023). Emicizumab should be considered for patients in case of poor venous access, problems with compliance, or a documented breakthrough bleeding despite optimised prophylaxis with factor concentrates (Medicinrådet 2023).

Dosing

For patients with moderate or severe phenotype haemophilia A, prophylaxis with FVIII concentrates is recommended at a dose and dosing interval that allows sufficient circulating factor to prevent haemarthrosis, and spontaneous and breakthrough bleeding, and to preserve musculoskeletal function based on individual needs and lifestyle (Srivastava et al. 2020, Nordic Hemophilia Council 2022). The overall goal of haemophilia prophylaxis in the Nordic countries is prevention of joint disease and intracranial bleeds (Nordic Hemophilia Council 2022).

Historically, the aim of prophylactic treatment of haemophilia A has been to convert a person with severe haemophilia (baseline FVIII level <1 IU/dL [1%]) to a bleeding phenotype typical of moderate or mild haemophilia by maintaining factor trough levels above 1 IU/dL (1%). These target trough levels have been limited by the short half-life of the available FVIII treatments not practically allowing for higher target levels. However, factor trough levels of 1–3 IU/dL (1%–3%) are insufficient to prevent all bleeds, and this regimen is today considered ineffective in preventing joint damage in the long run (Srivastava et al. 2020). Low factor trough levels allow occasional clinical and subclinical bleeds, resulting in gradual progression of joint disease over a lifespan (Srivastava et al. 2020). Therefore, many clinicians now prefer to target higher trough levels (Srivastava et al. 2020, Skinner et al. 2020, Malec and Matino 2023). A Nordic clinical expert in

haemophilia confirms that this is the case also in the Nordics (Sobi 2024a). According to a recent consensus statement from UK clinical experts in haemophilia A, the aim of prophylaxis should be to achieve a trough FVIII level ≥ 15 IU/dL (15%) and maintain a longer period with FVIII levels of more than 20-30 IU/dL (20-30%) to provide better bleed protection. The aspirational goal for PwHA according to these experts is to prevent all joint bleeds, which may be achieved by maintaining normalised FVIII levels (i.e. ≥50 IU/dL) (Laffan et al. 2024). Factor levels, independent of time, play a crucial role in reducing bleed rates. Higher factor VIII levels correlate with decreased risk of joint bleeding (Agosti et al. 2023). It is recognised today that trough factor levels are not the only pharmacokinetic parameter of importance when adjusting the dose of factor concentrates. Bleeding rates decline as the percent of time spent weekly with FVIII levels above 20-30 IU/dL increases. Area under the activity time curve (AUC), which is a measure of the total exposure to factor levels over the dosing interval, is also associated with increased protection against joint and non-joint bleeding (Valentino et al. 2016).

Personalisation

The WFH 2020 guidelines state that the trade-off in haemophilia prophylaxis is that higher trough levels may require higher doses or more frequent infusions of clotting factor concentrates. Therefore, dosing should be personalised based on the individual's activities, lifestyle, and PK handling of factor (Srivastava et al. 2020). PK-guided dosing is recommended on the basis that several studies have shown that bleeding and joint outcomes are significantly better when peaks and trough are personalised using PK-guided dosing compared with non-PK-guided dosing (Ferri Grazzi et al. 2022).

Based on a Delphi consensus statement published in 2017, tailoring dosing around physical activity was recommended, with a FVIII threshold of 3–5% appropriate for mild physical activity, 5–15% for higher-risk, and 15–30% for intensive physical activity (Iorio et al. 2017). A clinical expert in haemophilia based in the Nordics states that the lower FVIII threshold to prevent subclinical bleedings is 20%, but that higher levels are needed e.g. for patients practicing sports (Sobi 2024a). However, treatment personalisation involves PK monitoring requiring post-infusion blood sampling, which adds to the burden for PwHA (Lambert et al. 2018).

Limitations with current standard of care

Factor levels are limited by the short half-life of FVIII concentrates, and a major challenge with all current FVIII products is that they need to be administered quite frequently in order to keep trough levels high enough to prevent spontaneous bleeding (Soucie et al. 2018). Whereas EHL FVIII products offer improved dosing convenience over SHL FVIIIs, the half-life and AUC improvement is limited due to the VWF-imposed half-life ceiling, with EHL FVIIIs offering only a 1.4- to 1.6-fold increase in half-life and a 1.7 increase in AUC over SHL FVIIIs (Marchesini et al. 2021, Lissitchkov et al. 2022).

The frequency of factor infusions increases with the target factor level. In the rurioctocog alfa pegol PROPEL study, PwHA were randomized to target trough FVIII activity of 1-3% or 8-12%. Achieving trough FVIII activity of 8-12% during the 12-month study required a mean (SD) of 3.6 (1.2) infusions per week compared to 2.3 (0.6) in the 1-3% activity group (Klamroth et al. 2021). This high frequency of infusions contributes to a

considerable treatment burden for PwHA. Moreover, even in the FVIII activity 8-12% group, many patients failed to reach zero total and spontaneous bleeds (Klamroth et al. 2021).

Thus, despite availability of prophylactic treatment, many PwHA with moderate or severe haemophilia do not achieve the treatment goals and remain in the range of moderate to mild haemophilia for a considerable time of the week. Due to fluctuations in FVIII activity levels, bleedings still occur, and in the long run most PwHA – including patients with a mild phenotype – are facing joint damage and various degrees of disability (Zwagemaker et al. 2021, De la Corte-Rodriguez et al. 2022, Måseide et al. 2020).

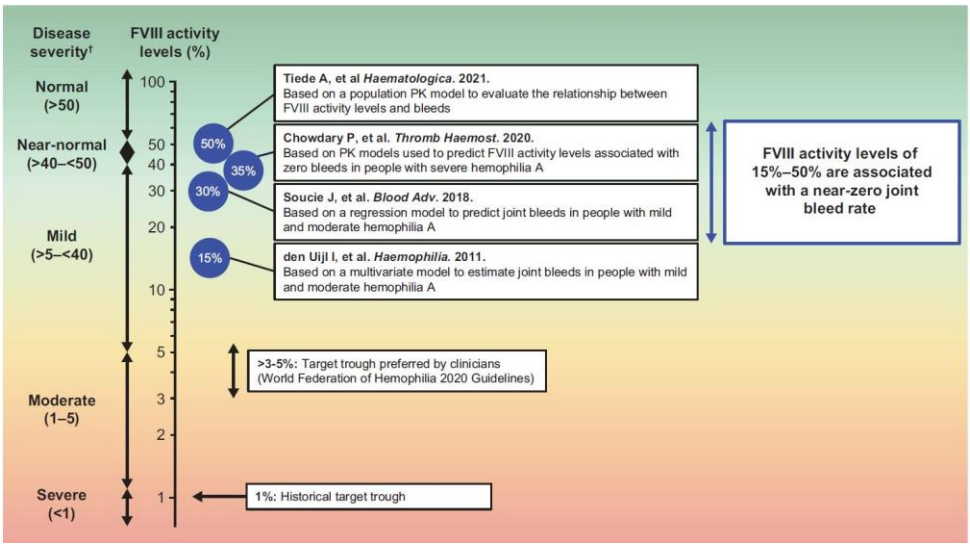
Relationship between factor levels and bleedings

As a rule of thumb, the higher the factor levels at all times, the less the bleeding. On average, joint bleeding rates decrease as FVIII activity increases, yet joint bleeds are prevalent even in PwHA with a mild bleeding phenotype (with FVIII levels 5–40 IU/dL), and the likelihood of joint bleeds depends on variables such as activity, lifestyle, and body build (Srivastava et al. 2020).

Current data suggest that FVIII activity levels of 15%–50% may be needed to achieve a near-zero joint bleed rate (Figure 2). Den Uijl et al. showed that for every 1% increase in baseline factor levels (in people with haemophilia not on prophylaxis), there is a decrease in bleeding frequency, and when baseline FVIII levels are above 15 IU/dL (15%), spontaneous bleeding is rare (den Uijl et al. 2011). This level may therefore be described as the minimal protective factor activity level. However, target FVIII activity levels of 15% are inadequate to prevent all joint bleeding in adults with haemophilia, and even at 20%, adult patients are predicted to have 1 joint haemorrhage per year (Soucie et al. 2018). For complete prevention of joint damage in PwHA, normalisation of FVIII levels are needed, i.e. levels in the range of 50 – 150 IU/dL (50-150%) (Laffan et al. 2024). A clinical expert in haemophilia based in the Nordics confirms that spontaneous bleedings can be avoided at factor activity levels of 15%, but that higher levels (at least 20 – 30 %) are needed to avoid traumatic bleeds, e.g. in relation to sport activities (Sobi 2024a). Nordic PwHA with a trough factor level of 4-5% may appear healthy and free of complications in the form of break-through bleeds, but they still experience subclinical bleedings detectable with MR. With such low trough levels there are no safety margin in case of trauma (Sobi 2024a).

In patients with severe haemophilia receiving FVIII replacement therapy, studies have shown that few patients experience bleeds at FVIII levels of >20 IU/dL, and at FVIII levels of >30 IU/dL, most patients have zero bleeds (Valentino et al. 2016, Chowdary et al. 2020, Benson et al. 2021). In a recent literature review, FVIII activity levels up to 50% are suggested in order to achieve a near-zero joint bleed rate (Figure 2) (Malec and Matino 2023).

Figure 2: FVIII activity levels associated with a near-zero bleed rate in haemophilia A



Note: Based on †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. FVIII activity levels of >40%–<50% are defined here as near-normal.

Abbreviations: FVIII, factor VIII; PK, pharmacokinetic.

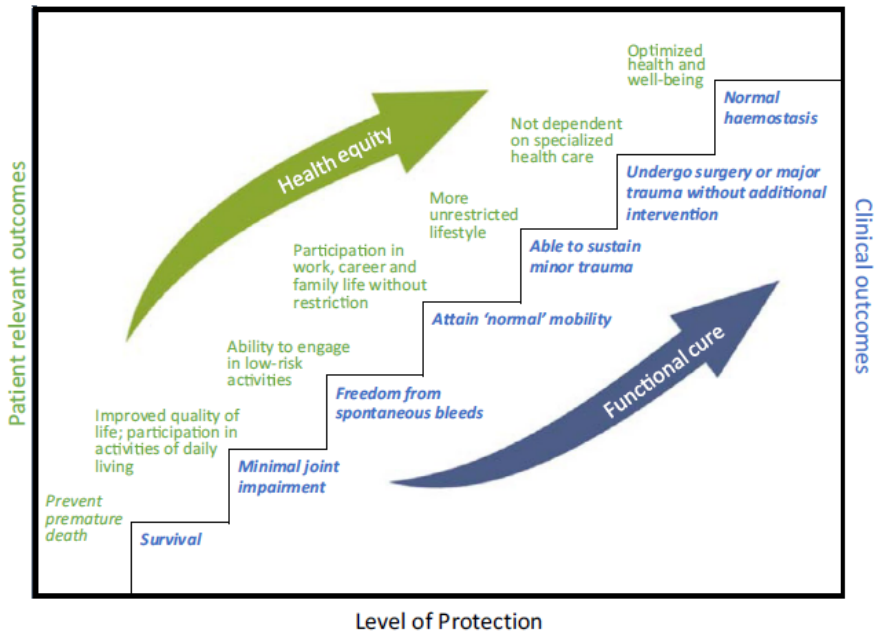
Sources: Figure from (Malec and Matino 2023). Sources cited in figure are (Tiede et al. 2021, Chowdary et al. 2020, Soucie et al. 2018, den Uijl et al. 2011, Srivastava et al. 2020)

Normalised haemostasis

In the WFH guidelines (2020), a definition of prophylaxis was proposed based on outcomes rather than doses of therapeutic products or time of initiation (Srivastava et al. 2020): “The regular administration of a haemostatic agent/agents with the goal of preventing bleeding in people with haemophilia while allowing them to lead active lives and achieve quality of life comparable to non-haemophilic individuals.”

To develop the definition of prophylaxis, a treatment model was proposed which, instead of clinical outcomes and FVIII levels, used clinical milestones correlated with activity and targeted outcomes (Skinner et al. 2020). The objective of the model was to “Encompass a vision shared by providers and PwHA alike, tracking clinical and patient centric outcomes in parallel, such that value is not limited to efficacy endpoints alone, but rather provides a clear path towards ‘normal haemostasis’ ” (Skinner et al. 2020).

Figure 3: Model of milestones towards normal haemostasis



Note: Level of protection on horizontal access. Medical outcome on right vertical access; patient-relevant outcome on left vertical access

Source: Skinner et al. 2020 (Skinner et al. 2020)

Sustaining FVIII levels near to the normal range at >40 IU/dL provides normalised haemostasis. The final treatment milestone of 'normal haemostasis' involves achieving FVIII activity at normal to near-normal levels that are sustainable over time (Skinner et al. 2020). High sustained factor levels have the potential to provide improved protection from bleeds, preserve joint health, and advance closer to the goal of achieving optimal function and health equity. However, achieving this may not be achievable with treatments currently available for PwHA (Table 5).

Table 5: Model of milestones towards normalised haemostasis and current treatments

Milestone	Outcome and achievability in context of current and upcoming treatments adapted from Skinner et al. (2020)
1. Sustain life	Prevent premature death • Achievable in PwHA who have access to current treatments
2. Minimal joint impairment	Participation in activities of daily living and improve HRQoL • Achievable in most PwHA who start prophylaxis early in life, but less so for those exposed to joint bleeds that have resulted in chronic damage before starting prophylaxis, or those that continue to experience joint bleeds despite prophylaxis
3. Freedom from spontaneous bleeds	Prevent bleeding and subclinical microbleeds, and enable participation in low-risk activities • Spontaneous bleeds still occur despite prophylaxis with current treatments, especially at factor activity levels below 15 IU/dL

4. Attain 'normal' mobility	No visible differences from the general population in terms of day-to-day activities, such as walking, cycling or working. • Achieving normal mobility may be possible with current treatments, but will require frequent administrations in order to keep factor activity levels above the minimum protective level of 15 IU/dL
5. Able to sustain minor trauma	Able to sustain minor trauma and lead a more unrestricted lifestyle • Achieving ability to sustain minor trauma will require factor activity levels exceeding the minimum protective level of 15 IU/dL at all times • Current management is on-demand FVIII therapy
6. Undergo surgery or major trauma without additional intervention	Undergo surgery or major trauma without additional intervention • Current management is to monitor FVIII levels and to supply required FVIII therapy
7. Normal haemostasis	Normalised haemostasis, resulting in active lives and achieve quality of life comparable to non-haemophilic individuals • SHL and EHL are limited due to half-life ceiling effect • Emicizumab provides FVIII-like activity of 15–20% • Once-weekly efanesoctocog alfa provides FVIII activity in the near normal (>40%) for most of the week

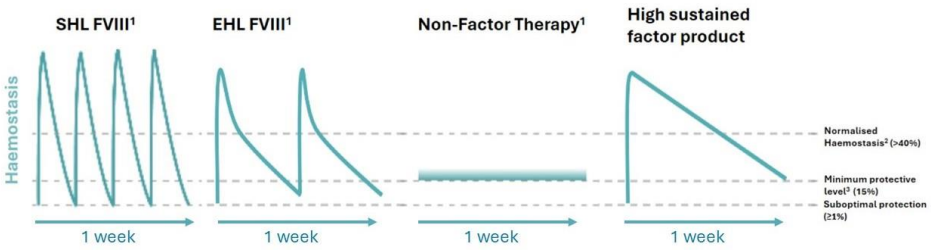
Abbreviations: EHL, Extended half-life; HRQoL, Health-related quality of life; IU, International unit; PwHA, Patients with haemophilia A; SHL, standard half-life.

Source: adapted from Skinner et al. 2020 (Skinner et al. 2020)

With currently available FVIII concentrates, FVIII activity levels fall below the minimum protective level of 15% for a significant part of the time. In the Nordics, minimum trough levels of 3-5% have typically been targeted in the past, although many clinicians nowadays aim for higher levels (Sobi 2024a). The non-factor therapy emicizumab keeps the FVIII activity at approximately 15%, which may be sufficient to keep spontaneous bleeds at low risk, but not to prevent haemorrhage associated with e.g. physical activity (Figure 4) (Schmitt et al. 2021, Broderick et al. 2012). As described above, trough levels are not the only pharmacokinetic parameter of importance. High factor levels are important for preventing bleeds during physical activity, and the total factor exposure over time measured by AUC is another important indicator of the level of bleed protection (Valentino et al. 2016). There is an urgent need for a high sustained factor treatment that keeps the FVIII activity levels above the minimum protective level at all times in the normalised haemostasis range for a significant part of the time, while at the same time not adding to the already high burden of treatment so that PwH can achieve a quality of life comparable to non-haemophilic individuals.

Historically, the main reasons that clinicians have not aimed for higher trough levels have been costs and treatment adherence. Although normalisation of haemostasis is not mentioned as a goal in the Nordic treatment guidelines, this is something that has become achievable only with modern treatment options such as efanesoctocog alfa. Future updates of Nordic and international treatment guidelines are expected to include a more aggressive treatment goal in the management of PwHA (Sobi 2024a).

Figure 4: PK profiles of different approaches to haemophilia therapy*



Abbreviations: EHL, extended half-life; FVIII, factor 8; PK, pharmacokinetic; SHL, standard half life.

*Dosing varies between therapy class; every other day to twice weekly for SHL factors, twice weekly for EHL factor, and weekly to monthly for non-factor therapies; EHL: Extended half-life; SHL: Standard half-life; NFT: Non-Factor Therapy

Sources: 1. (Skinner et al. 2020) , 2. (Srivastava et al. 2020), 3. (Soucie et al. 2018)

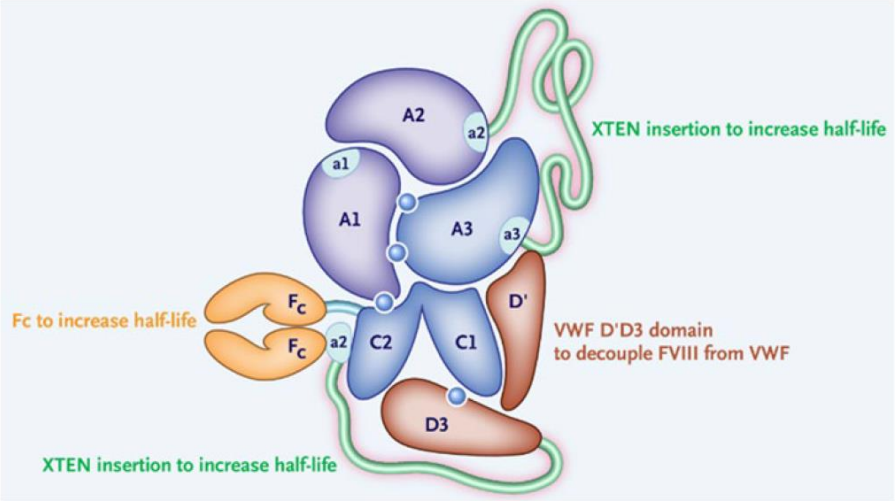
3.4 The intervention

Efanesoctocog alfa (Altuvoct) received a positive opinion by the CHMP recommending the granting of a marketing authorization on the 25th of April 2024 (European Medicines Agency 2024b). The full indication is:

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

Efanesoctocog alfa is a new class of FVIII replacement therapy designed to decouple recombinant FVIII from endogenous VWF and overcome the VWF imposed half-life ceiling. Efanesoctocog alfa is composed of a single recombinant FVIII protein and three additional components that contribute to its increased half-life: an Fc domain that facilitates recycling through the neonatal Fc receptor pathway, covalent linkage to a VWF D'D3 FVIII binding domain to decouple recombinant FVIII from endogenous VWF, and two XTEN polypeptides to shield efanesoctocog alfa from proteolytic degradation and clearance (Figure 5) (von Drygalski et al. 2023b).

Figure 5: Structure of efanesoctocog alfa

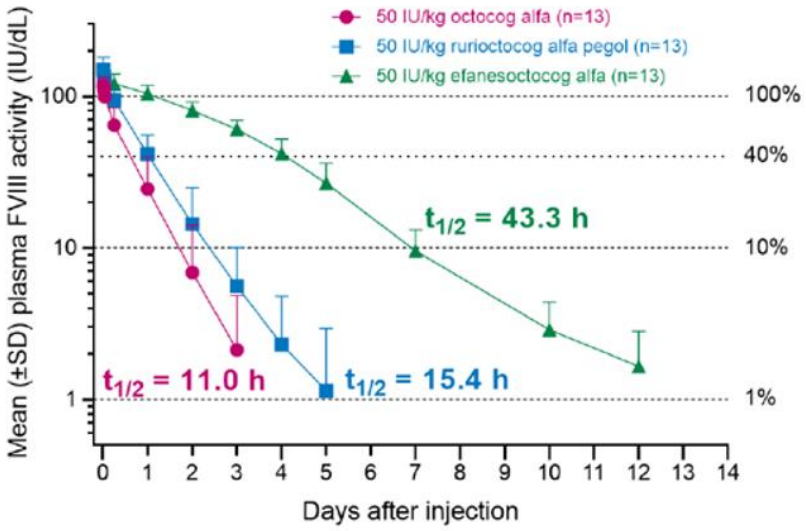


Abbreviations: a1, a2, a3, acidic region 1, 2, 3; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; FVIII, factor 8, VWF, von Willebrand factor.

Source: von Drygalski et al. 2023 (von Drygalski et al. 2023b)

In a PK/PD study, a single dose of efanesoctocog alfa resulted in a geometric mean half-life of 43.3 hours, which was up to four times longer than EHL rurioctocog alfa pegol (15.4 hours) and SHL octocog alfa (11.0 hours) (Figure 6, Table 6). The AUC_{inf} (AUC extrapolated to infinity) fold increase was 6.0 (90% CI: 5.3, 6.8) vs SHL octocog alfa and 3.6 (90% CI: 3.2, 4.1) vs EHL rurioctocog alfa pegol (Lissitchkov et al. 2022).

Figure 6: Sequential PK study: efanesoctocog alfa plasma half-life



Abbreviations: FVIII, Factor 8; IU, International unit; SD, Standard deviation; $t_{1/2}$, half-life.
Source: (Lissitchkov et al. 2023)

Table 6: Sequential PK study: PK parameter for efanesoctocog alfa versus octocog alfa and rurioctocog alfa pegol

PK parameter, Geometric mean	Octocog alfa n=13	Rurioctocog alfa pegol n=13	Efanesoctocog alfa N=13
$t_{1/2}$, h	11.0	15.4	43.3
AUC_{inf}, IU x h/dL	1670	2820	10100
C_{max}, IU/dL	118	148	139
Time >40 IU/dL post dose, days	<1	~1	4

Abbreviations: AUC_{inf}, Area under the activity time curve extrapolated to infinity; C_{max}, Maximum serum concentration; IU, International unit; PK, Pharmacokinetic; $t_{1/2}$, Half-life.

Source: (Lissitchkov et al. 2022)

At 26 weeks, similar results were obtained in a sequential PK subgroup (see Figure 14 in Section 6.1.4.5). The clinical development programme showed that once-weekly injections of efanesoctocog alfa provided high-sustained FVIII activity in the normal to near-normal range (>40 IU/dL) for a significant part of the week, with a mean of 15 IU/dL after 7 days. The geometric mean half-life was 47.0 hours (95% CI, 42.3 to 52.2), the steady state clearance 0.439 ml per hour per kilogram (95% CI, 0.390 to 0.493), the maximum factor VIII activity 151 IU/dL (95% CI: 137 to 167), and the AUC was 11,500 h × IU/dL (95% CI, 10,200, 13,000). Similar results were observed at 52 weeks, with a through level of 18 IU/dL (European Medicines Agency 2024a).

An overview of efanesoctocog alfa is found in Table 7.

Table 7: Overview of efanesoctocog alfa

Overview of intervention	
Therapeutic indication relevant for the assessment	[redacted]
Method of administration	i.v. infusion
Dosing	Once weekly
Dosing in the health economic model (including relative dose intensity)	[redacted]
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Continuous (life-long)
Necessary monitoring, both during administration and during the treatment period	None
Need for diagnostics or other tests (e.g. companion	None

Overview of intervention	
diagnostics). How are these included in the model?	
Package size(s)	250, 500, 750, 1000, 2000, 3000, 4000 IU

Abbreviations: FVIII, Factor 8; IU, International unit; NFT, Non-factor therapy; PwHA, Patients with haemophilia A.

3.4.1 The intervention in relation to Danish clinical practice

No additional diagnostic tests to those already used in routine care of haemophilia are required for use of efanesoctocog alfa.

Considering the limitations of existing treatment options in preventing long-term joint damage and disability described above (section 3.3), efanesoctocog alfa has the potential to improve treatment standards in all people with haemophilia A by achieving normalised haemostasis for a significant part of the week, and maintaining FVIII levels above the minimum protective level of 15 IU/dL at all times with a once weekly dosing (von Drygalski et al. 2023b). [redacted] As such, it constitutes a new class of treatment and an improved treatment option to other products already used in clinical practice, including SHLs, EHLs and emicizumab.

[redacted]

3.5 Choice of comparator(s)

Factor VIII concentrates used in accordance with current treatment guidelines (Nordic Hemophilia Council 2022, Srivastava et al. 2020) will result in factor trough levels in the range of baseline levels for moderate haemophilia (i.e. 1–5 IU/dL, or 1-5%). As described in section 3.3, patients treated this way might continue to experience breakthrough bleedings, subclinical bleedings and subsequent long-term joint damage. In contrast, efanesoctocog alfa will normalise factor levels by keeping them above 40 IU/dL (40%) for a significant part of the week and above the minimum protective level of 15 IU/dL (15%) at the end of the week, thereby minimizing the risk of bleedings. For SHLs and EHLs to achieve similar trough levels, high off label doses and frequent dosing intervals may be needed.

In contrast to SHL and EHL factor VIII concentrates, emicizumab has a mean (SD) elimination half-life of 26.9 (9.1) days, and is dosed subcutaneously every 1, 2, or 4 weeks. In the HAVEN I study of 112 people with severe haemophilia with inhibitors, once weekly emicizumab (1.5 mg/kg) provided a mean steady-state FVIII-like activity of approximately 20% (Schmitt et al. 2021), with a slightly lower level at approximately 15% with a 6 mg/kg dosing every 4 weeks (Schmitt et al. 2021). Notably, emicizumab provides factor-like activity, while efanesoctocog alfa directly replaces the missing factor.

Efanesoctocog alfa is the first factor replacement therapy in adult PwHA to maintain the FVIII activity level above the minimum protective level of 15% at all times (see section 3.4). Until now, emicizumab has been the only treatment currently available on the market in Denmark that, like efanesoctocog alfa, can provide a factor (like) activity level not falling below the minimum protective FVIII (like) activity level above 15% at all times at dosing according to label. This makes emicizumab the most suitable comparator to efanesoctocog alfa, despite emicizumab having a different administration route. This choice of comparator is supported also by a clinical expert in haemophilia based in the Nordics (Sobi 2024a). However, in contrast to emicizumab, efanesoctocog alfa maintains factor levels in the normal range for a significant part of the week. Our deliberate choice to compare with emicizumab 1.5 mg/kg once weekly dosing thus reflects a conservative approach. [redacted]

Overview of comparator	
Generic name	Emicizumab
ATC code	B02BX06
Mechanism of action	Emicizumab is a humanized monoclonal bispecific anti-FIXa/FX antibody that promotes thrombin formation by mimicking FVIIIa activity
Method of administration	s.c. injection
Dosing	3 mg/kg once weekly for 4 weeks (induction), followed by: • 1.5 mg/kg Q1W, or • 3 mg/kg Q2W, or • 6 mg/kg Q4W
Dosing in the health economic model (including relative dose intensity)	1.5 mg/kg Q1W
Should the pharmaceutical be administered with other medicines?	No (although Factor VIII concentrates may be needed for treatment of breakthrough bleedings or increase peak factor levels prior to physical activity or surgery)

Overview of comparator	
Treatment duration/ criteria for end of treatment	Continuous treatment (life-long)
Need for diagnostics or other tests (i.e. companion diagnostics)	None
Package size(s)	1 x 12 mg/0,4 ml 1 x 30 mg/1 ml 1 x 60 mg/0,4 ml 1 x 105 mg/0,7 ml 1 x 150 mg/1 ml 1 x 300 mg/2 ml

Abbreviations: FIXa, Factor 9a; FVIIIa, Factor 8a; FX, Factor 10; Q1W, Once weekly; Q2W, once every two weeks; Q4W, Once every four weeks.

3.6 Cost-effectiveness of the comparator(s)

Emicizumab was assessed by the DMC for patients with haemophilia A without inhibitors in 2019, but was at that time not recommended (Medicinrådet 2019). However, emicizumab was later included in the DMC treatment guidelines for the same indication (Medicinrådet 2023). Thus, emicizumab can be assumed to be cost effective for patients with haemophilia A without inhibitors.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

XTEND-1 is the pivotal study and the study used in the indirect comparison vs the comparator emicizumab. The primary endpoint was estimated in the Full Analysis Set with the use of a negative-binomial regression model. ABRs were calculated on the basis of the number of bleeding episodes during the efficacy period. If the upper limit of the 97.5% CI for the ABR in group A was ≤6, the intervention was considered to be effective. The intra-patient comparison of the ABR during prophylaxis in group A and the rate during pre-study prophylaxis was assessed using a negative-binomial regression model. Noninferiority and superiority of efanesoctocog alfa prophylaxis to pre-study prophylaxis were evaluated sequentially. The adjusted mean change from baseline to week 52 in physical health (Haem-A-QoL physical-health score), pain (PROMIS pain-intensity score 3a), and joint health (HJHS) were estimated by means of mixed effects models with repeated measures, as part of a prespecified hierarchical testing framework. All efficacy outcome measures included in the application are defined in Table 8. Additional outcome measures and definitions thereof are available on ClinicalTrials.gov (ClinicalTrials.gov 2023a).

