

Single Technology Appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Contents:

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Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

- 1. Company submission** from Pfizer
- 2. Company summary of information for patients (SIP)** from Pfizer
- 3. Clarification questions and company responses**
 - a. Company responses
 - b. Company response appendices
- 4. Patient group, professional group and NHS organisation submissions** from:
 - a. The Haemophilia Society
- 5. Expert personal perspectives** from:
 - a. Dr Mary Mathias – clinical expert, nominated by Pfizer
- 6. External Assessment Report** prepared by Warwick Evidence
- 7. External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Document B

Company evidence submission

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Company evidence submission template for marstacimab for the treatment of severe
haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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Abbreviations

Abbreviation	Definition
AAS	All Analysis Set
ABR	Annualised bleeding rate
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
AJBR	Annualised joint bleeding rate
ALT	Alanine transaminase
aPCC	Activated prothrombin complex concentrates
AS	Absolute shortfall
ASD	Absolute standardised difference
ATP	Active treatment phase
BMI	Body mass index
BNF	British National Formulary
BPI	Brief pain inventory
BSA	Business Services Authority
BSH	British Society for Haematology
BU	Bethesda units
CADTH	Canada's Drug and Health Technology Agency
CE	Conformité Européenne
CEA	Cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
DOT	Days of therapy
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
EHA	European Haematology Association
EHL	Extended half-life
EMA	European Medicines Agency
ES	Effective size
EU	European Union
FIX	Factor IX
FVIII	Factor VIII
FX	Factor X
GB	Great Britain
GBP	Great British Pounds
GEE	Generalised estimating equation
Haem-A-QoL	Haemophilia A Quality of Life for Adults
Haemo-QoL	Haemophilia Quality of Life Questionnaire for Children
HAL	Haemophilia Activities List

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Abbreviation	Definition
Hemo-TEM	Haemophilia Treatment Experience Measure
HIV	Human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
HLIQ	Haemophilia Life Impacts Questionnaire
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
IgG1	Immunoglobulin G1
IPD	Individual-level data
IQR	Interquartile range
ISTH	International Society on Thrombosis and Hemostasis
ITC	Indirect treatment comparison
IU	International units
IV	Intravenous
IVIG	Intravenous immunoglobulin
LPLV	Last patient last visit
LTE	Long-term extension
LTFU	Long term follow up
mAb	Monoclonal antibody
MAIC	Matching adjusted indirect comparison
MAR	Missing at random
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
mITT	Modified intention to treat
ML-NMR	Multi-level network meta-regression
NA	Not applicable
nAb	Neutralising antibodies
NHB	Net health benefit
NHD	National Haemophilia Database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMI	Network meta-interpolation
NR	Not recorded
OLE	Open label extension
OP	Observational phase
OR	Odds ratios
PAS	Patient Access Scheme
PCC	Prothrombin complex concentrates
pedHAL	Paediatric Haemophilia Activities List

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Abbreviation	Definition
P-FiQ	Pain, functional impairment and quality of life
PGIC-H	Patient global impression of change - haemophilia
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PS	Proportional shortfall
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QW	Once weekly
RCT	Randomised control trial
RP	Routine prophylaxis
RR	Rate ratios
RU	Resource use
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SHL	Standard half-life
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SOC	Standard of care
STA	Single technology appraisal
STC	Simulated treatment comparison
SW	South west
TBC	To be confirmed
TEAE	Treatment emergent adverse events
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TSD	Technical support document
Tx	Treatment
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centre Doctors' Organisation
US	United States
VAS	Visual analogue scale
WFH	World Federation of Hemophilia
WTP	Willingness-to-pay

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

- Haemophilia is a rare, lifelong, genetic disease that results in repeating bleeding episodes that can lead to long-term, progressive joint damage, pain and impaired mobility, with many patients reporting substantial impacts on anxiety and their ability to participate in activities of daily living¹
- There are two types of haemophilia, A and B, which are characterised by deficiencies in clotting factor levels; factor VIII (FVIII) for haemophilia A and factor IX (FIX) for haemophilia B. Although caused by different mutations the two types of haemophilia are largely indistinguishable with regards to clinical outcomes²
- Severe haemophilia is defined as having <1% of normal factor activity and is primarily managed by life-long regular intravenous (IV) infusions of factor prophylaxis, with extended half-life (EHL) products favoured in the UK over standard half-life (SHL) given the reduced frequency of administration.^{3, 4} In haemophilia A, emicizumab, a chimeric bispecific antibody that replaces the function of FVIII, is an increasingly common treatment option⁵
- However, there are limitations to the current treatment options; factor prophylaxis products require regular IV infusions which can be strenuous and time consuming, and emicizumab, although a subcutaneous (SC) therapy, is not an available treatment option for patients with haemophilia B.^{6, 7}
- There remains an unmet need for a convenient prophylaxis therapy, particularly in haemophilia B where there are no SC administration options, to reduce the burden of IV administration of factor replacement products.
- Marstacimab is a novel monoclonal antibody directed against the tissue factor pathway inhibitor (TFPI), the primary inhibitor of the extrinsic coagulation cascade. Marstacimab is delivered SC on a weekly basis, and offers patients a simpler self-administration treatment, via a pre-filled pen, removing the burden of IV factor infusions. Marstacimab is administered as a flat dose, further reducing the complexity of administration.

B.1.1 Decision problem

The objective of this appraisal is to determine the clinical and cost-effectiveness of marstacimab, in line with its anticipated marketing authorisation, for the [REDACTED]

The submission covers the technology's full marketing authorisation for this indication. The decision problem addressed in this submission, compared to that defined in the final scope issued by NICE, is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with severe haemophilia A or severe haemophilia B aged 12 years and over	People with severe haemophilia A, without FVIII inhibitors, or severe haemophilia B, without FIX inhibitors, aged 12 years and over	As per the technology's full marketing authorisation
Intervention	Marstacimab	Marstacimab	As per the final scope
Comparator(s)	For people with severe haemophilia A: - Established clinical management, including: - prophylaxis (with or without on-demand treatment) with FVIII replacement therapy (including efanesoctocog alfa – subject to NICE evaluation) - emicizumab (in accordance with National Health Service [NHS] England's clinical commissioning policies) For people with severe haemophilia B: - Established clinical management, including: - prophylaxis (with or without on-demand treatment) with FIX replacement therapy - Etranacogene dezaparvovec (subject to NICE evaluation) - Fidanacogene elaparvovec (subject to NICE evaluation)	For people with severe haemophilia A: - Established clinical management, including: - prophylaxis (with or without on-demand treatment) with FVIII replacement therapy - emicizumab (in accordance with NHS England's clinical commissioning policies) For people with severe haemophilia B: - Established clinical management, including: - prophylaxis (with or without on-demand treatment) with FIX replacement therapy	- The proposed comparators are in line with the NICE final scope - The NICE evaluations of efanesoctocog alfa and fidanacogene elaparvovec are still ongoing at the time of submission; these products are therefore not routinely used in clinical practice and as such, they are not considered relevant comparators in this evaluation⁸⁻¹⁰ - NICE have recently released final draft guidance recommending etranacogene dezaparvovec as a treatment option for patients with moderately severe or severe haemophilia B but final guidance is yet to be published.¹¹ Additionally, this recommendation included a managed access agreement. As per NICE guidelines, etranacogene dezaparvovec is therefore not considered established practice and is not a suitable comparator in this appraisal^{11, 12} - In line with the anticipated marketing authorisation for marstacimab, recombinant activated coagulation factor VII is not a relevant comparator in this evaluation

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	○ Recombinant activated coagulation factor VII (for people with inhibitors)		• On-demand treatment on its own is not recommended for use in patients with severe haemophilia, as per WFH and BSH guidelines.^{13, 14} Therefore, the decision problem addressed in the submission will consider on-demand treatment only in the context of treating bleeding events on top of prophylactic treatment regimens
Outcomes	The outcome measures to be considered include: • annualised bleeding rate (ABR) • need for on-demand treatment with FVIII or FIX injections • durability of response to treatment • complications of the disease (e.g. joint problems and joint surgeries) • mortality • adverse effects of treatment • health-related quality of life	Outcomes addressed in the submission include: • ABR (total bleeds and treated bleeds) • need for on-demand treatment with factor VIII or IX injections • durability of response to treatment • complications of the disease (e.g., joint health) • mortality • adverse effects of treatment • health-related quality of life	As per the final scope
Subgroups	If evidence allows subgroups will be considered based on: • Haemophilia type (A or B) • Development of inhibitors	Subgroups considered in the submission include: • Haemophilia type (A or B)	• Pre-planned subgroup analyses of the BASIS trial by haemophilia type (A or B) have been presented in Section B.2.8. These data also informed scenario analyses in the cost-effectiveness analysis. The small sample sizes and lack of powering associated with these subgroup analyses mean these should be interpreted with caution. • The anticipated licensed indication is for 'people with severe haemophilia A, without FVIII inhibitors, or severe haemophilia B, without FIX inhibitors, aged 12 years and over'. Therefore, only data from the

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			relevant population of patients in the BASIS trial without inhibitors are presented within this submission.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	As per the final scope	As per the final scope
Special considerations including issues related to equity or equality	None specified in the final scope.	This submission covers all people with severe haemophilia including females, people with HIV, or those with historical hepatitis B or hepatitis C infection	The Phase 3 BASIS trial did not include females. NICE should ensure that recommendations do not discriminate based on sex. Additionally, NICE should ensure that recommendations do not discriminate against people with HIV or historical hepatitis B or C infection

^a Severe haemophilia is defined as <1% of normal factor activity.

Abbreviations: ABR: annualised bleeding rate; BSH: British Society for Haematology; FIX: factor IX; FVIII: factor VIII; HIV: Human Immunodeficiency Virus; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life year; UK: United Kingdom; WFH: World Federation of Hemophilia.

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B.1.2 Description of the technology being evaluated

A description of the technology being appraised, marstacimab, is presented in Table 2. The draft Summary of Product Characteristics (SmPC) for marstacimab is provided in the reference pack accompanying this submission.

Table 2: Technology being appraised

UK approved name and brand name	Marstacimab (Brand name TBC)
Mechanism of action	Marstacimab is a human monoclonal immunoglobulin G1 (IgG1) antibody directed against the tissue factor pathway inhibitor (TFPI) protein, the primary inhibitor of the extrinsic coagulation cascade. Marstacimab inhibits the TFPI, which enhances the extrinsic pathway of clot formation and reduces/eliminates the need for replacement factor therapies (see Figure 2 below).
Marketing authorisation/CE mark status	At the time of submission, marstacimab is under regulatory review by the European Medicines Agency (EMA). The anticipated date of EMA Committee for Medicinal Products for Human Use (CHMP) opinion is [REDACTED], with European Union (EU) marketing authorisation anticipated in [REDACTED]. The anticipated date of GB marketing authorisation is [REDACTED].
Indications and any restriction(s) as described in the SmPC	The anticipated indication for marstacimab is for [REDACTED].⁵ • [REDACTED] • [REDACTED] Contraindications include hypersensitivity to the active substance or to any of the excipients listed below:⁵ • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]
Method of administration and dosage	Marstacimab is administered as a weekly subcutaneous (SC) injection from a pre-filled syringe. After training from a healthcare professional, individuals may self-inject in the recommended injection sites, the abdomen and thigh. The recommended dose for patients 12 years of age and older, weighing at least 35 kg, is an initial loading dose of 300 mg by SC injection followed thereafter by 150 mg by SC injection once weekly. [REDACTED]
Additional tests or investigations	NA – No additional tests or investigations are required prior to treatment with marstacimab.

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List price and average cost of a course of treatment	The list price for marstacimab is [REDACTED] per 150 mg pack.
Patient access scheme (if applicable)	A confidential simple discount Patient Access Scheme (PAS) would provide marstacimab at a fixed net price of [REDACTED] per 150 mg pack. This represents an approximate [REDACTED] discount from the list price.

Abbreviations: CE: Conformité Européene; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; EU: European Union; GB: Great Britain; FIX: Factor IX; FVIII: Factor VIII; IgG1: Immunoglobulin G1; kg: Kilogram; mg: Milligram; MHRA: Medicines and Healthcare products Regulatory Agency; NA: Not applicable; PAS: Patient Access Scheme; SC: subcutaneous; SmPC: summary of product characteristics; TBC: to be confirmed; TFPI: Tissue factor pathway inhibitor; UK: United Kingdom.

Source: Marstacimab draft SmPC.⁵

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Overview of the disease

Haemophilia is a rare, lifelong, genetic disease that results in repeated bleeding episodes that can lead to long-term, progressive joint damage, pain and impaired mobility, with many patients reporting substantial impacts on anxiety and their ability to participate in activities of daily living and live spontaneously

- Haemophilia is characterised by the impaired production of coagulation factors, which are required for proper blood clotting.¹ As an X-linked, recessive condition, haemophilia predominantly presents in males, however, females can also be affected and de novo, non-inherited, cases can arise.¹⁵
- The two primary forms of haemophilia, haemophilia A and B, are distinguished by the affected clotting factor. Individuals with haemophilia A have reduced activity of FVIII, while individuals with haemophilia B have reduced activity of FIX.¹⁶ FVIII and FIX are important constituents of the blood coagulation cascade; absence or deficiency of these proteins impairs fibrin production which delays clot formation once bleeding has occurred.^{17, 18}
- While haemophilia A and B are distinct diseases, caused by mutations in genes encoding different proteins, their clinical outcomes are largely indistinguishable, and both diseases are considered clinically similar.^{2,19}
- People with haemophilia present with prolonged and spontaneous bleeding episodes, the severity of which is related to the percentage of normal factor (FVIII or FIX) activity in an individual; severe haemophilia is defined as having <1% of normal factor activity.^{2, 13, 20}
- Haemophilia B is rarer than its counterpart, haemophilia A, accounting for 20% of all haemophilia cases.²¹ It has been estimated that there were 2,128 patients treated for severe haemophilia A and 329 treated for severe haemophilia B in the UK in 2022/2023.⁴
- Those with haemophilia experience repeat bleeding episodes into muscles, soft tissue and joints; long-term, progressive joint damage (arthropathy) can result following continued joint bleeds, resulting in substantial pain, reduced range of motion and poor mobility all of which contribute negatively to quality of life.^{13, 22-24}
- The physical impairment brought about by recurrent bleed episodes can limit individuals in their ability to participate in activities of daily living or the ability to live spontaneously.²⁴⁻²⁷
- A substantial psychological burden is associated with haemophilia; anxiety and depression are commonly reported due to the unpredictability of bleeding events, frustration with treatment and issues with venous access.^{6, 24, 27}

B.1.3.1.1 Haemophilia background and pathophysiology

Haemophilia is a rare, X-linked genetic disorder caused by a deficiency or absence of coagulation factors (FVIII or FIX), with disease severity that is defined by circulating levels of these factors

Haemophilia is a rare, lifelong genetic condition that affects blood clotting.¹ The reduced ability of the body to produce coagulation factors (referred to as factor[s] from here on), proteins that are essential for normal blood clotting, results in prolonged and spontaneous bleeding episodes.¹⁶ There are two primary forms of haemophilia: haemophilia A and the less common haemophilia B.¹⁹ The form of haemophilia that presents is dependent on the affected factor, with haemophilia A and haemophilia B characterised by an absence or deficiency of FVIII and FIX, respectively.¹⁹

FVIII deficiency is the result of mutation of the factor gene, *F8*, located on the X-chromosome at position Xq28, while FIX deficiency is the result of mutation of the factor gene, *F9*, located on the X-chromosome at position Xq27.1. As an X-chromosome-linked, recessive condition, haemophilia predominantly affects males. Although instances of more severe forms of haemophilia in females are rare, those carrying two mutated copies of the X chromosome present with symptomatic disease, while female carriers are largely asymptomatic.²⁸ Haemophilia can occur without family history of the disease; approximately one third of all haemophilia cases are not inherited, instead occurring *de novo*.

The stopping of bleeding (haemostasis) is a complex process involving the interaction of blood vessels, platelets (specialised human blood cells) which adhere to each other, and clotting factors. Primary haemostasis, the body's initial response to vascular injury, involves the build-up of platelet aggregates at the site of the damaged blood vessel to form a haemostatic plug; this temporarily blocks the disrupted vasculature.^{29, 30} Secondary haemostasis, the formation and deposition of insoluble fibrin (a clot forming protein) through the blood coagulation cascade, is required to form blood clots and permanently stop bleeding episodes.³¹

FVIII and FIX are key components in the intrinsic pathway of the blood coagulation cascade.³² Specifically, FIX works in the presence of its cofactor, FVIII, to activate factor X (FX), an important step in the activation cascade of several plasma factors which results in fibrin formation, ultimately contributing to the cessation of bleeding (Figure 1).^{17, 18}

TFPI is an early inhibitor of the extrinsic coagulation system, blocking FXa via the K2 domain and the tissue factor-FVIIa complex via the K1 domain.³³ Marstacimab acts by preventing this early inhibition of blood clotting by binding to TFPI, blocking its inhibitory effects (Figure 2).