Table 8 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Estimated Annualized Bleeding Rate (ABR) [primary outcome measure in XTEND-1, secondary outcome measure in XTEND-KIDS] **Annualized Bleeding Rate by Type of Bleed (Spontaneous, Traumatic and Unknown Type)** [secondary outcome measure in XTEND-1 and XTEND-kids] **Annualized Bleeding Rate by Location of Bleed (Joint, Muscle, Internal and Skin/Mucosa)** [secondary outcome measure in XTEND-1 and XTEND-kids] [ABR any bleeding, any treated bleeding, spontaneous treated bleeding, and joint treated bleeding included in MAIC]	Baseline to week 52	ABR is annualized number of treated bleeding episodes (BE) per participant per year. Treated Bleeding episode: any occurrence of hemorrhage that required administration of efanesoctocog alfa. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered ≤72 hours apart from previous injection were considered same bleeding episode. Any bleed at different location was considered as separate bleeding episode, regardless of time from last injection. Spontaneous bleeding: bleeding episode without contributing factor (definite trauma/antecedent "strenuous" activity). Traumatic bleeding: bleeding episode with known/believed reason for bleed. ABR=number of treated bleeding episodes during efficacy period (EP)/number of days during EP*365.25. EP reflects the sum of all intervals of time during which participants were treated with Efanesoctocog alfa according to the study arms and treatment regimens.	This outcome measure (OM) presents estimated results (i.e., results estimated by fitting negative binomial [NB] regression model on data collected during EP). A clinically meaningful effect on ABR was defined as an upper 97.5% CI of the estimated ABR of ≤6. The primary endpoint was estimated in the Full Analysis Set with the use of a negative-binomial regression model. ABRs were calculated on the basis of the number of bleeding episodes during the efficacy period. If the upper limit of the 97.5% CI for the ABR in group A was ≤6, the intervention was considered to be effective.
Intra-participant comparison of efanesoctocog alfa, non-inferiority followed by superiority	Historical prophylaxis: From 6 months (prior to entry into study EFC16293) until the day before enrollment in	Data from Study OBS16221 were used to perform an intra-participant comparison of ABR between weekly prophylactic treatment with	The key secondary endpoint of intrapatient comparison of annualized bleed rate (ABR) during weekly efanesoctocog alfa versus prestudy prophylaxis in Arm A was assessed using a negative binomial regression model. The

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
[key secondary outcome in XTEND-1]	EFC16293; efanesoctocog alfa prophylaxis: Baseline up to Week 52 of current study EFC16293	Efanesoctocog alfa and prestudy prophylactic treatment with a marketed FVIII product.	mean paired difference and 95% CI was estimated using the per protocol set (noninferiority, primary analysis) and the treatment considered noninferior if the upper limit of the 1-sided 97.5% CI of the intrapatient ABR difference was <4. If noninferiority is achieved, then superiority will be evaluated sequentially using a negative-binomial regression model as above. The paired ABR ratio and 95% CI will be estimated using the full analysis set, and the treatment will be considered superior if the upper limit of the 1-sided 97.5% CI of the intrapatient ABR difference is <1.
Change From Baseline in Patient Reported Outcomes Measurements Information Systems (PROMIS) Pain Intensity 3a Score [secondary outcome measure in XTEND-1 and XTEND-kids]	Baseline, Week 52	PROMIS is a system of reliable and precise measures of participant-reported heath status. PROMIS measures cover physical, mental and social health and can be used for many chronic conditions. PROMIS - Pain Intensity - Short Form 3a consisted of 3 questions, participants reported for the intensity of pain experienced in the past 7 days. Each question had 5 responses scored between 1 (had no pain) to 5 (very severe pain). Total PROMIS pain intensity 3a score range was from 3 (no pain) to 15 (very severe pain), where higher score indicated more intense pain. Total raw score was converted into a T-score which rescaled raw score into standardized score with mean of 50 and standard deviation (SD) of 10. Higher PROMIS T-score represented worst outcome. For PROMIS pain intensity 3a, T-score of 60 was one SD worse than average.	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change From Baseline in Hemophilia Joint Health Score (HJHS) Total Score [secondary outcome measure in XTEND-1 and XTEND-kids]	Baseline, Week 52	HJHS is a validated 11-item scoring tool developed for the assessment of joint health in participants with haemophilia. It comprised an evaluation of the elbows, knee and ankle joints: swelling (0 to 3), duration of swelling (0 and 1), muscle atrophy (0 to 2), crepitus on motion (0 to 2), flexion loss (0 to 3), extension loss (0 to 3), joint pain (0 to 2) and strength (0 to 4), in each item 0 = none and higher score = severe damage and global gait (walking, stairs, running, hopping on 1 leg) scored on scale ranged from 0 to 4, where 0 = all skills in normal limit and 4 = no skills within normal limits). Total HJHS score = sum of joint totals (0 to 120) + general gait (1 to 4) and ranged from 0 (no joint damage) to 124 (severe joint damage), where higher score indicated severe joint damage.	
Quality of life parameters			
Change From Baseline in Hemophilia-specific Health-related Quality of Life Questionnaire for Adults (Haem-A-QOL) Physical Health Domain Score [secondary outcome measure in XTEND-1 (patients ≥17 years of age)]	Baseline, Week 52	Haem-A-QoL is a participant-reported questionnaire designed for adult participants (≥17 years of age) with haemophilia; and consists of 46 items comprising 10 domains. Lower scores denoted better physical health. Change from baseline in physical Health domain score was reported in this OM.	
Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score	Baseline to week 52	Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score from baseline to Week 52 (≥ 4 years old and parent proxy for all ages)	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
[secondary outcome measure in XTEND-1 (patients <17 years of age) and XTEND-kids]			
EQ-5D-5L [exploratory outcome measure in XTEND-1]	Baseline to week 52	The EuroQoL 5-dimension 5-level (EQ-5D-5L) is used widely in clinical trials to assess 5 dimensions of health outcome (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) from a wide variety of interventions on a common scale, for purposes of converting into a single summary score of health state.	Translated patient reported outcomes questionnaires were distributed to adult and pediatric patients. The EQ 5D-5L was assessed for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L descriptive system was converted into a single index value, the EQ-5D index score.
Safety parameters			
Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAE) [secondary outcome measure in XTEND-1 and XTEND-kids]	Arm A: From Baseline (Day 1) up to 3 weeks post last dose of efanesoctocog alfa (i.e., up to Week 55); Arm B: On-demand: Baseline to Week 26 and Arm B: Prophylaxis: From Week 26 up to 3 weeks post last dose of efanesoctocog alfa in Week 52 (i.e., up to Week 55)	An adverse event (AE) was defined as any untoward medical occurrence in a participant who received study drug which did not necessarily have a causal relationship with the treatment. A serious AE (SAE) was defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was a medically important event. Treatment-emergent AEs were AEs that developed, worsened or became serious from Baseline (Day 1) up to 3 weeks post last dose.	
Number of Participants With Neutralizing Antibodies (Development of Inhibitors) Directed Against Factor VIII	Arm A: Baseline to Week 52; Arm B: On-demand - Baseline to Week 26,	Development of inhibitors was defined as an inhibitor result of >=0.6 bethesda unit per milliliter (BU/mL) that was confirmed by a second test result of >=0.6 BU/mL from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn. Both	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
[primary outcome measure in XTEND-kids, secondary outcome in XTEND-1]	Prophylaxis - Week 26 to 52	tests must have been performed by the central laboratory using the Nijmegen-modified Bethesda assay.	
Pharmacokinetic parameters			
Area under the plasma FVIII activity versus time curve (AUC_{0-tau}) [secondary outcome in XTEND-1]	Pre-dose, 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline); pre-dose, 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26 (Day 183)	AUC_{0-tau} was defined as area under the plasma concentration-time profile from time zero (pre-dose) to dosing interval. Only for participants who were enrolled in sequential PK subgroup of study, PK samples were collected for all timepoints at Baseline and at Week 26; however, participants did not receive Efanesoctocog alfa dose in week 2 and week 27.	Following a washout period of 4–5 days, 17 patients in Arm A underwent sequential blood sampling for measuring factor VIII (FVIII) activity at Week 1 and Week 26 (predose, and 15 minutes, 3 hours, 24 hours, 72 hours, 168 hours, 240 hours, and 336 hours post dose). All remaining patients underwent abbreviated sampling for FVIII activity at Week 1 (predose, and 15 minutes, 3 hours, 24 hours, 72 hours, and 168 hours post dose). Sampling for peak (15 minutes post dose) and trough (168 hours post dose) FVIII activity occurred at Weeks 4 and 13 (Arm A only), 26, 39, and 52.
Elimination half-life (plasma $t_{1/2}$) [secondary outcome measure in XTEND-1 and XTEND-kids]	Pre-dose, 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline); pre-dose, 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26	Plasma $t_{1/2}$ was the time measured for the plasma concentration of drug to decrease by one half. Only for participants who were enrolled in sequential PK subgroup of study, PK samples were collected for all timepoints at Baseline and at Week 26; however, participants did not receive efanesoctocog alfa dose in week 2 and week 27.	
Trough Concentration for efanesoctocog alfa (C_{trough})	Pre-dose at Baseline (Day 1) and Week 52	C_{trough} is the pre-dose concentration of a drug.	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
[secondary outcome measure in XTEND-1 and XTEND-kids]			

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Abbreviations: ABR, annualised bleeding rate; AE, adverse event; $AUC_{0\text{-}tau}$, Area under the plasma FVIII activity versus time curve; BE, bleeding episodes; BU, Bethesda unit; CI, Confidence interval; C_{trough}, trough level; EP, efficacy period; EQ-5D, EuroQoL 5-dimensional quality of life-questionnaire; FVIII, Factor 8; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; Haemo-QoL, Haemophilia-specific health-related quality of life questionnaire; HJHS, Haemophilia joint health score; MAIC, Matching-adjusted indirect comparison; OM, Outcome measure; PROMIS, Patient-Reported Outcomes Measurement Information System; SAE, serious adverse event; $t_{1/2}$, half-life; TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse event.

Validity of outcomes

The Haem-A-QoL Questionnaire was assessed in terms of reliability, validity, and sensitivity to change over time in adult males with haemophilia over a 6-month period, using trial data from two phase 3 clinical trials (A-LONG: rFVIIIFc, and B-LONG: rFIXFc) (von Mackensen et al. 2017). Internal consistency reliability was adequate (Cronbach's alpha > 0.70) for nine of the 10 Haem-A-QoL domains and for 'Total Score' in both trials at baseline (A-LONG, n = 133; B-LONG, n = 73). At baseline, several Haem-A-QoL domains and 'Total Score' demonstrated known-groups and convergent validity when compared with other trial measures, including the EQ-5D (items and total scores) and joint impairment. Change score correlations (baseline to 28 weeks) between the EQ-5D and the Haem-A-QoL 'Total Score', and 'Physical Health' and 'Feelings' domains were moderate in magnitude ($|r| \geq 0.33$; $P < 0.03$), demonstrating sensitivity to change for these outcome measures in A-LONG. The authors concluded that the analyses provide evidence of the reliability, validity and ability to detect change of the Haem-A-QoL to assess the HRQoL of adult males with severe haemophilia A and B in longitudinal clinical trials.

The Haemo-QoL questionnaire for children with haemophilia was developed and tested in six countries (France, Germany, Italy, the Netherlands, Spain and the United Kingdom) for psychometric properties in 339 children with haemophilia and their parents. Psychometric testing involved the examination of reliability and validity. The three age-group versions of the Haemo-QoL had acceptable internal consistency and retest reliability values, as well as possessing sufficient discriminant and convergent validity (von Mackensen et al. 2004).

The clinical validity of PROMIS was evaluated, by domain, across six clinical populations, including approximately 1,500 individuals at baseline and 1,300 at follow-up (Cook et al. 2016). The analyses reported in were conducted post hoc, pooling data across six studies, and accommodating the different designs of the six, within-condition, parent studies. Changes in T-scores, standardized response means, and effect sizes were calculated in each study. When a parent study design allowed, known groups validity was calculated using a linear mixed model. The results provide substantial support for the clinical validity of nine PROMIS measures in a range of chronic conditions.

HJHS has been validated for use in children and adults with haemophilia. Using a fully factorial design, four physiotherapists (from Canada, the United States and Sweden) examined eight boys with severe haemophilia A on two consecutive days using the HJHS. The boys ranged in age from 4-12 years and presented with variable joint damage. Six index joints (elbows, knees and ankles) were assessed on 11 impairment items including swelling, flexion and extension loss and gait. Concordance was measured by the intra-class correlation co-efficient. Reliability of the HJHS was excellent with an inter-observer co-efficient of 0.83 and a test-retest of 0.89 (Hilliard et al. 2006).

The convergent and discriminant construct validity of the HJHS version 2.1(HJHSv2.1) was studied in adults with haemophilia. rained physiotherapists scored the HJHS and World Federation of Hemophilia (WFH) joint score. Health history, the Functional Independence Scale of Hemophilia (FISH), Hemophilia Activities List (HAL), and Short-

Form McGill Pain Questionnaire (SF-MPQ) were also collected. he HJHS correlated strongly with WFH score (Spearman's rho [rs] = .95, P < .001). Moderate correlations were seen between the FISH (rs = .50, P < .001) and SF-MPQ Present Pain Intensity (rs = .50, P < .001), while a modest correlation was found with the HAL (rs = -.37, P < .001). The HJHS significantly differentiated between age groups (Kruskal-Wallis T = 35.02, P < .001) and disease severity in participants with haemophilia. The HJHS had high internal reliability (Cronbach's α = .88). The authors concluded that the HJHS shows evidence of strong convergent and discriminant construct validity to detect arthropathy in adults with haemophilia and is well suited for use in this population (St-Louis et al. 2022).

4. Health economic analysis

A [redacted] was performed to evaluate the [redacted] of efanesoctocog alfa compared to emicizumab.

The indirect treatment comparison based on pivotal trials shows a superior effect for efanesoctocog alfa compared to emicizumab on controlling bleeds (see section 7). [redacted] Assumptions are further described under their respective section.

The [redacted] is presented in this application along with all assumptions and a stand-alone version in Microsoft® Excel is attached.

4.1 Model structure

[redacted]

4.2 Model features

The features of the cost-comparison are presented in Table 9.

Table 9 Features of the economic model

Model features	Description	Justification
Patient population	[redacted]	[redacted]

Model features	Description	Justification
	[redacted]	
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	10 years	Previously accepted by AMGROS to include all relevant costs and benefits, Hemlibra 2019
Cycle length	[redacted]	[redacted]
Half-cycle correction	[redacted]	[redacted]
Discount rate	3.5%	DMC guidelines
Intervention	Efanesoctocog alfa	
Comparator(s)	Emicizumab	According to national treatment guideline
Outcomes	[redacted]	[redacted]

Abbreviations: DMC, Danish Medicines Council; EHL, Extended half-life; NA, Not applicable; SHL, Standard half-life.

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was conducted to identify phase 3 clinical trials of FVIII-replacement therapies and non-factor replacement therapies in patients with haemophilia A. The search was run in Medline, EMBASE and Cochrane clinical Trials register through the OvidSP gate using a search strategy constructed based on the inclusion/exclusion criteria presented in Appendix H. The last search was conducted September 6th, 2023, and identified a total of 65 publications corresponding to 49 unique trials. The SLR is summarized in Appendix H.

Only trials of the relevant comparator – emicizumab – with populations matching the XTEND-1 trial were of direct interest for the comparative analysis. Of the trials identified in the SLR, 7 investigated emicizumab (HAVEN I, II, III, IV, V, VI and VII). Of these, only HAVEN III included patients above age 12 with severe haemophilia A without inhibitors with data reported separately for patients with prior prophylactic treatment and was thus suitable for an indirect comparison vs efanesoctocog alfa using data from XTEND-1. Relevant literature included in the assessment is shown in Table 10.

Table 10 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Von Drygalski et al., (2023). Efanesoctocog alfa prophylaxis for patients with severe hemophilia A. New England Journal of Medicine, 388(4), 310-318. (von Drygalski et al. 2023b, ClinicalTrials.gov 2023a)	XTEND-1	NCT04161495	Start: 19/11/19 Completion: 03/02/22	Efanesoctocog alfa vs emicizumab
Safety, Efficacy and PK of BIVV001 in Pediatric Patients With Hemophilia A (ClinicalTrials.gov 2023b)	XTEND-Kids	NCT04759131	Start: 19/02/21 Completion: 18/01/23	Safety and efficacy study of efanesoctocog alfa in pediatric patients
Mahlangu et al. (2018). Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. New England Journal of Medicine, 379(9), 811-822. (Mahlangu et al. 2018b) Kiialainen et al. (2019). Effect of emicizumab prophylaxis on bone and joint health markers in people with haemophilia A without factor VIII inhibitors in the HAVEN 3 study. Haemophilia, 28(6), 1033-1043. (Kiialainen et al. 2022)	HAVEN III	NCT02847637	Start: 27/09/16 Completion: 12/05/22	Efanesoctocog alfa vs emicizumab

5.2 Literature used for the assessment of health-related quality of life

[redacted]

Table 11 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied

5.3 Literature used for inputs for the health economic model

[redacted]

Table 12 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied

6. Efficacy

6.1 Efficacy of efanesoctocog alfa compared to emicizumab for severe haemophilia A

6.1.1 Relevant studies

6.1.1.1 XTEND-1 (NCT04161495)

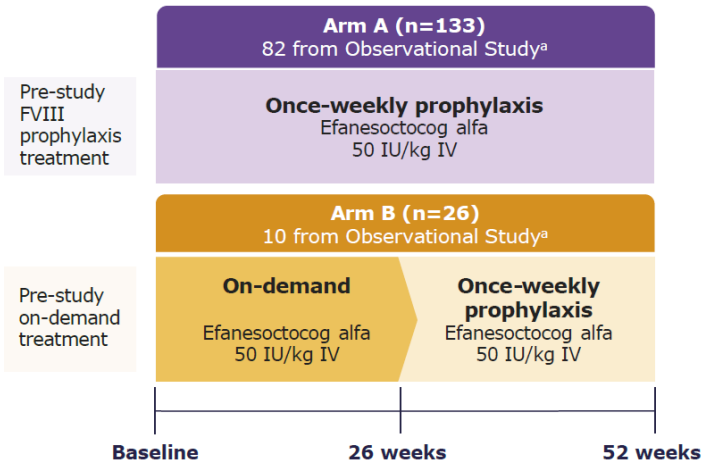
XTEND-1 was a Phase 3, global, open-label, study of the safety, efficacy, and PK of efanesoctocog alfa in previously treated people aged ≥12 years with severe haemophilia A (NCT04161495) (von Drygalski et al. 2023b). The study was conducted in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Spain, South Korea, Taiwan, UK, and USA.

Eligibility criteria were severe haemophilia A, defined as <1 IU/dL (<1%) endogenous FVIII or a documented genotype known to produce severe haemophilia A, and had received previous treatment for haemophilia A including any recombinant and/or plasma-derived FVIII product, or cryoprecipitate for at least 150 exposure days.

Eligible participants received efanesoctocog alfa 50 IU/kg once-weekly as a prophylaxis regimen for up to 52 weeks (Arm A), or received efanesoctocog alfa 50 IU/kg as an on-demand regimen for bleeding episodes for 26 weeks, and then efanesoctocog alfa 50 IU/kg once-weekly prophylaxis for another 26 weeks (Arm B) (Figure 7). In Arm B, participants were required to have ≥12 bleeding episodes in the previous 12 months, or ≥6 bleeding episodes in the previous 6 months.

Bleeding episodes were treated with a single dose of efanesoctocog alfa 50 IU/kg, and if the bleeding episode did not resolve, additional doses of efanesoctocog alfa 30 or 50 IU/kg could be administered every 2–3 days.

Figure 7: Phase 3, open-label, global study of people aged ≥12 years with severe haemophilia A: XTEND-1 study design



[a] A subset of participants in both arms A and B had enrolled in a 12-month observational pre-study.

Abbreviations: FVIII, Factor 8; IU, International unit; IV, intravenous.

Source: von Drygalski et al. 2023 (von Drygalski et al. 2023b)

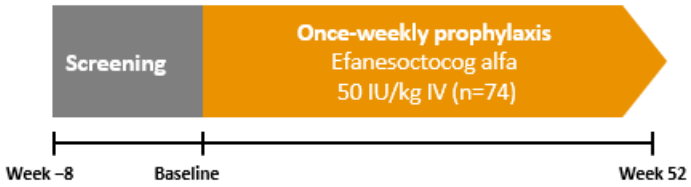
For the purposes of the indirect comparison of efanesoctocog alfa and emicizumab (section 7), only arm A of XTEND-1 is relevant (the population consists of PwHA with prior prophylaxis).

6.1.1.2 XTEND-Kids (NCT04759131)

The content of this methods chapter is based on the XTEND-Kids Clinical Study Report (CSR) (Sobi 2023) unless referenced otherwise. XTEND-Kids was a Phase 3, open-label, single-arm study of the safety, efficacy, and PK of IV administered efanesoctocog alfa in previously treated patients (PTPs) aged <12 years with severe haemophilia A (NCT04759131). The study comprised two age cohorts of children (<6 years and 6 to <12 years), and consisted of a screening period of up to 8 weeks, a 52-week open-label treatment period, and a 2- to 3-week safety follow-up period only for participants who did not enter the open-label extension study (Figure 8). The study was conducted in Australia, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, Taiwan, Turkey, UK, and USA.

Participants enrolled in this study were PTPs with severe haemophilia A defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia A. Previous treatment of haemophilia A (prophylaxis or on-demand) was defined as any recombinant and/or plasma-derived FVIII replacement product, or cryoprecipitate for at least 150 exposure days for patients aged 6 to <12 years and for at least 50 exposure days for patients aged <6 years.

Figure 8: Phase 3, open-label, single-arm study of people aged <12 years with severe haemophilia A: XTEND-Kids study design



Abbreviations: IU, International units.

Source: Malec et al. 2023 (Malec et al. 2023)

Participants with a history of a positive inhibitor test or with a positive inhibitor result at study screening were excluded.

The eligible participants received efanesoctocog alfa at a dose of 50 IU/kg IV once weekly for 52 weeks. The aim of the 50 IU/kg once-weekly treatment regimen was to provide high, sustained FVIII activity levels throughout the 7-day dosing interval and to decrease patient treatment burden compared with previous prophylactic FVIII replacement therapies.

Bleeding episodes were treated with a single dose of efanesoctocog alfa 50 IU/kg, and if the bleeding episode did not resolve, additional doses of efanesoctocog alfa 30 or 50 IU/kg could be administered every 2–3 days. For minor/moderate bleeding episodes within 2 to 3 days of a recent prophylactic dose, a 30 IU/kg dose could also be used.

XTEND-kids is not included in the comparison of efanesoctocog alfa vs emicizumab, as the patient population in XTEND-kids differ from that of HAVEN III. However, XTEND-kids is relevant as proof of efficacy and safety of efanesoctocog alfa in PwHA below the age of 12 years.

6.1.1.3 HAVEN III (NCT02847637)

HAVEN III is a randomized, global, multicentre, open-label, Phase 3 clinical study in participants with severe haemophilia A without inhibitors against Factor VIII (FVIII) who are 12 years or older. The study evaluates two prophylactic emicizumab regimens versus no prophylaxis in this population with emphasis on efficacy, safety, and pharmacokinetics (Mahlangu et al. 2018b).

Random assignment was applied where, in a 2:2:1 ratio, participants 12 years of age or older who had been receiving episodic treatment with factor VIII to receive a subcutaneous maintenance dose of emicizumab of 1.5 mg per kilogram of body weight per week (group A) or 3.0 mg per kilogram every 2 weeks (group B) or no prophylaxis (group C). The primary end point was the difference in rates of treated bleeding (group A vs. group C and group B vs. group C). Participants who had been receiving factor VIII prophylaxis received emicizumab at a maintenance dose of 1.5 mg per kilogram per

week (group D); intraindividual comparisons were performed in those who had participated in a noninterventional study (Mahlangu et al. 2018b).

A total of 152 participants were enrolled. The annualized bleeding rate was 1.5 events (95% confidence interval [CI], 0.9 to 2.5) in group A and 1.3 events (95% CI, 0.8 to 2.3) in group B, as compared with 38.2 events (95% CI, 22.9 to 63.8) in group C; thus, the rate was 96% lower in group A and 97% lower in group B (P<0.001 for both comparisons). A total of 56% of the participants in group A and 60% of those in group B had no treated bleeding events, as compared with those in group C, who all had treated bleeding events. In the intraindividual comparison involving 48 participants, emicizumab prophylaxis resulted in an annualized bleeding rate that was 68% lower than the rate with previous factor VIII prophylaxis (P<0.001). The most frequent adverse event was low-grade injection-site reaction. There were no thrombotic or thrombotic microangiopathy events, development of antidrug antibodies, or new development of factor VIII inhibitors (Mahlangu et al. 2018b).

For the purposes of the comparison between efanesoctocog alfa and emicizumab, [redacted]

Table 13 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
XTEND-1 NCT04161495 (von Drygalski et al. 2023b)	Multicentre, open-label, non-randomized, controlled, phase 3-trial	52 weeks	The patient population consisted of previously treated people aged ≥12 years with severe haemophilia A. Eligibility criteria were severe haemophilia A, defined as <1 IU/dL (<1%) endogenous FVIII or a documented genotype known to produce severe haemophilia A, and had received previous treatment for haemophilia A including any recombinant and/or plasma-derived FVIII product, or cryoprecipitate for at least 150 exposure days.	Arm A: prophylaxis, efanesoctocog alfa (n=133), 50 IU/kg, once weekly, up to 52 weeks Arm B: on-demand, then prophylaxis, efanesoctocog alfa (n=26), 50 IU/kg as needed for treatment of bleeding episodes from week 1 to week 26. At week 26, participants switched to prophylaxis treatment, 50 IU/kg, once weekly, until week 52	NA	See Appendix A
XTEND-kids NCT04759131 (ClinicalTrials.gov 2023b)	Multicentre, open-label, single-arm, phase 3-trial	52 weeks	The patient population consisted of previously treated patients aged <12 years with severe haemophilia A defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia A. Previous	The eligible participants received efanesoctocog alfa at a dose of 50 IU/kg IV once weekly for 52 weeks.	NA	See Appendix A

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			treatment of haemophilia A (prophylaxis or on-demand) was defined as any recombinant and/or plasma-derived FVIII replacement product, or cryoprecipitate for at least 150 exposure days for patients aged 6 to <12 years and for at least 50 exposure days for patients aged <6 years.			
HAVEN III NCT02847637 (Mahlangu et al. 2018b) (Kiialainen et al. 2019)	Randomized, multicentre, open-label, phase 3-trial	24 weeks	Eligible participants were 12 years of age or older with severe congenital haemophilia A (endogenous factor VIII activity, <1%), without current factor VIII inhibitors (<0.6 Bethesda units per milliliter), who were receiving episodic or prophylactic factor VIII infusions.	Subcutaneous maintenance dose of emicizumab of 1.5 mg per kilogram of body weight per week (group A) or 3.0 mg per kilogram every 2 weeks (group B) or no prophylaxis (group C) Participants who had been receiving factor VIII prophylaxis received emicizumab at a maintenance dose of 1.5 mg per kilogram per week (group D)	NA	See Appendix A

Abbreviations: FVIII, Factor 8; IU, International unit; NA, Not applicable.

6.1.2 Comparability of studies

The differences between the included studies and the method used to address these are presented in Section 7.

6.1.2.1 Comparability of patients across studies

Unadjusted data for XTEND-1 arm A and HAVEN III group D (the studies included in the ITC) are presented in Table 14 as well as XTEND-1 arm A data after matching. The method employed for the matching procedure is presented in Section 7.

Table 14: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (XTEND-1 arm A before and after matching to HAVEN III group D)

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

Abbreviations: ESS – Effective sample size, pts – patients, SD – Standard deviation, TJ – Target joint

Sources: (Kiialainen et al. 2019, Mahlangu et al. 2018b, von Drygalski et al. 2023b)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The economic model only includes body weight as a population parameter. The economic evaluation assumes a body weight of 75 kg to be representative of the Danish patient population. This bodyweight was found in a study by Funding et al. (Funding et al. 2023) and is in line with the Statens Institut for Folkesundhed data on bodyweight (SDU Dk 2024).

Table 15 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Patient body weight	75 (SDU Dk 2024)	75

6.1.4 Efficacy – results per XTEND-1

As described in section 3.7, following the analysis of the primary efficacy endpoint (ABR in Arm A) of XTEND-1, the key secondary endpoint (i.e. intra-patient comparison of efanesoctocog alfa versus prestudy FVIII prophylaxis [non-inferiority followed by superiority]), and the 3 selected secondary endpoints (Haem-A-QoL Physical Health, PROMIS Pain intensity 3a [past 7 days intensity of pain at its worst score], and HJHS total score) were analysed as part of a hierarchical testing procedure. The primary and key selected secondary efficacy endpoints were all met, thus demonstrating efficacy of efanesoctocog alfa prophylaxis in prevention of bleeds. Protection compared to standard of care prestudy FVIII prophylaxis was superior, with statistically significant and clinically meaningful improvement in physical functioning, pain, intensity, and joint health. Results for the primary and secondary endpoints with multiplicity adjustment, presented according to the hierarchical testing order, are summarized in Table 16.

There are two treatment arms in the XTEND-1 study; Arm A are pretreated with FVIII prophylaxis, whereas Arm B had a history of on-demand FVIII treatment. As the majority of patients with severe haemophilia A in the Nordics are treated with FVIII prophylaxis, only the results of Arm A are presented here. Results for patients in Arm A are also used in the MAIC vs the comparator (emicizumab).