Figure 1: The intrinsic and extrinsic pathways of the coagulation cascade

Intrinsic pathway

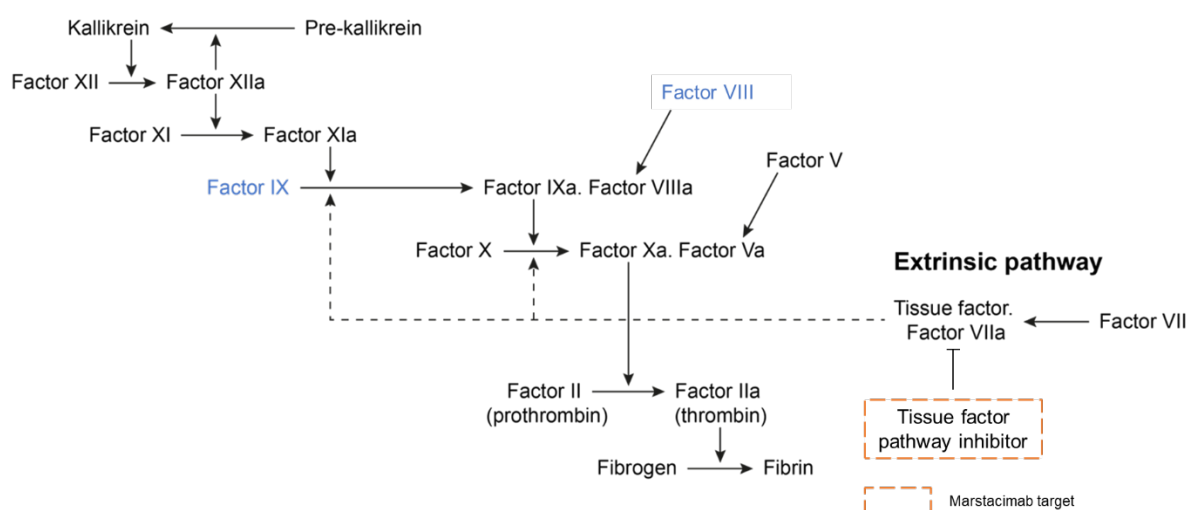
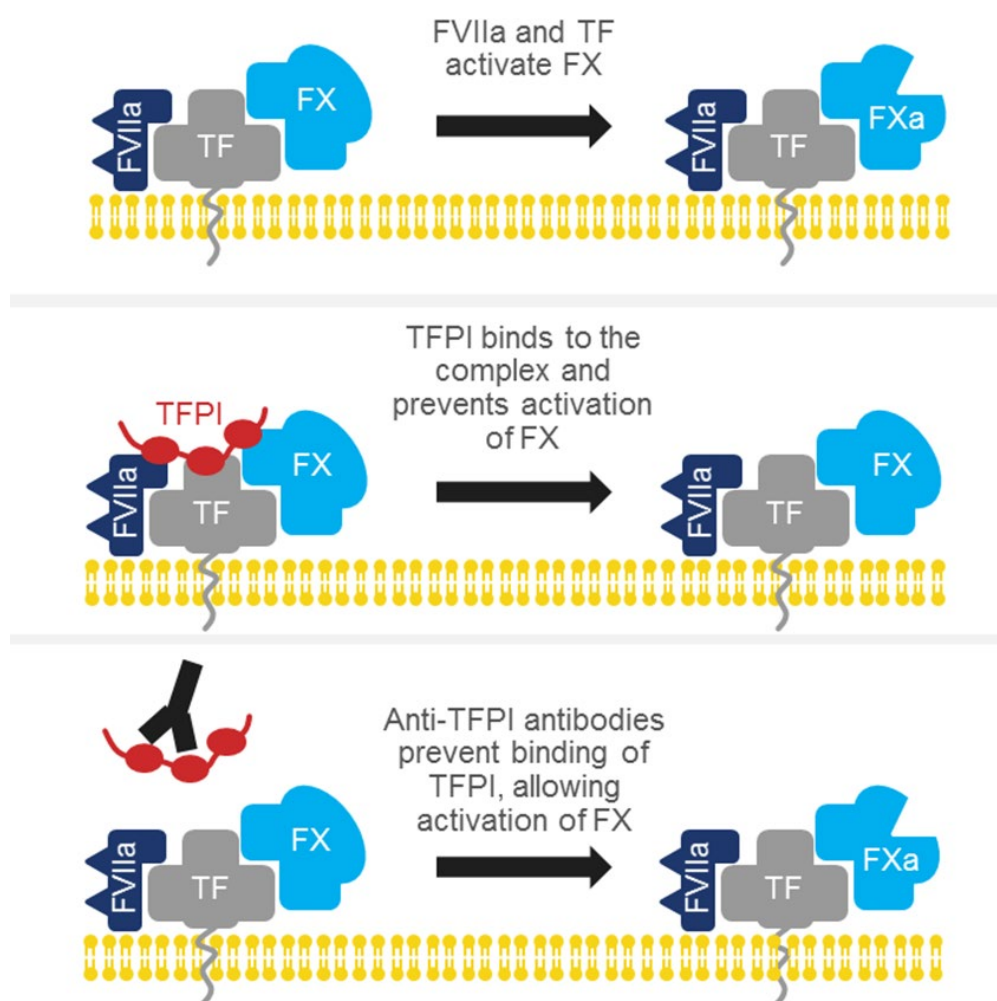


Figure 2: TFPI mechanism of action



Abbreviations: FVII: Factor VII; FX: Factor X; TF: tissue factor; TFPI: tissue factor pathway inhibitor.

Source: Adapted from Chowdary et al. 2018³⁴

In haemophilia, the formation of the haemostatic plug is unaffected, but reduced fibrin production due to factor deficiency causes impaired secondary haemostasis; this results in delayed clot formation and susceptibility to continued bleeding.³⁵ Consequently, people with haemophilia experience frequent and prolonged bleeding episodes. Depending on disease severity, these bleeding episodes can occur either spontaneously or following minor trauma; this can be acutely life-threatening and lead to debilitating long-term complications.^{36, 37}

B.1.3.1.2 Disease severity

The severity of haemophilia can be classified according to the plasma level of FVIII or FIX relative to normal plasma levels (Table 3). Factor activity in plasma is usually expressed either as a percentage (relative to normal human plasma) or in international units (IU) (relative to an international standard for FVIII or FIX in plasma). The normal factor activity in blood plasma is defined as 100 IU/decilitre (dL) (equivalent to 1 IU/mL [i.e., 100% of normal factor activity]). Factor activity levels lower than this usually correlate with an increased likelihood of bleeding events and injury. For patients with severe haemophilia (i.e. factor activity below 1% of normal [<1 IU/dL]), bleeding often presents spontaneously.^{2, 13, 20}

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Table 3: Classification of the severity of haemophilia according to circulating factor levels

Disease Severity	% of normal factor activity	Clinical presentation
Mild	5 to <40% (5 to < 40 IU/dL)	Bleeding typically occurs following injury, trauma, or surgery; spontaneous bleeding rare
Moderate	1 to <5% (1 to <5 IU/dL)	Infrequent spontaneous bleeding with prolonged bleeding following surgery or minor trauma
Severe	<1% (<1 IU/dL)	Frequent spontaneous bleeding into muscles or joints, with excessive bleeding following minor injuries or surgery

Abbreviations: dL: Decilitre; IU: International units.

Source: Srivastava et al. 2020¹³

B.1.3.1.3 Epidemiology

Severe haemophilia is a rare condition, with recent epidemiological data indicating that there were an estimated 2,457 adults treated in the UK in 2022/2023

Haemophilia A is more common than haemophilia B, with the former occurring in one in 5,000 live male births and the latter occurring in one in 30,000 live male births.¹⁵ Some global estimates have calculated the prevalence of haemophilia A to be 12.8 per 100,000 men and haemophilia B to be 2.69 per 100,000 men (based on data from Western European countries, the United States, and Canada).^{38, 39}

A key source of epidemiological information for people with severe haemophilia in the UK is derived from the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) National Haemophilia Database (NHD). The UKHCDO is an association of medical practitioners working within haemophilia centres in the UK. They manage the UK NHD which prospectively collects data for all people registered with a bleeding disorder in the UK, as well as the Haemtrack home therapy reporting system which allows individuals with haemophilia to report their treatments in real-time. The most recently available data from the NHD indicated that there were 2,128 patients treated for severe haemophilia A and 329 people treated for severe haemophilia B in the UK.⁴ The full breakdown of patients with haemophilia by severity is provided in Table 4.

Additionally, bespoke analysis of 2022/2023 UKHCDO data (12 years+ only), conducted for Pfizer, reports that there are [REDACTED] patients treated with severe haemophilia A and [REDACTED] treated with severe haemophilia B, in the UK. Of those with severe haemophilia A, [REDACTED] were aged 12 to 17 while [REDACTED] were aged 18+. Of those with severe haemophilia B, [REDACTED] were aged 12 to 17 while [REDACTED] were aged 18+.⁴⁰

Table 4: Breakdown of patients with haemophilia by severity in the UK, 2022/2023

	Haemophilia type	Total number of people by factor activity level (IU/dL)					
		<1	1–5	>5 and <40	≥40	Unknown	Total
Total number of patients in register	A	2,230	873	4,141	1,969	103	9,316
	B	374	351	893	417	34	2,069
Total number of treated patients	A	2,128	567	750	43	10	3,498
	B	329	194	202	8	-	733

Includes infant (<18) and adult patients (≥18).

Abbreviations: dL: Decilitre; IU: International Unit.

Source: Adapted from UKHCDO Annual Report 2023 and Bleeding Disorder Statistics for the Financial Year 2022/23.⁴

B.1.3.1.4 Overview of symptoms and clinical features

The primary clinical features of haemophilia are repeated episodes of bleeding into the muscles, soft tissue and joints. Patients with haemophilia have reduced life expectancy compared with the general population, and persistent bleeding into the joints can result in the development of long-term joint damage that is associated with joint pain, reduced range of movement and impaired mobility

Individuals with haemophilia A and B display comparable symptoms, of which the defining clinical feature is the repeated and prolonged bleeding events into muscles and soft tissue which can occur spontaneously (without an identifiable cause) or in response to trauma (e.g., following injury or surgery).^{13 22, 41, 42} Recurrent bleeding events can lead to inflammation, joint pain, diminished range of movement and poor mobility.²³

Approximately 70–80% of all bleeds occur into joints (haemarthrosis) which can lead to progressive haemophilic joint damage (arthropathy), an important long-term complication of bleeding.⁴³ Recurrent spontaneous and/or traumatic haemarthrosis aggravates joints, resulting in the development of chronic synovial inflammation (synovitis) – a joint that experiences chronic synovitis is known as a “target joint” – and joint arthropathy.^{44, 45} The severity of joint arthropathy, is proportional to the number of joint bleeds experienced by an individual, with permanent damage observed following three episodes of haemarthrosis into the same joint. Long term, irreversible, progressive joint destruction follows, ultimately causing substantial physical dysfunction and impairment in individuals with severe haemophilia.¹³

Asymptomatic (sub-clinical) microbleeds into joints have also been observed in individuals with haemophilia that do not present with clinically evident joint bleeds.⁴⁶ Studies have reported on individuals who, despite maintaining excellent bleed outcomes, report abnormalities consistent with microbleeds following magnetic resonance imaging.^{47, 48} Such asymptomatic leakage of small amounts of blood into a joint can contribute to joint arthropathy and damage over an individual’s lifetime.⁴⁶

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Those with haemophilia may also experience bleeding into muscles and abdominal organs, which can lead to organ rupture and further severe blood loss.⁴⁹ Long-term internal bleeding can also lead to the development of osteoporosis, the most common comorbidity of haemophilia. Reductions in bone mineral density are often observed in those with moderately severe to severe haemophilia, resulting in further chronic pain and an increased propensity for fractures in older individuals.^{50, 51}

Evidence suggests that people with haemophilia may have a higher mortality risk than the general population, with the risk of mortality linked to severity.^{52, 53} In the UKHCDO 2023 report, the median life expectancy of individuals with severe haemophilia A and B, who were actively registered between 1996 and 2023, was reported as 77 and 79 years, respectively, compared with a median life expectancy of 84 and 85 for individuals with mild haemophilia.⁴ Approximately 20% of deaths in people with haemophilia are caused by spontaneous intracranial bleeding,⁵⁴ which can additionally lead to seizures or impaired motor functioning in those surviving these debilitating incidents.^{13, 37}

B.1.3.1.5 Impacts of severe haemophilia on people living with the condition

Severe haemophilia has a substantial and wide-ranging physical and psychological impact on people living with the condition and their daily activities

Given the increased prevalence of haemophilia A compared with haemophilia B, there is a greater body of evidence describing the impacts of the condition on people with haemophilia A. Therefore, given the comparable disease profiles between haemophilia A and B, applicable data from those with haemophilia A are presented where appropriate, and where possible evidence from people with haemophilia B will also be discussed.

Impact of physical symptoms on quality of life

The recurrent bleeding episodes that characterise severe haemophilia can lead to progressive joint damage (arthropathy) and pain, resulting in physical impairment and negative impacts on quality of life

As described in B.1.3.1.4, repeated episodes of bleeding into muscle, soft tissue and joints are a central clinical feature of haemophilia.²² Bleeding into joints can result in the development of joint arthropathy,^{44, 45} in turn leading to joint pain, reduced range of movement and impaired mobility.²³ High bleeding rates, joint arthropathy and associated joint pain have each been shown to be key drivers of negative impacts on health related quality of life (HRQoL) in people with haemophilia and have been considered in turn below.²⁵

Bleeding as a driver of impacted HRQoL

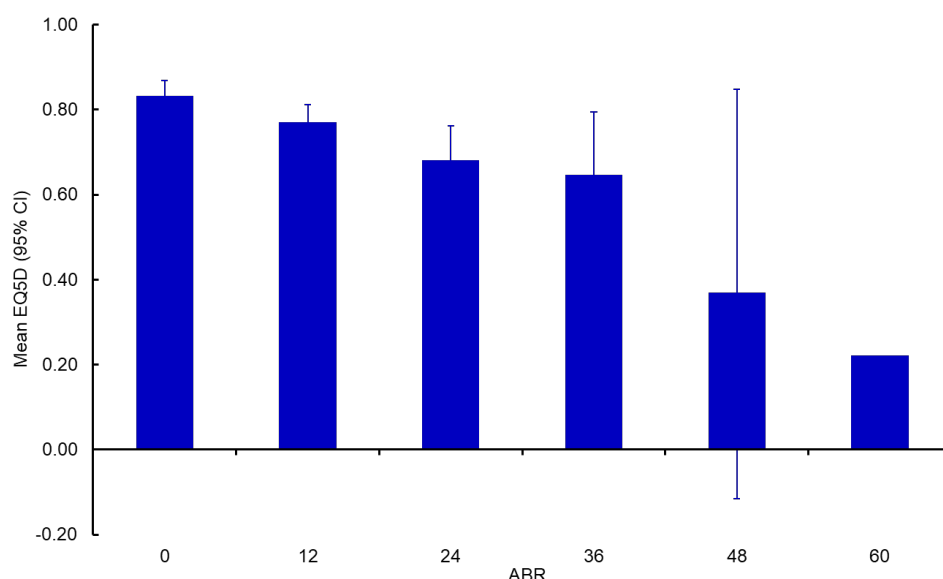
The Cost of Haemophilia across Europe – a Socioeconomic Survey (CHESS) study has been used as a dataset to determine the impact of bleeds on the HRQoL of people with haemophilia. CHESS was a real-world study in which individuals with haemophilia (n=996 with severe haemophilia A [78%]; n=289 with severe haemophilia B [22%]) and physicians from five European countries (including the UK) completed questionnaires between 2014 and 2015 on bleeding, joint status, QoL and haemophilia-related direct and indirect costs.⁴⁵

One study utilising a subset of data from CHESS (n=400 with haemophilia A; n=115 with haemophilia B) evaluated the relationship between bleeding rates (as assessed by ABR) and HRQoL (as measured using the EQ-5D-3L instrument).⁵⁵ Notably, individuals with zero bleeds

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(n=172) had significantly higher EQ-5D scores when compared with those with non-zero bleeds (mean scores: 0.84 versus 0.74; $p < 0.0001$), and an increase in ABRs was found to result in a statistically significant reduction in HRQoL (Figure 3).⁵⁵

Figure 3: Correlation of EQ-5D with ABR



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

Source: Adapted from Camp et al. 2016.⁵⁵

Furthermore, in a secondary analysis of the data from CHES, ABR was found to have a greater impact on utility index score than bleed severity in 404 participants with haemophilia A, highlighting that each bleeding event is significant to individuals.⁵⁶ Separately, discussions with UK patients with severe haemophilia B attending a workshop (n=5) and interviews (n=4) conducted by Haemnet on behalf of Pfizer in 2023 echoed the same conclusions, with bleeding rates driving negative impacts on HRQoL in this population:²⁴

“Having so many bleeds, it was so disruptive to my work, just to life in general”

Joint bleeds as a driver of impacted HRQoL

The development of joint arthropathy resulting from repeated bleeding episodes represents one of the most debilitating consequences of severe haemophilia and has been shown to be a key driver of quality-of-life impacts for people with the condition. A strong association between musculoskeletal complications caused by haemophilia and negative impacts on HRQoL has been observed in a further analysis of data from the CHES study (n=551 with severe haemophilia A and B).²⁶ In this study, participants with one or more target joints reported significantly worse HRQoL when compared with those with no recorded target joints (mean EQ-5D index score: 0.73 [Standard deviation (SD): 0.285] versus 0.87; SD: 0.179), with scores worsening as the number of target joints increased.²⁶ Furthermore, participants with severe haemophilia B interviewed in the Haemnet study raised the issue of joint health and the frustrations this causes on multiple occasions, demonstrating that the development of long-term joint damage and associated physical impairments also result in negative impacts on HRQoL:²⁴

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"My greatest regret in life is when my kids were young I couldn't kick a football with them and I still can't, and if I have grandkids I can't kick a football with them. I want to be able to do the things, I can't go on hikes with them, I can't go cycling with them because I don't have the range in my ankles. I'm not as fit as I used to be, I used to work out five times a week, I can't lift stuff now."

"Speaking as somebody who has long-term joint damage and, you know, really painful long-term joint damage, it really affects my mobility and so I can't be as spontaneous as I would like to be."

Pain as a driver of impacted HRQoL

Finally, pain associated with bleeding is another factor that can have a substantial impact on individuals with severe haemophilia. The CHES II real-world burden of illness study was conducted across five European countries between 2019–2020 and aimed to describe the burden of haemophilia following advances in the management and treatments of the disease since the original CHES study five years prior.^{57, 58} One analysis of the CHES II study focused on individuals with haemophilia A (moderate haemophilia A: n=190; severe haemophilia A: n=278) with problem joints, defined as joint damage presenting with chronic joint pain and/or limited range of movement due to compromised joint integrity. Patients with problem joints reported markedly lower EQ-5D scores, which decreased in patients with a greater number of problem joints.⁵⁹ An additional analysis of the CHES II study specifically focussed on people with severe haemophilia B receiving prophylaxis (n=75, with 29% from the UK). In this study, it was reported that 76% of participants had mild or moderate chronic pain and 5% endured severe chronic pain, with low EQ-5D scores (mean 0.67) measured across this cohort of individuals as a result.⁵⁸

Further insight into the prevalence and severity of pain experienced by people with haemophilia is provided by the pain, functional impairment and quality of life (P-FiQ) study, an observational cross-sectional assessment of adults in the United States with haemophilia (n=381) presenting for routine care.²⁵ This study assessed pain and functional impairment via the EQ-5D-5L overall Brief Pain Inventory (BPI; a validated and widely used means to assess pain). Severity scores for adult participants indicated substantial levels of pain, and as shown in Figure 4, pain due to haemophilia caused substantial interference across many aspects of the cohort's life, including the ability to enjoy life, work normally, sleep and walk, all of which are areas that individuals without the disease may take for granted.²⁵ Additionally, over three-quarters of participants in this study reported a history of pain and discomfort as measured by EQ-5D-5L, with higher median pain interference scores (indicating increased pain interference) for general activity, mood, walking and work, providing further evidence to show that the effects and causes of pain in those with haemophilia is multifaceted.⁶⁰

Figure 4: BPI pain interference composite scores in adults with haemophilia



BPI range: 0 to 10; lower scores indicated less pain interference, with scores ranging from 0 (“no pain” or “does not interfere”) to 10 (“pain as bad as you can imagine” or “complete interference”).

Abbreviations: BPI: brief pain inventory

Source: Adapted from Buckner et al. 2018.²⁵

Participants in the workshop and interviews conducted by Haemnet repeatedly raised the issue of pain and associated frustrations, including having to manage it constantly.²⁴ One patient described pain as “an occupational hazard”, noting that “you get pain whatever, don’t you, really, so you just deal with it”. The stoic attitude of people with haemophilia may often mask the true impact of the disease, however, one participant concisely summarised their future hopes by simply saying “I’d like to have less pain”.²⁴

Impact on daily living

The downstream physical impairment brought about by recurrent bleeding episodes can limit individuals in their ability to participate in activities of daily living that those not living with haemophilia may take for granted

The physical impairments that can develop as a result of bleeding are closely linked with challenges in performing routine activities of daily living, including physical activity and household tasks.²⁵ The aforementioned study analysing CHES II highlighted that 63% of participants reported an impact of haemophilia on their daily lives.⁵⁸ Personal care, work-related issues and leisure activities are also all detrimentally impacted by the functional impairment caused by haemophilia.²⁵ Fatigue, loss of enjoyment, and reduced leisure pursuits also correlate positively with the presence of target joints.²⁶

Similar themes were discussed in the Haemnet workshop and interviews with people with severe haemophilia B.²⁴ While haemophilia had affected the lives of participants to different degrees, all stated an impact of the disease on their family and relationships, education, employment and physical activities. Additionally, the participating individuals felt limited in their ability to travel, particularly due to the need to take medical products like liquids and syringes with them. The

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individuals noted travel was “frustrating” due to the requirement of travelling with liquids and syringes, with one stating:²⁴

“I hadn’t been out of the country until this year for nine years. Going out of a UK airport I feel like a criminal every time. Even though I’ve got the hospital letters, etc.”

Physical leisure activities were also significantly curtailed in individuals with haemophilia, despite a desire to be able to participate. One patient noted:²⁴

“My earliest memory of a consultant was [them saying] ‘you will not play football, you will not play cricket, you will not play rugby, you will not play basketball, you will not do PE at school’ and I was bored and I got fed up.”

Further evidence for the impact on daily living due to bleeds and subsequent physical burden is provided in a qualitative study involving nine members of The Haemophilia Society.²⁷ All participants reported that joint bleeds had a substantial impact on their physical well-being, with bleeds and associated comorbidities limiting mobility and independence, along with the inability to partake in activities of daily living, as emphasised by one participant:²⁷

“I’ve had a fair number of bleeding episodes, like knees, ankles, elbows, shoulders and hips and, later on, I’ve begun to suffer with arthritis which has obviously had a major impact on my mobility which effects all aspects of my life... especially doing things for myself.”

Psychological impacts

Beyond the physical aspects of the condition, anxiety and depression are commonly reported in people with severe haemophilia, highlighting how aspects of living with the condition can result in an additional psychological burden

Across the cohort of individuals with haemophilia A and B (n=515) in one secondary analysis of the CHES study, anxiety and depression were two of the most common dimensions in which ‘extreme’ problems were reported on the EQ-5D-3L instrument.²⁶ In a separate analysis of the CHES dataset (n=404 with severe haemophilia A), the relationship between bleeding and psychological impact was also stronger when considering the pain/discomfort and anxiety/depression domains of the EQ-5D-3L instrument, indicating that physical and psychological dimensions of bleeding also contribute to reductions in HRQoL.⁵⁶

Further evidence for the psychological impact of haemophilia can be drawn from the MIND study, an 11-year Nordic registry study that analysed longitudinal national data from 2007–2017 of people with haemophilia (n=3,246), which showed a higher use of antidepressants amongst those with the condition compared with those without the disorder.⁶¹

Additionally, during the Haemophilia Treatment Experience Measure (Hemo-TEM) study, which aimed to capture the broad range of treatment burden issues experienced by individuals with haemophilia (n=28 [93.3%] with severe haemophilia), individuals stated they felt worried, anxious and frustrated, with feelings of stress and being overwhelmed also reported.⁶ The cause for these psychological impacts was multifactorial, with participants noting venous access, the

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chance for infection, and potential development of inhibitors.⁶ Further underlying reasons for psychological impacts of the condition are expected to include anxiety relating to the unpredictability of bleeding events, concerns that the condition will progress and result in further damage and physical impairment, and the limitations on freedom because of the care required to manage the condition with IV factor infusions.

The psychological well-being of all participants as a result of their haemophilia was also noted by participants in the qualitative study involving members of The Haemophilia Society; anxiety was common due to the unpredictable nature of the disease, with strong feelings of uncertainty for the future also reported.²⁷ The inability to participate in activities that individuals valued, along with a lack of independence, were also cited as reasons for depression, with the inability to partake in activities independently also leading to a feeling of “*disempowerment*”.²⁷ Feelings of anger and frustration were further reiterated due to restrictions in activities of daily living and the lifelong nature of the disease:

“I think there are a lot of us who are angry and haemophilia is definitely frustrating, it can bring on an awful lot of anxiety”; “I sometimes feel ... why me and I do get angry because it’s not my fault that I’ve got this thing which now I have to live with every day because I know it’s not going to ever go away.”

Restrictions in social engagements and dependency on others were also cited to exacerbate feelings of depression, with participants also forced to stay home due to the physical impact of their disease, as reported by one participant:²⁷

“I’ve had all sorts of depression on and off for the last eight years. I felt so disempowered, a lot of the time couldn’t do anything for myself, have a shower, get dressed; I was in pain, bleeding, in a mess and couldn’t leave the house.”

Socioeconomic burden

Severe haemophilia is associated with a substantial socioeconomic burden resulting from reduced work opportunities and productivity

Haemophilia also represents a major economic burden to society and has a substantial impact on an individual’s employment status and productivity.⁶²⁻⁶⁴ People with haemophilia are up to four times more likely to be unemployed compared with non-haemophilia controls among people of working age.⁶² Those with the disease also participate less in full-time work compared with the general population, as reported in a study conducted in the Netherlands.⁶³ A substantial number of employed individuals with severe haemophilia (39%) were also reported to experience restrictions in performing their job due to pain and frequent absenteeism. This effect was reported in 19% of individuals with mild or moderate haemophilia.⁶³

Many participants in the qualitative study with members of The Haemophilia Society also mentioned the impact that bleeding had on their education, work and social life. Five individuals included in the study reported that their working lives were notably impacted, with three participants having to retire early due to their haemophilia.²⁷ One participant also mentioned:²⁷

“... you have no social life, you can’t leave the house, you can’t do anything by yourself.”

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Education and employment were also key themes of the workshop and interviews conducted by Haemnet on behalf of Pfizer. Participants stated that having haemophilia influenced their hopes and goals regarding employment and caused them to miss out on educational opportunities. Participants discussed the negative impacts on schooling and work:²⁴

“I was hardly ever at school; I was mainly in hospital and when I was at school I was bullied and if I wasn’t bullied, I was in detention... So my teachers didn’t really take much notice of me.”

“It [bleeding] was basically every month and I was having to have, like, a week off work and then come in in a wheelchair the next week, and it was just like ... it was crap.”

Furthermore, direct and indirect costs due to disease-related complications such as orthopaedic complications, transfusion-related infections (e.g. human immunodeficiency virus [HIV], Hepatitis C) and development of inhibitors can be substantial.⁶⁵ This is due to greater use of clotting factors, more frequent hospitalisations for bleeding, a greater need for surgical intervention (e.g., joint replacements) and the high cost of treating individuals with inhibitors to factor prophylaxis.^{65, 66} From an economic perspective, while the lifetime medical costs incurred to prevent and manage bleeding risk and the long-term consequences of joint damage are most notable for the NHS (as discussed in Section B.1.3.2), it is important to not overlook the negative impact of severe haemophilia on employment and the lives of those with the disease.^{6, 65}

B.1.3.2 Description of the clinical care pathway

Severe haemophilia A is primarily managed with emicizumab, a prophylactic monoclonal antibody treatment, while life-long IV infusions of FIX prophylaxis remains standard of care in haemophilia B

- Following its introduction in 2019, emicizumab self-administered as a once weekly SC injection has become the primary treatment for haemophilia A in NHS clinical practice.⁶⁷ This was confirmed by clinical experts participating in consultancy interviews who noted that emicizumab is now considered standard of care for haemophilia A.⁶⁸
- Whilst their use has declined following the introduction of emicizumab, prophylactic replacement therapies given as regular IV infusions remain an important treatment option in haemophilia A
- In the absence of newly recommended alternatives, standard of care in haemophilia B remains life-long regular IV administration of factor prophylaxis infusions to transiently raise circulating factor activity levels to prevent bleeding and preserve musculoskeletal function.¹⁴
- On-demand factor therapy is also available to resolve individual bleeds, for example following surgery or injury, and can be used in addition to prophylaxis or, rarely, on its own.¹³
- Factor prophylaxis therapies are available in two forms: SHL and EHL products. Haemophilia A SHL products require administration 3 to 4 times a week, while EHL products are typically administered twice weekly.⁶⁹⁻⁷⁵ In haemophilia B, SHL products can require administration twice per week, whilst EHL products are typically administered at frequencies from once a week to once every two weeks for those whose bleeding is well controlled.⁷⁶⁻⁷⁹
- In patients with haemophilia A, EHL and SHL products have similar market share, while in patients with haemophilia B, EHL products are favoured given they reduce the frequency of administration and the subsequent treatment burden, with their use increasing substantially over time.^{4, 80}

B.1.3.2.1 Overview of clinical care

Current clinical management of severe haemophilia primarily consists of life-long prophylaxis to prevent bleeding and preserve musculoskeletal function. Factor replacement remains a common form of prophylaxis, however prophylaxis with emicizumab is becoming more commonly used to treat patients with haemophilia A

Given that haemophilia is a life-long condition characterised by recurrent bleeding episodes that can lead to irreversible joint damage, the primary goals of current treatments are to reduce or prevent bleeding while allowing patients to lead active lives and achieve a quality of life comparable to individuals not affected by this condition.¹⁴

B.1.3.2.2 Factor replacement therapy

Routine factor replacement prophylaxis remains a mainstay of treatment for people with severe haemophilia, as recommended by the World Federation of Hemophilia (WFH).¹³ Prophylaxis treatment can significantly reduce joint bleeding and improve joint health as compared with on-demand therapy.

In the UK, there are currently no available NICE-recommended treatments for haemophilia. However, guidelines published by the BSH in 2020 recommend that factor replacement prophylaxis should be started before or immediately after the first joint bleed in a person with severe or moderate haemophilia with a baseline level 1–3 IU/dL; this will usually be early in life, prior to the age of three.¹⁴ UK clinical experts have confirmed that the BSH guidelines represent commonly followed clinical practice in the UK.⁶⁸

Currently available recombinant factor therapies include SHL and EHL products.^{13, 14} In haemophilia A, SHL products require administration 3 to 4 times a week, while EHL products are typically administered twice weekly.⁶⁹⁻⁷⁵ In haemophilia B, SHL products can require administration twice per week, whilst EHL products are typically administered at frequencies from once a week to once every two weeks for those whose bleeding is well controlled.⁷⁶⁻⁷⁹

Given EHL factor prophylaxis reduces the frequency of administration and the subsequent treatment burden compared with SHL products (see Section B.1.3.3.1), EHL products are favoured, especially in haemophilia B, as evidenced by their greater market share in the UK.⁴ In haemophilia A there is a greater balance between the use of EHL and SHL products, likely due to the reduced extension of effect for EHL products. FVIII EHL products have a half-life of approximately 19 hours (1.4 to 1.6 fold extension compared to FVIII SHL products), whereas FIX EHL products have a half-life of approximately 82 to 89 hours (3 to 5 fold extension compared to FIX SHL products).¹³

B.1.3.2.3 On-demand treatment

Management of haemophilia in the UK may also involve on-demand administration of factor replacement products, either on its own or in addition to emicizumab (for patients with haemophilia A only) or factor prophylaxis, with the aim of stopping bleeding once it has occurred, as may be required following trauma or surgery.⁸¹ However, administration of on-demand factor replacement without prophylaxis is rarely used as a treatment strategy in haemophilia, especially in patients with severe haemophilia. While on demand treatment is essential for reducing the pain and debilitating impact of individual bleeds, it does not significantly alter the bleeding profile and does not subsequently change the natural history of haemophilia leading to musculoskeletal

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damage and other complications from bleeding. On-demand therapy on its own has been demonstrated to be significantly less effective compared with factor prophylaxis at reducing ABR.^{82, 83} On-demand treatment on its own is therefore not recommended for use in severe haemophilia, as per WFH and BSH guidelines.^{13, 14}

As previously outlined in Section B.1.1, five UK clinical experts in haemophilia confirmed that on-demand use of factor replacement products alone are rarely used to treat severe haemophilia in the UK. One clinician estimated that 96% of patients with severe haemophilia are on prophylaxis, with patients only very rarely choosing on-demand therapy.⁶⁸ On-demand factor replacement treatment as standalone therapy has therefore not been considered relevant in this appraisal, in line with other recent NICE appraisals for severe haemophilia.^{10, 84}

B.1.3.2.4 Emicizumab

For decades, the standard of care for haemophilia was to use clotting factor replacements as prophylaxis to enhance homeostasis. However, non-factor replacement treatments have also been in development, with emicizumab being available in the UK for people with severe haemophilia A without inhibitors since 2019.⁸⁵ Since then, emicizumab has become the primary treatment option for patients with severe haemophilia A, with over half of UK patients estimated to have received emicizumab in 2023.⁸⁰ Emicizumab is a monoclonal immunoglobulin G4 (IgG4) antibody with a bispecific structure enabling it to bridge activated FIX and factor X, restoring the function of the missing FVIIIa and thus promoting the intrinsic pathway of blood clotting.⁶⁷

Like factor replacement therapies, emicizumab is given as prophylaxis, however is self-administered by SC injections instead of IV infusion. The recommended dose is 3 mg/kg once weekly for the first four weeks (loading dose), followed by a maintenance dose from Week 5, of either 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks.⁶⁷ Patients or caregivers may self-administer emicizumab after appropriate training from a healthcare provider.⁸⁶ Self-administration of emicizumab requires the individual to first determine their correct weight-based-dose and then draw this up into the SC syringe from the vials of product provided.⁶⁷

B.1.3.2.5 Current clinical management of haemophilia in the UK

Based on UK clinical recommendations developed by the BSH, and expert clinical opinion, prophylaxis is considered to represent the primary treatment option for adults with severe haemophilia in the UK.^{14, 68} For haemophilia A specifically, the monoclonal antibody emicizumab is an alternative prophylactic treatment to FVIII replacement. The products used to treat haemophilia in the UK and considered in this submission are presented in Figure 5.

Figure 5: Current clinical management of severe haemophilia in UK clinical practice

Haemophilia A SOC			Haemophilia B SOC	
mAb	Prophylactic FVIII replacement		Prophylactic FIX replacement	
	SHL products	EHL products	SHL products	EHL products
HEMLIBRA® (emicizumab-kxwh)	ADVATE® (octocog alfa)	ESPEROCT® (turoctocog alfa pegol)	BeneFIX® (nonacog alfa)	ALPROLIX® (eftrenonacog alfa)
	ReFacto AF® (moroctocog alfa)	ELOCTA® (efmoroctocog alfa)		IDELVION® (albutrepenonacog alfa)
	NovoEight® (turoctocog alfa)	ADYNOVI® (rurioctocog alfa pegol)		REFIXIA® (nonacog beta pegol)
	NUWIQ® (simoctocog alfa)			

Only SHL and EHL products with a market share of >1% in the UK are included in the diagram and as relevant comparators in this appraisal.

Some individuals may also administer factor replacement therapy on an on-demand basis to stop bleeding when it arises, as may occur following injury or local trauma, for example, following surgery.

Abbreviations: EHL: extended half-life; FIX: factor IX; FVIII: Factor VIII; mAb: monoclonal antibody; SHL: standard half-life; SOC: standard of care.

Source: [REDACTED];⁸⁰ UKHCDO Annual Report 2023 and Bleeding Disorder Statistics for the Financial Year 2022/23.⁴

Table 5 and Table 6 below present a breakdown of the products issued to treat people with haemophilia A and B in the UK in 2022/23, respectively, as reported by IQVIA market share analysis and the UKHCDO 2023 report.^{4, 80} Emicizumab has the greatest market share for products used by patients with haemophilia A, while similar proportions continue to use either EHL or SHL FVIII prophylaxes. While both SHL and EHL products are available to individuals with severe haemophilia B, prescriptions of EHL products far outweigh those for SHL products. These market share estimates were reflected in feedback received from UK clinical experts, who estimated that over 50% of patients with severe haemophilia A patients received emicizumab, whilst the use of EHL products greatly outweighed SHL products in both severe haemophilia A and B.⁶⁸

Market share data are often presented in terms of IU volumes for each product. However, as SHL products require a higher daily dose (in IU) than EHL products, using IU volumes to inform market share could artificially skew the results in favour of the SHLs. To correct for this, days of therapy (DOT) adjusts for the different dosing regimens of SHLs and EHLs ($\text{DOT} = \text{IU} / \text{daily dose}$) and standardises the IU data by the different daily doses for each product, facilitating a more accurate comparison of market shares. For emicizumab only, DOT market share was calculated using sales volume in mg, rather than IU.