Table 16: Results of the primary and secondary efficacy endpoints analysed as part of the hierarchical testing procedure demonstrating efficacy of efanesoctocog alfa

Outcome			
Primary endpoint		Arm A (N=133)	
ABR	Total number of treated bleeding episodes	86	
	Total participant-years followed	121.2	
	Mean ABR (SD)	0.71 (1.43)	
	Mean ABR, model based [a]	0.71	
	(95% CI)	(0.52; 0.97)	
Key secondary endpoint (hierarchical testing procedure)		Arm A	
Intra-participant comparison of ABR between efanesoctocog alfa prophylaxis and prestudy FVIII prophylaxis: non-inferiority analysis based on PPS	Comparison groups	**Historical prophylaxis (OBS16221) (N=77)**	**Efanesoctocog alfa prophylaxis (EFC16293) (N=77)**
	Mean ABR (95% CI) [b]	2.99 (2.03; 4.42)	0.69 (0.43; 1.12)
	Mean difference (95% CI) [b]		-2.30 (-3.49; -1.11)

Intra-participant comparison of ABR between efanesoctocog alfa prophylaxis and prestudy FVIII prophylaxis: superiority analysis based on FAS	Comparison groups	Historical Prophylaxis (OBS16221) (N=78)	Efanesoctocog alfa Prophylaxis (EFC16293) (N=78)
	Mean ABR (95% CI) [b]	2.96 (2.00; 4.37)	0.69 (0.43; 1.11)
	Rate ratio (95% CI) [b]		0.23 (0.13; 0.42)
	p-value (superiority) [c]		<0.0001
Physical functioning and pain (QoL)			
Secondary endpoints analysed as part of the hierarchical testing procedure		**Arm A (N=133)**	
Haem-A-QoL Physical Health	Baseline: mean (SD), number	37.02 (23.83), n=104	
	Week 52: mean (SD), number	29.66 (23.40), n=104	
	Change from B to Week 52:		
	Mean (SD), number	-6.79 (18.59), n=98	
	LS Mean (SE) [d]	-6.74 (1.71)	
	95% CI	(-10.13, -3.36)	
	p-value	0.0001	
PROMIS Pain Intensity 3a past 7 daysintensity of pain at its worst score	Baseline: mean (SD), number	2.47 (1.15), n=125	
	Week 52: mean (SD), number	2.21 (1.21), n=127	
	Change from B to Week 52		
	Mean (SD), number	-0.21 (1.20), n=119	
	LS Mean (SE) [d]	-0.21 (0.10)	
	95% CI	(-0.41, -0.02)	
	p-value	0.0276	
Joint health			
Secondary endpoint analysed as part of the hierarchical testing procedure		**Arm A (N=133)**	
HJHS total score	Baseline: mean (SD), number	18.1 (18.4), n=116	
	Week 52: mean (SD), number	16.5 (17.6), n=110	
	Change from B to Week 52:		
	Mean (SD), number	-1.5 (6.4), n=107	
	LS Mean (SE) [d]	-1.54 (0.59)	
	95% CI	(-2.70, -0.37)	
	p-value	0.0101	

[a] Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.

[b] Estimated using a negative binomial regression model with treatment (Efanesoctocog alfa prophylaxis vs historical prophylaxis) as covariate.

[c] P-value relates to the null hypothesis:rate ratio (Efanesoctocog alfa prophylaxis/historical prophylaxis) =1.

[d] The LS mean (SE) and 95% CI are estimated by mixed-effect model with repeated measures (MMRM) with visit as fixed effect, and baseline score as covariate.

Abbreviations: ABR; Annualised bleeding rate; CI, Confidence interval; FAS, Full analysis set; FVIII, Factor 8; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; HJHS, Haemophilia joint health score; LS, Least square; PPS, Per protocol set; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, Quality of life; SD, Standard deviation; SE, Standard error.

6.1.4.1 Annualised bleeding rate (ABR)

In Arm A, weekly prophylaxis with efanesoctocog alfa provided highly effective protection against bleeds and a clinically meaningful effect during a mean (SD) treatment period of 47.55 (8.77) weeks (Table 17) (von Drygalski et al. 2023b). The estimated mean ABR was 0.71 (95% CI: 0.52, 0.97) and the primary endpoint was met.

The estimated mean ABR was 0.26 (95% CI: 0.11; 0.57) in participants aged 12–17 years, 0.84 (95% CI: 0.60; 1.17) in participants 18–64 years, and 0.34 (95% CI: 0.05; 2.38) in participants ≥65 years. Overall, ABRs were consistently low with efanesoctocog alfa weekly prophylaxis across type and location of bleeding – 80.4% of patients had an ABR of zero for spontaneous bleeds and 72.2% of patients had an AjBR of zero during the study.

Table 17: Efanesoctocog alfa prophylaxis: ABR at Week 52 (primary endpoint)

Efanesoctocog alfa weekly prophylaxis and ABR	Arm A, n=133
Median ABR (SD)	0 (0–1.04)
Mean ABR, model based (95% CI)[a]	0.71 (0.52, 0.97)
Zero bleeding episodes	86 (65%)[b]

ABR, annualized bleed rate; SD, standard deviation; CI, confidence interval

[a]The mean ABR was estimated with the use of a negative-binomial model, with the total number of treated bleeding episodes during the efficacy period as the response variable and the log-transformed duration of the efficacy period (in years) as an offset variable.

[b]The median duration of administration of efanesoctocog alfa was 53.0 weeks (range, 2 to 63)

Abbreviations: ABR, Annualised bleeding rate; CI, Confidence interval; SD, Standard deviation.

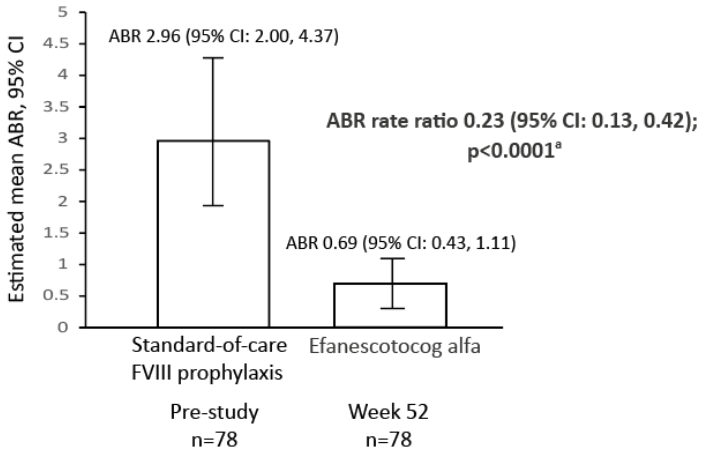
Source: (von Drygalski et al. 2023b)

Among 133 PwHA who received efanesoctocog alfa prophylaxis, 96 (72.2%) had no joint bleeds. During the study, the mean AjBR was 0.51 (95% CI: 0.36, 0.72). The improvements in AjBR and target joint resolution suggested an improvement of joint health (von Drygalski et al. 2023b).

6.1.4.2 Intra-participant comparison of ABR

The intra-patient analysis included 78 PwHA who participated in a pre-study with ≥6 months efficacy data on standard-of-care FVIII prophylaxis. In intra-patient comparison (n=78), during 12 months before efanesoctocog alfa prophylaxis in the pre-study, the mean (SD) number of bleeding episodes was 3.2 (5.4) (von Drygalski et al. 2023a). 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% (Figure 9). The ABR rate ratio showed superiority over standard-of-care FVIII prophylaxis, at 0.23 (95% CI, 0.13, 0.42; p<0.001).

Figure 9: Efanesoctocog alfa prophylaxis versus standard-of-care FVIII: intra-patient comparison of estimated mean ABR



[a]Estimated using a negative binomial regression model with efanescotocog alfa prophylaxis versus historical prophylaxis as covariate

ABR, annualized bleeding rate; CI, confidence interval

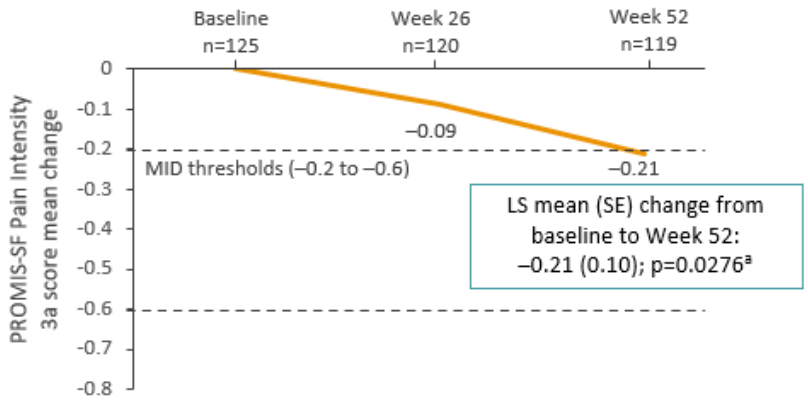
Abbreviations: ABR, Annualised bleeding rate; CI, Confidence interval; FVIII, Factor 8.

Source: (von Drygalski et al. 2023b)

6.1.4.3 PROMIS Pain Intensity 3a past 7 days

In Arm A (n=125), at baseline, the worst pain intensity in the past 7 days, measured using PROMIS-SF, was scored as at least moderate pain by 53.6% of participants (Wilson et al. 2022b). In participants aged ≥12 years (n=119), there was a significant improvement in Pain Intensity 3a first item score between baseline and Week 52 (Figure 10). The estimated mean Pain Intensity 3a first item score was -0.21 (95% CI: -0.41, -0.02; p=0.0276).

Figure 10: PROMIS-SF Pain Intensity 3a first item score at baseline and Week 52 (Arm A)



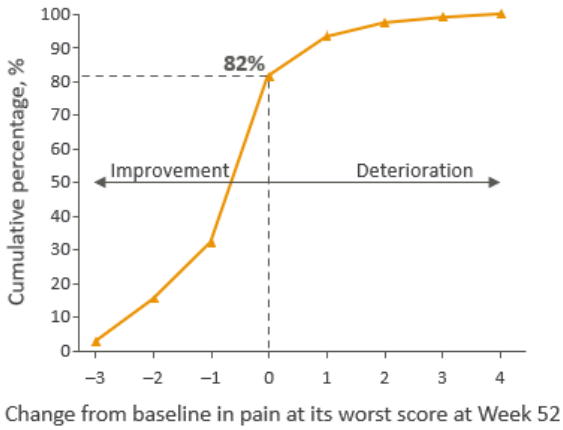
[a]The LS mean (SE) and 95% CI were estimated by mixed-effect model with repeated measures and visit as fixed effects, and baseline pain intensity score as covariate.

Abbreviations: CI, Confidence interval; LS, Least square; MID, Minimally important difference; PROMIS, Patient-Reported Outcomes Measurement Information System ; SE, Standard error; SF, Short form.

Source: (Sobi 2022)

Most participants (81.5%; 97/119) reported numeric improvement or maintained (change from baseline ≤0) pain intensity at Week 52 (Figure 11). More participants reported feeling no pain (37%) at Week 52 compared with baseline (29%).

Figure 11: PROMIS-SF Pain Intensity 3a first item scores: cumulative percentage of participants by change in score between baseline and Week 52 (Arm A)

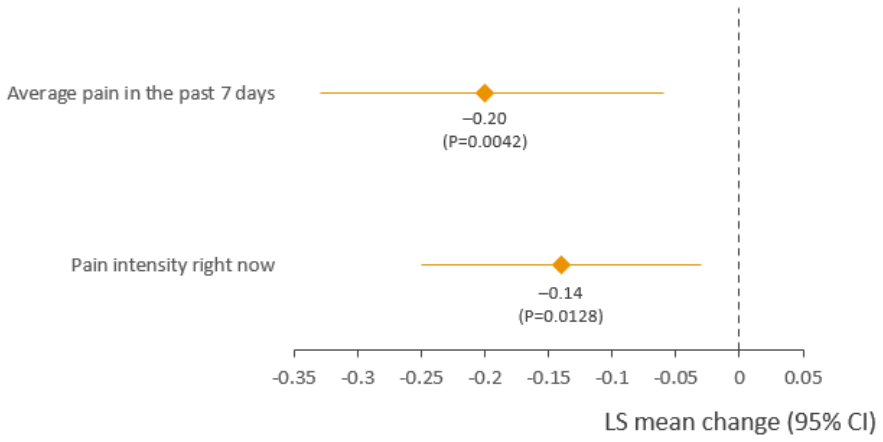


Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System; SF, Short form

Source: (Sobi 2022)

The Pain Intensity 3a total score changed from baseline to Week 52 in Arm A, with a LS mean of -1.94 (95% CI: -3.26, 0.63; p=0.0042). There were significant improvements between baseline and Week 52 for average pain intensity in the past 7 days and for pain right now (Figure 12).

Figure 12: Change in PROMIS-SF Pain Intensity LS means from baseline to Week 52 (Arm A)

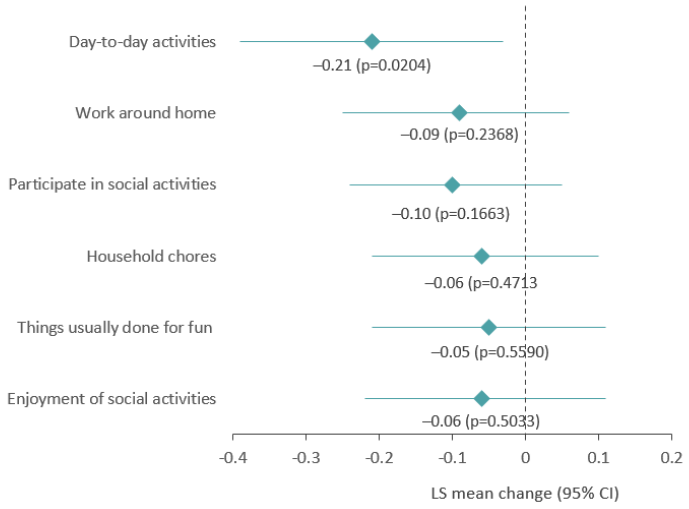


Abbreviations: CI, Confidence interval; LS, Least square; PROMIS, Patient-Reported Outcomes Measurement Information System ; SF, Short form

Source: (Sobi 2022)

In Arm A, 103 and 102 participants, respectively, completed the PROMIS-SF Physical Function questionnaire at baseline and at Week 52, and the mean (SD) score was 46.80 (8.82) at baseline and 47.35 (9.28) at Week 52. In participants aged ≥18 years, from baseline to Week 52, the Pain Interference 6a total score changed by -1.25 (6.90); LS mean change -1.16 (95% CI: -2.45, -0.14; p=0.0793). Of the six domains, there was a significant improvement in day-to-day activities (Figure 13).

Figure 13: Change in PROMIS-SF Pain Interference LS means from baseline to Week 52 (Arm A, aged ≥18 years)



Abbreviations: CI, Confidence interval; LS, Least square; PROMIS, Patient-Reported Outcomes Measurement Information System; SF, Short form

Source: (Sobi 2022)

6.1.4.4 HJHS total score

In Arm A, there was a significant improvement in HJHS from baseline to Week 52. The mean (SD) HJHS Total score at baseline was 18.1 (18.4), with an estimated mean change in HJHS Total score from baseline to Week 52 of -1.54 (95% CI: -2.70, -0.37; p=0.01). The domains of the HJHS with the greatest improvement from baseline to Week 52 were swelling, muscle atrophy, crepitus on motion, and flexion loss (von Drygalski et al. 2023b).

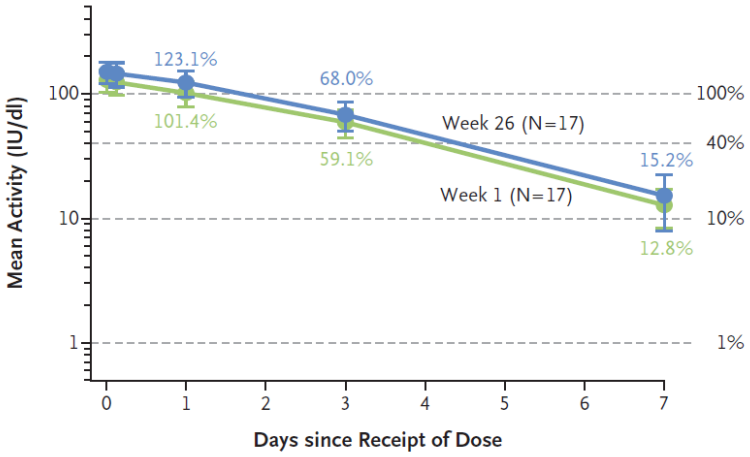
6.1.4.5 Trough FVIII levels and elimination plasma half-life

In the XTEND-1 study, the mean FVIII level was >40 IU/dL for 3 to 4 days after dosing, and was 15.2 IU/dL at the end of the 7-day dosing interval, showing that FVIII activity remains at protective levels in most participants for the full week.

A total of 17 participants who received efanesoctocog alfa prophylaxis in Arm A were included in the sequential PK subgroup analysis after approximately 26 weeks treatment (von Drygalski et al. 2023b). A single efanesoctocog alfa dose of 50 IU/kg resulted in mean FVIII activity in the normal to near-normal range (>40 IU/dL) for 3 to 4 days and mean FVIII activity of 15.2% at the end of the 7-day dosing interval (Figure 14) The geometric mean half-life was 47.0 hours (95% CI, 42.3 to 52.2), the steady state clearance 0.439 ml per hour per kilogram (95% CI, 0.390 to 0.493), the maximum factor VIII activity 151 IU/dL (95% CI: 137 to 167), and

the AUC was 11,500 h × IU/dL (95% CI, 10,200, 13,000). There was minimal accumulation of once-weekly efanesoctocog alfa.

Figure 14: Sequential PK analysis: FVIII level



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)

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 participants who underwent sequential blood sampling for pharmacokinetic assessment (sequential-pharmacokinetic subgroup). Bars indicate standard deviations. 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_{0-tau}, Area under the plasma FVIII activity versus time curve; CI, Confidence interval; FVIII, Factor 8; IU, International unit; PK, Pharmacokinetic.

Source: (von Drygalski et al. 2023b)

6.1.5 Efficacy – results per XTEND-Kids

XTEND-kids is not included in the [redacted] vs emicizumab. However, it serves as evidence of efficacy and safety in the patient population below 12 years of age.

In summary, similar to XTEND-1, once weekly efanesoctocog alfa maintained FVIII levels in the normal to near normal range for a significant part of the week and provided a clinically meaningful bleed control. Also, efanesoctocog alfa prophylaxis provided high protection from joint bleeds, leading to resolution of target joints. It was associated with stability in joint health and improved physical function, with positive implications for HRQoL.

Details of the efficacy outcomes of the XTEND-kids are presented in Appendix B.2.1.

6.1.6 Efficacy – results per HAVEN III

Haemophilia joint health scores (HJHS; v2.1) were evaluated at baseline and Weeks 49 and 97 in PwHA receiving emicizumab (n = 134), and at baseline and Weeks 49, 73 and 97 in PwHA who switched to emicizumab after 24 weeks of no prophylaxis (n = 17). Bone and joint biomarkers were measured in 117 PwHA at baseline and at Weeks 13, 25, 49 and 73. HJHS was lower for PwHA who were previously on FVIII prophylaxis, aged <40 years or had no target joints at baseline compared with PwHA who were receiving no prophylaxis, aged ≥40 years or with target joints. Clinically significant mean (95% confidence interval) improvements from baseline of -2.13 (-3.96, -.29) in HJHS joint-specific domains were observed at Week 49 in PwHA with at least one target joint at study entry (n = 71); these changes were maintained through Week 97. Improvements in HJHS from baseline were also observed for PwHA aged 12-39 years. Biomarkers of bone resorption/formation, cartilage degradation/synthesis, and inflammation did not change significantly during emicizumab prophylaxis (Kiialainen et al. 2019).

The annualized bleeding rate was 1.5 events (0.9, 2.5) in group A and 1.3 events (0.8, 2.3) in group B, as compared with 38.2 events (22.9, 63.8) in group C; thus, the rate was 96% lower in group A and 97% lower in group B (P<0.001 for both comparisons). A total of 56% of the participants in group A and 60% of those in group B had no treated bleeding events, as compared with those in group C, who all had treated bleeding events. In the intraindividual comparison involving 48 participants, emicizumab prophylaxis resulted in an annualized bleeding rate that was 68% lower than the rate with previous factor VIII prophylaxis (P<0.001). The most frequent adverse event was low-grade injection-site reaction. There were no thrombotic or thrombotic microangiopathy events, development of antidrug antibodies, or new development of factor VIII inhibitors (Mahlangu et al. 2018b).

Only group D of the HAVEN III trials consisted of a patient population with prior FVIII prophylaxis and was thus comparable to that of XTEND-1 Arm A. Hence, for the purposes of the indirect comparison between efanesoctocog alfa and emicizumab, results from Group A and Group B are not used (see section 7).

Table 18. Outcomes for HAVEN III

Characteristics	HAVEN III Group D
N	63
Follow-up time, mean (weeks)	Median duration: 33.7
ABR, mean (95%CI)	3.3 (2.2, 4.8)

ABR treated, mean (95%CI)	1.6 (1.1-2.4)
AsBR treated, mean (95%CI)	0.5 (0.2-0.9)
AjBR treated, mean (95%CI)	1.2 (0.7-2.0)
No any bleeds, n (%)	(44.4)
No treated bleeds, n (%)	(55.6)
No spontaneous treated bleeds, n (%)	(82.5)
No joint treated bleeds, n (%)	(68.3)
Haem-A-QoL Change in total score from baseline, mean (95%CI)	-
Haem-A-QoL Change in physical health score from baseline, mean (95%CI)	-
HJHS Change in total score from baseline, mean (95%CI)	-
HJHS Change in joint score from baseline, mean (95%CI)	-

Abbreviations: ABR – Annualized bleeding rate, AsBR – Annualized spontaneous bleeding rate, AjBR – Annualized joint bleeding rate; CI, Confidence interval; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; HJHS, Haemophilia joint health score.

7. Comparative analyses of efficacy

The main objective of the indirect comparison was to compare efficacy of prophylactic treatment with efanesoctocog alfa versus emicizumab. The analysis was primarily focused on patients without inhibitors who had previously been receiving prophylactic regimens, which was consistent with the expected patient population in Denmark, as well as the inclusion criteria for the Arm A of the XTEND-1 trial for efanesoctocog alfa.

The pivotal trial assessing efanesoctocog alfa was XTEND-1 designed as 2-arm, parallel-design, open-label, multicentre, non-randomised trial to determine the efficacy of efanesoctocog alfa as a prophylaxis treatment in patients 12 years or older with severe haemophilia A without inhibitors and with prior prophylactic or on demand treatment.

The comparator trial was a randomized multi-arm trial, which evaluated two prophylactic emicizumab regimens versus no prophylaxis in patients 12 years or older with severe haemophilia A without inhibitors against FVIII and with prior prophylactic or on demand treatment.

The XTEND-1 trial did not allow to form connected networks with the comparator trial, therefore an anchored comparison using either Bucher's indirect comparison or network meta-analysis was not feasible for the comparison between efanesoctocog alfa and

emicizumab. The relative efficacy in the disconnected studies was instead assessed using unanchored matching-adjusted indirect comparison (MAIC) as proposed in the NICE TSD 18 guidelines (Phillippo et al. 2016).

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.

One trial for emicizumab (HAVEN III (Kiialainen et al. 2019, Mahlangu et al. 2018a)) and one trial for efanesoctocog alfa (XTEND-1) in adolescent/adult patients with haemophilia A without inhibitors were included in the analysis. The comparison between efanesoctocog alfa and the comparator trial is feasible due to reporting from XTEND-1 trial for patients with prior prophylaxis (arm A), and the efanesoctocog alfa effects could be estimated using the same statistical methods as adopted in the comparator trial due to availability of Individual Patient Data (IPD) from XTEND-1 trial.

7.1.1 Differences in definitions of outcomes between studies

The definitions for bleeding events/episodes were reported for HAVEN III [emicizumab]. This trial applied the 72-hour rule, the same as the XTEND-1 trial. Bleeding, or any symptoms of bleeding at the same location, that occurs within 72 hours of the last injection used to treat a bleeding episode at that location were considered a part of the original bleeding event, and were counted as one bleeding episode towards the ABR. Any bleeding symptoms that began more than 72 hours from the last injection used to treat a bleeding episode at that location constituted a new bleeding event.

Two commonly used methods to compare incidence rates are the incidence rate ratio (IRR) and the mean difference (MD) in the incidence rates. Both methods produce qualitatively similar estimates and statistically consistent inference but differ in the interpretation of results. IRR gives clinically interpretable results on the relative scale (treatment results in % change in risk relative to comparator), while MD gives clinically interpretable results on the absolute scale (mean change in risk) (Guevara et al. 2004).

In the MAIC analyses, the model used to estimate the bleeding rate from XTEND-1 IPD depended on the method of estimation used in the comparator study (e.g.: negative binomial, crude mean (SD)), so that the same measure was used for treatment-effect comparison. In particular, the method of bleeding rate estimation also determined the method of outcome comparison.

The rates for comparators estimated using count model (e.g. negative binomial) 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.

Negative binomial regression model was used for HAVEN III (emicizumab).

None of the studies reported ABR estimated solely with Poisson regression, thus for consistency all incidence rate ratios between efanesoctocog alfa versus emicizumab were estimated using negative binomial regression model for relevant scenarios.

Table 19: Comparison of definitions for bleeding outcomes

Trial	Bleeding-related definitions	ABR estimation	ABR reporting
Efanesoctocog alfa			
XTEND-1	• A standardized definition of a *bleeding episode* based on ISTH criteria • Bleeding episodes are classified as *spontaneous* when there is no known contributing factor, such as a definite trauma or antecedent "strenuous" activity. • Efficacy outcomes were reported for both, total and treated bleeds ABR	Negative-binomial regression model	**All bleeds**: ABR, ABR=0, AsBR, AjBR, AjBR=0 **Treated bleeds**: ABR, ABR=0, AsBR, AjBR, AjBR=0
Emicizumab			
HAVEN III	• A standardized definition of a *bleeding episode* based on ISTH criteria • *Treated bleed*: if it was directly followed by a haemophilia medication without an intervening bleed and irrespective of the time between the treatment and the preceding bleed. A bleed and the first treatment thereafter were considered to be pairs (i.e., one treatment belonged to one bleed only), with the following exception: if multiple bleeds occurred on the same calendar day, the subsequent treatment was considered to apply for each of these multiple bleeds (which were, however, counted as separate bleeds). Bleeds due to surgery/ procedure were not included in the primary analysis. • *Target joint*: a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which ≥3 bleeds occur over a 24-week period. • Efficacy outcomes were reported for both, total and treated bleeds ABR	Negative binomial-regression model including stratification factor (<9 or ≥9 bleeding events in the previous 24 weeks) and accounted for various follow-up times to determine the bleeding rate per day, which was then converted to an ABR	**All bleeds**: ABR, ABR=0 **Treated bleeds**: ABR, ABR=0, AsBR, AjBR, AjBR=0

Abbreviations: ABR, Annualised bleeding rate; AjBR, Annualised joint bleeding rate; AsBR, Annualised spontaneous bleeding rate; ISTH=International Society on Thrombosis and Haemostasis.

Additional assumptions:

* - Due to limited reporting presence of untreated bleeds could not be ruled out, thus XTEND-1 total bleeds will be used for comparison

** - 'All bleeds' (treated or not treated) was assumed based on definition from primary outcome

7.1.2 Method of synthesis

The method of synthesis is described in Appendix C.

7.1.3 Results from the comparative analysis – efanesoctocog alfa vs emicizumab Q1W (prior PHX)

7.1.3.1 Clinical data

Emicizumab Q1W was assessed in arm D of the HAVEN III trial on 63 patients with severe haemophilia, who had been receiving prophylactic treatment prior to enrolment. Based on the available publication the age of participants ranged from 13 to 68 years, while the body weight ranged from 52.8 to 139 kg.

Arm A of the XTEND-1 trial was compared with arm D of the HAVEN III study, since both cohorts recruited patients receiving prophylactic treatment prior to enrolment. Fourteen out of 133 XTEND-1 arm A participants with age and/or body weight outside the ranges reported in the corresponding HAVEN III cohort were excluded from the analysis, so that 119 patients receiving efanesoctocog alfa were finally included in the MAIC (Table 20).

Table 20 Pre-selection of XTEND-1 patients with comparable baseline characteristics

Arm of the HAVEN III trial	Range of baseline variables		XTEND-1 IPD			
	Age (years)	Body weight (kg)	Arm (N)	Age (years)	Body weight (kg)	Patients remaining after restrictions (N)
ARM D (prior PHX)	13-68	52.8-139	Arm A (133)	12-72	33.9-132.8	119

Abbreviations: IPD, Individual patient data; PHX, Prophylaxis.

7.1.3.2 Matching of baseline characteristics

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 1 target joint, and
    - Proportion of patients with 2+ 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 was reduced from 119 to 76 patients following matching, which corresponds to 64% of the initial sample (Table 21).

Table 21 Matching of baseline characteristics between XTEND-1 arm A and HAVEN III arm D

Variables	XTEND-1 arm A baseline			HAVEN III 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 w/ 0 TJ	78.2%	n/a		58.7%	n/a	58.7%	n/a		
% pts w/ 1 TJ	5.9%			12.7%	n/a	12.7%			
% pts w/ 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, pts – patients, SD – Standard deviation, TJ – Target joint

7.1.3.3 Outcomes

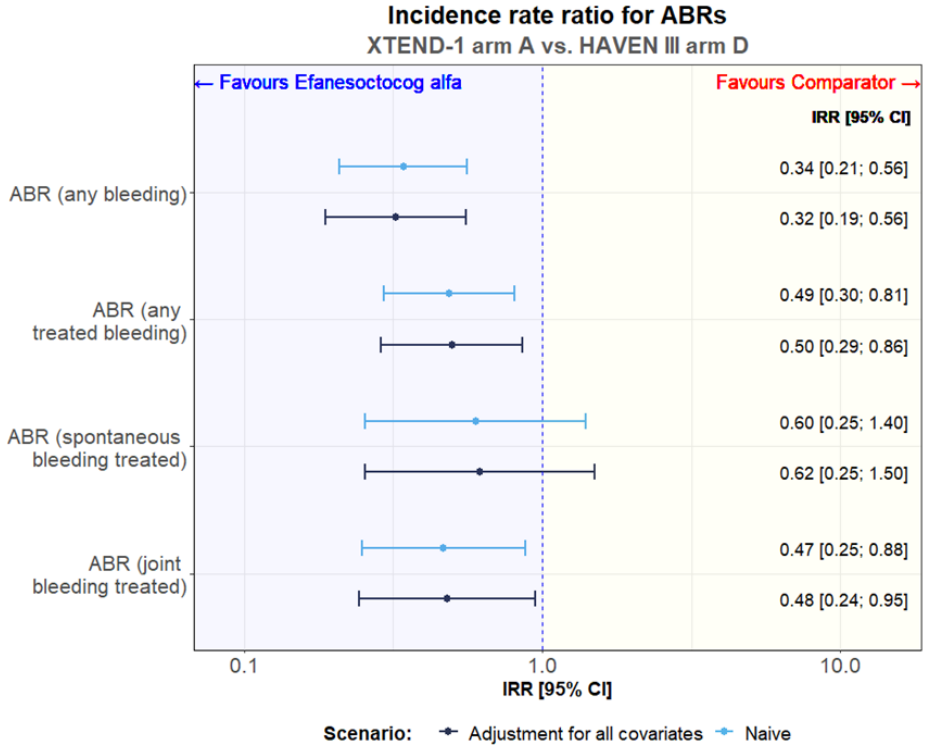
The comparison between prophylactic regimens of efanesoctocog alfa and emicizumab Q1W in patients receiving prior prophylactic was feasible for the ABRs for:

- any bleeding episodes (treated and untreated),
- treated bleeding episodes,
- spontaneous treated bleeding episodes, and
- joint treated bleeding episodes.