Table 5: Products issued to treat people with haemophilia A

Product		IQVIA Sales Volume Data (Apr 2023–Apr 2024)		UKHCDO 2023 Annual Report (2022/23)	
		IU ^a	DOT	IU ^a	DOT
mAb	Emicizumab	█	█	NA	43.75%
FVIII EHL	Esperoct®	█	█	23.57%	13.21%
	Elocta®	█	█	19.81%	11.10%
	ADYNOVI®	█	█	1.92%	1.05%
FVIII SHL	Advate®	█	█	27.21%	15.89%
	ReFacto AF®	█	█	15.95%	9.31%
	NovoEight®	█	█	8.95%	4.18%
	Nuwiq®	█	█	2.59%	1.51%

^a Emicizumab is dosed in mg, not IU, so market shares calculated by IU exclude this treatment.

Abbreviations: DOT: Days of therapy; EHL: Extended half-life; FVIII: Factor VIII; IU: International unit; mAB: monoclonal antibody; SHL: Standard half-life; UKHCDO: United Kingdom Haemophilia Centres Doctors' Organisation.

Source: █⁸⁰ UKHCDO Annual Report 2023 and Bleeding Disorder Statistics for the Financial Year 2022/23.⁴

Table 6: Products issued to treat people with haemophilia B

Product		IQVIA Sales Volume Data (Apr 2023–Apr 2024)		UKHCDO 2023 Annual Report (2022/23)	
		IU	DOT	IU	DOT
FIX EHL	Alprolix®	█	█	42.91%	46.70%
	Idelvion®	█	█	11.83%	15.10%
	Refixia®	█	█	10.84%	14.80%
FIX SHL	BeneFix®	█	█	34.42%	23.40%

Abbreviations: DOT: Days of therapy; EHL: Extended half-life; FIX: Factor IX; IU: International unit; mAB: monoclonal antibody; SHL: Standard half-life; UKHCDO: United Kingdom Haemophilia Centres Doctors' Organisation.

Source: █ UKHCDO Annual Report 2023 and Bleeding Disorder Statistics for the Financial Year 2022/23.⁴

B.1.3.3 Unmet need

A substantial unmet need exists for an efficacious therapy with a novel mechanism of action and a convenient and simple method of administration

- Factor prophylaxis treatment is associated with substantial administration burden; the need for frequent self-administered IV infusions greatly interferes with an individual's ability to take part in day-to-day activities that others without the condition may take for granted.^{6,84} This is particularly true for people with haemophilia B for whom there is no SC treatment option currently available.^{6, 13, 87}
- The high costs of the lifetime use of factor products that require regular IV administration means that disease management is associated with substantial direct treatment costs for the NHS.^{45, 58}
- People with severe forms of haemophilia remain at risk of spontaneous, prolonged bleeding, particularly into the joints, despite regular use of factor prophylaxis.
- While emicizumab offers an effective treatment option with a different mechanism of action to factor replacement therapies, issues around complicated dosing and administration practices remain. Furthermore, emicizumab is not available to patients with haemophilia B
- The administration of both emicizumab and factor prophylaxis requires prescribing clinicians to perform weight-based dosing calculations. Patients taking emicizumab must then draw up the solution into a syringe from vials themselves. Additionally, regular factor replacement therapy is challenging for older adults with limited venous access, who have already endured many years of injections. Treatment administration difficulties can additionally lead to issues with treatment adherence.^{13, 88, 89}
- There is an unmet need for an easy-to-use and conveniently self-administered prophylactic for all individuals with severe haemophilia.

B.1.3.3.1 Treatment burden associated with current SOC

The current approach to clinical management of lifelong, regular IV infusions of factor products results in a substantial treatment burden

Beyond the physical and psychological burden and impacts on activities of daily living experienced by many people with severe haemophilia, current clinical management with factor prophylaxis (discussed in detail in Section B.1.3.2) imposes a substantial treatment burden for people with the condition. Factor prophylaxis for both haemophilia A and B requires frequent IV infusions of FVIII or FIX over the lifetime of an individual to maintain sufficient circulating levels and prevent bleeds.¹³ As individuals are primarily responsible for their administration of factor prophylaxis, such frequent and time consuming infusions can substantially interfere with opportunities to take part in day-to-day activities that others without the condition may take for granted.¹³ The effect of treatment burden interfering with daily life was identified in the Hemo-TEM study; participants reported that travel and social activities were often impacted and that they had to stop activities to treat bleeds.⁶ Consequently, people with more severe haemophilia requiring regular IV infusions (every 1 to 3 days) are unable to easily plan their lives, especially when travelling, and they are not afforded the opportunity to live as spontaneously in their day-to-day lives.²⁴ Treatment also affected participant's employment as it caused them to arrive at work late or leave work early. These impacts were also identified by five clinical experts in the Hemo-TEM study who confirmed treatment regimens may negatively impact a patient's ability to travel and participate in social activities.⁶

Self-administration of factor therapies is a complicated and time-consuming process, requiring dexterity and phlebotomy capabilities and the need to regularly endure painful injections.⁶ Venous access has been identified as a key barrier to the administration of prophylaxis for people with haemophilia, given the requirement for frequent venous infusion with factor

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replacement products.¹³ In a multicentre prospective study conducted in France (n=450) venous access was judged to be difficult in 37% of haemophilia patients, most commonly due to poor vein condition (33%), young patient age (25%), patients being overweight (19%), and difficulty in locating veins (16%).⁹⁰ Regular factor prophylaxis thus inflicts further burden on those with limited venous access, a significant challenge for older adults with haemophilia who have endured many years of injections.^{13, 88}

These challenges compound the emotional impacts of haemophilia on individuals, resulting in experiences of frustration and anger in relation to their treatment regimen, particularly due to the interference it has on daily life and the ability to travel (see Section B.1.3.1 for further detail on the impact current treatments have on patients' daily living).⁶

Whilst the development of long-acting EHL FIX prophylaxis has reduced treatment burden in patients with haemophilia B to an extent, the more modest half-life extension seen with EHL FVIII treatments means this remains an issue in haemophilia A. IV administration of factor prophylaxis can take from 2 to >50 minutes depending on the product and preparation required, which creates a significant time burden and can be hard to fit around daily life.⁹¹ Additionally, the processes associated with factor product storage and administration can be time consuming, with 33% of patients in a survey of 200 individuals with haemophilia A considering the process of storing, preparing, and mixing FVIII product to be disruptive to their daily routine.⁹² A confounding effect from the burdensome treatment schedules of EHL and SHL factor prophylaxes is a potential impact on patients' ability to adhere to the treatment regimen.⁸⁹ Poor adherence has in turn been associated with negative impacts on clinical outcomes, including an increased risk of breakthrough bleeding episodes and target joint bleeds, which may then lead to subsequent worsening of joint damage and HRQoL.^{13, 93}

As a more convenient subcutaneous administration, emicizumab is becoming the treatment of choice for patients with severe haemophilia A. However, the by-weight dosing of emicizumab adds complexity to the administration process.⁷ While prescribing clinicians make the calculation regarding the dose required, it is up to the patient to draw this exact dose up into the SC syringe from the vials of product provided.⁶⁷ Given that emicizumab is only available in four vial sizes with differing concentrations, producing the correct dose for injection can lead to wastage of product if the exact dose does not meet the vial size.⁷

B.1.3.3.2 Limited treatment outcomes with current prophylaxis

A need exists for a new and effective therapy that can address limitations associated with current management of severe haemophilia with factor prophylaxis, including sub-optimal treatment outcomes

Despite regular use of factor prophylaxis, people with severe forms of haemophilia remain at risk of spontaneous, prolonged bleeding, particularly into the joints.¹³ A retrospective analysis of the UK NHD (n=36 with severe haemophilia B) has highlighted that 70% of individuals with haemophilia B do not remain haemarthrosis-free annually.⁹⁴ The risk of spontaneous or breakthrough bleeding remains, and suboptimal outcomes are evident, further reinforcing that current clinical prophylactic management of haemophilia is inadequate and fails to fully address the needs of individuals.^{13, 95-97} Taken together, this evidence highlights that an unmet need exists for a therapy that can provide greater reductions in bleeding rates, therefore increasing protection from the development of long-term joint damage and associated negative impacts on HRQoL.¹³

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B.1.3.4 Proposed positioning of marstacimab

Marstacimab is an innovative monoclonal antibody therapy that offers a practical pre-filled SC, self-administered, prophylactic therapy for individuals with severe haemophilia A and B

Marstacimab is anticipated to be indicated for [REDACTED]

With a once weekly, pre-filled SC, fixed-dose regimen, marstacimab prophylaxis offers a more manageable therapy compared with currently available invasive IV factor replacement products. A switch from IV to SC administration for haemophilia treatment products has been shown to improve patient quality of life. Results of a web based survey administered to male adults and their caregivers in the US indicated that both groups preferred treatments administered via SC injection rather than IV infusion.⁹⁸ Additionally, as marstacimab is given as a single injection from a pre-filled syringe, it would eliminate the need for complicated weight-based dosing calculations and the requirement for patients to prepare and draw up their own dose of factor therapy or emicizumab. Lessening the burden of administration with routine marstacimab prophylaxis could therefore improve confidence in self-administration, as well as adherence, thereby having a positive effect on patient outcomes.

As described in detail in Section B.2, in a Phase 3 clinical study, marstacimab has been demonstrated to be superior to routine prophylactic treatment in an intra-patient comparison, as measured by ABR of treated bleeds. This efficacy was maintained long-term (up to 16 months post treatment initiation [based on currently available open-label trial data]), with numerical improvement in participant quality of life compared with those on prophylactic factor replacement therapy. In addition to durable efficacy, the overall safety profile continues to be acceptable.

The mechanism of action of marstacimab enables it to provide all people with severe haemophilia, regardless of whether they have haemophilia A or B, access to a conveniently administered prophylactic therapy. Its novel mechanism of action, combined with its simple, fixed-dose, pre-filled SC method of administration, separates marstacimab from current products on the market. Ultimately, the introduction of marstacimab would fulfil an important unmet need for a simple and effective treatment option able to improve bleeding rates for patients, reduce the physical and psychological impacts of the treatment-associated and economic burdens of current management, and widen the range of treatment options available.

B.1.4 Equality considerations

Whilst the BASIS trial only recruited male participants, a very small number of females may also be living with severe haemophilia. It is expected that this appraisal will not exclude any people protected by equality legislation, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Separately, it is worth noting that individuals with active hepatitis B or C, or HIV uncontrolled by antiretroviral drugs (evidenced by CD4+ cell count of ≤ 200 mm³ or viral load >20 copies/mL) at the time of enrolment were ineligible for the marstacimab trials, which may present an equality consideration for the Committee.

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B.2 Clinical effectiveness

- A systematic literature review (SLR) was conducted to identify evidence on clinical efficacy, including safety, of current therapies for people with severe haemophilia A or B, without a history of factor (FVIII or FIX) inhibitors
- The Phase 3 BASIS study represents the pivotal clinical trial demonstrating the efficacy and safety of marstacimab prophylaxis compared to factor prophylaxis in patients with severe haemophilia A and B
- Weekly marstacimab prophylaxis was demonstrated in BASIS to be an effective treatment option, providing a statistically significant, 35.2% (95% CI: 5.6%, 55.6%; $p = 0.0376$) reduction in the primary endpoint, ABR_{treat} , compared with the observational period of the trial where patients received SOC factor prophylaxis.
- The mean ABR reductions observed with marstacimab were generally consistent across haemophilia A and B and age groups for those with prior routine prophylaxis, with all point estimates for a difference <2.5 (non-inferiority margin for the ABR of treated bleeds).
- Data from BASIS are supported by its open label extension (OLE) which is following trial participants for up to an additional 7 years of participation; currently up to an additional 16 month of data are available from the OLE. Data presented from an average of 6 months of follow up indicate a further numerical reduction in ABR_{treat} for patients receiving long-term marstacimab prophylaxis in the OLE, compared to patients from the BASIS trial active treatment phase (ATP)
- In the absence of direct comparative efficacy versus emicizumab, an unanchored simulated treatment comparison (STC) was conducted using data from the BASIS and HAVEN 3 trials. Results from this indirect treatment comparison (ITC) showed that the efficacy of marstacimab is comparable to that of emicizumab with respect to the control of total and treated bleeding rates, however no results reached statistical significance
- BASIS demonstrated that marstacimab is well tolerated with no notable safety findings. Marstacimab exhibited an acceptable safety profile when compared with factor prophylaxis
- Overall, weekly marstacimab prophylaxis offers patients with severe haemophilia A or B the option of a convenient and effective treatment able to reduce bleeds and improve quality of life compared to currently available factor prophylaxis

B.2.1 Identification and selection of relevant studies

A *de novo* SLR of the published literature was conducted. The SLR aimed to identify evidence on the burden of illness and the clinical efficacy and safety of current therapies for adults and adolescents with severe haemophilia A and moderately severe to severe haemophilia B without a history of factor VIII or IX inhibitors. The SLR was wider in scope than the proposed indication in this submission, as it additionally included patients with moderately severe haemophilia B. This reflects the enrolment protocol for the BASIS trial, which ultimately did not enrol any patients with moderately severe haemophilia B.

The review focused on clinical outcomes data derived from Phase 2/3 and single-arm randomised clinical trials (RCTs), non-RCTs and observational studies (including prospective and retrospective cohort studies and cross-sectional analyses).

The SLR was conducted in accordance with the high-quality standards required by NICE, as well as standards set forth in other established guidelines (i.e. Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] and the Cochrane Handbook for Systematic Reviews of Interventions).^{99, 100}

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The SLR was conducted on the 4th August 2020 (original SLR) and subsequently updated on the 21st August 2023 and 17th May 2024, with a similar review methodology utilised in each iteration. A total of 79 unique trials reported in 333 records were included in the SLR. 46 trials included patients with haemophilia A, 27 included patients with haemophilia B, and 6 included patients with haemophilia A and patients with haemophilia B. Sample size ranged from 2 patients to 216 patients, with the majority reporting on populations under 100 patients.

Full details of the SLR search strategy, study selection process and results are presented in Appendix D.1.

B.2.2 List of relevant clinical effectiveness evidence

Two unique trials were found in the SLR that reported clinical evidence for marstacimab: one Phase 3 trial, BASIS, and a Phase 2, dose-investigation trial.^{101, 102}

The primary evidence source for the efficacy and safety of marstacimab is the Phase 3 BASIS trial (NCT03938792).¹⁰¹ BASIS is an ongoing Phase 3, one-way, cross-over, open-label, multi-centre study in adolescent and adult patients with severe haemophilia A or moderately severe to severe haemophilia B with or without inhibitors comparing marstacimab versus routine factor prophylaxis. The study compared treatment with patients prescribed on-demand or prophylaxis factor replacement therapy during a 6 month, lead-in, observational phase (OP) with a 12 month ATP, during which patients received prophylactic marstacimab.

An OLE study (NCT05145127) of the BASIS trial provides further supportive data for the clinical evidence base of marstacimab. The OLE is assessing the long-term safety, tolerability, and efficacy of prophylaxis treatment with marstacimab in patients who successfully completed participation in the BASIS trial.¹⁰³

This submission focuses on the marstacimab Phase 3 clinical programme (consisting of the BASIS trial and the OLE). An overview of the key clinical evidence from the BASIS trial and OLE is presented in Table 7. The methodology and results of the BASIS trial are presented in Section B.2.3 onwards.

Table 7: Clinical effectiveness evidence

Study	Phase 3 BASIS study (NCT03938792)	OLE Study (NCT05145127)
Study design	Phase 3, one-way, cross-over, open-label, multi-centre study	Phase 3, interventional, open-label extension study
Population	Adult and adolescent (aged 12 to 74 years) males with a diagnosis of severe haemophilia A (FVIII activity <1%) or moderately severe to severe haemophilia B (FIX activity ≤2% respectively) with or without inhibitors	Patients from the BASIS trial who did not require early termination
Intervention(s)	Marstacimab; 300 mg SC loading dose followed by 150 mg once weekly. After 6 months, individual participants who met protocol-specified dose escalation criteria based upon breakthrough bleeding, may have had their dose increased to 300 mg SC once weekly, based on clinician judgement.	

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Study	Phase 3 BASIS study (NCT03938792)	OLE Study (NCT05145127)
Comparator(s)	Prior SOC treatment during the 6-month OP with either prophylactic or on-demand factor replacement therapy	NA
Number of patients	179 screened 128 entered the OP 116 entered the ATP	111 completed BASIS study 108 planned to participate in OLE 88 entered the OLE as of the interim data cut-off of 10th March 2023
Planned follow-up	12 month ATP phase, 1 month follow-up for safety monitoring	7 years
Duration of analysis completed	45-day screening period, 6 month OP, 12 month ATP	Data cut-off 10th March 2023, median treatment duration of 193.0 days (range, 34.0-483.0 days)
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	No
Rationale if study not used in model	NA	The study provides supportive long-term evidence for the safety and efficacy of marstacimab, however the reduced sample size (N=58 received routine prophylaxis in the BASIS trial OP and continued on to the OLE at interim data analysis cut-off of 10 th March 2023) and lack of a comparator arm means results are too limited to directly inform the model
Reported outcomes specified in the decision problem	Primary outcome: ABR for treated bleeding events Key secondary outcomes: ABR for treated joint bleeds - ABR for treated spontaneous bleeds - ABR for total bleeds - ABR for treated target joint bleeds - Change in joints as measured by HJHS Number of patients with no treated bleeds PROs: - HAL/pedHAL	

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Study	Phase 3 BASIS study (NCT03938792)	OLE Study (NCT05145127)
	• Patient global impression of change – haemophilia (PGIC-H) HRQoLs: • Haem-A-QoL/Haemo-QoL • EQ-5D-5L Safety: • AEs • SAEs	
All other reported outcomes	NA	NA

Endpoints in bold are those that are used to inform the cost-effectiveness model.

Abbreviations: ABR: annualised bleeding rate; AE: adverse event; ATP: active treatment phase; FIX: Factor IX; FVIII: Factor VIII; Haem-A-QoL: Haemophilia A Quality of Life for adults; Haemo-QoL: Haemophilia Quality of Life Questionnaire for Children; HAL: Hemophilia Activities List; HJHS: Haemophilia Joint Health Score; mg: milligrams; NA: not applicable; OLE: open-label extension; OP: observational phase; pedHAL: Pediatric Hemophilia Activities List; PGIC-H: patient global impression of change – haemophilia; SAE: serious adverse event; SC: subcutaneous; SOC: standard of care.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023; Pfizer marstacimab Phase 3 BASIS trial protocol, 2022; Pfizer marstacimab Phase 3 OLE trial protocol; Pfizer marstacimab Phase 3 OLE trial CSR.¹⁰⁴⁻¹⁰⁷

B.2.3 Marstacimab Phase 3 clinical trial programme (BASIS)

B.2.3.1 Summary of methodology of the relevant clinical effectiveness evidence

BASIS, and its OLE study, represent the pivotal clinical trials demonstrating the efficacy and safety of patients receiving weekly marstacimab prophylaxis compared with factor prophylaxis

- In BASIS, a Phase 3, one-way, crossover, open-label, multicentre study, adult male patients with severe haemophilia A or B received their SOC factor prophylaxis treatment (N=91) during a 6 month OP; 83 patients subsequently progressed to the 12 month ATP where they received weekly SC marstacimab prophylaxis
- Trial outcomes in the modified intention to treat (mITT) population, those who completed OP and received at least one dose of marstacimab in ATP, were measured at the end of the 12 month ATP
- The primary outcome measure for BASIS was ABR_{treat}, the number of treated bleeding episodes experienced by patients during the 12 month ATP compared to during the 6 month OP. Further secondary outcomes included ABR_{treat} for specific bleed types: spontaneous, joint, and target joint. PROs were also recorded
- Trial patients had a mean age of 33 years, with 78% (N=65) diagnosed with severe haemophilia A and 22% (N=18) diagnosed with severe haemophilia B. Additionally, the trial included 17 (21%) adolescent patients aged 12 to 17 years
- UK clinicians consulted as part of this submission considered that the BASIS trial had enrolled a more severe patient population than other haemophilia trials, with patients also slightly younger and lower weight than the average patient in UK practice⁶⁸

B.2.3.1.1 Trial design and methodology

The BASIS trial provides the primary clinical evidence base for marstacimab. BASIS is a Phase 3, one-way, crossover, open-label, multi-centre study in adolescent and adult patients that has

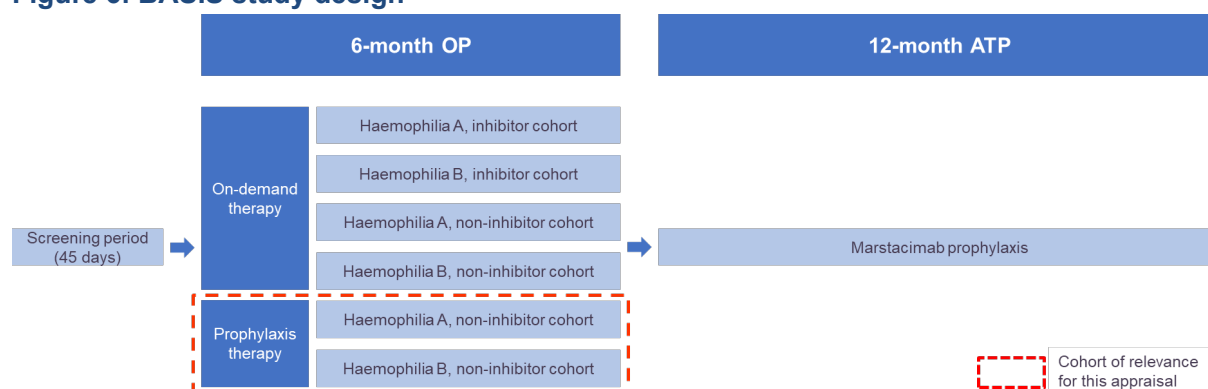
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demonstrated the efficacy, safety, and tolerability of marstacimab for routine prophylaxis in male patients aged 12 to 74 years with severe haemophilia A (coagulation FVIII activity < 1%) or severe haemophilia B (coagulation FIX activity < 1%) without inhibitors. The BASIS trial enrolment protocol included patients with moderately severe haemophilia B, but ultimately only enrolled patients with severe disease.

The BASIS trial included two cohorts which were split based on whether they received on demand factor therapy (N=37 at OP entry) or factor prophylaxis (N=91 at OP entry), during the 6 month OP. As patients with severe haemophilia A or B primarily use factor prophylaxis to manage their condition (Section B.1.3.2.5), this submission will present BASIS trial data for the pre-specified cohort of patients who received factor prophylaxis during the OP only. Additionally, a subset of patients with haemophilia develop neutralising antibodies (nAb), also known as inhibitors, directed against FVIII or FIX. Those with inhibitors are likely to have a reduced effectiveness of factor replacement therapy. The BASIS trial inclusion criteria specified that patients with severe haemophilia A or B both with or without inhibitors were eligible for the trial. However, the marketing authorisation for marstacimab is anticipated to specify that marstacimab is indicated for patients without FVIII or FIX inhibitors. In the cohort of patients receiving prophylactic factor therapy during the OP, which is the focus of this submission, no patients had inhibitors.

In BASIS, individuals received their current standard of care treatment, prophylactic factor replacement therapy, during a 6-month lead-in OP. Eligible patients then progressed to the ATP where they received a 300 mg loading dose followed by a 150 mg once weekly SC injection of marstacimab prophylaxis. Patients were followed for 12 months in the ATP to evaluate efficacy and safety endpoints. A schematic of the BASIS trial design is presented in Figure 6.

Figure 6: BASIS study design



Source: Adapted from Pfizer marstacimab Phase 3 BASIS trial CSR, 2023.¹⁰⁴

A summary of the BASIS trial methodology is presented in Table 8. Additional eligibility criteria for the BASIS trial are presented in Appendix M.1.1.

Table 8: Summary of the BASIS trial

Trial name	BASIS (NCT03938792)
Location	52 sites in 19 countries: Bulgaria (2 sites), Canada (3 sites), China (3 sites), Croatia (1 site), France (1 site), Hong Kong (2 sites), India (3 sites), Italy (3 sites), Japan (2 sites), Republic of Korea (3 sites), Mexico (1 site), Oman (2 sites), Russian Federation (1 site), Saudi Arabia (1 site), Serbia (5 sites), South Africa (1 site), Spain (5 sites), Turkey (11 sites), and the US (2 sites).

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Trial design	One-way, cross-over, open-label, multi-centre, Phase 3 study
Comparator	Patients' SOC prescribed prophylaxis or on demand factor replacement therapy received during the OP
Eligibility criteria for patients^a	Inclusion criteria: • Male • Adult or adolescent (aged 12 to <75 years) • Diagnosis of severe haemophilia A (FVIII <1%) or moderately severe to severe haemophilia B (FIX ≤2%) • Minimum weight of 35 kg at screening • Patients enrolled in the 'non-inhibitor cohort' also met the following inclusion criteria: ○ No detectable or documented history of inhibitors ○ Patients on FVIII/FIX routine prophylaxis who have demonstrated at least 80% compliance with scheduled prophylaxis regimen during 6 months prior to enrolment and are willing to continue to receive routine prophylaxis treatment with FVIII/FIX replacement during the OP ○ Patients with on-demand treatment regimen with ≥6 acute bleeding episodes (spontaneous or traumatic) that required coagulation factor infusion during the 6 months period prior to enrolment and willing to continue to receive on demand treatment during the OP Exclusion Criteria: • Previous or current treatment for and/or history of coronary artery diseases, venous or arterial thrombosis or ischemic disease • Known planned surgical procedure during the planned study period • Known haemostatic defect other than haemophilia A or B • Abnormal renal or hepatic function • Current unstable liver or biliary disease • Abnormal hematologic parameters • Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, • Current routine prophylaxis with bypassing agent or non-coagulation non-factor- replacement therapy, or any previous treatment with a gene therapy product for treatment of haemophilia (patients treated with prophylaxis using bypassing agents or who had prior treatment with non-factor products may be considered on a case-by-case basis). • Regular, concomitant therapy with immunomodulatory drugs • Ongoing or planned use of immune tolerance induction during the OP or ATP, or prophylaxis with FVIII or FIX replacement at any time after initiation of treatment with study intervention during the active treatment phase • Previous exposure to marstacimab • Participation in other studies involving investigational drug(s) or investigational vaccines within 30 days (or as determined by local requirements) or 5 half-lives prior to study entry and/or during study participation. • CD4 cell count ≤200/uL if human immunodeficiency virus (HIV)-positive • Screening electrocardiogram that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results. • Individuals with hypersensitivity or an allergic reaction to hamster protein or other components of the study intervention.

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	Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.
Study drugs	Marstacimab; 300 mg SC loading dose followed by 150 mg once weekly. After 6 months, participants who met protocol-specified dose escalation criteria were eligible to receive the 300 mg SC once weekly dose, based on clinician judgment. Escalation criteria included patients (weighing ≥ 50 kg) experiencing two or more spontaneous bleeds (joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of FVIII or FIX over a 6 month period, in the absence of a confirmed FVIII or FIX inhibitor, respectively.
Permitted and disallowed concomitant medication	Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, or herbal supplements) that the patient is receiving at the time of screening or receives during the study was recorded. Prohibited medications (all study phases): - Immunomodulatory medications (eg, IVIG, routine systemic corticosteroids, rituximab) and emicizumab. Bypassing agent therapy was not permitted at any time for the Non-Inhibitor Cohort. Prohibited medications (ATP): - Prophylaxis treatment with FVIII- or FIX-replacement, or any use of bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT) - Systemic antifibrinolytic agents or medications known to influence platelet function (eg, aspirin or certain non-steroidal anti-inflammatory drugs) required a washout of ≥ 120 hours prior to administration of study intervention Any breakthrough bleed during the study should have been stabilised using the patients standard haemostatic treatment regimen which may include factor replacement therapy.
Primary outcome	ABR for treated bleeds at 12 months post-marstacimab initiation (ATP) versus SOC factor replacement therapy use in the OP
Secondary outcomes	The key secondary outcomes for the BASIS trial were: - Annualised joint bleeding rate (AJBR), spontaneous bleeds, target joint bleeds and total bleeds (treated and untreated) at 12 months post-marstacimab initiation (ATP) versus SOC factor replacement therapy use in the OP - Number of patients with no treated bleeds - Change in joints as measured by HJHS at 12 months post-marstacimab initiation (ATP) versus SOC factor replacement therapy use in the OP The following endpoints compared patient reported outcomes and quality of life assessments at 12 months post-marstacimab initiation (ATP) versus SOC factor replacement therapy use in the OP: - HAL/pedHAL - PGIC-H - Haem-A-QoL/Haemo-QoL - EQ-5D-5L The following safety and tolerability outcomes were also explored: - Incidence of AEs and SAEs - Incidence and severity of thrombotic events

	• Incidence and severity of injection site reaction • Patients with clinically significant changes from baseline • Incidence of clinically significant laboratory value abnormalities • Incidence of severe hypersensitivity and anaphylactic reactions • Number of patients with clinically significant changes from baseline in vital signs • Incidence and severity of thrombotic microangiopathy • Incidence of disseminated intravascular coagulation/consumption coagulopathy • Incidence of anti-drug antibody (ADA) against marstacimab • Incidence of clinically significant persistent neutralizing antibody (nAb) against marstacimab
Exploratory endpoints	• The number of target joints at baseline, at the end of the 6 month OP and after the 12 month ATP ◦ A target joint is defined as a major joint (eg, hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (3 or more spontaneous bleeds into a single joint within a consecutive 6 month period). The number of target joints is derived from the eDiary via counting joints that meet the definition of a target joint during the treatment period. • Total coagulation factor consumption during the ATP versus the OP
Pre-specified subgroups	No pre-specified subgroups within the prior prophylaxis, non inhibitor cohort were included in the BASIS trial protocol. The study was not powered to draw statistical conclusions on subgroups

^a Additional eligibility criteria required for the ‘inhibitor cohort’ are not reported here as they are not of direct relevance to the decision problem addressed in this submission.

Abbreviations: ABR: annualised bleeding rate; ADA: anti-drug antibody; AE: adverse event; AJBR: annualised joint bleeding rate; aPCC: activated Prothrombin Complex Concentrates; ATP: active treatment phase; BU: Bethesda units; CD4: cluster of differentiation 4; FIX: Factor IX; FVIII: Factor VIII; Haem-A-QoL: Haemophilia A Quality of Life for adults; Haemo-QoL: Haemophilia Quality of Life Questionnaire for Children; HAL: Haemophilia Activities List; HIV: human immunodeficiency virus; HJHS: Haemophilia Joint Health Score; IV: intravenous; IVIG: intravenous immunoglobulin kg: kilogram; LPLV: last patient last visit; mL: millilitre; nAb: neutralising antibody; OP: observational phase; PCC: Prothrombin Complex Concentrates; pedHAL: Pediatric Hemophilia Activities List; PGIC-H: patient global impression of change – haemophilia; SAE: serious adverse event; SOC: standard of care; uL: microlitre; US: United States.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023; Pfizer marstacimab Phase 3 BASIS trial protocol, 2022.^{104, 105}

Definitions and clinical relevance of trial outcomes

Overview of efficacy measures: ABR and HJHS

In the BASIS trial, ABR was measured according to two definitions, ABR_{treat} and ABR_{total}. The primary endpoint, ABR_{treat}, involved counting of all treated bleeds experienced by patients and was defined as the number of treated bleeding episodes during the 12-month ATP. Furthermore, ABR_{treat} was also assessed for specific bleed types, including for spontaneous, joint, and target joint bleeds.

ABR_{total} during the 12-month ATP, a key secondary endpoint, was defined similarly to ABR_{treat} except that both treated and untreated bleeding was counted.

As the primary aim of haemophilia treatment is to reduce bleeding and given that acute bleeds have a significant impact on quality of life and also contribute to deterioration of joint health and

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future complications, measurements of ABR are directly relevant as key benefits for patients. ABR_{treat} quantifies the proportion of bleeds that are most severe and thus require treatment with on-demand factor replacement therapies, whilst ABR_{total} additionally reflects those bleeds which, whilst not requiring treatment, still prove burdensome for patients.

An additional efficacy endpoint in the BASIS trial was the HJHS. The HJHS provides a measure of joint health for the joints most commonly affected in haemophilia, namely the knees, ankles and elbows, and enables tracking of joint health over time. Different aspects of joint health are evaluated, and for each of the six joints, the following items are scored: swelling (scored from 0–3), duration of swelling (0–1), muscle atrophy (0–2), crepitus on motion (0–2), flexion loss (0–3), extension loss (0–3), joint pain (0–2), and strength (0–4). The maximum score for each individual joint is 20, with gait also scored from 0–4, resulting in a maximum total score of 124; higher scores indicate worse joint health. The HJHS was not included in the BASIS trial's testing hierarchy.

Overview of PRO and HRQoL measures used in BASIS

Data from a number of HRQoL instruments and PROs were collected in BASIS:

- **EQ-5D-5L** is a generic HRQoL measure used in the assessment of QALYs. The EQ-5D measurement is NICE's preferred method for measuring HRQoL.¹²
 - The EQ-5D-5L instrument measures 5 dimensions of health on a 5-point scale including Mobility, Self-care, Usual activities, Pain/discomfort and Anxiety/depression.
 - Also included is a visual analogue scale (VAS) anchored by worst and best imaginable health on a 0 to 100 scale where patients are asked to indicate where on the scale they rate their current health.
 - EQ-5D results can be used to generate utility values, where 1.0 represents perfect health and 0.0 represents death, which can then be applied in an economic analysis to calculate the QALYs associated with an intervention (see Section B.3.3).
- **Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)** and **Haemophilia Quality of Life Questionnaire for Adolescents (Haemo-QoL)** are disease specific measures of HRQoL intended for adults and adolescents with haemophilia, respectively.
 - The instruments use a 4-week recall period to assess health across 10 domains consisting of 46 items in the adult version and 12 domains consisting of 77 items in the adolescent version. The 10 domains and the number of items within each domain of the adult version are as follows: Physical Health (5); Feelings (4); View of Self (5); Sport/Leisure (5); Work/school (4); Dealing with Haemophilia (3); Treatment (8); Future (5); Family Planning (4); and Partnership and Sexuality (3). The 12 domains and the number of items within each domain of the adolescent version are as follows: Physical Health (7); Feelings (8); Attitude/View (10); Family (8); Friends (4); Other people (6); Sport and School (9); Coping/Dealing (7); Treatment (8); Perceived Support (4); Future (4); Relationship (2).
 - These items are rated by the patients as either 'never', 'seldom', 'sometimes', 'often' or 'always'; for other items, 'not applicable' is also an option. Scores are calculated by domain and a single total score is determined, ranging from 0 to 100, with higher scored reflecting lower quality of life.

- **Haemophilia Activities List 2.0 (HAL2) and Pediatric Hemophilia Activities List (pedHAL)** are multiple domain measures of the impact of haemophilia on functional abilities in adults and children, respectively.
 - The seven domains of the adult instrument contain 42 items in total, as follows: Lying/sitting/kneeling/standing (8); Lower (leg) functioning (9); Upper (arm) functioning (4); Transportation (3); Self-care (5); Household tasks (6); and Sports/Leisure (7).
 - The seven domains of the paediatric instrument contain 53 items in total, as follows: Sitting/Kneeling/Standing (10); Functions of the Legs (11); Functions of the Arms (6); Use of Transportation (3); Self-Care (9); Household Task (3); Leisure Activities and Sports (11).
 - Scoring can be done by domain, components (Activities involving the Upper Extremities, Basic activities involving the Lower Extremities and Complex activities involving the Lower Extremities) or a standardised total score.

Patient Global Impression of Change – Hemophilia (PGIC-H) is a single-item assessment of an individual's overall impression of the change in their life due to haemophilia. The assessment can be taken by adults and adolescents.