All ABRs in HAVEN III 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.

Efanesoctocog alfa compared to emicizumab Q1W (prior PHX) was associated with significantly lower rate of any bleeding (treated and untreated), any treated bleeding, and joint treated bleeding. There was no evidence for significant differences regarding frequency of treated spontaneous bleeding (Figure 15).

Figure 15 Comparison of ABRs between efanesoctocog alfa and emicizumab Q1W



Abbreviations: ABR – Annualized bleeding rate, CI – Confidence interval, IRR – Incidence rate ratio

7.1.3.4 Summary of the results from the comparative analysis

The comparison was conducted versus the following regimen in the HAVEN III trial:

- Emicizumab once weekly (EMI Q1W) in patients receiving prior prophylaxis (PHX)

Efanesoctocog alfa was associated with significantly lower incidence of any bleeds (treated and untreated) compared with EMI Q1W prior PHX. The results for ABR (any treated bleeding) and ABR (joint treated bleeding) versus EMI Q1W prior PHX were also statistically significant (Table 22, Table 23).

The comparison regarding the proportion of patients without bleeds during the follow-up was not attempted due to different observation periods between XTEND-1 (arm A: 52w) and HAVEN III (group D on prior PHX: 33.7w) studies.

Table 22 Summary of the results from the comparative analysis of efanesoctocog alfa vs. emicizumab for adult patients without inhibitors and prior prophylaxis

Results for comparison between efanesoctocog alfa *versus* emicizumab (HAVEN III)	
Endpoint	***vs.* EMI Q1W (prior PHX)**
ABR (any bleeding) (IRR)	**0.32 [0.19; 0.56]**
ABR (any treated bleeding) (IRR)	**0.50 [0.29; 0.86]**
ABR (spontaneous treated bleeding) (IRR)	0.62 [0.25; 1.50]
ABR (joint treated bleeding) (IRR)	**0.48 [0.24; 0.95]**

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

Abbreviations: ABR – Annualized Bleeding Rate, EMI – Emicizumab, HJHS - Haemophilia Joint Health Score, O-D – on-demand, PHX – prophylaxis, QxW – every x week, IRR – Incidence rate ratio, MD – Mean difference

Table 23 Results from the comparative analysis of efanesoctocog alfa vs. emicizumab for adult patients without inhibitors and prior prophylaxis

Outcome measure	Efanesoctocog alfa (N=133) 52 weeks	Emicizumab once weekly (N=48) 33.7 weeks	Results, IRR (95% CI), naive comparison	Results, IRR (95% CI), adjusted for all covariates
ABR (any bleeding), mean (95% CI)	1.11 (0.83, 1.48)[a]	3.3 (2.2, 4.8)[b]	0.34 (0.21, 0.56)	0.32 (0.19, 0.56)
ABR (any treated bleeding) , mean (95% CI)	0.71 (0.52, 0.97)[a]	1.6 (1.1, 2.4)[b]	0.49 (0.30, 0.81)	0.50 (0.29, 0.86)
ABR (spontaneous treated bleeding) , mean (95% CI)	0.27 (0.18, 0.41)[a]	0.5 (0.2, 0.9)[b]	0.60 (0.25, 1.40)	0.62 (0.25, 1.50)
ABR (joint treated bleeding) , mean (95% CI)	0.51 (0.36, 0.72)[a]	1.2 (0.7, 2.0)[b]	0.47 (0.25, 0.88)	0.48 (0.24, 0.95)

[a]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.

[b]The annualized bleeding rate was calculated with the use of a negative binomial-regression model.

Abbreviations: ABR – Annualized Bleeding Rate, CI – Confidence interval, EMI – Emicizumab, HJHS - Haemophilia Joint Health Score, O-D – on-demand, PHX – prophylaxis, QxW – every x week, IRR – Incidence rate ratio, MD – Mean difference, SD – Standard deviation.

Sources: (Sobi 2022, Mahlangu et al. 2018a)

7.1.3.5 Limitations of the analyses

The objective of this analysis was to compare efficacy between efanesoctocog alfa and emicizumab. The comparison was based on the results of the pivotal XTEND-1 trial, which did not form evidence connections with the HAVEN III trial assessing emicizumab. Therefore, to minimise the risk of bias associated with imbalanced effect modifiers and prognostic factors across studies, a population-adjusted comparison using MAIC was used, as recommended by the NICE DSU guidelines.

The unanchored comparisons are inherently associated with several 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 trial, since the matching can be carried out only against reported aggregated data.

The credibility of MAIC depends also on the similarity of populations across trials, since insufficient overlapping of baseline characteristics lead to a massive loss of information expressed with a huge drop in effective sample size. As a consequence, the estimates drawn based on very small amount of data may not be reliable. In this analysis the effective sample for most of the analyses did not drop below 50% of initial sample, which can be considered as acceptable compared to other published analyses in which 80% drop of effective sample size was not infrequent (Phillippo et al. 2016).

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

[redacted]

8.1.1.1 Extrapolation of [effect measure 1]

[redacted]

Table 24 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	[redacted]

8.1.2 Calculation of transition probabilities

[redacted]

Table 25 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence		
	Death		

8.2 Presentation of efficacy data from [additional documentation]

[redacted]

8.3 Modelling effects of subsequent treatments

[redacted]

8.4 Other assumptions regarding efficacy in the model

[redacted]

8.5 Overview of modelled average treatment length and time in model health state

[redacted]

Table 26 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	[redacted]	[redacted]	[redacted]
[Name of comparator]	[redacted]	[redacted]	[redacted]

Table 27 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
[Intervention]	XXXX	XXXX	XXXX
[Comparator]	XXXX	XXXX	XXXX

9. Safety

9.1 Safety data from the clinical documentation

XTEND-1 (arm A)

Inhibitor development to FVIII was not detected, and there were no reports of serious allergic reactions, anaphylaxis, or vascular thrombotic events (von Drygalski et al. 2023b). By Nijmegen-modified Bethesda assay, among participants with ≥50 exposure days to efanesoctocog alfa, the incidence of inhibitor development to FVIII was 0.0% (95% CI: 0.0, 3.3).

A total of 11 participants (7%) were positive for pre-existing antidrug antibodies before receiving efanesoctocog alfa, with no discernible effect on any PK variable that was assessed in comparison with the antibody-negative population on day 1 of the study. During the study, transient antidrug antibodies developed in 4 participants (3%). In all 4 cases there was no effect observed during the study on the PK profile, the pattern of bleeding, or the clinical efficacy.

Among 133 participants in the Safety Analysis Set, 108 (81.2%) reported 394 TEAEs. Two (1.3%) participants discontinued treatment due to a TEAE (Table 28). The most frequently reported (>3% of participants overall) TEAEs were: headache (n=32, 20.1%), arthralgia (n=26, 16.4%), fall (n=10, 6.3%), back pain (n=9, 5.7%), COVID-19 and fatigue

(n=7, 4.4%, each), contusion, haemophilic arthropathy, and nasopharyngitis (n=6, 3.8% each), and joint injury, pain in extremity and toothache (n=5, 3.1%, each).

Common TEAEs (>10%) by SOC were musculoskeletal and connective tissue disorders (n=56, 35.2%), nervous system disorders (n=43, 27.0%), injury, poisoning and procedural complications (n=30, 18.9%), infections and infestations (n=34, 21.4%), general disorders and administration site conditions (n=20, 12.6%), gastrointestinal disorders (n=22, 13.8%), and investigations (n=18, 11.3%). Of the 133 patients, TESAEs were reported in 13 (9.8%) participants.

HAVEN III (group D)

For emicizumab, 236 TEAEs occurred in the 63 patients in HAVEN III group D. The most common event was injection-site reactions (32% of patients). Number of TESAEs was 10, and no patients discontinued treatment due to AEs. No new factor VIII inhibitors developed in participants receiving emicizumab (Mahlangu et al. 2018b).

XTEND-kids

In general, the safety profile of efanesoctocog alfa was similar in XTEND-kids to XTEND-1. As XTEND-kids is not included in the comparative efficacy analysis vs emicizumab, detailed safety data is not presented here but in Appendix B.2.2.

Table 28 Overview of safety events*

	Efanesoctocog alfa (N=74) (XTEND-kids)	Efanesoctocog alfa (N=133) (XTEND-1 Arm A)	Emicizumab (N=63) (HAVEN III group D)	Difference, % (95 % CI)
Number of adverse events, n	255	358	236	NA
Number and proportion of patients with ≥1 adverse events, n (%)	62 (83.8)	108 (81.2)	Not available	NA
Number of serious adverse events, n	10	16	10	NA
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	9 (12.2)	13 (9.8)	Not available	NA
Number of CTCAE grade ≥ 3 events, n	Not available	Not available	Not available	NA
Number and proportion of patients with ≥ 1	Not available	Not available	Not available	NA

	Efanesoctocog alfa (N=74) (XTEND-kids)	Efanesoctocog alfa (N=133) (XTEND-1 Arm A)	Emicizumab (N=63) (HAVEN III group D)	Difference, % (95 % CI)
CTCAE grade 3 events, n (%)				
Number of adverse reactions, n	Not available	Not available	Not available	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	3 (4.1)	8 (6.0)	Not available	NA
Number and proportion of patients who had a dose reduction, n (%)	Not available	Not available	None (4 patients had dose increased to 3.0 mg weekly)	NA
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	2 (2.7)	9 (6.7)	0	NA
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	0	2 (1.5%)	0	NA

*For efanesoctocog alfa, assessment was made at 52 weeks. Median (range) exposure time for emicizumab group D was 33.1 weeks (18.0–48.1) (Mahlangu et al. 2018b)

Note: Between-group differences were calculated between XTEND-1 (Arm A) and HAVEN III (group D)

Abbreviations: CI, Confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; NA, Not applicable.

There were few TESAEs reported in XTEND-1 and HAVEN III. In XTEND-1 (arm A), haemophilic arthropathy was reported in 2 (1.3%) participants and all other TESAEs were reported in 1 (0.8%) patient each (Appendix E) (Sobi 2022). Due to the low frequence, no events are reported for XTEND-1 in Table 29. The majority of TESAEs were assessed by the Investigator as mild to moderate in severity and not related to efanesoctocog alfa. Also for HAVEN III (group D), the number of TESAEs was low, however bleedings occurred in ≥ 5% patients and is therefore reported in Table 29 (Mahlangu et al. 2018b).

Table 29 Serious adverse events in XTEND-1 and HAVEN III with frequency ≥ 5%*

Adverse events	Efanesoctocog alfa (N=133) (XTEND-1 Arm A)		Emicizumab (N=63) (HAVEN III)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Bleeding, n (%)	-	-	4 (6.3)	Not reported

* For efanesoctocog alfa, assessment was made at 52 weeks (Sobi 2022). Median (range) exposure time for emicizumab group D was 33.1 weeks (18.0–48.1) (Mahlangu et al. 2018b)

Safety data is not used in the health economic model as TESAEs are few and relatively mild for both efanesoctocog alfa and emicizumab. Therefore, Table 30 is left blank.

Table 30 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)	NA	NA	NA	NA
[Add a new row for each adverse event included in the model]	NA	NA	NA	NA

Abbreviations: NA, Not applicable.

9.2 Safety data from external literature applied in the health economic model

[redacted]

Table 31 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	NA	NA	NA	NA	NA	NA	NA	NA

10. Documentation of health-related quality of life (HRQoL)

[redacted]

Table 32 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	XTEND-1	Exploratory
Haem-A-QoL	XTEND-1 (patients aged ≥17 years)	Clinical effectiveness
Haemo-QoL Kids short version	XTEND-1 (patients aged <17 years) XTEND-kids	Clinical effectiveness

Abbreviations: Haem-A-QoL, Hemophilia-specific Health-related Quality of Life Questionnaire for Adults; Haemo-QoL, Hemophilia Quality of Life Questionnaire (Haemo-QoL).

10.1 Presentation of the health-related quality of life instrument Haem-A-QoL

10.1.1 Study design and measuring instruments

In the Phase 3, XTEND-1 study (study design described in section 6.1.1.1), the Haem-A-QoL was used to assess haemophilia-related QoL across all 10 domains, with a focus on the physical health sub-scores.

Haem-A-QoL is a participant-reported questionnaire designed for adult participants (≥ years of age) with haemophilia; and consisted of 46 items comprising 10 domains (physical health [5 items], feelings [4 items], view of self [5 items], sports and leisure [5 items], work and school [4 items], dealing with haemophilia [3 items], treatment [8 items], future [5 items], family planning [4 items], partnership and sexuality [3 items]). Items were rated along five response options: never, rarely, sometimes, often, or all the time. Raw score for physical health domain were transformed to a scale ranged from 0 to 100, where lower scores denoted better physical health. Change from baseline in physical Health domain score was reported in the study (ClinicalTrials.gov 2023a).

Haemo-QoL kids short version is used to measure physical and emotional impacts on quality of life in children & adolescent with haemophilia. It was administered to children & their caregivers. Short version for children containing 16 items (4 to 7 years) and 35 items (8 to <12 years) were selected in this study. This version covers 9 dimensions relevant for children's HRQoL (physical health, feelings, view of yourself,

family, friends, other people, sports and school, dealing with haemophilia & treatment). Items were rated along 5 response options: never, seldom, sometimes, often and always, higher scores=greater impairment. Raw score for each domain were transformed to scale ranged between 0 to 100, where lower score=better HRQoL. Haem- A-QoL total score=average of all domain scores and ranged from 0 to 100, where lower scores=better QoL (ClinicalTrials.gov 2023b).

10.1.2 Data collection

Haem-A-QoL assessments were made at baseline and at week 52 in XTEND-1 (patients ≥17 years of age). In Arm A, the change from baseline to Week 52 in Haem-A-QoL Physical Health score (selected secondary endpoint) was analysed as part of the hierarchical testing procedure using an MMRM model.

Haemo-QoL assessments were made at baseline and at week 52 in XTEND-1 (patients <17 years of age) and in XTEND-kids. Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score and physical health domain score from baseline to Week 52 (≥4 years old) and via parent proxy version (≥4 years old). In the study, 21 participants were aged 4 to <6 years, 16 participants aged 6 to 7 years, and 20 participants aged 8 to <12 years.

Table 33 Pattern of missing data and completion

Study	Time point	HRQoL population N
XTEND-1 >17 years **Haem-A-QoL**	**52 weeks**	133
XTEND-1 kids <8 years **Haemo-QoL kids**	**52 weeks**	37
XTEND-1 kids 8 to <12 years **Haemo-QoL kids**	**52 weeks**	14
XTEND-1 **EQ-5D-5L**	**52 weeks**	122

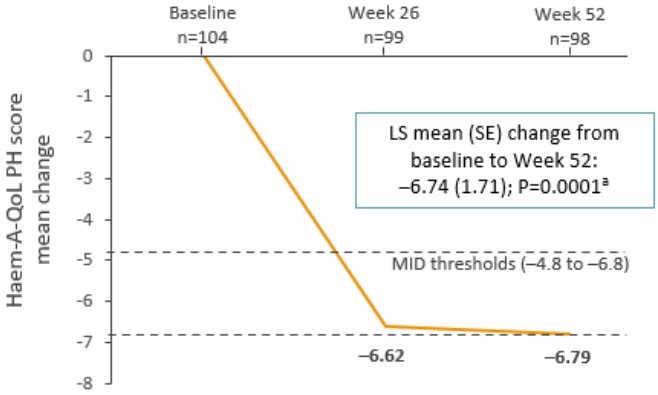
10.1.3 HRQoL results

XTEND-1

In 98 participants aged ≥17 years who received efanesoctocog alfa prophylaxis, 71.4% had physical health scores that were maintained or improved over 12 months, and efanesoctocog alfa demonstrated a clinically meaningful and statistically significant improvement in physical health scores from baseline to the end of the study. Improvements in physical functioning were seen for 7/10 domains, with the greatest change observed for physical health, followed by the view of yourself domain, and treatment domain in participants who received efanesoctocog alfa prophylaxis.

The LS mean for change in Physical Health scores from baseline to Week 52 was -6.74 (95% CI: -10.13, -3.36; p=0.0001) (Figure 16) (Wilson et al. 2023).

Figure 16: Mean change in Haem-A-QoL physical health scores from baseline to Week 52 (Arm A, aged ≥17 years)



[a]The LS mean (SE) and 95% CI were estimated by mixed-effect model with repeated measures and visit as fixed effects, and baseline Haem-A-QoL Physical Health score as covariate

CI, confidence interval; LS, least square; MID, minimally important difference; PH, physical health; SE, standard error; QoL, quality-of-life

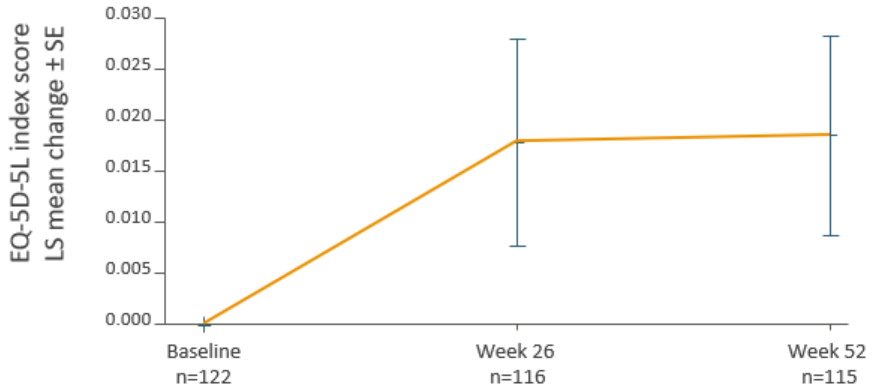
Source: (Wilson et al. 2022a)

In Arm A (n=110), the mean (SD) change in Haem-A-QoL total score from baseline to Week 52 was -4.56 (11.15). Apart from physical health, the greatest improvements in mean (SD) scores were observed in the domains of view of yourself at -7.40 (18.25) and treatment at -5.99 (15.10). Significant improvements were observed in 7/10 domains of the Haem-A-QoL (Wilson et al. 2023).

In Arm A, all 18 participants aged 13–16 years completed the Haemo-QoL questionnaire at baseline, Week 26, and Week 52. The mean (SD) change from baseline to Week 52 was -2.18 (22.05). From baseline to Week 52, there was an improvement in mean (SD) total score change of -3.45 (8.83). The greatest improvements were observed in the domains of support participants felt they were receiving, friends, sports and school. Results in participants aged 12 years (n=5) were generally consistent with results in participants aged 13–16 years.

In Arm A, 122 participants completed the EQ-5D-5L questionnaire at baseline, 127 at Week 26 and 126 at Week 52. The baseline EQ-VAS mean (SD) score was 81.66 (15.53), and the mean (SD) change in EQ-VAS score from baseline to Week 52 was 0.83 (13.18).

Figure 17 Mean change in EQ-5D index score from baseline to Week 52 (Arm A)



The mean (SD) EQ-5D index score at Week 52 was 0.80 (0.18), and the mean (SD) change from baseline to Week 52 in EQ-5D index score was 0.02 (0.13) suggesting that QoL measured using the EQ-5D was stable from baseline to end of study, Figure 17.

The proportion of participants who had improvement from baseline to Week 52 was greatest in the mobility (23.5%), pain/discomfort (20.9%), and usual activities (19.1%) domains. Overall, between baseline and Week 52, 35 (30.4%) participants reported improvement in at least one dimension (with no worsening in any other dimension), 26 (22.6%) reported worsening in at least one dimension (with no improvement in any other dimension), 44 (38.3%) reported no change (all dimensions stable), and 10 (8.7%) reported mixed change.

XTEND-kids

XTEND-kids is not included in the comparative effectiveness analysis vs emicizumab and is therefore not reported here in detail. In summary, efanesoctocog alfa prophylaxis was associated with improvements based on Haemo-QoL and EQ-5D. More details are presented in Appendix B.2.3.

Table 34 HRQoL [instrument 1] summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]					

10.2 Health state utility values (HSUVs) used in the health economic model

[redacted]

10.2.1 HSUV calculation

[redacted]

10.2.1.1 Mapping

[redacted]

10.2.2 Disutility calculation

[redacted]

10.2.3 HSUV results

[redacted]

Table 35 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

10.3 Presentation of the health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

[redacted]

10.3.1 Study design

10.3.2 Data collection

10.3.3 HRQoL Results

10.3.4 HSUV and disutility results

Table 36 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

Table 37 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

11. Resource use and associated costs

[redacted]

Justifications for inclusion or exclusion of each [redacted] category is described under each subheading.

11.1 Pharmaceutical costs (intervention and comparator)

Included drug acquisition costs are presented in Table 38. Prices are sourced from Medicinpriser.dk. Vial combinations were generated by creating all possible combinations of vials between 0 and 10 vials per vial type. Cost and wastage were assigned to each combination. The script for generation of vials is included in the health economic model. Vial combinations chosen were based on the combination with the lowest amount of wastage to reduce costs, and if multiple combinations resulted in the same amount of wastage, then the combination with the fewest number of vials was selected.

Table 38 Pharmaceutical costs used in the model

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]
Efanesoctocog alfa	250 IU	1 stk.	2 235,00 DKK
	500 IU	1 stk.	4 470,00 DKK
	750 IU	1 stk.	6 705,00 DKK
	1000 IU	1 stk.	8 940,00 DKK
	2000 IU	1 stk.	17 880,00 DKK
	3000 IU	1 stk.	26 820,00 DKK
	4000 IU	1 stk.	35 760,00 DKK
Emicizumab	12 mg/0,4 ml	1 stk. inj.væske, opløsning	6 095,32 DKK

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]
	30 mg/1 ml	1 stk. inj.væske, opløsning	15 254,99 DKK
	60 mg/0,4 ml	1 stk. inj.væske, opløsning	30 489,48 DKK
	105 mg/0,7 ml	1 stk. inj.væske, opløsning	53 340,13 DKK
	150 mg/1 ml	1 stk. inj.væske, opløsning	76 191,51 DKK
	300 mg/2 ml	1 stk. inj.væske, opløsning	152 383,02 DKK

11.2 Pharmaceutical costs – co-administration

Not applicable.

11.3 Administration costs

Efanesoctocog is administered through intravenous injection and emicizumab is administered as a subcutaneous injection. Both are self-administered at home by the patient or caregiver (European Medicines Agency 2024a, European Medicines Agency 2023). Self-administration at home is assumed to be a negligible cost relative to drug acquisition cost and was therefore not included in the analysis.

Table 39 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable				

11.4 Disease management costs

No disease management costs were included in the analysis.

Table 40 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable				

11.5 Costs associated with management of adverse events

Not included as the incidence of adverse events were infrequent and mild. No serious adverse events occurring in ≥5% of patients were reported for efanesoctocog alfa (see section 9).

Table 41 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Not applicable		

11.6 Subsequent treatment costs

Not Applicable

Table 42 Pharmaceutical costs of subsequent treatments

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Not applicable					

11.7 Patient costs

Neither administration of intervention or comparator require healthcare personnel supervision or health-care visits, therefore loss of leisure time and transportation costs were excluded from the analysis.

Table 43 Patient costs used in the model

Activity	Time spent [hours]	Patient time cost per hour	Transportation cost per administration
Not applicable			

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

The base case settings are presented in Table 44.

Table 44 Base case overview

Feature	Description
Comparator	Emicizumab once weekly
Type of model	[redacted]
Time horizon	10 years
Discounting	3.5%
Treatment line	2nd line. Subsequent treatment lines not included.
Measurement and valuation of health effects	[redacted]
Costs included	Pharmaceutical costs
Dosage of pharmaceutical	Based on weight
Average time on treatment	Full time horizon
Inclusion of waste	Yes
Patient body weight	75 kg
Efanesoctocog alfa dosing	50 IU/kg body weight
Efanesoctocog alfa weekly dosing	3750 IU: 1 vial 3000 IU 1 vial 750 IU
Emicizumab dosing	1.5 mg/kg body weight
Emicizumab weekly dosing	112,5 mg: 2 vials 12 mg/0,4 ml 1 vial 30 mg/1 ml 1 vial 60 mg/0,4 ml
Emicizumab loading phase	Excluded

12.1.1 Base case results

The results from the base case analysis are presented in Table 45. Results are calculated with the base case settings as described previously in Table 44. All costs are presented in 2024 DKK.

The results show that efanesoctocog alfa is cost saving over the ten-year time horizon, resulting in per patient savings of XXXXXXXXXX DKK at AIP prices. With annual savings of XXXXXXXXX DKK.

Table 45 Base case results, discounted estimates

	Efanesoctocog alfa	Emicizumab	Difference
Pharmaceutical costs	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
Total costs	XXXXXXXXXX	XXXXXXXXXX	XXXXXXCXXXX
Incremental costs		XXXXXXXXXX	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

A deterministic one-way sensitivity analysis was performed on key parameters. The results are presented in Table 47. The sensitivity analysis shows that efanesoctocog alfa is cost-saving under the different assumptions. The different vial combinations are shown in Table 46 for each scenario and the base case.

Table 46 Emicizumab vial combinations used in the base case and scenarios

Scenario	Notes	12 mg /0,4 ml	30 mg /1 ml	60 mg /0,4 ml	105 mg /0,7 ml	150 mg /1 ml	300 mg /2 ml
Base case	-	2	1	1	0	0	0
Patient's body weight	-	3	1	1	0	0	0
Emicizumab loading phase	Week 1-4	0	0	2	1	0	0
	Week +4	2	1	1	0	0	0
Emicizumab dosing schedule	Q1W	2	1	1	0	0	0
	Q2W	0	0	1	1	0	0
	Q4W	0	0	0	0	1	1

The first analysis varies body weight to the observed body weight in the XTEND-1 trial of 81 kg. In this scenario 1 vial of 3000 IU, 1 vial of 1000 IU, and 1 vial of 250 IU was used for efanesoctocog alfa dosing. For emicizumab 3 vials of 12 mg/0,4 ml, 1 vial of 30 mg/ml, and 1 vial of 60 mg/0,4ml were used.

In the second analysis emicizumab induction phase is included, consisting of four weeks of 3 mg/kg body weight. For this analysis the weekly cost for the first four weeks of the year is calculated using 2 vials 60 mg/ml, 0,4 ml and 1 vial 105 mg/ml, 0,7 ml. The costs for the remainder of the year are calculated as in the base case scenario.

In the third scenario all the different dosing intervals were included as the equally weighted average of the three dosing intervals. Q1W was calculated using 2 vial of 12 mg/ml, 1 vial of 30 mg/ml, and 1 vial of 60 mg/ml, 0,4 ml. Q2W was calculated using 2 vials 60 mg/ml, 0,4 ml and 1 vial 105 mg/ml, 0,7 ml. Lastly, Q4W was calculated using 1 vials of 150 mg/ml, 1 ml and 1 vial of 300 mg/ml, 2 ml.

Table 47 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)
Base case	NA	NA	XXXXXXXXXX
Patient's body weight	81 kg	Observed mean baseline body weight in XTEND-1	XXXXXXXXXX
Emicizumab loading phase	Inclusion of loading phase	Recommended dosing	XXXXXXXXXX
Emicizumab dosing schedule	Equally weighted average of Q1W, Q2W, and Q4W	Includes all available dosing frequency options	XXXXXXXXXX

12.2.2 Probabilistic sensitivity analyses

No probabilistic sensitivity analysis was done as it was not deemed relevant for the decision problem.

13. Budget impact analysis

Number of patients

The expected number of patients is shown in Table 48. The numbers are calculated as in section 3.2. Mortality is not included in the calculations. Of the XXX initial patients, under a non-recommendation scenario, emicizumab is assumed to have a market share of XXX in year one, which increases by XXXX points per year up to an estimated XXX at year 5. In the recommended scenario, emicizumab and efanesoctocog alfa are assumed to equally share the market share of emicizumab under the non-recommendation scenario (XXX each in year 1, increasing to XXX each in year 5).

Table 48 Number of new patients expected to be treated over the next five-year period if the pharmaceutical is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Efanesoctocog alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: patient numbers are rounded to nearest whole number.

Budget impact

Results of the budget impact analysis are presented in Table 49. Settings are those of the base case in section 12.1, excluding discounting. Results are presented on an annual basis and not accumulated. In summary, calculations assume 75 kg hypothetical patients on a weekly dosing schedule without a loading phase for emicizumab.