- The PGIC-H measures the patient's overall impression of change in their life with haemophilia in a 7-point ordinal scale with lower scores indicating better change; 1: greatly improved, 2: moderately improved, 3: slightly improved, 4: no change, 5: slightly worsened, 6: moderately worsened, and 7: greatly worsened.

Baseline characteristics

A total of 128 patients were enrolled in the OP. 91 patients with prior prophylactic treatment using factor replacement entered the study, and were included in the All Analysis Set (AAS) (see Section B.2.4). Of the 91 patients treated with factor replacement prophylaxis, 84 (92.3%) completed the 6 month OP and 7 (7.7%) discontinued during the OP (5 patients no longer met eligibility criteria and 2 patients due to protocol deviations).

Of the 84 patients who completed the OP, 83 patients entered the ATP, of whom 78 (94.0%) completed the 12 month ATP and 5 (6.0%) discontinued (4 patients withdrew by subject [subject initiated withdrawal unrelated to AEs] and 1 patient due to AE [not treatment related]).

Baseline characteristics for patients treated with prior factor prophylaxis in the OP of the trial who continued to the ATP of the trial are provided in Table 9. Baseline disease characteristics for this mITT BASIS factor prophylaxis cohort are presented in Table 10.

The proportion of patients with haemophilia A and B were comparable to UKHCDO data for 2022/23, with haemophilia B patients making up 21.7% of individuals in the BASIS trial and 14.3% of individuals in UK clinical practice.⁴ Clinical experts consulted as part of this appraisal noted however that the age (■■■ years) and weight (■■■ kg) of patients from the UKHCDO dataset were more reflective of patients in the UK, with the population in the BASIS trial being younger and lower weight. The advisors additionally noted that the BASIS trial may have enrolled a more phenotypically severe group of patients and included an overrepresentation of Asian patients compared with the UK, but did not consider this difference to be a prognostic variable or treatment effect modifier.⁶⁸

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Table 9: Baseline demographic characteristics in BASIS for patients treated with factor prophylaxis in the trial OP (17th April 2023 data cut-off; mITT analysis set)

Characteristic	Patients treated with prior factor prophylaxis in the OP (N=83)
Age, years	
Mean (SD)	32.6 (14.81)
Median (Min, Max)	31.0 (13.0, 66.0)
Sex, n (%)	
Male	83 (100.0)
Race, n (%)	
Asian	36 (43.4)
Black or African American	1 (1.2)
White	45 (54.2)
Not reported	1 (1.2)
Ethnicity, n (%)	
Hispanic or Latino or Spanish origin	9 (10.8)
Not Hispanic or Latino or Spanish origin	74 (89.2)
Estimated glomerular filtration rate	
≥ 90	62 (74.7)
≥ 60 to < 90	19 (22.9)
≥ 30 to < 60	0 (0.0)
<30	0 (0.0)
Missing	2 (2.4)
Weight, kg	
Mean (SD)	69.1 (15.32)
Median (Range)	69.0 (35.0, 120.0)
Height, cm	
Mean (SD)	170.5 (8.43)
Median (Range)	170.7 (141.0, 185.0)
Body mass index, kg/m²	
Mean (SD)	23.6 (4.25)
Median (Range)	23.5 (15.2, 36.0)

Abbreviations: cm: centimetre; kg: kilogram; m: meter; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2024.¹⁰⁴

Table 10: Baseline disease characteristics in BASIS for patients treated with factor prophylaxis in the trial OP (17th April 2023 data cut-off; mITT analysis set)

Characteristic	Patients treated with prior factor prophylaxis in the OP (N=83)
Haemophilia Type, n (%)	
Haemophilia A	65 (78.3)
Haemophilia B	18 (21.7)
Age and Haemophilia Type, n (%)	
Adolescents (≥12 to <18 years) Haemophilia A	13 (15.7)
Adolescents (≥12 to <18 years) Haemophilia B	4 (4.8)
Adults (≥18 years) Haemophilia A	52 (62.7)
Adults (≥18 years) Haemophilia B	14 (16.9)
ISTH Disease Severity, n (%)	
Mild	0
Moderate	0
Severe	83 (100.0)
Number of Target Joints at Baseline, n (%)	
0	36 (43.4)
1	19 (22.9)
2	15 (18.1)
≥3	13 (15.7)

Abbreviations: ISTH: International Society on Thrombosis and Haemostasis; mITT: Modified intention to treat; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2024.¹⁰⁴

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

B.2.4.1 Analysis sets in the BASIS trial

The definitions of the BASIS study populations considered in this submission are presented in Table 11.

Table 11: Trial populations used for the analysis of endpoints in the BASIS study; participants who received prophylaxis during the OP

Analysis set	Definition
Enrolled (N=91)	All patients who signed the informed consent form (ICF) and met all inclusion/exclusion criteria. Patients entered the OP
All safety (N=91)	Patients in the non-inhibitor cohort with prophylaxis in the OP who received at least one prophylactic or on-demand treatment during the OP (OP baseline)
Marstacimab safety (N=83)	Patients who received at least one dose of marstacimab in the ATP
mITT (N=83)	Patients who completed the OP and received at least one dose of marstacimab in the ATP. Patients who changed from a non-inhibitor cohort to inhibitor cohort on or before the ATP Day -7 testing were excluded from the mITT

Abbreviations: ATP: active treatment phase; ICF: informed consent form; mITT: modified intention to treat; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial protocol, 2022.¹⁰⁵

The population used in the analysis of the primary and secondary efficacy endpoints relating to bleeds was the mITT population, whilst safety analyses used the marstacimab safety set.

Statistical analysis

The primary efficacy hypothesis in BASIS was to demonstrate non-inferiority in ABR_{treat} following 12 months of treatment with marstacimab in the ATP compared with routine factor prophylaxis in the OP. Details on the statistical analysis of the primary efficacy endpoint are presented in Table 12.

Table 12: Statistical methods for the primary analysis of ABR_{treat} in BASIS

Hypothesis objective	- Marstacimab was considered non-inferior to prior prophylaxis treatment if the upper bound of the 2-sided 95% confidence interval for the difference (ATP minus OP) in ABR was less than the non-inferiority boundary of 2.5 - The primary objective for ABR was considered to have been met if non-inferiority was demonstrated.
Statistical analysis	- Marstacimab was compared with prior routine prophylaxis for various bleeding count endpoints (treated, spontaneous, joint, target joint[s], and all bleeds), using a repeated measure negative binomial regression model via generalised estimating equation (GEE) approach with identity link function. If the non-inferiority on ABR_{treat} was established, subsequent testing for superiority was conducted. - The estimated mean ABR_{treat} difference and its 2-sided 95% CI obtained from the analysis model are presented along with the conventional p-value (for the null hypothesis that the difference is 0). The following were also presented by

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	treatment for each endpoint: number of patients, the model-based mean ABR and its 2-sided 95% CI, the median and the IQR of the calculated ABR per patient per treatment, and n (%) of patients with 0, 1, 2, >=3 treated bleeding.
Sample size, power calculation	60 evaluable patients were planned for the comparison of marstacimab compared with routine factor prophylaxis for non-inferiority. - This sample size was derived via simulation under a range of scenarios. In the simulation, bleeding counts were generated from a negative binomial distribution. The mean bleeds over 6 months for routine prophylaxis was initially assumed as 2.5 with an added scenario of 2.35. The mean bleeds over 12 months for marstacimab was initially assumed as 4 with 2 additional scenarios of 2.67 and 3.46, the point estimate and the upper bound of the 1-sided 80% CI, respectively, from a Phase 2 study evaluating marstacimab. The variance was assumed as 6 times the mean for each scenario; the correlation between the 2 bleeding counts at OP and ATP from the same patient was assumed as 0.2. - Full details of the derivation of sample sizes are provided in the BASIS trial statistical analysis plan (SAP).

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; GEE: generalised estimating equation; ICF: informed consent form; IQR: interquartile range; OP: observational phase; SAP statistical analysis plan.

Source: Pfizer marstacimab Phase 3 BASIS trial Statistical Analysis Plan, 2022.¹⁰⁸

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the pivotal trial for marstacimab (BASIS) was performed using a modified version of the Downs and Black Checklist.¹⁰⁹ In this checklist, up to one point can be awarded for 26 questions and up to 2 for one question giving a maximum of 28 points per trial. Overall, the results of the BASIS trial can be considered to be both internally and externally valid, with a score of 21 which falls within the “good” category.

Table 13: Quality assessment of the BASIS trial

Item		Response	Score
Reporting			
Q1	Hypothesis/aim/objective clearly described	Yes = 1, No = 0	1
Q2	Main outcomes in Introduction or Methods	Yes = 1, No = 0	1
Q3	Patient characteristics clearly described	Yes = 1, No = 0	1
Q4	Interventions of interest clearly described	Yes = 1, No = 0	1
Q5	Principal confounders clearly described	Yes = 2, Partially = 1, No = 0	0
Q6	Main findings clearly described	Yes = 1, No = 0	1
Q7	Estimates of random variability provided for main outcomes	Yes = 1, No = 0	1
Q8	All adverse events of intervention reported	Yes = 1, No = 0	1
Q9	Characteristics of patients lost to follow-up described	Yes = 1, No = 0	1
Q10	Probability values reported for main outcomes	Yes = 1, No = 0	1
External Validity			
Q11	Subjects asked to participate were representative of source population	Yes = 1, No = 0, Unclear = 0	1

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Item		Response	Score
Q12	Subjects prepared to participate were representative of source population	Yes = 1, No = 0, Unclear = 0	1
Q13	Location and delivery of study treatment was representative of source population	Yes = 1, No = 0, Unclear = 0	1
Internal Validity – Bias and Confounding			
Q14	Study participants blinded to treatment	Yes = 1, No = 0, Unclear = 0	0
Q15	Blinded outcome assessment	Yes = 1, No = 0, Unclear = 0	0
Q16	Any data dredging clearly described	Yes = 1, No = 0, Unclear = 0	1
Q17	Analyses adjust for differing lengths of follow-up	Yes = 1, No = 0, Unclear = 0	1
Q18	Appropriate statistical tests performed	Yes = 1, No = 0, Unclear = 0	1
Q19	Compliance with interventions was reliable	Yes = 1, No = 0, Unclear = 0	1
Q20	Outcome measures were reliable and valid	Yes = 1, No = 0, Unclear = 0	1
Q21	All participants recruited from the same source population	Yes = 1, No = 0, Unclear = 0	1
Q22	All participants recruited over the same time period	Yes = 1, No = 0, Unclear = 0	1
Q23	Participants randomised to treatment(s)	Yes = 1, No = 0, Unclear = 0	0
Q24	Allocation of treatment concealed from investigators and participants	Yes = 1, No = 0, Unclear = 0	0
Q25	Adequate adjustment for confounding	Yes = 1, No = 0, Unclear = 0	0
Q26	Losses to follow-up taken into account	Yes = 1, No = 0, Unclear = 0	1
Power			
Q27	Sample size calculation was reported	Yes = 1, No = 0, Unclear = 0	1
Total			21

B.2.6 Clinical effectiveness results of the relevant studies

Marstacimab was demonstrated in BASIS to be an effective treatment option, providing significant reductions in ABR_{treat} , the primary endpoint

- Marstacimab prophylaxis demonstrated non-inferiority and superiority over routine prophylaxis as measured by ABR_{treat} . A statistically significant reduction of 35.2% (95% CI: 5.6%, 55.6%; $p=0.0376$) in the primary outcome of ABR_{treat} was achieved following 12 months of marstacimab prophylaxis in the ATP compared with 6 months of factor prophylaxis in the OP
- Marstacimab also demonstrated non-inferiority to factor prophylaxis in all bleed-related secondary efficacy outcomes, reducing the rates of annualised joint bleeding rate ($AJBR_{treat}$), $ABR_{target\ joint}$, $ABR_{spontaneous}$ and ABR_{total} from the OP to the ATP
- A comparable HJHS total score was reported in patients receiving marstacimab prophylaxis or factor prophylaxis, with a -2.0 and -2.2 estimated median difference measured for marstacimab prophylaxis compared with the 6 month OP value at 6 months and 12 months of the ATP, respectively
- Marstacimab demonstrated non-inferiority to factor prophylaxis in Haem-A-QoL for both total score and physical health score. Additionally, results from the BASIS trial indicate that marstacimab demonstrated non-inferiority in both the EQ-5D-5L index score and EQ-VAS score as compared to prior routine prophylaxis, indicating preservation of patient health status

The BASIS trial provides the primary clinical evidence base for marstacimab and details the efficacy, safety, and tolerability of marstacimab for routine prophylaxis in male patients aged 12 and over with severe haemophilia A (coagulation FVIII activity < 1%) or severe haemophilia B (coagulation FIX activity < 1%) without inhibitors. During the 6 month BASIS trial OP, participants received their SOC factor treatment either on-demand or as prophylaxis, followed by treatment with marstacimab in the 12 month ATP. As explained in Section B.1.3.2.3, on-demand factor treatment is very rarely prescribed in isolation to treat severe haemophilia, whilst factor prophylaxis represents an important treatment option. As such, the section below focuses on the outcomes reported by patients who received factor prophylaxis in the OP.

As noted in Table 8, Section B.2.3.1.1, patients meeting prespecified dose escalation criteria were permitted to receive a maintenance dose of 300 mg marstacimab administered weekly. All efficacy analyses prespecified in the BASIS trial protocol censored the bleeding records on or after a dose escalation to 300 mg for the eleven patients in the trial who received a dose escalation. The data presented in Section B.2.6 are aligned with this prespecified trial analyses.

However, for the purposes of the cost-effectiveness analysis presented in Section B.3 of this submission, it was considered that costs and efficacy estimates should include bleeding data for those patients who received dose escalation, as specified in the draft marstacimab SmPC, to align with the possibility of dose escalation in NHS clinical practice. Additionally, given the model structure (detailed in Section B.3.1.2) considers both a bleed and a non-bleed health state, ABR_{treat} and $AJBR_{treat}$ were analysed post-hoc to reflect the rates amongst those who experienced at least one bleeding event (i.e. excluding those patients with zero treated bleeds). Outputs from these post-hoc analyses that inform the economic model are presented in Section B.2.9 and Appendix N.

B.2.6.1 Primary endpoint

As described in Section B.1.3.1.4, the primary clinical manifestation of haemophilia is bleeding with the most severe bleeding events requiring treatment. Therefore, the annualised bleeding rate of treated bleeds, the primary endpoint of the BASIS trial, is a clinically meaningful outcome

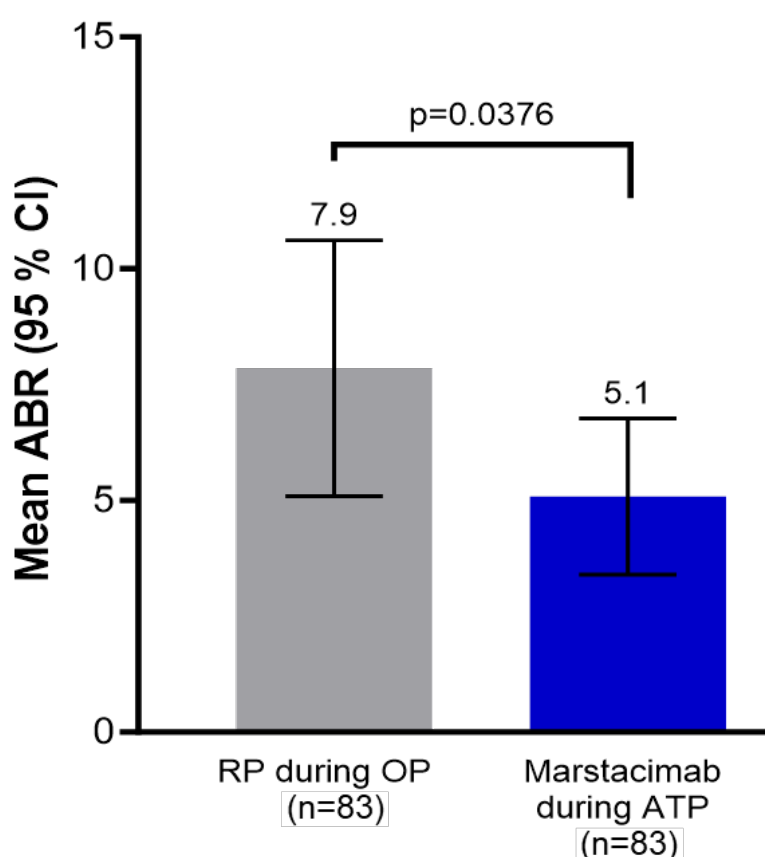
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to determine the efficacy of marstacimab at reducing the number of bleeding episodes, compared with factor prophylaxis.

Annualised bleeding rate for treated bleeds (ABR_{treat})

In the mITT set, marstacimab demonstrated non-inferiority and superiority over factor prophylaxis as measured by ABR_{treat} . The mean model-derived ABR_{treat} was 5.08 (95% CI: 3.40, 6.77) for marstacimab prophylaxis during the 12 month ATP compared with 7.85 (95% CI: 5.09, 10.61) for routine prophylaxis during the 6 month OP. This represented a reduction in estimated ABR_{treat} of -2.77 (95% CI: -5.37 , -0.16), equating to a 35.2% (95% CI: 5.6, 55.6) decrease. ABR_{treat} data are presented in Figure 7 and Table 14.

Figure 7: Comparison of model-derived^a ABR_{treat} after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)



Bleeding records on or after a dose escalation to 300 mg for the eleven patients in the trial who received a dose escalation are censored from these data;

^a Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: modified intention to treat; OP: observational phase; RP: routine prophylaxis.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Table 14: Comparison of ABR_{treat} after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

	Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
ABR_{treat}		
Mean (SD)	7.88 (12.914)	5.17 (8.041)
Median (range)	2.16 (0.00, 59.51)	2.02 (0.00, 35.51)
Categorical Summary		
Completed the Phase, n (%)	83 (100.0)	78 (94.0)
0 bleed, n (%)	33 (39.8)	29 (34.9)
1 bleed, n (%)	9 (10.8)	7 (8.4)
2 bleeds, n (%)	11 (13.3)	9 (10.8)
≥ 3 bleeds, n (%)	30 (36.1)	33 (39.8)
Discontinued the Phase, n (%)	0 (0.0)	5 (6.0)
Model-derived ABR_{treat}		
Estimate ^a (95% CI)	7.85 (5.09, 10.61)	5.08 (3.40, 6.77)
Treatment difference		
Estimates (95% CI) ^b	-	-2.77 (-5.37, -0.16)
p-value ^c	-	0.0376
Percentage reduction		
Estimates ^d (95% CI)	-	35.2% (5.6, 55.6)

Bleeding records on or after a dose escalation to 300 mg for the eleven patients in the trial who received a dose escalation are censored from these data;

^a Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

^b Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 2.5. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

^c P-value for the null hypothesis of difference = 0.

^d Supplemental statistics derived as (1-ratio)*100; The ratio and 95% CI were obtained from a repeated measure negative binomial regression model via generalised estimating equation approach with log link function. The working correlation was set as unstructured. The model used the number of bleeds as a response variable, treatment (marstacimab prophylaxis or routine prophylaxis) as a factor, and log time on treatment as an offset variable to account for different duration on treatment.

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Assessment of ABR_{treat} in patients who had their marstacimab dose increased during the ATP

Eleven patients (13%) in the BASIS trial who received prior prophylaxis during the OP had their weekly marstacimab dose increased from 150 mg to 300 mg during the ATP due to insufficient clinical response, based on clinician judgement of the dose escalation criteria. The median durations for 150 mg treatment was 251.0 days, with a subsequent median duration of 108.0 days on the increased dose 300 mg treatment. The mean ABR_{treat} were 14.03 (before dose increase) and 3.42 (on or after dose increase) with additional data presented in Appendix M.2.

Separate post-hoc analyses used to inform the model, based on ABR_{treat} for all patients who received marstacimab during the ATP, including dose escalated patients, and who experienced at least one bleeding event, are presented in Section B.2.9.

B.2.6.2 Secondary endpoints

Incidence of joint bleeds

Results from the BASIS trial indicate that the incidence of joint bleeds (treated) with marstacimab treatment was non-inferior to that observed during the OP with prior routine prophylaxis. The model derived treated AJBR_{treat} was 4.13 (95% CI: 2.59, 5.67) for marstacimab prophylaxis during the ATP compared with 5.66 (95% CI: 3.33, 7.98) for prior routine prophylaxis during the OP, with a resulting estimated reduction in AJBR_{treat} of -1.53 (95% CI: -3.70, 0.64; Table 15). Additionally, 39.8% of patients (33 out of 83) did not have any treated joint bleeds.

Table 15: Comparison of treated AJBR_{treat} after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

	Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
AJBR_{treat}		
Mean (SD)	5.68 (10.901)	4.20 (7.304)
Median (range)	1.89 (0.00, 55.89)	1.02 (0.00, 33.48)
Categorical Summary		
Completed the Phase, n (%)	83 (100.0)	78 (94.0)
0 bleed, n (%)	40 (48.2)	33 (39.8)
1 bleed, n (%)	12 (14.5)	9 (10.8)
2 bleeds, n (%)	8 (9.6)	9 (10.8)
≥ 3 bleeds, n (%)	23 (27.7)	27 (32.5)
Discontinued the Phase, n (%)	0 (0.0)	5 (6.0)
Model-derived AJBR_{treat}		
Estimate ^a (95% CI)	5.66 (3.33, 7.98)	4.13 (2.59, 5.67)
Treatment difference		
Estimates (95% CI) ^b	-	-1.53 (-3.70, 0.64)
p-value ^c	-	0.1680

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Bleeding records on or after a dose escalation to 300 mg for the eleven patients in the trial who received a dose escalation are censored from these data;

^a Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

^b Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 2.5. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

^c P-value for the null hypothesis of difference = 0.

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Incidence of target joint bleeds

As with treated joint bleeds, results from the BASIS trial indicate that the incidence of target joint bleeds (treated) with marstacimab treatment was non-inferior to that observed during the OP with prior routine prophylaxis.

The model derived treated $ABR_{\text{target joint}}$ was 2.51 (95% CI: 1.25, 3.76) for marstacimab prophylaxis during the ATP compared with 3.36 (95% CI: 1.59, 5.14) for prior routine prophylaxis during the OP, with a resulting estimated reduction in $ABR_{\text{target joint}}$ of -0.86 (95% CI: -2.41 , 0.70 ; Table 16). Additionally, 65.1% of patients (54 out of 83) did not have any treated target joint bleeds while receiving marstacimab during the ATP.

Table 16: Comparison of treated $ABR_{\text{target joint}}$ after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

	Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
Treated $ABR_{\text{target joint}}$		
Mean (SD)	3.38 (8.317)	2.55 (5.954)
Median (range)	0.00 (0.00, 38.86)	0.00 (0.00, 27.24)
Categorical Summary		
Completed the Phase, n (%)	83 (100.0)	78 (94.0)
0 bleed, n (%)	62 (74.7)	54 (65.1)
1 bleed, n (%)	4 (4.8)	6 (7.2)
2 bleeds, n (%)	3 (3.6)	4 (4.8)
≥ 3 bleeds, n (%)	14 (16.9)	14 (16.9)
Discontinued the Phase, n (%)	0 (0.0)	5 (6.0)
Model-derived treated $ABR_{\text{target joint}}$		
Estimate ^a (95% CI)	3.36 (1.59, 5.14)	2.51 (1.25, 3.76)
Treatment difference		
Estimates (95% CI) ^b	-	-0.86 (-2.41 , 0.70)
p-value ^c	-	0.2811

Bleeding records on or after a dose escalation to 300 mg for the eleven patients in the trial who received a dose escalation are censored from these data;

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^a Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

^b Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 1.2. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

^c P-value for the null hypothesis of difference = 0.

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Incidence of spontaneous bleeds

Results from the BASIS trial indicate that the incidence of spontaneous bleeds with marstacimab treatment was non-inferior to that observed during the OP with prior routine prophylaxis.

The model derived treated $ABR_{spontaneous}$ was 3.78 (95% CI: 2.25, 5.31) for marstacimab prophylaxis during the ATP compared with 5.86 (95% CI: 3.54, 8.19) for prior routine prophylaxis during the OP, with a resulting estimated reduction in $ABR_{spontaneous}$ of -2.09 (95% CI: -4.23, 0.06; Table 17). Additionally, 42.2% of patients (35 out of 83) did not have any treated spontaneous bleeds.

Table 17: Comparison of treated $ABR_{spontaneous}$ after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

	Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
$ABR_{spontaneous}$		
Mean (SD)	5.89 (10.868)	3.85 (7.262)
Median (range)	1.94 (0.00, 53.89)	0.00 (35.51)
Categorical Summary		
Completed the Phase, n (%)	83 (100.0)	78 (94.0)
0 bleed, n (%)	40 (48.2)	35 (42.2)
1 bleed, n (%)	12 (14.5)	12 (14.5)
2 bleeds, n (%)	7 (8.4)	6 (7.2)
≥ 3 bleeds, n (%)	24 (28.9)	25 (30.1)
Discontinued the Phase, n (%)	0 (0.0)	5 (6.0)
Model-derived ABR for all bleeds		
Estimate ^a (95% CI)	5.86 (3.54, 8.19)	3.78 (2.25, 5.31)
Treatment difference		
Estimates (95% CI) ^b	-	-2.09 (-4.23, 0.06)
p-value ^c	-	0.0566

Bleeding records on or after a dose escalation to 300 mg for the eleven patients in the trial who received a dose escalation are censored from these data;

^a Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

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^b Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 2.5. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

^c P-value for the null hypothesis of difference = 0.

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Incidence of total bleeds (treated and untreated)

Marstacimab treatment was also demonstrated to be non-inferior to prior routine prophylaxis with respect to the incidence of total bleeds (treated and untreated).

The model derived treated ABR_{total} was 5.97 (95% CI: 4.13, 7.81) for marstacimab prophylaxis during the ATP compared with 8.84 (95% CI: 5.97, 11.72) for prior routine prophylaxis during the OP, with a resulting estimated median reduction in ABR_{total} of -2.87 (95% CI: -5.61, -0.12; Table 18). Additionally, 26.5% of patients receiving marstacimab in the ATP (22 out of 83) did not have any bleeds (treated and untreated).

Table 18: Comparison of treated ABR_{total} after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

	Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
ABR_{total}		
Mean (SD)	8.87 (13.462)	6.06 (8.733)
Median (range)	3.91 (0.00, 59.51)	2.89 (0.00, 37.54)
Categorical Summary		
Completed the Phase, n (%)	83 (100.0)	78 (94.0)
0 bleed, n (%)	28 (33.7)	22 (26.5)
1 bleed, n (%)	9 (10.8)	10 (12.0)
2 bleeds, n (%)	13 (15.7)	7 (8.4)
≥ 3 bleeds, n (%)	33 (39.8)	39 (47.0)
Discontinued the Phase, n (%)	0 (0.0)	5 (6.0)
Model-derived ABR_{total}		
Estimate ^a (95% CI)	8.84 (5.97, 11.72)	5.97 (4.13, 7.81)
Treatment difference		
Estimates (95% CI) ^b	-	-2.87 (-5.61, -0.12)
p-value ^c	-	0.0406

Bleeding records on or after a dose escalation to 300 mg for the eleven patients in the trial who received a dose escalation are censored from these data;

^a Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

^b Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 2.9. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

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^c P-value for the null hypothesis of difference = 0.

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Haemophilia Joint Health Score (HJHS)

As detailed in section B.2.3.1, the HJHS provides a measure of joint health for the joints most commonly affected in haemophilia, namely the knees, ankles and elbows, and enables tracking of joint health over time. HJHS was assessed at both Month 6 and Month 12 in the ATP. Given that the reference treatment duration in the OP was 6 months, while marstacimab prophylaxis was administered for 12 months during the ATP, the main comparison timepoint between the OP and ATP is at 6 months. Where 12 month data from the ATP is presented it is compared to 6 month results from the OP. It should also be noted that for HJHS, data from marstacimab dose escalated patients in the ATP are not censored.

The median change from baseline in HJHS total score at 6 months was –0.6 (95% CI: –2.2, 1.0) for marstacimab prophylaxis during the ATP compared with 1.3 (95% CI: –0.7, 3.3) for routine prophylaxis during the OP, representing a median difference in decrease between treatments of –2.0 (95% CI: –4.3, 0.3). This difference corresponds to an observed effect size of 0.11 SD units, indicating a similar effect of marstacimab compared to routine prophylactic treatment. Results are presented in Table 19.

Table 19: Analysis of change from baseline in HJHS at baseline after 6 months of routine factor prophylaxis during the observational phase and after 6 and 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

		Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
Change from baseline at 6 months of treatment	Non-parametric summary ^a		
	Median (95% CI)	1.3 (–0.7, 3.3)	–0.6 (–2.2, 1.0)
	Treatment comparison		
	Estimated Median Difference (95% CI)		–2.0 (–4.3, 0.3)
	p-value		0.0835
	Effect size ^b		0.11
Change from baseline at 12 months of treatment	Non-parametric summary ^a		
	Median (95% CI)	1.3 (–0.7, 3.3)	–0.9 (–2.5, 0.7)
	Treatment comparison		
	Estimated Median Difference (95% CI)	-	–2.2 (–4.8, 0.3)
	p-value	-	0.0836

These data are irrespective of rescue medication use, dose modification, and/or the preventive treatment for medical/dental procedures.

^a Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on missing at random (MAR) assumption.

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^b Effect Size (ES) is calculated as [estimated median difference] / (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.

Abbreviations: ATP: active treatment phase; CI: confidence interval; ES: effect size; HJHS: Haemophilia Joint Health Score; MAR: missing at random; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Number of target joints (exploratory endpoint)

As discussed in Section B.1.3.1.4, one of the defining clinical features of haemophilia is recurrent haemarthrosis, which aggravates joints and can result in the development of chronic synovitis. Any joint with chronic synovitis is known as a target joint; as these are common in people with severe haemophilia, the BASIS trial investigated the number of target joints following marstacimab prophylaxis compared with factor prophylaxis baseline.^{44, 45} A target joint is defined as a major joint (eg, hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (three or more spontaneous bleeds into a single joint within a consecutive 6 month period). The number of target joints is derived from the eDiary via counting joints that meet the definition of a target joint during the treatment period.

At baseline, the mean number of target joints was 1.2 with this decreasing to 0.3 after 6 months of routine prophylaxis in the OP and remaining at 0.3 after 12 months of marstacimab prophylaxis in the ATP (Table 20).

Table 20: Summary of the number of target joints at baseline, after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

	Baseline (N=83)	Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
Mean (SD)	1.2 (1.54)	0.3 (0.72)	0.3 (0.91)
Median (range)	1.0 (0.0, 8.0)	0.0 (0.0, 4.0)	0.0 (0.0, 5.0)

Abbreviations: ATP: active treatment phase; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

B.2.6.3 Health-related quality of life and other PROs

A secondary objective of the BASIS trial was to evaluate the effect of marstacimab on health-related quality of life (HRQoL) as measured by both disease specific and patient reported outcome (PRO) measures. PRO measures were completed at scheduled office visits via an electronic tablet.¹⁰⁵ Overall, marstacimab is comparable or non-inferior to routine prophylactic factor treatment with respect to disease specific and general patient reported health related quality of life (HRQoL) outcomes.

PRO measures were assessed at Month 6 and Month 12 in the ATP. Given that the reference treatment duration in the OP was 6 months, while marstacimab prophylaxis was administered for 12 months during the ATP, the main comparison timepoint between the OP and ATP is at 6 months. Where 12 month data from the ATP is presented it is compared to 6 month results from the OP. It should also be noted that for all PROs, data from marstacimab dose escalated patients in the ATP are not censored.

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Haem-A-QoL and Haemo-QoL

The Haem-A-QoL and Haemo-QoL surveys are disease-specific measures of HRQoL in individuals with haemophilia. Each of the total or domain scores of Haem-A-QoL and Haemo-QoL range from 0 to 100, with lower scores indicating better haemophilia QoL.

Change from baseline in Total Score

As reported in Table 21, the estimated median change from baseline at 6 months on the Haem-A-QoL total score (adults ≥ 17 years; N=63) was -3.7 (95% CI: $-6.8, -0.6$) for marstacimab prophylaxis during the ATP compared with -1.2 (95% CI: $-3.5, 1.1$) for prior routine prophylaxis during the OP, with a resulting estimated median difference between treatments of -2.8 (95% CI: $-6.6, 1.0$). These results demonstrate the non-inferiority of marstacimab compared to prior routine prophylaxis. The observed effect size of 0.17 SD units indicates a similar effect of marstacimab compared to routine prophylaxis.

Table 21: Non-parametric analysis of change from baseline in total score of Haem-A-QoL for adult patients, after 6 months of routine factor prophylaxis during the observational phase and after 6 and 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

Total Score		Routine prophylaxis during OP (N=63)	Marstacimab prophylaxis during ATP (N=63)
Change from baseline at 6 months of treatment	Non-parametric summary ^a		
	Median (95% CI)	-1.2 ($-3.5, 1.1$)	-3.7 ($-6.8, -0.6$)
	Treatment comparison:		
	Estimated Median Difference (95% CI) ^b	-	-2.8 ($-6.6, 1.0$)
	p-value	-	0.1493
	Effect size ^c	-	0.17
Change from baseline at 12 months of treatment	Non-parametric summary ^a		
	Median (95% CI)	-1.2 ($-3.5, 1.1$)	-4.9 ($-8.1, -1.7$)
	Treatment comparison:		
	Estimated Median Difference (95% CI) ^b	-	-3.7 ($-8.3, 0.9$)
	p-value	-	0.1113

These data are irrespective of rescue medication use, dose modification, and/or the preventive treatment for medical/dental procedures.

^a Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.

^b Non-inferiority criterion for the total score was upper bound of 95% CI < 7 .

^c Effect Size (ES) is calculated as [estimated median difference] / (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.

Abbreviations: ATP: active treatment phase; CI: confidence interval; ES: effect size; Haem-A-QoL; Haemophilia Adult Quality of Life Questionnaire; MAR: missing at random; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

For the Haemo-QoL (adolescents 12 to <17 years; N=20) total score, the estimated median change from baseline at 6 months was –5.0 (95% CI: –10.5, 0.4) for marstacimab prophylaxis during the ATP compared with 0.8 (95% CI: –6.2, 7.8) for prior routine prophylaxis during the OP. This resulted in an estimated median difference between treatments of –6.5 (95% CI: –15.2, 2.2), corresponding to an observed effect size of 0.58 SD units. Full results are presented in Table 22.

Table 22: Non-parametric analysis of change from baseline in total score of Haemo-QoL for adolescent patients, after 6 months of routine factor prophylaxis during the observational phase and after 6 and 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

Total Score		Routine prophylaxis during OP (N=20)	Marstacimab prophylaxis during ATP (N=20)
Change from baseline at 6 months of treatment	Non-parametric summary ^a		
	Median (95% CI)	0.8 (–6.2, 7.8)	–5.0 (–10.5, 0.4)
	Treatment comparison:		
	Estimated Median Difference (95% CI)	-	–6.5 (–15.2, 2.2)
	p-value	-	0.1418
	Effect size ^b	-	0.58
Change from baseline at 12 months of treatment	Non-parametric summary ^a		
	Median (95% CI)	0.8 (–6.2, 7.8)	–4.2 (–10.1, 1.6)
	Treatment comparison:		
	Estimated Median Difference (95% CI)	-	–4.8 (–13.1, 3.4)
	p-value	-	0.2509

These data are irrespective of rescue medication use, dose modification, and/or the preventive treatment for medical/dental procedures.

^a Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.

^b Effect Size (ES) is calculated as [estimated median difference] / (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.

Abbreviations: ATP: active treatment phase; CI: confidence interval; ES: effect size; MAR: missing at random; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Change from baseline in physical health

As reported in Table 23, the estimated median change from baseline in Haem-A-QoL physical health score (adults ≥17 years; N=63) was –6.1 (95% CI: –12.6, 0.4) for marstacimab prophylaxis during the ATP compared with –3.0 (95% CI: –8.2, 2.2) for prior routine prophylaxis during the OP. This resulted in a median difference between treatments of –2.2 (95% CI: –9.1, 4.6), indicating the non-inferiority of marstacimab compared to prior routine prophylaxis.