Table 49 Expected budget impact of recommending the pharmaceutical for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 50 Main characteristics of XTEND-1

Trial name: XTEND-1		**NCT number: NCT04161495**
Objective	To evaluate the efficacy of efanesoctocog alfa as a prophylaxis treatment in prophylaxis treatment arm.	
Publications – title, author, journal, year	Efanesoctocog alfa prophylaxis for patients with severe hemophilia A, Von Drygalski, A., Chowdary, P., Kulkarni, R., Susen, S., Konkle, B. A., Oldenburg, J., ... & Knobe, K., New England Journal of Medicine, 2023	
Study type and design	Multicentre, open-label, non-randomized, controlled, phase 3-trial, completed	
Sample size (n)	159	
Main inclusion criteria	• Participant, male or female, must be equal to or greater than 12 years of age inclusive, at the time of signing the informed consent. • Severe haemophilia A, defined as less than (<) 1 international units per decilitre (IU/dL) (<1 percent [%]) endogenous FVIII activity as documented either by central laboratory testing at Screening or in historical medical records from a clinical laboratory demonstrating <1% FVIII coagulant activity (FVIII:C) or a documented genotype known to produce severe haemophilia A. • Previous treatment for haemophilia A (prophylaxis or on demand) with any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 exposure days. • Current regimen included one of the following: o Prophylactic treatment regimen with a FVIII product or prophylactic emicizumab therapy for at least 6 months during the previous 12 months. Appropriate washout time needs to be taken into account. o On-demand regimen with a FVIII product with a history of at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrolment. • On-demand participant was accepted to move to a prophylaxis treatment regimen after 26-week on-demand period. • Willingness and ability of the participant or surrogate (a caregiver or a family member greater than or equal to [>=] 18 years of age) to complete training in the use of the study electronic Patient Diary (ePD) and to use the ePD throughout the study.	

Trial name: XTEND-1	NCT number: NCT04161495
	• Ability of the participant or his or her legally authorized representative (e.g., parent or legal guardian) to understand the purpose and risks of the study, willing and able to comply with study requirements and provide signed and dated informed consent or assent (as applicable) and authorization to use protected health information in accordance with national and local participant privacy regulations.
Main exclusion criteria	• Clinically significant liver disease. • Serious active bacterial or viral infection (other than chronic hepatitis or HIV) present within 30 days of screening. • Other known coagulation disorder(s) in addition to haemophilia A. • History of hypersensitivity or anaphylaxis associated with any FVIII product. • Positive inhibitor results, defined as >=0.6 Bethesda unit per millilitre (BU/mL) at screening. History of a positive inhibitor test defined as >=0.6 BU/mL. Family history of inhibitors would not exclude the participant. • Use of Emicizumab within the 20 weeks prior to screening. • Major surgery within 8 weeks prior to screening.
Intervention	Arm A: prophylaxis, efanesoctocog alfa (n=133), 50 IU/kg, once weekly, up to 52 weeks Arm B: on-demand, then prophylaxis, efanesoctocog alfa (n=26), 50 IU/kg as needed for treatment of bleeding episodes from week 1 to week 26. At week 26, participants switched to prophylaxis treatment, 50 IU/kg, once weekly, until week 52
Comparator(s)	N/A
Follow-up time	52 weeks
Is the study used in the health economic model?	No. However it is used in the ITC demonstrating relative efficacy vs emicizumab. [redacted]
Primary, secondary and exploratory endpoints	Primary outcome: • Estimated mean ABR during 52 weeks of efanesoctocog alfa prophylaxis (Arm A) Key secondary outcomes (Arm A): • Intra-patient comparison of ABR for efanesoctocog alfa prophylaxis versus pre-study standard-of-care FVIII prophylaxis

Trial name: XTEND-1	NCT number: NCT04161495

- Changes from baseline to Week 52 in Haem-A-QoL physical health score
- Changes from baseline to Week 52 in PROMIS Pain Intensity 3a
- Changes from baseline to Week 52 in HJHS score

Secondary outcomes (analysis set):

ABR, bleeding, and FVIII activity

- Arm A: intra-patient comparison of efanesoctocog alfa weekly prophylaxis treatment versus the historical prophylaxis ABR for patients who participated in an observational pre-study
- Both arms: ABR by type and location for prophylaxis treatment
- Both arms: ABR for all bleeding episodes (including untreated bleeding episodes) for prophylaxis treatment
- Arm B: intra-patient comparison of ABR during the weekly prophylaxis treatment period versus the ABR during the on-demand treatment period
- Arm A: percentage of participants who maintain FVIII activity levels >1%, >5%, >10%, >15%, and >20%

Bleeding episodes

- Both arms: number of injections and dose of efanesoctocog alfa to treat a bleeding episode during prophylaxis and on-demand regimens
- Both arms: Percentage of bleeding episodes treated with a single injection of efanesoctocog alfa during prophylaxis and on-demand regimens
- Both arms: assessment of response to efanesoctocog alfa treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale per study arm and treatment regimen
- Both arms: physician's global assessment (PGA) of participant's response to efanesoctocog alfa treatment based on a 4-point response scale per study arm and treatment regimen:
- At each visit, physicians provided an assessment of the participant's response to efanesoctocog alfa using a 4-point scale of excellent, effective, partially effective, or ineffective

Efanesoctocog alfa consumption

- Both arms: total annualized efanesoctocog alfa consumption per participant per study arm and treatment regimen

Joint health

Trial name: XTEND-1	NCT number: NCT04161495

- Arm A: Change from baseline to Week 52 in total score and domain scores (e.g., swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS)
- Arm A: Annualized Joint Bleeding Rate (AjBR) per study arm and treatment regimen
- Arm A: Target joint resolution at Week 52, based on ISTH criteria
    - 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

Quality of Life

- Arm A: changes in Haem-A-QoL (≥17 years old) total score and physical health score measures from baseline to Week 52
- Arm A: changes in PROMIS Pain Intensity 3a from baseline to Week 52
- Arm A: changes in PROMIS SF Physical Function (≥18 years old) measures from baseline to Week 52

Interoperative management

- Both arms: investigator's or surgeon's assessment of participant's haemostatic response on the ISTH 4-point response for surgical procedures scale
- Both arms: Number of injections and dose to maintain haemostasis during perioperative period for major surgery
- Both arms: efanesoctocog alfa consumption during perioperative period for major surgery
- Both arms: number and type of blood component transfusions used during perioperative period for major surgery

Both arms: estimated blood loss during perioperative period for major surgery

Method of analysis	The primary endpoint was estimated in the Full Analysis Set with the use of a negative-binomial regression model. ABRs were calculated on the basis of the number of bleeding episodes during the efficacy period. If the upper limit of the 97.5% CI for the ABR in group A was ≤6, the intervention was considered to be effective. The intra-patient comparison of the ABR during prophylaxis in group A and the rate during pre-study prophylaxis was assessed using a negative-binomial regression model. Noninferiority and superiority of efanesoctocog alfa prophylaxis to pre-study prophylaxis were evaluated sequentially. The adjusted mean change from baseline to week 52 in physical health (Haem-A-QoL physical-health score), pain (PROMIS pain-intensity score 3a), and joint health (HJHS) were estimated by means of mixed effects models with repeated measures, as part of a prespecified hierarchical testing framework.

Trial name: XTEND-1		NCT number: NCT04161495
Subgroup analyses	Surgery subgroup	
Other relevant information		

Source: (ClinicalTrials.gov 2023a)

Table 51 Main characteristics of XTEND-kids

Trial name: XTEND-Kids		NCT number: NCT04759131
Objective	To evaluate the safety of efanesoctocog alfa in previously treated pediatric subjects with haemophilia A	
Publications – title, author, journal, year	NA	
Study type and design	Multicentre, open-label, single-arm, phase 3-trial, completed	
Sample size (n)	75	
Main inclusion criteria	• Participant must be younger than 12 years of age, at the time of signing the informed consent • Severe haemophilia A defined as <1 IU/dL (<1%) endogenous FVIII as documented either by central laboratory testing at Screening or in historical medical records from a clinical laboratory demonstrating <1% FVIII coagulant activity (FVIII:C) or a documented genotype known to produce severe haemophilia A. • Previous treatment for haemophilia A (prophylaxis or on-demand) with any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 EDs for patients aged 6-11 years and above 50 EDs for patients aged <6 years • Weight above or equal to 10 kg.	
Main exclusion criteria	• History of hypersensitivity or anaphylaxis associated with any FVIII product. • History of a positive inhibitor (to FVIII) test defined as ≥0.6 BU/mL, or any value greater than or equal to the lower sensitivity cut-off for laboratories with cut-offs for inhibitor detection between 0.7 and 1.0 BU/mL, or clinical signs or symptoms of decreased response to FVIII administrations. Family history of inhibitors will not exclude the participant.	

Trial name: XTEND-Kids	NCT number: NCT04759131
	• Positive inhibitor test result, defined as ≥0.6 BU/mL at Screening.
Intervention	The eligible participants received efanesoctocog alfa at a dose of 50 IU/kg IV once weekly for 52 weeks.
Comparator(s)	N/A
Follow-up time	52 weeks
Is the study used in the health economic model?	No The study serves as proof of efficacy and safety in PwHA below 12 years of age
Primary, secondary and exploratory endpoints	Primary outcome measure: • Occurrence of inhibitor development. Time Frame: Baseline to 52 weeks. Secondary outcome measures: • Annualized bleeding rate (ABR) levels [Time Frame: baseline to week 52] • Annualized bleeding rate (ABR) for treated, for untreated, for all bleeding episodes. • Annualized bleeding rate (ABR) by type of bleed [Time Frame: baseline to week 52] • ABR by type of bleed such as spontaneous or traumatic • Annualized bleeding rate (ABR) by location of bleed [Time Frame: baseline to week 52] • ABR by location of bleed such as joint, muscle, internal, or skin/mucosa • Percentage of participants who maintain FVIII activity above prespecified levels [Time Frame: baseline to week 52] • Number of injection and dose of efanesoctocog alfa to treat a bleeding episode [Time Frame: baseline to week 52] • Percentage of bleeding episodes treated with a single injection of efanesoctocog alfa [Time Frame: baseline to week 52] • Assessment of response to efanesoctocog alfa treatment of individual bleeding episodes [Time Frame: 52 weeks] • Assessment of response to efanesoctocog alfa treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale. • Physician's global assessment of the participant's response based on efanesoctocog alfa treatment [Time Frame: baseline to week 52]

Trial name: XTEND-Kids	NCT number: NCT04759131

- Physician's global assessment (PGA) of participant's response to efanesoctocog alfa treatment based on a 4-point response scale
- Total annualized efanesoctocog alfa consumption [Time Frame: baseline to week 52]
- Annualized Joint Bleeding Rate (AjBR) [Time Frame: baseline to week 52]
- Target joint resolution [Time Frame: At week 52]
- Target joint resolution at week 52, based on ISTH criteria.
- Change in Haemophilia Joint Health Score (HJHS) total score and domain scores [Time Frame: baseline to week 52]
- Change from baseline to week 52 in total score and domain scores (e.g., swelling and strength) assessed by the HJHS.
- Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score [Time Frame: baseline to week 52]
- Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score from baseline to Week 52 (≥ 4 years old and parent proxy for all ages)
- Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) physical health domain scores from [Time Frame: baseline to week 52]
- Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) physical health domain scores from baseline to Week 52 (≥ 4 years old and parent proxy for all ages)
- Investigators' or Surgeons' assessment of participant's haemostatic response to efanesoctocog alfa treatment [Time Frame: baseline to week 52]
- Investigators' or Surgeons' assessment of participant's haemostatic response to efanesoctocog alfa treatment on the ISTH 4 point response for surgical procedures scale
- Number of injections and dose to maintain haemostasis during perioperative period for major surgery [Time Frame: baseline to week 52]
- Total efanesoctocog alfa consumption during perioperative period for major surgery [Time Frame: baseline to week 52]
- Number of blood component transfusions used during perioperative period for major surgery [Time Frame: baseline to week 52]

Trial name: XTEND-Kids	NCT number: NCT04759131
	• Type of blood component transfusions used during perioperative period for major surgery [Time Frame: baseline to week 52] • Estimated blood loss during perioperative period for major surgery [Time Frame: baseline to week 52] • Number of participants with occurrence of adverse events (AEs) and serious adverse events (SAEs) [Time Frame: baseline to week 52] • Participants with occurrence of adverse events (AEs) and serious adverse events (SAEs) • Number of participants with occurrence of embolic and thrombotic events [Time Frame: baseline to week 52] • PK parameter: Maximum activity (Cmax) [Time Frame: baseline to week 52] • PK parameter: Elimination half-life (t1/2) [Time Frame: baseline (day 1)] • PK parameter: Total clearance (CL) [Time Frame: baseline (day 1)] • PK parameter: Total clearance at steady state (CLss) [Time Frame: baseline (day 1)] • PK parameter: dose-normalised area under the activity-time curve (DNAUC) [Time Frame: baseline (day 1)] • PK parameter: Area under the activity time curve (AUC) [Time Frame: baseline (day 1)] • PK parameter: Volume of distribution at steady state (Vss) [Time Frame: baseline (day 1)] • PK parameter: Mean residence time (MRT) [Time Frame: baseline (day 1)] • PK parameter: Incremental recovery (IR) [Time Frame: baseline to week 52] • PK parameter: Trough activity (Ctrough) [Time Frame: baseline to week 52] PK parameter: Time above predefined FVIII activity levels [Time Frame: baseline (day 1)]
Method of analysis	The methods presented in this section are based on the XTEND-Kids Statistical Analysis Plan (SAP).(SANOFI 2023) The primary endpoint for this study was the occurrence of inhibitor development, defined as an inhibitor result of >0.6 BU/mL that is confirmed by a second test result from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn. The overall incidence of positive inhibitor formation was calculated as the number of

Trial name: XTEND-Kids	NCT number: NCT04759131
	participants with an inhibitor divided by the number of participants who reached exposure day (ED) milestone or who had an inhibitor. The primary analysis of inhibitor development was based on all participants who have reached at least 50 EDs and had at least one inhibitor test performed at or beyond this milestone. The incidence of positive inhibitor formation was summarised for each age cohort and overall, and an exact 95% confidence interval (CI) was calculated using the Clopper-Pearson method for each incidence. The mean and 95% CI of annualised bleeding rate (ABR) was estimated using a Negative-Binomial model based on the number of treated bleeding episodes during the efficacy period as response variable, log-transformed duration of efficacy period as offset variable to account for variable duration. ABR was summarised descriptively for the treated bleeds by type and location, and the estimated mean ABR and the corresponding 95% CI were provided, for each subset, using the same method as specified above. The results were presented by age cohort and overall. Sensitivity analysis of the ABR was performed using the Per Protocol Set, as well as using the Full Analysis Set including participants with an efficacy period of at least 26 weeks. ABR was summarised descriptively by type (overall, spontaneous, traumatic) and location (overall, joint). Patient/parent reported outcomes using the Hemophilia Joint Health Score (HJHS), Haemo-QoL, PROMIS instruments (pain intensity, pain interference, physical activity) and EuroQoL-Youth (EQ-5D-Y) were summarised descriptively for the actual value and change from baseline for each age cohort and overall.
Subgroup analyses	Surgery subgroup
Other relevant information	

Source: (ClinicalTrials.gov 2023b)

Table 52 Main characteristics of HAVEN III

Trial name: HAVEN III	NCT number: NCT02847637
Objective	HAVEN III is a randomized, global, multicenter, open-label, Phase 3 clinical study in participants with severe haemophilia A without inhibitors against Factor VIII (FVIII) who are 12 years or older. The study evaluates two prophylactic emicizumab regimens versus no prophylaxis in this population with emphasis on efficacy, safety, and pharmacokinetics.

Trial name: HAVEN III	NCT number: NCT02847637
Publications – title, author, journal, year	Mahlangu, J., Oldenburg, J., Paz-Priel, I., Negrier, C., Niggli, M., Mancuso, M. E., Schmitt, C., Jiménez-Yuste, V., Kempton, C. & Dhalluin, C. 2018. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *New England Journal of Medicine,* 379**,** 811-822. Kiialainen, A., Niggli, M., Kempton, C. L., Castaman, G., Chang, T. Y., Paz-Priel, I., Adamkewicz, J. I. & Levy, G. G. 2019. Bone and joint health markers in persons with hemophilia A (PwHA) treated with emicizumab in HAVEN 3. American Society of Hematology Washington, DC.
Study type and design	**HAVEN III** is composed of a RCT recruiting patients previously treated with OD regimen, and a non-randomised study assessing patients, who received PHX before enrolment. Participants of the RCT were allocated to 2 different prophylactic regimens (1.5 mg/kg/week or 3.0 mg/kg every 2 weeks) and an OD treatment. Those, allocated to non-RCT arm were receiving prophylaxis with 1.5 mg/kg/week regimen.
Sample size (n)	63 (Group D)
Main inclusion criteria	• Body weight >/= 40 kilogram (kg) at the time of screening • Diagnosis of severe congenital haemophilia A • Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks • Adequate hematologic function • Adequate hepatic function • Adequate renal function • For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of less than (<) 1 percent (%) per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug
Main exclusion criteria	• Inherited or acquired bleeding disorder other than haemophilia A • Previous or current treatment for thromboembolic disease or signs of thromboembolic disease • Conditions that may increase risk of bleeding or thrombosis • History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection • Known human immunodeficiency virus (HIV) infection with cluster of differentiation (CD) 4 count <200 cells per microliter (cells/mcL) within 24 weeks prior to screening. Participants with HIV infection who has CD4 greater than (>) 200 and meet all other criteria are eligible

Trial name: HAVEN III	NCT number: NCT02847637
	• Use of systemic immunomodulators at enrolment or planned use during the study, with the exception of anti-retroviral therapy • Participants who are at high risk for thrombotic microangiopathy (TMA) (for example, have a previous medical or family history of TMA), in the investigator's judgment • Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the participant's safe participation in and completion of the study • Planned surgery (excluding minor procedures) during the study • Receipt of emicizumab in a prior investigational study; an investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration; a non-haemophilia-related investigational drug concurrently, within last 30 days or 5 half-lives, whichever is shorter • Pregnant or lactating, or intending to become pregnant during the study
Intervention	The study compared emicizumab prophylaxis 1.5 mg/kg/wk, 3 mg/kg/2wk, 1.5 mg/kg/wk and on demand treatment
Comparator(s)	Se above
Follow-up time	Median follow-up: 33.7 weeks
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary outcome measure (current): • Annualized bleeding rate for treated bleeds. Time frame: Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks). Primary outcome measure (original): • Number of bleeds over time. Time Frame: 24 weeks Secondary outcome measures (current): • Annualized Bleeding Rate (ABR) for All Bleeds. Time Frame: From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks) • Annualized Bleeding Rate (ABR) for Treated Joint Bleeds. Time Frame: From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)

Trial name: HAVEN III	NCT number: NCT02847637

- Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds. Time Frame: From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)
- Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds. Time Frame: From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)
- Intra-Participant Comparison of ABR for Treated Bleeds on Study Versus Pre-Study in Participants From the Non-Interventional Study Population Previously Treated With Factor VIII (FVIII) Prophylaxis (NISP). Time Frame: Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for Dnisp-FVIII Prophylaxis: 30.07 [5.0-45.1] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for Dnisp-Emicizumab Prophylaxis: 33.71 [20.1-48.6] weeks)
- Intra-Participant Comparison of ABR for All Bleeds on Study Versus Pre-Study in Participants From the Non-Interventional Study Population Previously Treated With FVIII Prophylaxis (NISP). Time Frame: Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for Dnisp-FVIII Prophylaxis: 30.07 [5.0-45.1] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for Dnisp-Emicizumab Prophylaxis: 33.71 [20.1-48.6] weeks)
- Intra-Participant Comparison of ABR for Treated Bleeds on Study Versus Pre-Study in Participants From the NIS Population Previously Treated With Episodic FVIII (NISE). Time Frame: Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for A+Bnise-FVIII Episodic: 25.71 [15.4-40.9] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for A+Bnise-Emicizumab: 34.71 [24.1-50.6] weeks)
- Intra-Participant Comparison of ABR for All Bleeds on Study Versus Pre-Study in Participants From the NIS Population Previously Treated With Episodic FVIII (NISE). Time Frame: Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for A+Bnise-FVIII Episodic: 25.71 [15.4-40.9] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for A+Bnise-Emicizumab: 34.71 [24.1-50.6] weeks)
- Hemophilia A Quality of Life (Haem-A-QoL) Questionnaire Physical Health Sub score for Adult Participants (≥18 Years of Age) in the Randomized Population at Week 25. Time Frame: Baseline, Week 25
- Haem-A-QoL Questionnaire Total Score for Adult Participants (≥18 Years of Age) in the Randomized Population at Week 25. Time Frame: Baseline, Week 25

- European Quality of Life 5-Dimensions-5 Levels (EQ-5D-5L) Questionnaire Visual Analogue Scale (VAS) Score in the Randomized Population at Week 25. Time Frame: Baseline, Week 25
- EQ-5D-5L Questionnaire Index Utility Score in the Randomized Population at Week 25. Time Frame: Baseline, Week 25
- Haemophilia-Specific Quality of Life - Short Form (Haemo-QoL-SF) Questionnaire Score in Adolescent Participants (12 to 17 Years of Age) in the Randomized Population at Week 25. Time Frame: Week 25
- Percentage of Participants With at Least One Adverse Event During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Percentage of Participants With at Least One Grade ≥3 Adverse Event During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Percentage of Participants With at Least One Adverse Event Leading to Withdrawal From Treatment During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Percentage of Participants With at Least One Adverse Event of Changes From Baseline in Vital Signs During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Percentage of Participants With at Least One Adverse Event of Changes From Baseline in Physical Examination Findings During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Percentage of Participants With at Least One Adverse Event of Abnormal Laboratory Values During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-

25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

- Percentage of Participants With at Least One Local Injection-Site Reaction During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Percentage of Participants With at Least One Thromboembolic Event During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Percentage of Participants With at Least One Thrombotic Microangiopathy During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Percentage of Participants With at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction During the First 24 Weeks of the Study, Primary Analysis. Time Frame: From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)
- Safety Summary of the Percentage of Emicizumab-Treated Participants With at Least One Adverse Event During the Study. Time Frame: From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)
- Long-Term Efficacy of Emicizumab: Model-Based Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants. Time Frame: From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)
- Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants. Time Frame: From start of emicizumab treatment to study completion, dose up-titration, or

change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

- Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants. Time Frame: From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)
- Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants. Time Frame: 1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks
- Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants. Time Frame: 1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks
- Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for All Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants. Time Frame: 1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks
- Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for All Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants. Time Frame: 1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks
- Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Spontaneous Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants. Time Frame: 1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks
- Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Spontaneous Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants. Time Frame: 1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204,

Trial name: HAVEN III	NCT number: NCT02847637
	205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks • Percentage of Participants with Anti-Emicizumab Antibodies at Any Time Post-Baseline During the Study. Time Frame: From Baseline to discontinuation from study (median [min-max] observation period for all emicizumab participants: 262.3 [14.4-288.3] weeks) • Percentage of Participants With De Novo Development of Factor VIII (FVIII) Inhibitors. Time Frame: From Baseline to discontinuation from study (median [min-max] observation period for all emicizumab participants: 262.3 [14.4-288.3] weeks) • Trough Plasma Concentration (Ctrough) of Emicizumab. Time Frame: Predose at Weeks 1, 2, 3, 4, 5, 7, 9, 13, 17, 21, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181, 193, 205, 217, 229, 241, 253, 265, and 277 Secondary outcome measures (original): • Reduction in number of bleeds over time. Time Frame: Baseline, 24 weeks • Reduction in number of joint bleeds over time. Time Frame: Baseline, 24 weeks • Reduction in number of target joint bleeds over time. Time Frame: Baseline, 24 weeks • Health related quality of life scores. Time Frame: 24 weeks • Trough plasma concentration (Ctrough) of emicizumab. Time Frame: (Pre-dose) Every week during Weeks 1-4, every 2 weeks during Weeks 5-8, every 4 weeks during Weeks 9-24, every 8 weeks during Weeks 25-48, every 12 weeks thereafter (maximum up to 2 years)
Method of analysis	For bleeding-related end points, comparisons of bleeding rate (which were calculated over the entire efficacy period) were performed with the use of a negative binomial-regression model. The model included the stratification factor (<9 or ≥9 bleeding events in the previous 24 weeks) and accounted for various follow-up times to determine the bleeding rate per day, which was converted to an annualized bleeding rate. The intraindividual comparison (without stratification as a covariate) included the participant component in the model.
Subgroup analyses	
Other relevant information	

Source: (Mahlangu et al. 2018a, Kiialainen et al. 2019)

Appendix B. Efficacy results per study

B.1 Results per XTEND-1

Table 53 Results per XTEND-1 (Arm A)

Results of XTEND-1 (NCT04161495)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ABR - Total number of treated bleeding episodes	Efanesocto cog alfa prophylaxis	133	86 64.7% (55.9, 72.8)							Counts, single arm no comparative analysis performed	(von Drygalski et al. 2023b)
ABR - Mean ABR (SD)	Efanesocto cog alfa prophylaxis	133	0.71 (1.43)							Counts, single arm no comparative analysis performed	(von Drygalski et al. 2023b)

Results of XTEND-1 (NCT04161495)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Zero bleeding episodes	Efanesoctocog alfa prophylaxis	133	86 64.7% (55.9, 72.8)							Counts, single arm no comparative analysis performed	(von Drygalski et al. 2023b)
Intra-participant comparison of ABR between efanesoctocog alfa prophylaxis and prestudy FVIII prophylaxis: non-inferiority analysis based on PPS -	Historical prophylaxis	77	2.99 (2.03, 4.42)	-2.30	(-3.49, -1.11)					Estimated using a negative binomial regression model with treatment (Efanesoctocog alfa prophylaxis vs historical prophylaxis) as covariate.	(von Drygalski et al. 2023b)
	Efanesoctocog alfa prophylaxis	77	0.69 (0.43, 1.12)								

Results of XTEND-1 (NCT04161495)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean ABR											
Intra-participant comparison of ABR between Efanesoctocog alfa prophylaxis and prestudy FVIII prophylaxis: superiority analysis based on FAS – Mean ABR	Historical prophylaxis	78	2.96 (2.00, 4.37)				0.23	0.13, 0.42	<0.0001	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 (BIVV001 prophylaxis/historical prophylaxis) =1.	(von Drygalski et al. 2023b)
	Efanesoctocog alfa prophylaxis	78	0.69 (0.43, 1.11)								

Results of XTEND-1 (NCT04161495)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
HJHS total score	Efanesoctocog alfa prophylaxis	133	LS Mean: -1.54 (-2.70, -0.37) p-value: 0.0101							The LS mean (SE) and 95% CI are estimated by mixed-effect model with repeated measures (MMRM) with visit as) fixed effect, and baseline score as covariate.	(von Drygalski et al. 2023b)

Abbreviations: ABR – Annualized Bleeding Rate, HJHS - Haemophilia joint health scores.

B.2 Results per XTEND-kids

Table 54 Results per XTEND-kids

Results of XTEND-KIDS (NCT04759131)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean ABR, model based (95% CI)	Efanesocto cog alfa	74	0.89 (0.56, 1.42)							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.	(Sobi 2023)
Median ABR (Q1; Q3)	Efanesocto cog alfa	74	0.00 (0.00, 1.02)								(Sobi 2023)
Zero bleeding episodes	Efanesocto cog alfa	74	47 63.5% (51.5, 74.4)								(Sobi 2023)

Results of XTEND-KIDS (NCT04759131)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean AsBR, model based (95% CI)	Efanesocto cog alfa	74	0.16 (0.06, 0.30)							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.	(Sobi 2023)
Median AsBR (Q1; Q3)	Efanesocto cog alfa	74	0.00 (0.00, 0.00)								(Sobi 2023)
Zero spontaneous bleeding episodes	Efanesocto cog alfa	74	65 87.8% (78.2, 94.3)								(Sobi 2023)

Abbreviations: ABR – Annualized Bleeding Rate, AsBR - annualised spontaneous bleeding rate.

B.2.1 Efficacy

B.2.1.1 FVIII inhibitor development

The primary endpoint was the occurrence of inhibitor development to FVIII. No FVIII inhibitor development was detected during the one-year study. The incidence of inhibitor development to FVIII was 0.0% (95% CI: 0.0 to 5.5) in participants with ≥50 exposure days to efanesoctocog alfa (Malec et al. 2023).

B.2.1.2 Annualised bleeding rate

Efanesoctocog alfa was effective for routine prophylaxis in children under 12 years of age with severe haemophilia A. Once-weekly efanesoctocog alfa 50 IU/kg routine prophylaxis resulted in an overall estimated mean ABR of 0.89 (95% CI: 0.56 to 1.42) in the study participants (Table 55). Low ABRs were observed in both age cohorts. The majority of the participants (63.5%) across both age cohorts reported no bleeding episodes (Malec et al. 2023).

Table 55: Efanesoctocog alfa weekly prophylaxis and ABR

Efanesoctocog alfa weekly prophylaxis and ABR	<6 years (N=38)	6 to <12 years (N=36)	Overall (N=74)
Overall ABR			
Mean ABR, model based (95% CI)[a]	0.48 (0.30; 0.77)	1.33 (0.64; 2.76)	0.89 (0.56; 1.42)
Median ABR (Q1; Q3))	0.00 (0.00; 1.00)	0.00 (0.00; 1.51)	0.00 (0.00; 1.02)
Zero bleeding episodes	24 (63.2)	23 (63.9)	47 (63.5)
Spontaneous bleeds			
Mean AsBR, model based (95% CI)[a]	0.17 (0.08; 0.38)	0.14 (0.04; 0.53)	0.16 (0.06; 0.30)
Median AsBR (Q1; Q3))	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)
Zero spontaneous bleeding episodes	32 (84.2)	33 (91.7)	65 (87.8)

Abbreviations: ABR, annualised bleed rate; AsBR, annualised spontaneous bleed rate; CI, confidence interval; Q1, first quartile; Q3, third quartile; SD, standard deviation.

[a] Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.

Source: **(Sobi 2023)**

Overall, 74 participants in the full analysis set had a total of 42 treated joint bleeds. The mean AJBR was 0.59 (95% CI: 0.27 to 1.28), with 0.19 (95% CI: 0.06 to 0.62) in the <6

years of age cohort, and 0.99 (95% CI: 0.38 to 2.60) in the 6 to <12 years of age cohort. Of the 74 participants who had an efficacy period, 61 (82.4%) participants reported no joint bleeds.

B.2.1.3 PROMIS

PROMIS data for Pain intensity, Pain interference and Physical activity were collected at Baseline, Week 26 and Week 52 in participants aged 8 to <12 years and by parents of participants 5 to 12 years. Lower scores represent lower level of pain, and hence a negative change from baseline represents improvement.

PROMIS Pediatric Pain Intensity 1a

No change was observed in the mean PROMIS Pediatric Pain Intensity 1a score among the participants in the 6 to <12 years age group, while a slight reduction was observed among the parents of this age group and the parents of the <6 age group (Table 56). The PROMIS instrument on pain intensity uses an 11-point Numeric Rating Scale (NRS) ranging in value from 0 to 10, with 0 indicating no pain and 10 indicating worse pain.

Table 56: Summary of mean change in PROMIS Pediatric Pain Intensity 1a score from baseline to Week 52

Group	PROMIS Pediatric Pain Intensity 1a*
<6 years old (parents of participants ≥5 years)	
Mean (SD) at baseline	1.20 (2.25) (n=10)
Mean (SD) change from Baseline to Week 52	-0.44 (2.65) (n=9)
6 to <12 years old (participants aged ≥8 years)	
Mean (SD) at baseline	1.71 (2.52) (n=14)
Mean (SD) change from Baseline to Week 52	0.00 (2.98) (n=10)
Parents of 6 to <12 years old (parents of participants ≥5 years)	
Mean (SD) at baseline	1.05 (1.84) (n=19)
Mean (SD) change from Baseline to Week 52	-0.75 (2.53) (n=12)

Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation

* The PROMIS instrument on pain intensity uses an 11-point Numeric Rating Scale (NRS) ranging in value from 0 to 10, with 0 indicating no pain and 10 indicating worse pain

Source: (Sobi 2023)

PROMIS Pediatric-SF Pain interference

A slight reduction in the mean PROMIS Pediatric-SF Pain interference 8a score was observed among the participants in the 6 to <12 years age group, the parents of this age group, and the parents of the <6 age group (Table 57). The PROMIS instrument on pain interference includes eight questions each of which has five answer options ranging from pain interfering "never" to "almost always" on relevant aspects of a person's life including mobility, sleep and mood.

Table 57: Summary of mean change in PROMIS Pediatric-SF Pain interference 8a T score from baseline to Week 52

Group	PROMIS Pediatric-SF Pain interference 8a*
<6 years old (parents of participants ≥5 years)	
Mean (SD) at baseline	43.31 (8.42) (n=13)
Mean (SD) change from Baseline to Week 52	-0.45 (7.89) (n=11)
6 to <12 years old (participants aged ≥8 years)	
Mean (SD) at baseline	42.52 (11.85) (n=14)
Mean (SD) change from Baseline to Week 52	-1.46 (7.61) (n=10)
6 to <12 years old (parents of participants ≥5 years)	
Mean (SD) at baseline	45.25 (8.17) (n=20)
Mean (SD) change from Baseline to Week 52	-1.92 (10.74) (n=12)

Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation

* The PROMIS instrument on pain interference includes eight questions each of which has five answer options ranging from pain interfering "never" to "almost always" on relevant aspects of a person's life including mobility, sleep and mood. All questions must be answered in order to produce a valid total score. The total raw score is converted into a T-score for each participant, which rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore, a person with a T-score of 40 is one SD below the mean.

Source: (Sobi 2023)

PROMIS Pediatric-SF Physical function

The PROMIS-SF Physical Function score reflects the ability to perform activities of daily living. A slight deterioration in the mean score was observed among the parents of the <6 age group and the participants in the 6 to <12 years age group observed some reduction, a small improvement among the parents of the 6 to <12 year group (Table 58).

Table 58: Summary of mean change in PROMIS-SF Physical Function score from baseline to Week 52

Group	PROMIS-SF Physical Function
<6 years old (parents of participants ≥5 years)	
Mean (SD) at baseline	50.93 (3.47) (n=8)
Mean (SD) change from Baseline to Week 52	3.96 (6.73) (n=7)
6 to <12 years old (participants aged ≥8 years)	
Mean (SD) at baseline	51.71 (10.44) (n=14)
Mean (SD) change from Baseline to Week 52	0.78 (10.48) (n=10)
6 to <12 years old (parents of participants <12 years)	
Mean (SD) at baseline	50.74 (10.55) (n=18)
Mean (SD) change from Baseline to Week 52	-1.36 (12.15) (n=10)

Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; SF, Short form.

Source: (Sobi 2023)

B.2.1.4 HJHS

The HJHS was used in participants aged ≥4 years at Baseline, Week 26 and Week 52. 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 on motion, flexion loss, extension loss, joint pain, and strength. Gait was scored based on walking and climbing stairs. The total score was the sum of scores from all 6 joints plus the gait score (range 0 to 124, highest score being the most severe disease) (Sobi 2023).

In the <6 years of age cohort, the mean (SD) HJHS Total score at Baseline was 2.4 (7.1) in 20 participants that were aged ≥4 years. The mean change (SD) in HJHS Total score from baseline to Week 52 was 0.2 (8.3) in 18 participants. In the 6 to <12 years of age cohort, the mean (SD) HJHS Total score at Baseline was 2.1 (4.5) in 35 participants. The mean change (SD) in HJHS Total score from baseline to Week 52 was -1.1 (4.3) in 33 participants (Sobi 2023).

B.2.1.5 Trough FVIII levels and elimination plasma half-life

At steady state, the analysis of time above specified FVIII activity levels showed a mean (SD) time above near-normal levels (>40 IU/dL) of 3 days and time above 10 IU/dL of approximately 7 days, indicating high sustained FVIII activity over a weekly dosing interval of efanesoctocog alfa. The mean (SD) terminal half-life of efanesoctocog alfa was 42.4 (3.70) hours and 38.0 (3.72) hours in 6 to <12 years and <6 years of age cohorts, respectively.

B.2.2 Safety

All 74 participants enrolled in the study received at least one dose of efanesoctocog alfa and were included in the Safety Analysis Set (Sobi 2023). There were 73 (98.6%) participants treated for at least 39 weeks and 56 (75.7%) participants treated for at least 52 weeks. The mean (SD) total number of exposure days per participant was 52.5 (7.2) and 66 (89.2%) participants achieved at least 50 exposure days.

The primary endpoint was the occurrence of inhibitor development to FVIII, and no FVIII inhibitor was detected during the study. By Nijmegen-modified Bethesda assay, the incidence of inhibitor development to FVIII was 0.0% (95% CI: 0.0 to 5.5) in participants with ≥50 exposure days to efanesoctocog alfa. There were no reports of serious allergic reaction, anaphylaxis, or embolic and thrombotic events, and no clinically meaningful patterns or trends identified in laboratory or vital sign parameters.

Three (4.1%) participants were positive samples for anti-drug antibodies at Baseline before receiving efanesoctocog alfa, all in the <6 years of age cohort, but all of them were tested negative for anti-drug antibodies later in the study.

Of the 74 participants in the Safety Analysis Set (Table 28), 62 (83.8%) experienced a total of 255 TEAEs: 33 (86.8%) participants in the <6 years of age cohort experienced 146 TEAEs and 29 (80.6%) participants in the 6 to <12 years of age cohort experienced 108 TEAEs. In the surgery subgroup, 1 TEAE was reported in 1 (50.0%) participant. Overall, 10 TESAE were reported in 9 (12.2%) participants, including 5 participants aged <6 years and 4 participants aged 6 to <12 years (Appendix E). No TEAEs resulting in death or leading to treatment discontinuation were reported.

The majority of TEAEs were assessed by the Investigator as mild in severity and not related to efanesoctocog alfa. Subgroup analyses of TEAEs by predefined intrinsic factors were generally consistent with TEAEs in the overall study population. No unique patterns

or trends were identified in any subgroup, and there were no unique safety findings identified during the major surgery/rehabilitation period.

The most frequently reported TEAEs (>5% of participants overall) were SARS-CoV-2 test positive and upper respiratory tract infection (11 [14.9%] participants, each), pyrexia (9 [12.2%] participants), asymptomatic COVID-19 (7 [9.5%] participants), gastroenteritis viral, nasopharyngitis, and head injury (6 [8.1%] participants, each), vomiting, arthralgia and pain in extremity (5 [6.8%] participants, each), viral infection, viral upper respiratory tract infection, contusion, and diarrhoea (4 [5.4%] participants, each) (Sobi 2023).

B.2.3 Quality of life

Disease-specific quality of life data were collected at Baseline, Week 26, and Week 52 in participants aged 4 to 7 years, in participants aged 8 to <12 years, and in respective caregivers via 4 separate Haemo-QoL questionnaires. Lower scores represent better quality of life, and therefore a negative change from baseline represents improvement during the course of the study. In the study, 21 participants were aged 4 to <6 years, 16 participants aged 6 to 7 years, and 20 participants aged 8 to <12 years. An improvement was observed in the mean Haemo-QoL score in all age cohorts, apart from 4 trial participants in the 6 to 7 years age cohort where the mean (SD) change from Baseline showed 4.69 (5.41) unit increase in the Haemo-QoL total score at 52 weeks (Table 59).

Table 59: Summary of mean change in Haemo-QoL total scores from baseline to Week 52

Group	Haemo-QoL total score		
4 to 7 years old	**4 to <6 years (n=21)**	**6 to 7 years (n=16)**	**4 to 7 years (n=37)**
Mean (SD) change from Baseline to Week 52	-5.31 (10.83) (n=10)	4.69 (5.41) (n=4)	-2.46 (10.49) (n=14)
Parents of 4 to 7 years old	**4 to <6 years (n=21)**	**6 to 7 years (n=16)**	**4 to 7 years (n=37)**
Mean (SD) change from Baseline to Week 52	-3.21 (12.23) (n=19)	-1.17 (11.08) (n=4)	-2.85 (11.82) (n=23)
8 to <12 years old		**8 to <12 years (n=20)**	
Mean (SD) change from Baseline to Week 52		-9.79 (12.18) (n=10)	

SD, standard deviation

Source: (Sobi 2023)

An improvement was observed in the mean Haemo-QoL physical health domain score among the study participants and their parents (Table 60). Data were only analysed from the 8 to <12 years age group and their parents.

Table 60: Summary of mean change in Haemo-QoL physical health domain score from baseline to Week 52

Group	Haemo-QoL physical health score
8 to <12 years old	
Mean (SD) at baseline	19.64 (19.12) (n=14)
Mean (SD) change from Baseline to Week 52	-10.63 (14.75) (n=10)
Parents of 8 to <12 years old	
Mean (SD) at baseline	16.35 (15.00) (n=13)
Mean (SD) change from Baseline to Week 52	-7.64 (11.60) (n=9)

SD, standard deviation

Source: (Sobi 2023)

The EuroQol-5D-Youth (EQ-5D-Y) child version and its parent of participant version were collected for participants aged 8 to <12 years and participants aged 4 to 7 years, respectively, at Baseline, Week 26 and Week 52.

The EQ 5D-Y was assessed for mobility, looking after myself, doing usual activities, having pain or discomfort, and feeling worried, sad or unhappy. Overall, participants or their parents reported no problems from baseline to end of study across all dimensions. Of note, the percentage of participants who reported feeling a bit worried (or very), sad or unhappy decreased from 34.5% (including 3.4% very worried) and 21.4% to 13.8% and 5.9% in parents of participants aged 4 to <6 years and participants aged 8 to <12 years, respectively.

B.3 Results per HAVEN III

Table 61 Results per HAVEN III (group D)

Results of HAVEN-3 (NCT02847637)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized rate of bleeding events, model-based (95%). Bleeding events treated with FVIII therapy	Emicizumab Once weekly	36	1.5 (0.9 - 2.5)				Rate ratio: 0.04	0.02 – 0.08		Assessed using a negative binomial (NB) regression model with the number of bleeds as a function of randomization and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor.	
	Control No prophylaxis	18	38.2 (22.9 - 63.8)								
Annualized rate of bleeding	Emicizumab Once weekly	36	2.5 (1.6 - 3.9)				0.05	0.03 - 0.10		Assessed using a negative binomial (NB) regression model with the number of	

Results of HAVEN-3 (NCT02847637)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
events, model-based (95%). All bleeding events, regardless of treatment with FVIII therapy	Control No prophylaxis	18	47.6 (28.5 - 79.6)							bleeds as a function of randomization and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor.	
Annualized Bleeding Rate (ABR) for Treated Joint Bleeds	Emicizumab Once weekly	36	1.1 (0.59 - 1.89)				0.04	0.02 – 0.09	<0.0001	Assessed using a negative binomial (NB) regression model with the number of bleeds as a function of randomization and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to	
	Control No prophylaxis	18	26.5 (14.67 - 47.79)								

Results of HAVEN-3 (NCT02847637)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										study entry as a stratification factor.	
Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds	Emicizumab Once weekly	36	1.0 (0.48 - 1.91)				0.06	0.025 - 0.151	<0.0001	Assessed using a negative binomial (NB) regression model with the number of bleeds as a function of randomization and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor.	
	Control No prophylaxis	18	15.6 (7.60 - 31.91)								

Appendix C. Comparative analysis of efficacy

C.1 Method of synthesis

The XTEND-1 trial assessing efanesoctocog alfa is a 2-arm, parallel-design, non-randomised trial. Patients who had been previously receiving FVIII prophylaxis were allocated to efanesoctocog alfa prophylaxis for 52 weeks (Arm A). Those receiving on demand treatment were allocated to ARM B, in which they were receiving on demand efanesoctocog alfa for 26 weeks followed by prophylaxis with the same substance. The design of the XTEND-1 trial does not allow to form connected networks with the comparator trial (HAVEN III), therefore an anchored comparison with methods such as Bucher's indirect comparison or network meta-analysis is not feasible for the comparison between efanesoctocog alfa and emicizumab.

According to the algorithm presented in the NICE DSU TSD 18 document, a population-adjusted indirect comparison shall be considered to compare the interventions which does not have a connected network with any of the comparator treatment regimen and cannot be compared through common anchor (which would require RCTs with common comparator). The treatment vs comparator comparison is meaningful on the assumption that the population distributions for the interventions being compared are similar enough. The population-adjusted ITC methods minimise the risk of bias through balancing of the between-treatment differences in baseline characteristics. The effects of interventions assessed in disconnected studies was compared after imposing constraints on XTEND-1 population based on comparator study inclusion/exclusion criteria and reported ranges of baseline characteristics values, followed by using methods proposed in the NICE TSD 18 guidelines: unanchored matching-adjusted indirect comparison (MAIC) and simulated treatment comparisons (STC) (Phillippo et al. 2016). A potentially even better balancing in baseline characteristics resulted in a further reduction of the risk of bias can be obtained in the case of access to patient-level data for both compared studies. According to NICE DSU TSD 17 document a method to consider, similar to MAIC, is the propensity score matching (PSM) method which estimate the probability of treatment assignment as a function of a set of observable covariates and the probabilities are used for weighting patients according to similarity in baseline characteristics to estimate the average treatment effect (Dias et al. 2011).

Unanchored indirect comparison is used when networks are disconnected and only single arms from respective trials can be used. An unanchored indirect comparison uses evidence from a treatment A arm (e.g., efanesoctocog alfa in XTEND-1) to generate an estimate $\hat{Y}_{A(B)}$ of absolute response in the population of the trial assessing comparator (B). This is compared with the estimates reported in the comparator trial $\hat{Y}_{B(B)}$. The unbiased estimator of the relative effect between A and B is

$$\hat{d}_{AB} = g(\hat{Y}_{B(B)}) - g(\hat{Y}_{A(B)})$$

To compare efanesoctocog alfa with other treatments for haemophilia A, SANOFI/SOBI provided C-C with patient-level data from XTEND-1 trial. For almost all studies assessing comparators only aggregated data regarding baseline characteristics and outcomes were available, therefore the comparison between efanesoctocog alfa and other therapies is feasible only with methods designed for indirect treatment comparison of disconnected evidence, such as MAIC and STC. Using MAIC, each patient from XTEND-1 trial was assigned with weights based on similarity to aggregated characteristics of respective arms assessing each comparator regimen. The effect estimates from the XTEND-1 trial was recalculated using assigned weights to estimate the effect of efanesoctocog alfa in the population of the comparator trial.

Matching-Adjusted Indirect Comparison (MAIC) is a non-parametric likelihood reweighting method, which allows the propensity score logistic regression model to be estimated without access to IPD in one study.

The method is dedicated to compare two treatments assessed in different studies (study A and study B). It can be used when IPD for one trial (A) are available and aggregated outcomes are reported for comparator (B). Ideally, a full joint distribution of X covariates in the population of study B is known however, reporting on aggregated data is usually restricted to an average treatment effect and a summary statistics of patient baseline characteristics. This means that only mean/median and standard deviation for continuous covariates, and proportion of individuals with a binary/categorical trait can be used in analysis.

To compare mean estimates between outcomes of treatments A and B using standard statistical methods, between-trial imbalances in patient characteristics should be adjusted for, including all effect modifiers and prognostic factors.

The proceeding step is the estimation of weights w_i using logistic regression as

$$\log(w_i) = \alpha_0 + {\alpha_1}^T {X_i}^{EM},$$

where ${X_i}^{EM}$ is the covariate vector for the i-th individual. However, due to the lack of IPD in B trial a method of moments instead of standard tools is used to estimate $\hat{\alpha}_1$. This is equivalent to minimising

$$\sum_{i=1}^{N_A} e^{{\alpha_1}^T {X_i}^{EM}},$$

when ${\bar{X}_B}^{EM} = 0$. To satisfy that condition, centred versions of effect modifiers are created by subtracting ${\bar{X}_B}^{EM}$ from X^{EM} in both trials.

Each individual receiving treatment A is assigned the weight estimated as the odds ratio of being enrolled in B trial versus A trial. As a result, the weighted average characteristics of study A participants match the aggregated baseline characteristics of study B. Then, treatment effects observed in A trial are recalculated by means of estimated weights and can be compared with the outcomes reported in B trial. The estimator of mean outcome on treatment A in study B population is expressed by the formula

$$\hat{Y}_{A(B)} = \frac{\sum_{i=1}^{N_A} Y_i e^{\hat{\alpha}_1{}^T X_i}}{\sum_{i=1}^{N_A} e^{\hat{\alpha}_1{}^T X_i}},$$

where Y_i denotes outcome observed for i-th individual in study A population.

There is no generally applicable formula for standard error of the weighted average. The precision of re-weighted effects therefore was estimated with bootstrap method (Gatz and Smith 1995).

C.1.1 Dealing with observations with extraordinary large weights

Distribution of the assigned weights was recorded and presented using adequate bar charts. The base-case analysis was conducted with unmodified weights, regardless of the distribution. In case when one or more patients was assigned with weights >10 a sensitivity analysis was conducted after capping the extraordinarily high weights at 10.

C.1.2 Effective sample size

The effective sample size (ESS) of the population formed by weighting of the XTEND-1 cohort was estimated following Signorovitch et al. (Signorovitch et al. 2010).

$$ESS = \frac{\left(\sum_{t=A,B} \sum_{i=1}^{N_{t(AB)}} \widehat{w}_{it}\right)^2}{\sum_{t=A,B} \sum_{i=1}^{N_{t(AB)}} \widehat{w}_{it}{}^2}$$

Small sample sizes indicate poor overlapping of the populations, which may lead to unstable results and biased estimates.

C.2 MAIC results

Results of the MAIC are summarised in Table 62.

Table 62 Comparative analysis of studies comparing Efanesoctocog alfa to Emicizumab for patients with haemophilia A

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
ABR (any bleeding) (IRR)	XTEND-1 (Arm A) HAVEN III (Group D)	NA	NA	NA	RRR: 0.32	0.19–0.56		Matching-Adjusted Indirect Comparison (MAIC), a non-parametric likelihood reweighting method using IPD data from the XTEND-1 trial.	[redacted]
ABR (any treated bleeding) (IRR)	XTEND-1 (Arm A) HAVEN III (Group D)	NA	NA	NA	RRR: 0.50	0.29-0.86	0.50	Matching-Adjusted Indirect Comparison (MAIC), a non-parametric likelihood reweighting method using IPD data from the XTEND-1 trial.	[redacted]
ABR (spontaneous treated bleeding) (IRR)	XTEND-1 (Arm A) HAVEN III (Group D)	NA	NA	NA	RRR: 0.62	0.25-1.50		Matching-Adjusted Indirect Comparison (MAIC), a non-parametric likelihood reweighting method using	[redacted]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
								IPD data from the XTEND-1 trial.	
ABR (joint treated bleeding) (IRR)	XTEND-1 (Arm A) HAVEN III (Group D)	NA	NA	NA	RRR: 0.48	0.24-0.95		Matching-Adjusted Indirect Comparison (MAIC), a non-parametric likelihood reweighting method using IPD data from the XTEND-1 trial.	■

Appendix D. Extrapolation

Not applicable

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

All serious adverse events in XTEND-1 (arm A) and XTEND-kids are reported in Table 63

Table 63: Serious adverse events in XTEND-1 (arm A) and XTEND-kids by SOC PT

TESAE	XTEND-1 (arm A) N=133	XTEND-kids N=74
CARDIAC DISORDERS		
Angina pectoris	1 (0.8)	-
GASTROINTESTINAL DISORDERS		
Eosinophilic oesophagitis	-	1 (1.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Vascular device occlusion	-	1 (1.4)
INFECTIONS AND INFESTATIONS		
Vascular device infection	-	2 (2.7)
Bacteraemia	-	1 (1.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Head injury	-	1 (1.4)
INVESTIGATIONS		
Blood glucose increased	1 (0.8)	-
CD4 lymphocytes decreased	1 (0.8)	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Combined tibia-fibula fracture	1 (0.8)	-
Traumatic haemorrhage	1 (0.8)	-
METABOLISM AND NUTRITION DISORDERS		
Dehydration	-	1 (1.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthropathy	1 (0.8)	-
Haemophilic arthropathy	2 (1.5)	-

Mobility decreased	1 (0.8)	-
NEOPLASMS BENIGN, MALIGNANT ANDUNSPECIFIED (INCL CYSTS AND POLYPS)		-
Basal cell carcinoma	1 (0.8)	
NERVOUS SYSTEM DISORDERS		
Cubital tunnel syndrome	1 (0.8)	-
Status epilepticus	1 (0.8)	-
Ulnar tunnel syndrome	1 (0.8)	-
PRODUCT ISSUES		
Device breakage	1 (0.8)	-
Device malfunction	-.	1 (1.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Asthma	-	1 (1.4)
SURGICAL AND MEDICAL PROCEDURES		
Central venous catheter removal	1 (0.8)	-
Circumcision	-	1 (1.4)

SOC, system organ class; TESAE, treatment-emergent serious adverse event; PT, preferred term
Note 1: Percentages are based on the number of participants in the Safety Analysis Set.
2: Events are coded using MedDRA version 25.1.
3: Participants are counted once if they reported multiple events in the same system organ class or preferred term.
4: Table sorted by SOC internationally agreed order and decreasing frequency of PT in the overall group.
5: AEs which occur during a major surgical/rehabilitation period are excluded from this table, but AEs which occur on the day of the major surgical/rehabilitation period starts will be included.

Source: (Sobi 2022, Sobi 2023)

Appendix F. Health-related quality of life

Not applicable

Appendix G. Probabilistic sensitivity analyses

Not applicable

Table 64. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution

Appendix H. Literature searches for the clinical assessment Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of efanesoctocog alfa and relevant comparators for the treatment of patients with haemophilia A in 2022. This SLR was later updated to include publications up until September 2023. In total, the updated SLR identified 176 publications reporting on 105 unique studies, of which 65 publications reporting on 49 unique studies were included for full data extraction. Methods and results are presented and described in the following sections. Search strings and results are presented separately for the two data cuts.

Table 65 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	Database inception to date of search	Original search: 10.02.2021 Updated search: 06.09.2023
MEDLINE Daily, In-Process & Other Non-indexed citations, and e-pub ahead-of-print			
Cochrane library- Cochrane Central Register of Controlled Trials			
Cochrane library – Cochrane Database of Systematic Reviews			

Table 66 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinical trial registries	United States National Institutes of Health (NIH) trial registry & results database (https://clinicaltrials.gov/) World Health Organization International Clinical Trials Registry Platform (WHO	Electronic search	10.02.2021 06.09.2023 (update)

Source name	Location/source	Search strategy	Date of search
	ICTRP: https://www.who.int/ictrp/search/en/).		
Previous HTA submissions	National Institute for Health and Care Excellence (NICE) Scottish Medicines Consortium (SMC) National Centre for Pharmacoeconomics (NCPE) Pharmaceutical Benefits Advisory Committee (PBAC) Canadian Agency for Drugs and Technologies in Health (CADTH) Haute Autorité de Santé (HAS) German Institute for Quality and Efficiency in Health Care (IQWiG) Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA]) Institute for Clinical and Economic Review (ICER).	Electronic search	10.02.2021 06.09.2023 (update)

Table 67 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
European Hematology Association (EHA)	https://ehaweb.org/	Manual search	NA Not available	10.02.2021 06.09.2023 (update)
World Federation of Hemophilia (WFH)	https://wfh.org/	Manual search	NA Not available	10.02.2021 06.09.2023 (update)

Abbreviations. NA, Not applicable.

Additionally, Bibliographic reference lists of included studies, relevant SLRs, and of relevant HTA documents were screened. Relevant unpublished clinical study reports (CSRs) provided by Sobi were also eligible for inclusion.

H.1.1 Search strategies

The first tables cover the original search of date 02.10.2021 (also indicated in table captions). The latter tables cover the updated search dated 06.09.2023.

Table 68 of search strategy table for Embase - Search 02.10.2021

No.	Query	Results
#1	("hemophilia A" or "haemophilia A" or "congenital Factor VIII deficiency" or "hemophilia type a" or "haemophilia type a").ab,ti.	16,800
#2	exp hemophilia a/	21,915
#3	"classical hemophilia".ab,ti OR "classical haemophilia".ab,ti OR "classic hemophilia".ab,ti OR "classic haemophilia".ab,ti	216
#4	("factor viii" adj4 deficien*).ab,ti. or ("factor 8" adj4 deficien*).ab,ti. or ("factor eight" adj4 deficien*).ab,ti.	1,723
#5	(hemophilia.ti OR haemophilia.ti) NOT (("hemophilia B" or "haemophilia B" or "congenital Factor IX deficiency" or "hemophilia type b" or "haemophilia type b" or "christmas disease").ab,ti. OR exp hemophilia b/ OR (("factor ix" adj4 deficien*) or ("factor 9" adj4 deficien*) or ("factor nine" adj4 deficien*) or ("fix" adj4 deficien*)).ab,ti.)	15,771
#6	or/1-5	29,126
#7	(acquired hemophilia).ab,ti.	1,241
#8	6 not 7	28,010
#9	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or PLACEBOS/	1,870,439
#10	(clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	0
#11	((clinical adj trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$)).tw.	931,879
#12	(phase ii$ or phase iii$ or phase iv$ or phase 2$ or phase 3$ or phase 4$).tw.	234,415
#13	Non Randomized Controlled Trials as Topic/ or (Non randomi?ed adj3 trial?).tw. or (Nonrandomi?ed adj3 trial?).tw. or "Quasi Experimental".tw.	37,719
#14	(single arm or open label).tw.	97,083
#15	case report.tw. or letter/ or historical article/ or review.tw.	3,546,349
#16	(or/9-14) not 15	1,974,134

No.	Query	Results
#17	exp animal/	26,734,150
#18	nonhuman/	6,460,191
#19	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).tw.	4,859,320
#20	or/17-19	28,742,415
#21	exp Human/ or "Human Experiment"/	21,974,016
#22	20 NOT (20 AND 21)	6,769,386
#23	8 AND 16 NOT 22	2,623
#24	limit 23 to English	2,540
#25	limit 24 to yr="1980-Current"	2,529
#26	remove duplicates from 25	2,490

Table 69 of search strategy table for Medline - Search 02.10.2021

No.	Query	Results
#1	("hemophilia A" or "haemophilia A" or "congenital Factor VIII deficiency" or "hemophilia type a" or "haemophilia type a").ab,ti.	8,529
#2	exp hemophilia a/	20,882
#3	"classical hemophilia".ab,ti OR "classical haemophilia".ab,ti OR "classic hemophilia".ab,ti OR "classic haemophilia".ab,ti	215
#4	("factor viii" adj4 deficien*).ab,ti. or ("factor 8" adj4 deficien*).ab,ti. or ("factor eight" adj4 deficien*).ab,ti.	1,055
#5	(hemophilia.ti OR haemophilia.ti) NOT (("hemophilia B" or "haemophilia B" or "congenital Factor IX deficiency" or "hemophilia type b" or "haemophilia type b" or "christmas disease").ab,ti. OR exp hemophilia b/ OR (("factor ix" adj4 deficien*) or ("factor 9" adj4 deficien*) or ("factor nine" adj4 deficien*) or ("fix" adj4 deficien*)).ab,ti.)	10,768
#6	or/1-5	23,505
#7	(acquired hemophilia).ab,ti.	644
#8	6 not 7	22,913

No.	Query	Results
#9	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or PLACEBOS/	1,207,059
#10	(clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	1,038,712
#11	((clinical adj trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$)).tw.	645,243
#12	(phase ii$ or phase iii$ or phase iv$ or phase 2$ or phase 3$ or phase 4$).tw.	122,890
#13	Non Randomized Controlled Trials as Topic/ or (Non randomi?ed adj3 trial?).tw. or (Nonrandomi?ed adj3 trial?).tw. or "Quasi Experimental".tw.	20,976
#14	(single arm or open label).tw.	50,074
#15	case report.tw. or letter/ or historical article/ or review.tw.	3,366,434
#16	(or/9-14) not 15	1,538,120
#17	exp animal/	23,803,587
#18	nonhuman/	0
#19	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).tw.	4,200,626
#20	or/17-19	24,164,260
#21	exp Human/ or "Human Experiment"/	21,974,016
#22	20 NOT (20 AND 21)	6,769,386
#23	8 AND 16 NOT 22	1,607
#24	limit 23 to English	1,527
#25	limit 24 to yr="1980-Current"	1,489
#26	remove duplicates from 25	1,481

Table 70 of search strategy table for Cochrane - Search 02.10.2021

No.	Query	Results
#1	("hemophilia A" or "haemophilia A" or "congenital Factor VIII deficiency" or "hemophilia type a" or "haemophilia type a").ab,ti.	1,354
#2	exp hemophilia a/	428
#3	"classical hemophilia".ab,ti OR "classical haemophilia".ab,ti OR "classic hemophilia".ab,ti OR "classic haemophilia".ab,ti	0
#4	("factor viii" adj4 deficien*).ab,ti. or ("factor 8" adj4 deficien*).ab,ti. or ("factor eight" adj4 deficien*).ab,ti.	52
#5	(hemophilia.ti OR haemophilia.ti) NOT (("hemophilia B" or "haemophilia B" or "congenital Factor IX deficiency" or "hemophilia type b" or "haemophilia type b" or "christmas disease").ab,ti. OR exp hemophilia b/ OR (("factor ix" adj4 deficien*) or ("factor 9" adj4 deficien*) or ("factor nine" adj4 deficien*) or ("fix" adj4 deficien*)).ab,ti.)	707
#6	or/1-5	1,540
#7	(acquired hemophilia).ab,ti.	13
#8	6 not 7	1,527
#9	limit 8 to English	939
#10	limit 9 to yr="1980-Current"	914
#11	remove duplicates from 10	884

Table 71 of search strategy table for Embase – Search 06.09.2023

No.	Query	Results
#1	(“hemophilia A” or “haemophilia A” or “congenital Factor VIII deficiency” or “hemophilia type a” or “haemophilia type a”).ab,ti.	20145
#2	exp hemophilia a/	25625
#3	(“classical hemophilia” or “classical haemophilia” or “classic hemophilia” or “classic haemophilia”).ab,ti.	216
#4	((“factor viii” adj4 deficien*) or (“factor 8” adj4 deficien*) or (“factor eight” adj4 deficien*)).ab,ti.	2011
#5	(hemophilia or haemophilia).ti. not ((“hemophilia B” or “haemophilia B” or “congenital Factor IX deficiency” or “hemophilia type b” or “haemophilia type b” or “ nglish s disease”).ab,ti. Or exp hemophilia b/ or ((“factor ix” adj4 deficien*) or	18238

No.	Query	Results
	(“factor 9” adj4 deficien*) or (“factor nine” adj4 deficien*) or (“fix” adj4 deficien*)).ab,ti.)	
#6	or/1-5	33619
#7	acquired hemophilia.ab,ti.	1560
#8	6 not 7	32194
#9	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or PLACEBOS/	2157922
#10	(clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	0
#11	((clinical adj trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$)).tw.	1119297
#12	(phase ii$ or phase iii$ or phase iv$ or phase 2$ or phase 3$ or phase 4$).tw.	288456
#13	Non Randomized Controlled Trials as Topic/ or (Non randomi?ed adj3 trial?).tw. or (Nonrandomi?ed adj3 trial?).tw. or “Quasi Experimental”.tw.	48909
#14	(single arm or open label).tw.	127429
#15	case report.tw. or letter/ or historical article/ or review.tw.	4276517
#16	(or/9-14) not 15	2276691
#17	8 and 16	3365
#18	animal/	1632873
#19	nonhuman/	7437200
#20	exp animal experiment/	3070451
#21	exp experimental animal/	819370
#22	animal model/	1709448
#23	exp rodent/	4027643
#24	(rat or rats or mouse or mice).ti.	1610946
#25	or/18-24	9945082
#26	human/ and 25	2802031

No.	Query	Results
#27	25 not 26	7143051
#28	17 not 27	3285
#29	limit 28 to english language	3194
#30	limit 29 to dc=20210210-20230906	693

Table 72 of search strategy table for Medline - Search 06.09.2023

No.	Query	Results
#1	("hemophilia A" or "haemophilia A" or "congenital Factor VIII deficiency" or "hemophilia type a" or "haemophilia type a").ab,ti.	10006
#2	exp hemophilia a/	22898
#3	("classical hemophilia" or "classical haemophilia" or "classic hemophilia" or "classic haemophilia").ab,ti.	221
#4	(("factor viii" adj4 deficien*) or ("factor 8" adj4 deficien*) or ("factor eight" adj4 deficien*)).ab,ti.	1196
#5	(hemophilia or haemophilia).ti. not (("hemophilia B" or "haemophilia B" or "congenital Factor IX deficiency" or "hemophilia type b" or "haemophilia type b" or "christmas disease").ab,ti. or exp hemophilia b/ or (("factor ix" adj4 deficien*) or ("factor 9" adj4 deficien*) or ("factor nine" adj4 deficien*) or ("fix" adj4 deficien*)).ab,ti.)	12219
#6	or/1-5	25759
#7	acquired hemophilia.ab,ti.	844
#8	6 not 7	24974
#9	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or PLACEBOS/	1330894
#10	(clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	1169511
#11	((clinical adj trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$)).tw.	780169
#12	(phase ii$ or phase iii$ or phase iv$ or phase 2$ or phase 3$ or phase 4$).tw.	148286

No.	Query	Results
#13	Non Randomized Controlled Trials as Topic/ or (Non randomi?ed adj3 trial?).tw. or (Nonrandomi?ed adj3 trial?).tw. or "Quasi Experimental".tw.	29368
#14	(single arm or open label).tw.	65389
#15	case report.tw. or letter/ or historical article/ or review.tw.	4038721
#16	(or/9-14) not 15	1746168
#17	8 and 16	1868
#18	animals/	7319299
#19	exp animals, laboratory/	952522
#20	exp animal experimentation/	10354
#21	exp models, animal/	642536
#22	exp rodentia/	3555130
#23	(rat or rats or mouse or mice).ti.	1444691
#24	or/18-23	7434033
#25	humans/ and 24	2209139
#26	24 not 25	5224894
#27	17 not 26	1851
#28	limit 27 to english language	1767
#29	limit 28 to ed=20210210-20230906	224

Table 73 of search strategy table for Cochrane - Search 06.09.2023

No.	Query	Results
#1	("hemophilia A" or "haemophilia A" or "congenital Factor VIII deficiency" or "hemophilia type a" or "haemophilia type a").ab,ti.	964
#2	exp hemophilia a/	652
#3	("classical hemophilia" or "classical haemophilia" or "classic hemophilia" or "classic haemophilia").ab,ti.	0

No.	Query	Results
#4	(("factor viii" adj4 deficien*) or ("factor 8" adj4 deficien*) or ("factor eight" adj4 deficien*)).ab,ti.	63
#5	(hemophilia or haemophilia).ti. not (("hemophilia B" or "haemophilia B" or "congenital Factor IX deficiency" or "hemophilia type b" or "haemophilia type b" or "christmas disease").ab,ti. or exp hemophilia b/ or (("factor ix" adj4 deficien*) or ("factor 9" adj4 deficien*) or ("factor nine" adj4 deficien*) or ("fix" adj4 deficien*)).ab,ti.)	827
#6	or/1-5	1342
#7	acquired hemophilia.ab,ti.	10
#8	6 not 7	1332
#9	limit 8 to english language [Limit not valid in CDSR; records were retained]	1314
#10	limit 9 to yr="2021 -Current"	166

H.1.2 Systematic selection of studies

Two independent reviewers screened citations by title/abstract, with any conflicts resolved by a third, more senior investigator. Full-text articles were screened by two independent reviewers against the selection criteria to ensure the methodology and results were relevant. Disputes regarding eligibility were referred to a third, more senior investigator.

The pre-specified inclusion and exclusion criteria are detailed in Table 74.

Table 74 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients or patient subgroup with hemophilia A with or without inhibitors	• Acquired hemophilia • Patients with conditions other than hemophilia A with or without inhibitors • Not in humans • Subpopulations (e.g., undergoing surgery, undergoing knee replacement, hemarthroses, dental extraction, circumcision, pregnancy, obesity)

Intervention	• Prophylaxis or on-demand use of: 1) non-factor replacement therapies (e.g., emicizumab, fitusiran, anti-TFPI [anti-tissue factor pathway inhibitor] and gene therapies), and 2) FVIII-replacement therapies, including standard half-life (SHL) and extended half-life (EHL) recombinant therapies (e.g., Efanesoctocog alfa, antihemophilic factor [recombinant], PEGylated; GlycoPEGylated-exei; single chain)	• Interventions others than prophylaxis or on-demand use of 1) non-factor replacement therapies (e.g., emicizumab, fitusiran, anti-TFPI [anti-tissue factor pathway inhibitor] and gene therapies), and 2) FVIII-replacement therapies, including standard half-life and extended half-life recombinant therapies (e.g., Efanesoctocog alfa, 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.
Comparators	NIL	NIL
Outcomes	• Annualized bleeding rate • Annualized spontaneous bleeding rate (AsBR) • Annualized joint bleeding rate (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/publication type	• Phase III randomized controlled trials (RCTs) and non-RCTs (single arm trials, and open label extension trials)	• Observational studies • Systematic literature reviews, meta-analyses (for bibliography check only) • Case reports or editorial comments

		• Non-phase III studies (including phase I, I/II, II, and IV)
Language restrictions	English language publications	Non-English language publications

H.1.2.1 Data collection process

Data was extracted from the relevant full-text publications identified in the current SLR 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 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 shown below.

Table 75 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., randomization ratio, stratification factors, cross-over) Trial duration/follow-up Blinding Sample size	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	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 patient-reported outcome (PRO) measures (e.g., Haem-A-QoL) HJHS/mHJHS

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	Infections (e.g., HIV, HCV)		

H.1.2.2 Results

Figure 18 shows the PRISMA diagram for the study selection in the original SLR datacut 02.10.2021. Of the 3,551 unique records identified in literature search, 1,184 conference abstracts and 24 publications prior to 1988 were excluded. A total of 2,343 citations were assessed for eligibility based on title and abstract. During the full-text review, 187 publications were further assessed for eligibility. A total of 102 publications met the inclusion/exclusion criteria. A total of 39 publications corresponding to 32 unique trials were extracted. The PRISMA diagram from the updated search is shown in Figure 19. The updated search included 63 eligible publications. Data was extracted from 26 of these, which were added to the original 39 publications. In total, data was extracted from 65 publications corresponding to 49 unique trials. Publications that were assessed as eligible but without extraction were not extracted because of the following reasons: terminated trials/interventions (e.g., the early termination of EPIC trial for Advate due to protocol deviation), pooled results for a mixed populations (e.g., Haemophilia A and B, with and without inhibitors), geographically limited trial populations (e.g., a subpopulation of the trials or trials conducted in a single Asian country), extension studies, and only reported on PROs that were not commonly available across studies (e.g., treatment satisfaction). See section H.1.2.3.

For the purpose of this Danish submission, an additional selection of studies to report in the efficacy and safety sections was made, see last part of PRISMA Figure 19. Only 3 studies of relevance for the assessment of efanesoctocog alfa and emicizumab, for the relevant population (patients above age 12 with severe haemophilia A without inhibitors and with data reported separately for patients with prior prophylactic treatment), were included. Although not representing the relevant patient population, an additional study was also added to support the Danish submission, considering it is of value for assessment of safety (XTEND-Kids).

Figure 18 PRISMA diagram of search 02.10.2021

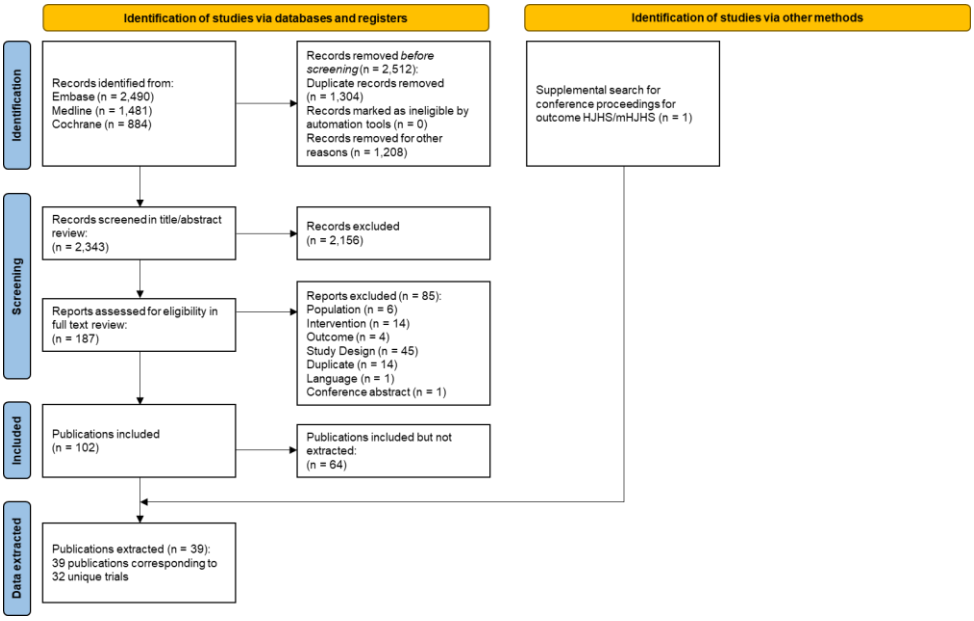
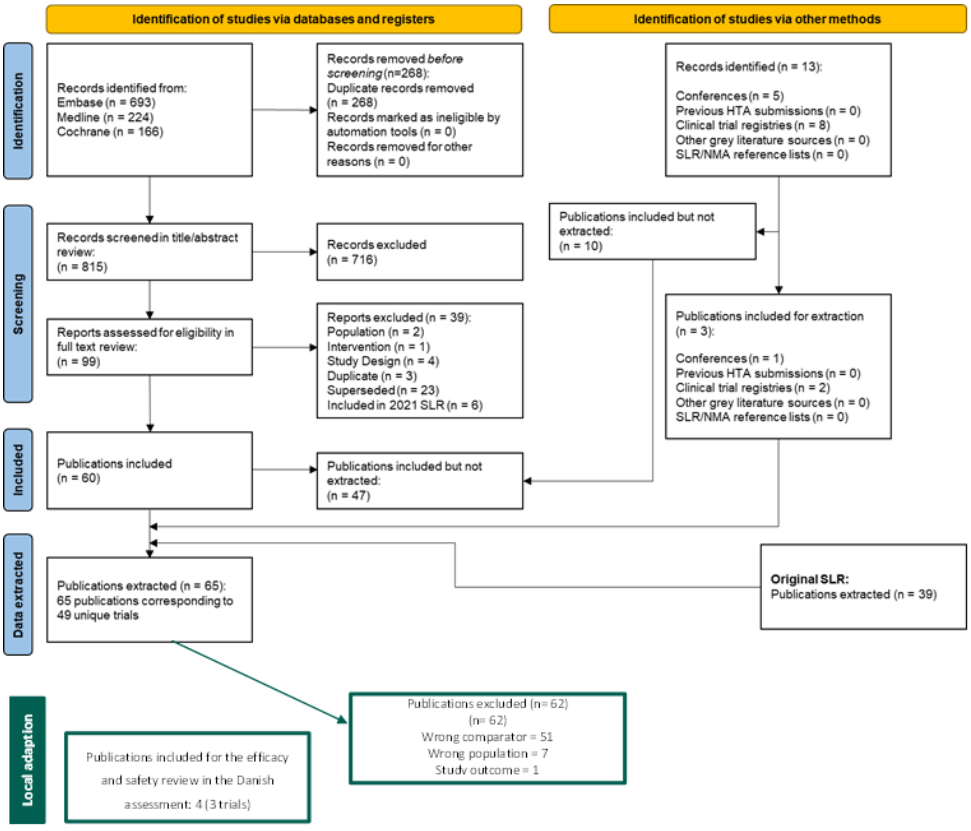


Figure 19 PRISMA diagram of search 06.09.2023



H.1.2.3 Studies excluded from MAIC analyses

The global SLR was used as the basis for the global indirect treatment comparison (ITC). The excluded publications are listed below in Table 76. See section H.1.2.4 for additional exclusion grounds for the Danish assessment.

Table 76 Publications (N=85 + 39 in update) excluded for the ITC

First Author	Year	Title	Reason for exclusion
Abildgaard CF	1991	Immunologic safety of recombinant factor VIII. The rFactor VIII Clinical Trial Group.	Study design
Kitchen C	2000	Human coagulation factor FVIIa (recombinant) in the management of limb-threatening bleeds unresponsive to alternative therapies: results from the NovoSeven emergency-use programme in patients with severe haemophilia or with acquired inhibitors.	Population
Aygoren-Pursun E	1997	A multicenter pharmacosurveillance study for the evaluation of the efficacy and safety of recombinant factor VIII in the treatment of patients with hemophilia A. German Kogenate Study Group.	Study design
Batlle J	1999	Induction of immune tolerance with recombinant factor VIII in haemophilia A patients with inhibitors.	Study design
Bidlingmaier C	2006	Continuous infusion of factor concentrates in children with haemophilia A in comparison with bolus injections.	Intervention
Blanchette VS	2008	Plasma and albumin-free recombinant factor VIII: pharmacokinetics, efficacy and safety in previously treated pediatric patients.	Study design
Brackmann HH	1993	Two years' experience with two recombinant factor VIII concentrates.	Study design
Chistolini A	1991	Intranasal DDAVP: biological and clinical evaluation in mild factor VIII deficiency.	Intervention
Chowdary P	2020	Modeling to Predict Factor VIII Levels Associated with Zero Bleeds in Patients with Severe Hemophilia A Initiated on Tertiary Prophylaxis.	Study design
Chozie NA	2019	Comparison of the efficacy and safety of 12-month low-dose factor VIII tertiary prophylaxis vs on-demand treatment in severe haemophilia A children.	Intervention
Chuansumrit A	2000	Controlling acute bleeding episodes with recombinant factor VIIa in haemophiliacs with inhibitor: continuous infusion and bolus injection.	Study design
Chuansumrit A	1995	Prophylactic treatment for hemophilia A patients: a pilot study.	Intervention
Crivianu-Gaita V	2016	Pilot study of once-a-day prophylaxis for youth and young adults with severe haemophilia A.	Study design
Dargaud Y	2018	Individual thrombin generation and spontaneous bleeding rate during personalized prophylaxis with	Outcome

		Nuwiq R (human-cl rhFVIII) in previously treated patients with severe haemophilia A.	
Feldman BM	2006	Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study.	Study design
Gill JC	2002	Evaluation of high concentration intranasal and intravenous desmopressin in pediatric patients with mild hemophilia A or mild-to-moderate type 1 von Willebrand disease.	Intervention
Gomperts E	1994	Recombinate study.	Study design
Hawkins TE	1995	Treatment of haemophilia A by continuous factor VIII infusion.	Study design
Hay CR	2012	The principal results of the International Immune Tolerance Study: a randomized dose comparison.	Intervention
Hilliard P	2013	Musculoskeletal health of subjects with hemophilia A treated with tailored prophylaxis: Canadian Hemophilia Primary Prophylaxis (CHPS) Study.	Study design
Inbal A	2012	Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency.	Population
John MJ	2020	Turoctocog alfa is safe for the treatment of Indian patients with hemophilia A: Guardian 10 trial results.	Study design
Kavakli K	1997	Prophylactic therapy for hemophilia in a developing country, Turkey.	Intervention
Kempton CL	2012	Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A.	Study design
Kessler CM	1994	Factor VIII inhibitors--an algorithmic approach to treatment.	Study design
Key NS	1998	Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors.	Outcome
Kohler M	1989	Subcutaneous injection of desmopressin (DDAVP): evaluation of a new, more concentrated preparation.	Intervention
Kurnik K	2010	New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development.	Intervention
Lalezari S	2014	Patient characteristics that influence efficacy of prophylaxis with rFVIII-FS three times per week: a subgroup analysis of the LIPLONG study.	Study design
Leissinger C	2001	High-dose DDAVP intranasal spray (Stimate) for the prevention and treatment of bleeding in patients with mild haemophilia A, mild or moderate type 1 von Willebrand disease and symptomatic carriers of haemophilia A.	Intervention

Lindley CM	1994	Pharmacokinetics and pharmacodynamics of recombinant factor VIIa.	Study design
Lindvall K	2012	Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy.	Intervention
Lissitchkov T	2017	PK-guided personalized prophylaxis with Nuwiq R (human-cl rhFVIII) in adults with severe haemophilia A.	Duplicate
Liu H	2017	An Open-label, Single-dose, Pharmacokinetic Study of Factor VIII Activity After Administration of Moroctocog Alfa (AF-CC) in Male Chinese Patients With Hemophilia A.	Study design
Manco-Johnson MJ	2007	Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia.	Study design
Mauser-Bunschoten EP	1994	Clinical course of factor VIII inhibitors developed after exposure to a pasteurised Dutch concentrate compared to classic inhibitors in hemophilia A.	Study design
Negrier C	1994	The use of porcine factor VIII in France.	Population
Page MJ	2000	Patient/caregiver assessment of convenience in the use of recombinant activated factor VII (rVIIa; NovoSeven) in home therapy.	Study design
Peerlinck K	1993	A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate.	Intervention
Pennington JE	1991	Design of clinical studies with recombinant factor VIII. The rFactor VIII Clinical Trial Group.	Study design
Peyvandi F	2016	A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A.	Study design
Powell J	2012	Efficacy and safety of prophylaxis with once-weekly BAY 79-4980 compared with thrice-weekly rFVIII-FS in haemophilia A patients. A randomised, active-controlled, double-blind study.	Study design
Qi X	2014	Evaluating and monitoring the efficacy of recombinant activated factor VIIa in patients with haemophilia and inhibitors.	Population
Rice KM	1996	NovoSeven (recombinant factor VIIa) in centeral nervous systems bleeds.	Study design
Rocino A	1994	Hemofil-M study.	Study design
Santagostino E	2001	Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors.	Population
Scharrer I	1999	Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency.	Population
Seremetis SV	1994	The clinical use of factor VIIa in the treatment of factor VIII inhibitor patients.	Study design

Valentino LA	2012	A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management.	Study design
Verma SP	2016	A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia - A success story from a resource limited country.	Intervention
White GC 2nd	1997	A multicenter study of recombinant factor VIII (Recombinate) in previously treated patients with hemophilia A. The Recombinate Previously Treated Patient Study Group.	Study design
Wu R	2017	A prospective study of health-related quality of life of boys with severe haemophilia A in China: comparing on-demand to prophylaxis treatment.	Study design
Yoshioka A	2003	Clinical evaluation of a recombinant factor VIII preparation (Kreuz et al.) in previously untreated patients with hemophilia A.	Study design
Abshire T.C	2000	Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy. Results of a multicenter, international, clinical investigation.	Duplicate
Aygoren-Pursun E	1997	A multicenter pharmacosurveillance study for the evaluation of the efficacy and safety of recombinant factor VIII in the treatment of patients with hemophilia A.	Duplicate
Sattler L	2020	Switch vers un facteur VIII recombinant fusionne avec un fragment Fc Experience chez 30 patients hemophiles A, Switching toward the use of recombinant factor VIII Fc fusion protein Study among 30 patients with severe hemophilia A.	LANG
Dargaud Y	2018	Individual thrombin generation and spontaneous bleeding rate during personalized prophylaxis with Nuwiq (human-cl rhFVIII) in previously treated patients with severe haemophilia A.	Duplicate
Ducore J	2017	Safety and dose-dependency of eptacog beta (activated) in a dose escalation study of non-bleeding congenital haemophilia A or B patients, with or without inhibitors.	Study design
Driessler F	2017	Evaluation of recombinant factor VIII Fc (Eloctate) activity by thromboelastometry in a multicenter phase 3 clinical trial and correlation with bleeding phenotype.	Outcome
Klukowska A	2016	Novel, human cell line-derived recombinant factor VIII (Human-cl rhFVIII, Nuwiq) in children with severe haemophilia A: Efficacy, safety and pharmacokinetics.	Duplicate
Lissitchkov T	2016	Novel, human cell line-derived recombinant factor VIII (human-cl rhFVIII; Nuwiq) in adults with severe haemophilia A: Efficacy and safety.	Duplicate

Tiede A	2016	Prophylaxis vs. on-demand treatment with Nuwiq (Human-cl rhFVIII) in adults with severe haemophilia A.	Duplicate
Valentino L.A	2016	Association of peak factor VIII levels and area under the curve with bleeding in patients with haemophilia A on every third day pharmacokinetic-guided prophylaxis.	Study design
Martinowitz U	2011	Bioequivalence between two serum-free recombinant factor VIII preparations (N8 and ADVATE)--an open-label, sequential dosing pharmacokinetic study in patients with severe haemophilia A.	Study design
De Podesta Haje D	2011	Orthopaedic evaluation in children with severe haemophilia A or B submitted to primary prophylaxis therapy in a coagulopathy treatment centre.	Intervention
Young G	2008	Single 270mugkg-1 -dose rFVIIa vs. standard 90mugkg-1 -dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: A randomized comparison.	Duplicate
Nowak-Gottl U	2008	Potential role of prophylactic treatment for prevention of joint disease in hemophilia A.	Study design
Tarantino M.D	2004	Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: Pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A1.	Duplicate
Petrini P	2001	What factor should influence the dosage and interval of prophylactic treatment in patients with severe haemophilia A and B?.	Study design
Yoshioka A	2001	Safety and efficacy of a new recombinant FVIII formulated with sucrose (fFVIII-FS) in patients with haemophilia A: A long-term, multicentre clinical study in Japan.	Duplicate
Liesner R.J	1996	The impact of prophylactic treatment on children with severe haemophilia.	Study design
Lusher J.M	1998	A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors.	Duplicate
White II G.C.	1997	A multicenter study of recombinant factor VIII (Recombinate) in previously treated patients with hemophilia A.	Duplicate
Bray G.L.	1994	A multicenter study of recombinant factor VIII (recombinate): Safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A.	Duplicate
Ingerslev J		Home treatment with recombinant activated factor VII: results from one centre	Outcome

Lusher JM		Recombinant activated factor VII for treatment of intramuscular haemorrhages: a comparison of early versus late treatment	Study design
Eshghi P		A prospective crossover triple-blind controlled trial on the safety and efficacy of Iranian recombinant FVIII (Safacto(R)) versus plasma derived FVIII; a pilot study	Duplicate
		Trial Results Reveal Greater Risk of Inhibitor Formation in Patients With Hemophilia A Receiving Recombinant Factor VIII Than in Patients Receiving Plasma-Derived Factor VIII	Study design
		Emicizumab (hemlibraA[degrees]) in haemophilia A: a first-choice preventive treatment for patients with factor VIII inhibitors	Study design
Horling FM		Immunogenicity of BAX 855 in previously treated patients with congenital severe hemophilia A	Publication type
Anthony, D	2016	On-demand recombinant factor VIII for people with haemophilia A (Structured abstract)	Study design
Stachnik, J	2016	Recombinant antihemophilic factor VIII (Structured abstract)	Study design
NHS Quality Improvement Scotland	2016	The use of recombinant factor VIIa (rFVIIa) in people with haemophilia who develop inhibitors (Structured abstract)	Study design
HAYES Inc	2016	NovoSeven Coagulation Factor VIIa (Recombinant) (Novo Nordisk Inc.) for the prevention of bleeding in patients with congenital hemophilia A or B (Factor VIII or IX deficiency hemophilia) (Structured abstract)	Study design
Berntorp, E	2016	Treatment of hemophilia A and B and von willebrand disease (Structured abstract)	Study design
Hermans	2022	Emicizumab prophylaxis for the treatment of people with moderate or mild hemophilia A without factor VIII inhibitors: Results from the primary analysis of the HAVEN 6 Study	Superseded
VonDrygalski	2022	Efficacy, safety, and pharmacokinetics of once-weekly efanesoctocog alfa (BIVV001) prophylaxis in previously treated patients with severe hemophilia A: Results from the phase 3 XTEND-1 study	Superseded
JimenezYuste	2022	Concizumab prophylaxis in patients with haemophilia A or B with inhibitors: Efficacy and safety results from the primary analysis of the phase 3 explorer7 Trial	Superseded
Liu	2022	Comparative effectiveness of valoctocogene roxaparvovec and prophylactic factor VIII replacement estimated through propensity scoring	Study design
Mahlangu	2022	Relationship between transgene-produced FVIII and bleeding rates 2 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8-1	Superseded

Carcao	2022	A post hoc analysis of individuals with severe hemophilia A and inhibitors from the PUPs A-LONG study	Superseded
Rangarajan	2022	Fitusiran, an investigational siRNA therapeutic targeting antithrombin: Analysis of antithrombin levels and thrombin generation from a phase 3 study in people with hemophilia A or B with inhibitors	Superseded
Pipe	2023	EMICIZUMAB FOR THE TREATMENT OF INFANTS WITH SEVERE HEMOPHILIA A: INTERIM ANALYSIS OF HAVEN 7	Duplicate
Bauer	2023	Pharmacokinetic-Pharmacodynamic Comparison of Recombinant and Plasma-Derived von Willebrand Factor in Patients with von Willebrand Disease Type 3	Study design
Male	2023	The safety and efficacy of N8-GP (turoctocog alfa pegol) in previously untreated pediatric patients with hemophilia A	Superseded
Malec	2023	Recombinant factor VIII Fc fusion protein for first-time immune tolerance induction: final results of the verITI-8 study	Study design
Oldenburg	2023	Emicizumab prophylaxis for the treatment of people with moderate or mild Hemophilia A without Factor VIII inhibitors: Results from the primary analysis of the HAVEN 6 study	Superseded
Boggio	2023	Rptacog beta efficacy at 24 hours postinfusion for mild or moderate bleeds in individuals with hemophilia a or b and inhibitors	Study design
Mathias	2023	Subcutaneous concizumab prophylaxis in patients with haemophilia a or b with inhibitors: efficacy and safety results by haemophilia subtype from the phase 3 explorer7 trial	Superseded
Malangu	2022	Efficacy and safety of valoctocogene roxaparvovec gene transfer for severe hemophilia A: Results from the GENEr8-1 two-year analysis	Superseded
Gomber	2022	Twice Weekly Vs. Thrice Weekly Low-Dose Prophylactic Factor VIII Therapy in Children with Hemophilia A: An Open Label Randomized Trial	Intervention
Negrier	2022	Emicizumab prophylaxis in people with mild or moderate haemophilia a without factor viii inhibitors: results from the interim analysis of the haven 6 study	Superseded
O'Mahony	2022	Impact of valoctocogene roxaparvovec gene transfer for severe haemophilia a on health-related quality of life	Superseded
Escobar	2021	PERSEPT 3: A phase 3 clinical trial to evaluate the haemostatic efficacy of eptacog beta (recombinant human FVIIa) in perioperative care in subjects with haemophilia A or B with inhibitors	Population

Mancuso	2021	Decreased Bleeding Rates in Patients with Hemophilia A Switching from Standard-Half-Life FVIII to BAY 94-9027 Prophylaxis	Included in original SLR
Jimenez-Yuste	2021	Second interim analysis results from the STASEY trial: A single-arm, multicentre, open-label, phase III clinical trial to evaluate the safety and tolerability of emicizumab prophylaxis in persons with haemophilia A (PwHA) with FVIII inhibitors	Superseded
Srivastava	2021	Fitusiran, an Investigational siRNA Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: First Results from a Phase 3 Study to Evaluate Efficacy and Safety in People with Hemophilia a or B without Inhibitors (ATLAS-A/B)	Superseded
Sidonio	2021	Rurioctocog alfa pegol use in immune tolerance induction: Interim results from an open-label multicenter clinical trial in previously untreated patients with severe hemophilia a	Superseded
Sidonio	2021	Immunogenicity, efficacy and safety of rurioctocog alfa pegol in previously untreated patients with severe hemophilia a: Interim results from an open-label multicenter clinical trial	Superseded
Young	2021	Efficacy and safety of fitusiran prophylaxis, an sirna therapeutic, in a multicenter phase 3 study (ATLAS-INH) in people with hemophilia a or b, with inhibitors (PWHI)	Superseded
Negrier	2021	Emicizumab prophylaxis in persons with mild or moderate hemophilia a: Results from the interim analysis of the haven 6 study	Superseded
Ranjan	2021	The Safety and Efficacy of N8-GP in Previously Untreated Patients with Severe Haemophilia A: Interim Results from the Main and Extension Phases of Pathfinder 6	Superseded
Jimenez-Yuste	2021	Final analysis of the stasey trial: A single-arm, multicenter, open-label, phase III clinical trial evaluating the safety and tolerability of emicizumab prophylaxis in persons with hemophilia A (PWHA) with factor (F)VIII inhibitors	Superseded
Ozelo	2021	Efficacy and safety of valoctocogene roxaparvovec adeno-associated virus gene transfer for severe hemophilia a: Results from the phase 3 gener8-1 trial	Superseded
Ahuja	2021	BAY 94-9027 provided effective long-term prophylaxis in pediatric patients aged >= 12 years at the end of the protect viii kids extension study, indicating consistent safety of treatment into adolescence	Duplicate
Callaghan	2021	Safety and efficacy of emicizumab in persons with haemophilia a with/without FVIII inhibitors: Pooled data from four phase III studies (Haven 1-4)	Duplicate
Kenet	2020	Improvement of efficacy outcomes in patients who switched from sucrose-formulated rFVIII to BAY 81-8973 prophylaxis in the LEOPOLD clinical trials	Superseded

vonMackensen	2020	Determining meaningful health-related quality-of-life improvement in persons with haemophilia A using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)	Included in original SLR
Santagostino	2019	Interim Analysis of the Extension Study with rVIII-SingleChain in Previously Untreated Patients (PUPs) with Severe Hemophilia A (CSL627-3001)	Superseded
Hampton	2022	Clinical outcomes after joint surgery in patients on turoctocog alfa pegol (N8-GP) prophylaxis: A post hoc analysis.	Population
Chowdary	2020	Long-term safety and efficacy results from the phase 3b, open-label, multicentre Continuation study of rurioctocog alfa pegol for prophylaxis in previously treated patients with severe haemophilia A.	Included in original SLR
Giangrande	2020	Long-term safety and efficacy of N8-GP in previously treated adults and adolescents with hemophilia A: Final results from pathfinder2.	Included in original SLR
Kenet	2020	Continued benefit demonstrated with BAY 81-8973 prophylaxis in previously treated children with severe haemophilia A: Interim analysis from the LEOPOLD Kids extension study.	Included in original SLR
Yang	2020	Safety and Efficacy of Moroctocog Alfa (AF-CC) in Chinese Patients with Hemophilia A: Results of Two Open-Label Studies	Included in original SLR

H.1.2.4 Included studies

For this application, only the comparative analysis vs the relevant comparator – emicizumab – was of interest. Hence, only studies of emicizumab with a study population that matched that of the XTEND-1 study were relevant for inclusion. Of the 32 unique trials included in the SLR data synthesis, one trial (two publications) of emicizumab was eventually included in the MAIC. Other trials of emicizumab were identified but not included due to non-matching study populations. See section 5.1 for more details.

The XTEND-1 trial assessing efanesoctocog alfa is a 2-arm, parallel-design, non-randomised trial. Patients who had been previously receiving FVIII prophylaxis were allocated to efanesoctocog alfa prophylaxis for 52 weeks (Arm A). Those receiving on demand treatment were allocated to ARM B, in which they were receiving on demand efanesoctocog alfa for 26 weeks followed by prophylaxis with the same substance.

Emicizumab Q1W was assessed in arm A of the HAVEN III trial on 36 patients, with severe haemophilia, who had been receiving on-demand treatment prior to enrolment. Emicizumab Q1W was assessed in arm D of the HAVEN III trial on 63 patients, with severe haemophilia, who had been receiving prophylactic treatment prior to enrolment.

Table 77 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
von Drygalski	Determine the efficacy, safety, and pharmacokinetics of efanesoctocog alfa for routine prophylaxis, treatment of bleeding episodes, and perioperative management in previously treated adults and adolescents with severe hemophilia A.	Phase 3, multicenter tria	≥12y severe hemophilia A without inhibitors	Prophylaxis: 50 IU/kg once weekly for 52 weeks On-demand: on-demand dose regimen of 50 IU/kg for 26 weeks, followed by prophylactic regimen of 50 IU/kg once weekly for 26 weeks	Mean annualized bleeding rate in group A, 52 weeks	intrapatient comparison of the annualized bleeding rate during prophylaxis, treatment of bleeding episodes, safety, pharmacokinetics, and changes in physical health, pain, and joint health, 52 weeks
Mahlangu 2018	To assess the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis in persons who have hemophilia A without inhibitors.	Phase 3, multicenter tria	≥12y severe congenital hemophilia A or hemophilia A with FVIII inhibitors	3 kg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously Prophylaxis every two weeks and pre-study on-demand FVIII:	Difference (expressed as a ratio) in the rate of treated bleeding events, 24 weeks	All bleeding events (treated and not treated), spontaneous and joint bleeding events, and the score on the Haem-A-QoL physical health subscale, 24 weeks

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
				3 kg/kg/week subcutaneously for 4 weeks, followed by 3 mg/kg subcutaneously every two weeks No Prophylaxis and pre-study on-demand FVIII: no prophylaxis for at least 4 weeks have the opportunity to switch to emicizumab prophylaxis after 24 weeks on-study Prophylaxis once weekly and pre-study FVIII prophylaxis: 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously		

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Kiialainen 2019	To explore the potential effect of emicizumab prophylaxis on bone and joint health beyond bleed prevention, by measured joint health scores and bone and joint biomarkers in HAVEN 3	Phase 3, multicenter tria	≥12y severe congenital hemophilia A or hemophilia A with FVIII inhibitors	3 kg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously Prophylaxis every two weeks and pre-study on-demand FVIII: 3 kg/kg/week subcutaneously for 4 weeks, followed by 3 mg/kg subcutaneously every two weeks No Prophylaxis and pre-study on-demand FVIII: no166rophylaxis for at least 4 weeks have the opportunity to switch to emicizumab prophylaxis after 24 weeks on-study	Hemophilia joint health scores (HJHS; v2.1), 49 weeks.	Biomarkers of bone formation (osteocalcin [OC], N-terminal propeptide of type I procollagen [P1NP]), bone resorption (C-terminal telopeptide of type I collagen [CTXI]), osteoblasts (osteoprotegerin), osteoclastogenesis (soluble receptor activator of nuclear factor- kappaB Ligand [sRANKL]), cartilage turnover (cartilage oligomeric matrix protein [COMP]), and inflammation (interleukin 1 beta, interleukin 6, and tumor necrosis factor) were measured in 117 PwHA (Table 1) receiving emicizumab at baseline and after 3,

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
				Prophylaxis once weekly and pre-study FVIII prophylaxis: 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously		6, 12, and 18 months of treatment

Studies included in the full SLR are listed below in Table 78.

Table 78: List of studies included in the SLR

Treatment name	Trial name/Registration number (if available)	Trial phase	Single vs. multiple arms	Population	Adult vs. Adolescent vs. Children	Inhibitors vs. no inhibitors vs. both	Author, year (AGID)
Adults and adolescents without inhibitors							
Standard half-life products							
Kogenate FS	SPINART NCT00623480	3b/4	Multiple	12-50 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Manco-Johnson 2017 (Manco-Johnson et al. 2017) Manco-Johnson 2013 (Manco-Johnson et al. 2013)
Kovaltry	LEOPOLD I NCT01029340	3	Multiple	12 to 65 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Saxena 2016 (Saxena et al. 2016)
Kovaltry	LEOPOLD II NCT01233258	2/3	Multiple	12 to 65 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Kavakli 2015 (Kavakli et al. 2015)
NovoEight	Guardian 1 NCT00840086	3	Single	≥12 years old, hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Lentz 2013 (Lentz et al. 2013) Santagostino 2014 (Santagostino et al. 2014)
Nuwiq	NR	3	Single	Ages >18 years with severe hemophilia A without inhibitors	Adult, Adolescent	No inhibitors	Lissitchkov 2016 (Lissitchkov et al. 2016)
Nuwiq	NuPreviq NCT01863758	3	Single	≥18 years old, severe hemophilia A, without inhibitors	Adult	No inhibitors	Lissitchkov 2017 (Lissitchkov et al. 2017)
Xyntha	NR	NR	Single	≥12 years old, hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Recht 2009(Recht et al. 2009)
Extended half-life products							

Adynovate	PROLONG-ATE NCT01736475	2/3	Multiple	12-65 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Konkle 2015 (Konkle et al. 2015)
Adynovate	PROPEL NCT02585960	3	Multiple	<12 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Klamroth 2021 (Klamroth et al. 2021)
Afstyla	AFFINITY NCT01486927	2/3	Multiple	12 to 65 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Mahlangu 2016 (Mahlangu et al. 2016)
Eloctate	A-LONG NCT01181128	3	Multiple	≥12 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Wyrwich 2016 (Wyrwich et al. 2016) Mahlangu 2014 (Mahlangu et al. 2014) Shapiro 2017 (Shapiro et al. 2017)
Esperoct	Pathfinder 2 NCT01480180	3	Multiple	≥12 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Giangrande 2017(Giangrande et al. 2017) Kearney 2019 (Kearney et al. 2019)
Hemlibra	HAVEN 3 NCT02847637	3	Multiple	≥12 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Mahlangu 2018 (Mahlangu et al. 2018a) Kiialainen 2019(Kiialainen et al. 2019)
Jivi	PROTECT VIII NCT01580293	2/3	Multiple	12–65 years old, severe hemophilia A, without inhibitors	Adult, Adolescent	No inhibitors	Reding 2017 (Reding et al. 2017)
Adults and adolescents with inhibitors							
Non-factor replacement therapy							
Hemlibra	HAVEN 1 NCT02622321	3	Multiple	≥12 years old, hemophilia A, with inhibitors	Adult, Adolescent	Inhibitors	Oldenburg 2019 (Oldenburg et al. 2019) Oldenburg 2017 (Oldenburg et al. 2017)
Adult, Adolescent, and children without inhibitors							
Standard half-life products							
Advate	NR	NR	Single	≥10 years old, severe or moderately	Adult, Adolescent, Children	No inhibitors	Tarantino 2004 (Tarantino et al. 2004)

				severe hemophilia A, without inhibitors			
Refacto	Refacto Phase 3 study group (PTP study)	3	Single	> 7 years old, severe hemophilia A, without inhibitors	Adult, Adolescent, Children	No inhibitors	Courter 2001a (Courter and Bedrosian 2001a) Lusher 2003 (Lusher et al. 2003)
Children without inhibitors							
Standard half-life products							
Kogenate FS	NR	3	Single	≤4 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Kreuz 2005 (Kreuz et al. 2005)
Kovaltry	LEOPOLD Kids NCT01311648	3	Single	≤12 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Ljung 2016 (Ljung et al. 2016)
NovoEight	Guardian 3 NCT01138501	3	Single	<12 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Kulkarni 2013 (Kulkarni et al. 2013) Santagostino 2014 (Santagostino et al. 2014)
NovoEight	Guardian 4 NCT01493778	3	Single	<6 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Yaish 2020 (Yaish et al. 2020)
Nuwiq	GENA-03	3	Single	2–12 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Klukowska 2016 (Klukowska et al. 2016)
Recombinate	NR	NR	Single	2-50 months, severe hemophilia A, without inhibitors	Children	No inhibitors	Bray 1994 (Bray et al. 1994)
Refacto	Refacto Phase 3 study group (PUP study)	3	Single	0-52 months, severe hemophilia A, without inhibitors	Children	No inhibitors	Courter 2001b (Courter and Bedrosian 2001b) Lusher 2003 (Lusher et al. 2003)
Extended half-life products							

Adynovate	NCT02210091	3	Single	<12 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Mullins 2017 (Mullins et al. 2017)
Afstyla	NCT02093897	3	Single	<12 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Stasyshyn 2017 (Stasyshyn et al. 2017)
Eloctate	Kids A-LONG NCT01458106	3	Single	<12 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Young 2015 (Young et al. 2015)
Esperoct	Pathfinder 5 NCT01731600	3	Single	<12 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Meunier 2017 (Meunier et al. 2017) Kearney 2019 (Kearney et al. 2019)
Jivi	PROTECT VIII Kids NCT01775618	2/3	Single	<12 years old, severe hemophilia A, without inhibitors	Children	No inhibitors	Santagostino 2020 (Santagostino et al. 2020)
Xyntha	NR	NR	Single	Includes 2 studies: 1) <6 years old, severe hemophilia A patients, without inhibitors 2) 6-12 years old, severe hemophilia A patients, without inhibitors	Children	No inhibitors	Rusen 2018(Rusen et al. 2018)
Children with inhibitors							
Non-factor replacement therapy							
Hemlibra	HAVEN 2 NCT02795767	3	Multiple	Up to 17 years old, severe hemophilia A, without inhibitors	Children	Inhibitors	Young 2019 (Young et al. 2019)

H.1.3 Quality assessment

Each RCT identified in the SLR underwent a comprehensive quality assessment using guidelines from NICE (National Institute for Health and Care Excellence (NICE) 2015). This 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?

In the original SLR a total of 32 clinical trials corresponding to 39 publications were extracted for an ITC feasibility assessment. All trials were open label, including 20 single-arm trials and 12 trials with multiple arms (8 trials were randomized controlled). A total of 14 treatments were assessed, including 9 SHL treatments (i.e., Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Refacto, and Xyntha), 4 EHL treatments (i.e., Adynovate, Eloctate, Esperoct, Jivi) and one non-factor replacement therapy (i.e., Hemlibra). Publications included from early years (e.g., prior to 2010) were all for SHL treatments. The first publication of the EHL treatments included in the SLR was for Eloctate in 2014. The first publication of the non-factor replacement therapy included in the SLR was for Hemlibra in 2017. Publications in the latest year of 2020 were a mix of SHL, EHL and non-factor replacement therapies. All treatments were evaluated for prophylactic use and ten of them (i.e., Adynovate, Afstyla, Eloctate, Esperoct, Hemlibra, Jivi, Kogenate FS, Kovaltry, Recombinate, and Refacto) for which trials also included an on-demand or no prophylaxis treatment arm.

Variations in baseline characteristics were observed across trials. Age, race, prior treatments (on-demand vs. prophylaxis) and severity of disease were commonly reported while number of bleeds or joint bleeds prior to the trial entry was only reported in about one third of the studies. While most patients included in the trials were White and had severe hemophilia A as indicated by <1% of FVIII level (e.g., the percent of patients with severe hemophilia A ranged from 92.9% to 100% across treatment groups among trials of adults and adolescents without inhibitors), the percent of patients receiving on-demand vs. prophylaxis treatments prior to the trial entry in the prophylaxis arms varied across trials.

Bleeding outcomes were most reported, whereas PROs and HJHS were only reported in few studies. ABR was the most reported bleeding outcomes, followed by AsBR and AjBR. In the prophylaxis arms, the median ABR for all bleeds ranged from 0 to 4.0 among adults and adolescents without inhibitors who were treated with SHL, from 0 to 4.1 among adults and adolescents without inhibitors who were treated with EHL, from 0.6 to 1.6 among adults and adolescents without inhibitors who were treated with non-factor replacement therapy, from 1.9 to 3.0 among children without inhibitors who were treated with SHL, from 2.0 to 2.9 among children without inhibitors who were treated with EHL and from 0 to 1.6 among children with inhibitors who were treated with non-factor replacement therapy. In the on-demand/no prophylaxis arms, the median ABR for

all bleeds ranged from 19.6 to 60.0 among patients without inhibitor and was not available for patients with inhibitor. PROs (i.e., Haem-A-QoL) were reported in six publications of eight trials. Overall, mean changes in the Haem-A-QoL total score and physical score showed a greater improvement in the prophylaxis arms compared to the on-demand arms. HJHS was reported in one conference proceeding for Hemlibra HAVEN 3 trial. Compared to baseline, mean HJHS total score was reduced by 2.25 and mean HJHS score of joint-specific domain was reduced by 2.23.

Despite multiple strengths of this SLR, it is important to consider potential limitations. For instance, it is possible that not all relevant studies were captured through the search strategy. Publications not indexed accordingly or by our search date may have been missed. Searches were limited from 1988 to the date the search was conducted and thus, relevant studies prior to this period or published very recently might not have been included. Furthermore, only studies published in English were reviewed. Screening by reviewers may have missed relevant articles, although reviews by two independent reviewers, with adjudication by a third reviewer, was intended to minimize any discordance.

This SLR suggests that prophylaxis treatments are effective in reducing bleeding events and improve quality of life for patients with severe haemophilia A. However, quality of life measures (e.g., Haem-A-QoL) were not well reported across trials. In addition, certain outcomes like treated bleeds were recently introduced and only reported in trials conducted in recent years. Clinical trials conducted after this SLR search data and real-world studies could provide additional insights on the clinical efficacy of treatments.

In the updated SLR a total, 13 RCTs were identified that were considered and reported sufficient methodological information to be quality assessed.

Table 79 Risk of bias assessment original SLR

Study (AG ID)	Was the randomization method adequate?	Was the allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	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)?	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 intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
HAVEN 3 (766)	Yes: Randomization 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 randomized 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 randomized treatment arms (3% in Emicizumab once-weekly prophylaxis vs. 3% in Emicizumab every-2-weeks prophylaxis vs. 6% in No prophylaxis).	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: Although intention-to-treat analysis was not explicitly mentioned, the analysis was performed within the groups patients were randomized 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.
SPINART (788 and 786)	Yes: Randomization was centralized and managed by use of a customized interactive voice response system. Patients were stratified on the basis of the presence or absence of target joints and	Yes: Interactive voice response system suggests that next allocation was not predictable.	Unclear: The treatment groups were similar in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label.	No: The rates of study discontinuation were the same (17%) in the on demand and prophylaxis treatment groups.	No: There was no evidence of selective reporting. All specified outcomes	Yes: The analysis included an intention-to-treat analysis. There were missing data in the severity of bleeding event; however, there is no mention of how

	bleeding frequency within the preceding 6 months.					were reported.	missing data were handled.
PROTECT VIII (1086)	Yes: Patients eligible for randomization were assigned to treatment groups based on randomization generated by the sponsor's randomization management system.	Unclear: There is no in-depth discussion about allocation methods.	Unclear: The randomized treatment groups were similar in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label.	No: The rates of study discontinuation were the same (2%) in the two randomized treatment groups.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing data were not mentioned in the study.
LEOPOLD II (548)	Yes: Patient assignment was performed using a centralized telephone interactive voice response system or interactive web response system.	Yes: Centralized telephone interactive voice response system or interactive web response system suggests that next allocation was not predictable.	Unclear: The randomized treatment groups were similar other than some differences in race and prior bleeds in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label.	Unclear: The rates of study discontinuation were similar in the six randomized treatment groups. The discontinuation rates in the 4 treatment groups ranged from 6% to 9% and two treatment groups had 0% study discontinuation rate. The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing data were not mentioned in the study.

LEOPOLD I (1161)	Yes: The sequence of the products was randomized by a system generated by the sponsor's randomization management group; patient assignment was performed using a centralized interactive response system.	Yes: Centralized interactive response system suggests that next allocation was not predictable.	Unclear: The baseline characteristics between the randomized treatment groups were not presented.	No: The study was open-label.	Unclear: The rate of study discontinuation was higher in the intraindividual comparison of the clinical efficacy of prophylaxis using potency labelling based on the chromogenic substrate assay per European Pharmacopoeia (CS/EP) group (6%) compared to the adjusted by a predefined factor to mimic results obtained with the one-stage assay (CS/ADJ) group (0%). The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing data were not mentioned in the study.
HAVEN I (961 and 959)	Yes: Randomization was conducted centrally by a vendor via interactive voice/web response system. Permutated blocks method was used and randomization was stratified by bleeds in the prior 24 weeks.	Yes: Interactive voice/web response system suggests that next allocation was not predictable.	Unclear: The randomized treatment groups were similar in baseline characteristics other than some differences in hemophilia severity at baseline and historical titer of factor VIII inhibitor, but no statistical analysis was conducted.	No: The study was open-label.	Unclear: The rate of study discontinuation was higher in the Emicizumab Prophylaxis (11%) compared to the No Prophylaxis group (0%). The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: Although intention-to-treat analysis was not explicitly mentioned, the analysis was performed within the groups patients were randomized to. Missing data were not mentioned in the study.
PROPEL (1596)	Unclear: There is no in-depth discussion about randomization methods.	Unclear: There is no in-depth discussion about randomization methods.	Unclear: The randomized treatment groups were similar in baseline characteristics other than some differences in hmophilic arthropathy, hepatitis C virus and human immunodeficiency virus at baseline, but no statistical analysis was conducted.	No: The study was open-label.	Unclear: The rate of study discontinuation was higher in the target FVIII trough level ~10% group (14%) compared to the target FVIII trough level 1-3% group (2%). The primary endpoint analysis in the full analysis set accounted for discontinuation.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing bleed data were imputed using a multiple imputation technique.

A-LONG (769, 1432, 1212)	Unclear: There is no in-depth discussion about randomization methods.	Unclear: There is no in-depth discussion about randomization methods.	Unclear: The randomized treatment groups were similar in baseline characteristics other than some differences in race, human immunodeficiency virus, 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: Intention-to-treat 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.

The quality assessment of the studies from the updated SLR is provided below in Table 80.

Table 80 Risk of bias assessment updated SLR

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 once-weekly prophylaxis vs. 3% in Emicizumab every-2-weeks prophylaxis vs. 6% in No prophylaxis).	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: Although intention-to-treat 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.

SPINART	Yes: Randomisation was centralized and managed by use of a customized interactive voice response system. Patients were stratified on the basis of the presence or absence of target joints and bleeding frequency within the preceding 6 months.	Yes: Interactive voice response system suggests that next allocation was not predictable.	Unclear: The treatment groups were similar in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label.	No: The rates of study discontinuation were the same (17%) in the on demand and prophylaxis treatment groups.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. There were missing data in the severity of bleeding event; however, there is no mention of how missing data were handled.
PROTECT VIII	Yes: Patients eligible for randomisation were assigned to treatment groups based on randomisation generated by the sponsor's randomisation management system.	Unclear: There is no in-depth discussion about allocation methods.	Unclear: The randomised treatment groups were similar in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label.	No: The rates of study discontinuation were the same (2%) in the two randomised treatment groups.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing data were not mentioned in the study.
LEOPOLD II	Yes: Patient assignment was performed using a centralized telephone interactive voice response system or interactive web response system.	Yes: Centralized telephone interactive voice response system or interactive web response system suggests that next allocation was not predictable.	Unclear: The randomised treatment groups were similar other than some differences in race and prior bleeds in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label.	Unclear: The rates of study discontinuation were similar in the six randomised treatment groups. The discontinuation rates in the 4 treatment groups ranged from 6% to 9% and two treatment groups had 0% study discontinuation rate. The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing data were not mentioned in the study.

LEOPOLD I	Yes: The sequence of the products was randomised by a system generated by the sponsor's randomisation management group; patient assignment was performed using a centralized interactive response system.	Yes: Centralized interactive response system suggests that next allocation was not predictable.	Unclear: The baseline characteristics between the randomised treatment groups were not presented.	No: The study was open-label.	Unclear: The rate of study discontinuation was higher in the intraindividual comparison of the clinical efficacy of prophylaxis using potency labelling based on the chromogenic substrate assay per European Pharmacopoeia (CS/EP) group (6%) compared to the adjusted by a predefined factor to mimic results obtained with the one-stage assay (CS/ADJ) group (0%). The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing data were not mentioned in the study.
HAVEN I	Yes: Randomisation was conducted centrally by a vendor via interactive voice/web response system. Permutated blocks method was used and randomisation was stratified by bleeds in the prior 24 weeks.	Yes: Interactive voice/web response system suggests that next allocation was not predictable.	Unclear: The randomised treatment groups were similar in baseline characteristics other than some differences in haemophilia severity at baseline and historical titer of factor VIII inhibitor, but no statistical analysis was conducted.	No: The study was open-label.	Unclear: The rate of study discontinuation was higher in the Emicizumab Prophylaxis (11%) compared to the No Prophylaxis group (0%). The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: Although intention-to-treat analysis was not explicitly mentioned, the analysis was performed within the groups patients were randomised to. Missing data were not mentioned in the study.

PROPEL	Unclear: There is no in-depth discussion about randomisation methods.	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 hmophilic arthropathy, hepatitis C virus and human immunodeficiency virus at baseline, but no statistical analysis was conducted.	No: The study was open-label.	Unclear: The rate of study discontinuation was higher in the target FVIII trough level ~10% group (14%) compared to the target FVIII trough level 1-3% group (2%). The primary endpoint analysis in the full analysis set accounted for discontinuation.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing bleed data were imputed using a multiple imputation technique.
A-LONG	Unclear: There is no in-depth discussion about randomisation methods.	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, human immunodeficiency virus, 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: Intention-to-treat 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.
ATLAS-A/B	Yes. Randomisation was conducted using an interactive response system. Randomisation was stratified by the number of bleeds in the 6 months before screening and haemophilia type.	Yes. Interactive response system suggests that next allocation was not predictable.	Unclear: The treatment groups were similar in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label	Unclear: The rate of study discontinuation was higher in the Fitusiran Prophylaxis (11/80 patients) compared to the On Demand group (3/40 patients). The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing data were imputed using a multiple imputation technique.

ATLAS-INH	Yes: Randomisation was conducted by an external vendor via an interactive response system. Permuted block randomisation was used, and randomisation was stratified by the number of bleeding episodes in the 6 months before screening (≤10 or >10).	Yes. Interactive response system suggests that next allocation was not predictable.	Unclear: The treatment groups were similar in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label	Unclear: The rate of study discontinuation was higher in the Fitusiran Prophylaxis (5/38 patients) compared to the On Demand group (0/19 patients). The reasons for discontinuation were well documented; only one was related to an adverse event.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis. Missing data were imputed using a multiple imputation technique.
Explorer 7	Yes. Randomisation was conducted using an interactive web response system. Randomisation was stratified by the number of bleeds in the 24 weeks before screening (<9 vs ≥9 bleeding episodes). and haemophilia type.	Yes. Interactive response system suggests that next allocation was not predictable.	Unclear: The treatment groups were similar in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label	Unclear: The rate of study discontinuation was higher in the prophylaxis (6/33 patients) compared to the on-demand group (6/19 patients). The reasons for discontinuation were well documented.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes. The analysis used the full analysis set and missing data were handled using a mixed model for repeated measured
HAVEN 5	Yes. Randomisation was conducted using an interactive voice/web response system. Randomisation was stratified by the number of bleeds in the 24 weeks before screening (<9 vs ≥9 bleeding episodes).	Yes. Interactive response system suggests that next allocation was not predictable.	Unclear: The treatment groups were similar in baseline characteristics, but no statistical analysis was conducted.	No: The study was open-label	No: There were no drop-outs in any of the treatment groups in the study.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Yes: The analysis included an intention-to-treat analysis and recording of missing data was not required.

NCT00543439	Yes: Randomisation was conducted centrally by a vendor via interactive voice/web response system and stratified by haemophilia A severity.	Yes: Interactive voice/web response system suggests that next allocation was not predictable.	Unclear: The randomised treatment groups were similar in baseline characteristics, however, only age, sex and race were reported in the trial registry record.	No: The study was open-label.	No: The rates of study discontinuation were very similar between the treatment groups.	No: There was no evidence of selective reporting. All specified outcomes were reported.	Unclear: The analysis reported an intention-to-treat analysis, however, the methods to account for missing data are inadequately described.

H.1.4 Unpublished data

No unpublished data was used in the MAIC.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

[redacted]

Table 81 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion

Abbreviations:

Table 82 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Table 83 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search

I.1.1 Search strategies

Table 84 Search strategy for [name of database]

Query	Results

I.1.2 Quality assessment and generalizability of estimates

[redacted]

I.1.3 Unpublished data

Not applicable

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

NA

J.1.1 Ex. Systematic search for […]

NA

Table 85 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
NA			

NA

J.1.2 Ex. Targeted literature search for [estimates]

NA

Table 86 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NA			

NA

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