Table 23: Non-parametric analysis of change from baseline in physical health score of Haem-A-QoL, after 6 months of routine factor prophylaxis during the observational phase and after 6 and 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

Physical Health Score		Routine prophylaxis during OP (N=63)	Marstacimab prophylaxis during ATP (N=63)
Change from baseline at 6 months of treatment	Non-parametric summary^a		
	Median (95% CI)	−3.0 (−8.2, 2.2)	−6.1 (−12.6, 0.4)
	Treatment comparison:		
	Estimated Median Difference (95% CI) ^b	-	−2.2 (−9.1, 4.6)
	p-value	-	0.5223
	Effect size ^c	-	0.08
Change from baseline at 12 months of treatment	Non-parametric summary^a		
	Median (95% CI)	−3.0 (−8.2, 2.2)	−8.3 (−15.4, −1.3)
	Treatment comparison:		
	Estimated Median Difference (95% CI) ^b	-	−5.0 (−12.4, 2.4)
	p-value	-	0.1848

These data are irrespective of rescue medication use, dose modification, and/or the preventive treatment for medical/dental procedures.

^a Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.

^b Non-inferiority criterion for the physical health score was upper bound of 95% CI < 10.

^c Effect Size (ES) is calculated as [estimated median difference] / (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.

Abbreviations: ATP: active treatment phase; CI: confidence interval; ES: effect size; Haem-A-QoL; Haemophilia Adult Quality of Life Questionnaire; MAR: missing at random; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

For the Haemo-QoL (adolescents 12 to <17 years; N=20) physical health score, the estimated median change from baseline at 6 months was −17.9 (95% CI: −27.7, −5.4) for marstacimab prophylaxis during the ATP compared with −0.9 (95% CI: −14.3, 12.5) for prior routine prophylaxis during the OP, resulting in an estimated median difference in change from baseline scores of −18.7 (95% CI: −35.7, 5.4) between ATP and OP groups. This difference corresponds to the observed effect size of 0.78 SD units, indicating a large effect of marstacimab over routine prophylaxis. Full results are presented in Table 24.

Table 24: Non-parametric analysis of change from baseline in physical health score of Haemo-QoL, after 6 months of routine factor prophylaxis during the observational phase and after 6 and 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

Physical Health Score		Routine prophylaxis during OP (N=20)	Marstacimab prophylaxis during ATP (N=20)
Change from baseline at 6 months of treatment	Non-parametric summary^a		
	Median (95% CI)	−0.9 (−14.3, 12.5)	−17.9 (−27.7, −5.4)
	Treatment comparison:		
	Estimated Median Difference (95% CI)	-	−18.7 (−35.7, 5.4)
	p-value	-	0.1353
	Effect size ^b	-	0.78
Change from baseline at 12 months of treatment	Non-parametric summary^a		
	Median (95% CI)	−0.9 (−14.3, 12.5)	−17.9 (−28.6, −4.5)
	Treatment comparison:		
	Estimated Median Difference (95% CI)	-	−14.3 (−31.2, 0.0)
	p-value	-	0.0430

These data are irrespective of rescue medication use, dose modification, and/or the preventive treatment for medical/dental procedures.

^a Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.

^b Effect Size (ES) is calculated as [estimated median difference] / (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.

Abbreviations: ATP: active treatment phase; CI: confidence interval; ES: effect size; MAR: missing at random; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

EQ-5D-5L and EQ-Visual Analogue Scale

Results from the BASIS trial indicate that change from baseline at 6 months with marstacimab prophylaxis was non-inferior to that with prior routine prophylaxis, with respect to EQ-5D-5L and EQ-visual analogue scale (VAS) index scores. In both patient questionnaires, a higher score indicates better health states.

The estimated change in EQ-5D-5L index score from baseline to 6 months was 0.0752 (95% CI: 0.0178, 0.1325) for marstacimab prophylaxis during the ATP and 0.0300 (95% CI: −0.0140, 0.0740) for prior routine prophylaxis during the OP, a difference between treatments of 0.0223 (95% CI: −0.0432, 0.0877; Table 25). These results demonstrated the non-inferiority of marstacimab compared to prior routine prophylaxis. The difference of 0.0223 corresponds to the observed effect size of 0.12 SD units, indicating a similar effect of marstacimab compared to routine prophylaxis.

Table 25: Non-parametric analysis of change from baseline in EQ-5D-5L score, after 6 months of routine factor prophylaxis during the observational phase and after 6 and 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

EQ-5D-5L Index		Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
Change from baseline at 6 months of treatment	Non-parametric summary^a		
	Median (95% CI)	0.0300 (-0.0140, 0.0740)	0.0752 (0.0178, 0.1325)
	Treatment comparison:		
	Estimated Median Difference (95% CI) ^b	-	0.0223 (-0.0432, 0.0877)
	p-value	-	0.5050
	Effect size ^c	-	0.12
Change from baseline at 12 months of treatment	Non-parametric summary^a		
	Median (95% CI)	0.0300 (-0.0140, 0.0740)	0.0640 (0.0088, 0.1192)
	Treatment comparison:		
	Estimated Median Difference (95% CI) ^b	-	0.0226 (-0.0421, 0.0874)
	p-value	-	0.4932

These data are irrespective of rescue medication use, dose modification, and/or the preventive treatment for medical/dental procedures.

^a Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.

^b Non-inferiority criterion for the EQ-5D-5L index was lower bound of 95% CI > -0.1.

^c Effect Size (ES) is calculated as [estimated median difference] / (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.

Abbreviations: ATP: active treatment phase; CI: confidence interval; ES: effect size; MAR: missing at random; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

The estimated median change in EQ-VAS index score from baseline to 6 months was 4.5 (95% CI: 1.4, 7.7) for marstacimab prophylaxis during the ATP and 3.0 (95% CI: -0.6, 6.6) for prior routine prophylaxis during the OP, a difference between treatments of 0.6 (95% CI: -4.0, 5.1; Table 26). These results demonstrated the non-inferiority of marstacimab compared to prior routine prophylaxis. The difference of 0.6 corresponds to the observed effect size of 0.03 SD units, indicating a similar effect of marstacimab compared to routine prophylaxis.

Table 26: Non-parametric analysis of change from baseline in ED-VAS score, after 6 months of routine factor prophylaxis during the observational phase and after 6 and 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)

EQ-VAS		Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
Change from baseline at 6 months of treatment	Non-parametric summary^a		
	Median (95% CI)	3.0 (−0.6, 6.6)	4.5 (1.4, 7.7)
	Treatment comparison:		
	Estimated Median Difference (95% CI) ^b	-	0.6 (−4.0, 5.1)
	p-value	-	0.8006
	Effect size ^c	-	0.03
Change from baseline at 12 months of treatment	Non-parametric summary^a		
	Median (95% CI)	3.0 (−0.6, 6.6)	3.0 (−0.2, 6.2)
	Treatment comparison:		
	Estimated Median Difference (95% CI) ^b	-	−1.5 (−6.9, 3.8)
	p-value	-	0.5776

These data are irrespective of rescue medication use, dose modification, and/or the preventive treatment for medical/dental procedures.

^a Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.

^b Non-inferiority criterion for the EQ-VAS index was lower bound of 95% CI > −9.5.

^c Effect Size (ES) is calculated as [estimated median difference] / (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.

Abbreviations: ATP: active treatment phase; CI: confidence interval; EQ-VAS: EQ-visual analogue scale; ES: effect size; MAR: missing at random; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Patient Global Impression of Change-Haemophilia

The patient global impression of change-haemophilia (PGIC-H) is a single item assessment of an individual's overall impression of the change in their life due to haemophilia. The PGIC-H was assessed at two timepoints during the BASIS trial; after 6 months of routine prophylaxis in the OP and after 6 months of receiving marstacimab during the ATP.

After 6 months of routine prophylaxis in the OP the median PGIC-H was 3.5 (95% CI: 3.0, 3.9) compared with 1.8 (95% CI: 1.4, 2.3) after 6 months of marstacimab prophylaxis in the ATP. The median difference of −1.8 (95% CI: −2.2, −1.4) indicates marstacimab prophylaxis improved PGIC-H compared with prior routine prophylaxis.¹⁰⁴

Haemophilia Activities List

Marstacimab prophylaxis was comparable to prior routine prophylaxis for self-perceived functional abilities as assessed by the HAL2 and the PedHAL. For both instruments, scores range from 0 to 100 with higher scores indicating a better functional status.

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For HAL2 (adults ≥ 17 years; N=63) total score, the estimated median change from baseline at 6 months was 2.1 (95% CI: -1.0, 5.1) for marstacimab prophylaxis during the ATP compared with -0.6 (95% CI: -3.0, 1.8) for prior routine prophylaxis during the OP, with a resulting estimated median difference in change from baseline scores of 2.0 (95% CI: -1.8, 5.7) between treatments.¹⁰⁴

For the pedHAL (adolescents 12 to <17 years; N=20) total score, the estimated median change from baseline at 6 months was 5.3 (95% CI: -4.7, 15.3) for marstacimab prophylaxis during the ATP compared with -1.7 (95% CI: -9.8, 6.3) for prior routine prophylaxis during the OP, with the resulting estimated median difference in change from baseline scores of 6.7 (95% CI: -9.3, 22.7) between treatments.¹⁰⁴

Haemophilia Life Impacts Questionnaire (Exploratory Endpoint)

Improvements in most haemophilia life impacts questionnaire (HLIQ) domains related to life impacts associated with living with and receiving treatment for haemophilia were also observed. For example, from baseline to Year 1, the proportion of patients reporting that haemophilia was not on their mind at all increased from 16.0% to 26.7%. Detailed results of the HLIQ are presented in Appendix M.2.3.

B.2.7 Supportive clinical efficacy results – Phase 3 Open Label Extension Study

Data from BASIS are supported by evidence from its OLE study, demonstrating continued durability of efficacy

March 2023 data-cut:

- Fifty-nine patients who had received prophylaxis in the BASIS trial OP and completed the ATP without early termination were enrolled in the Phase 3 OLE where they continued to receive weekly SC marstacimab prophylaxis up to an additional 16 months. One patient withdrew from the OLE
- Of the 58 OLE patients analysed, 77.6% had haemophilia A and 22.4% had haemophilia B
- In terms of the primary endpoint, model derived ABR_{treat} further decreased from 5.08 (95% CI: 3.40, 6.77) in the BASIS ATP to 2.27 (95% CI: 1.40, 3.67) in the OLE, although the OLE was not powered to detect differences between outcomes in the ATP and OLE
- Further reductions in $AJBR_{treat}$, $ABR_{target\ joint}$, $ABR_{spontaneous}$ and ABR_{total} were also detected for patients receiving marstacimab prophylaxis during the OLE
- Additionally, marstacimab prophylaxis preserved joint health as assessed by HJHS at Day 180, with a -2.7 mean change from OLE baseline in the prior prophylaxis group (n=24)

October 2023 interim data-cut:

- Seventy-five patients who had received prophylaxis in the BASIS trial OP and completed the ATP without early termination were enrolled in the Phase 3 OLE where they continued to receive weekly SC marstacimab prophylaxis up to an additional 23 months.
- Of the 75 OLE patients, 77.3% had haemophilia A and 22.7% had haemophilia B
- In terms of the primary endpoint, model derived ABR_{treat} further decreased from 5.08 (95% CI: 3.40, 6.77) in the BASIS ATP to 2.79 (95% CI: 1.95, 3.98) in the OLE, although the OLE was not powered to detect differences between outcomes in the ATP and OLE.
- There were no new safety signals and no reports of thromboembolic events

The clinical results from the OLE support the Phase 3 BASIS trial data in demonstrating that marstacimab is noninferior and superior in the primary endpoint of ABR_{treat} for patients with prior prophylactic treatment of severe haemophilia. In the OLE, long term efficacy of marstacimab was

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maintained when administered beyond the 12 month BASIS study and up to an additional 16 months.

B.2.7.1 Study overview

The Phase 3 OLE study was an extension of the BASIS trial designed to evaluate the long-term safety, tolerability, and efficacy of marstacimab prophylaxis in patients with severe haemophilia. The OLE recruited patients from the BASIS trial who did not require early termination. Patients would remain on their 150 mg weekly SC dose of marstacimab, with potential dosage escalation to 300 mg SC weekly prescribed to patients meeting dose escalation criteria (as detailed in Table 8). Patient inclusion and exclusion criteria remained the same as the BASIS trial.

As of the interim data analysis cut-off of 10th March 2023, 88 patients had enrolled in the OLE. 29 patients had prior on-demand treatment and 59 patients had prior prophylaxis treatment during the OP. Two patients, one receiving prior on demand factor therapy and one receiving prophylaxis, discontinued from the OLE study due to patient withdrawal. One patient who received prior prophylaxis was not included in the safety analysis set reported herein, as their data was not available by the 10th March 2023 interim data cut-off. Of the 58 OLE patients who received prophylaxis in the BASIS trial OP and included in the OLE safety analysis set, 45 (77.6%) had haemophilia A and 13 (22.4%) had haemophilia B.

A more recent analysis comprising of a 4-month safety update was conducted in October 2023. This was a limited data cut primarily assessing safety. Data for the main trial endpoints were analysed but data on all trial endpoints were not assessed as part of this data-cut. Results have recently presented at the European Haematology Association meeting (June 13-16 2024).

At the time of the October 2023 data cut-off, 107 of 116 (92.2%) of non-inhibitor participants from the pivotal study had enrolled in the OLE study (32 from the prior on-demand group and 75 from the prior prophylaxis group). Of the 75 OLE patients who received prophylaxis in the BASIS trial OP, 58 (77.3%) had haemophilia A and 17 (22.7%) had haemophilia B.¹¹⁰

Further demographics and baseline characteristics for the OLE patients with prior prophylaxis at OP are presented in Appendix M.1.2.

B.2.7.2 Efficacy endpoints

Original Submission – March 2023 OLE data cut

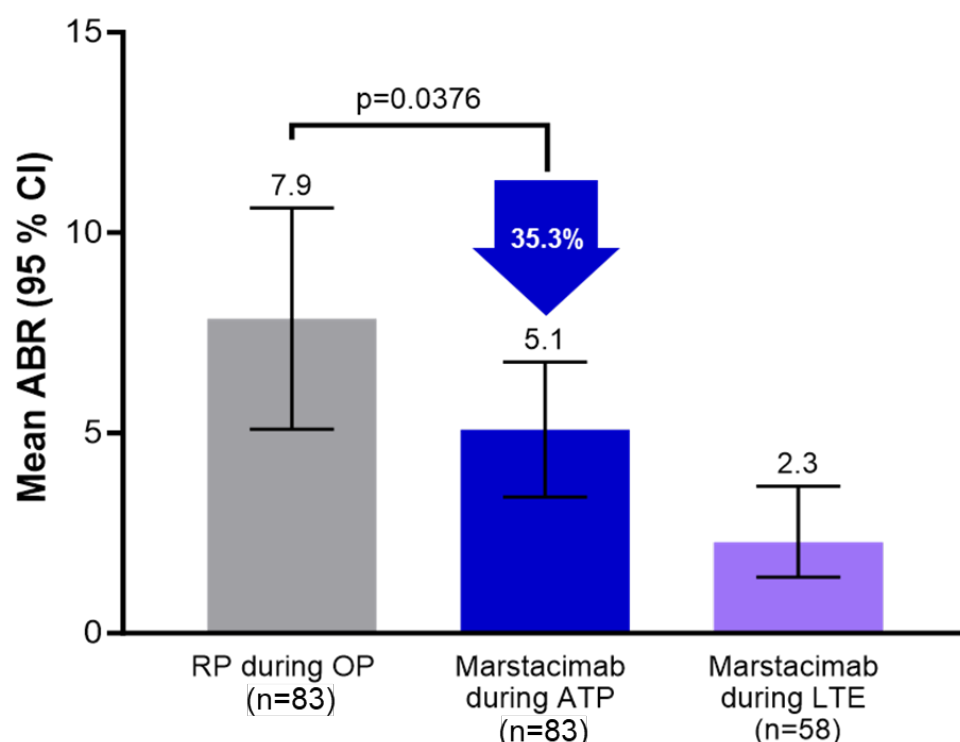
At the interim analysis data cut-off of 10th March 2023, 58 patients with haemophilia A or B, previously treated with prophylaxis in the BASIS trial OP, were treated with marstacimab, with a median treatment duration of 180.0 days (34.0 to 483.0 days) beyond the 12 month BASIS trial ATP. The mean percentage of missed doses was 1.2% indicating good adherence with study medication administration. As of the interim analysis data cut-off, four participants had their dose escalated from 150 mg weekly (QW) to 300 mg QW during the OLE; this is in addition to 10 participants in the BASIS trial who had their dose escalated to 300 mg QW and continued on this dose during the OLE (all eleven BASIS trial participants who had dose escalation of marstacimab continued to the OLE, however for one patient, their data were not available at the time of the interim analysis). The median exposure on the 300 mg QW dose of marstacimab was 98.0 days. All efficacy endpoints reported from the OLE includes data from individuals who received a dose escalation of marstacimab during the BASIS trial ATP or the OLE.

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Primary endpoint – ABR_{treat}

The long-term efficacy of marstacimab was maintained when administered beyond 12 months, up to an additional 16 months, in the OLE as measured by ABR_{treat}. The mean model derived ABR_{treat} was 2.27 (95% CI: 1.40, 3.67) for marstacimab prophylaxis during the OLE, in those previously receiving prophylaxis during the BASIS trial OP (Figure 8, Table 27).

Figure 8: Comparison of model-derived ABR_{treat} after 6 months of routine factor prophylaxis during the observational phase,^a after 12 months of marstacimab prophylaxis in the active treatment phase^a and after marstacimab prophylaxis therapy during the OLE^b



^a 17th April 2023 data cut-off, mITT analysis set; ^b 10th March 2023 data cut-off, safety analysis set

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; LTE: long-term extension study; mITT: Modified intention to treat; OP: observational phase; RP: routine prophylaxis.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023, Pfizer marstacimab Phase 3 OLE CSR, 2023^{104, 107}

Table 27: Comparison of ABR_{treat} after 12 months of marstacimab prophylaxis in the BASIS trial active treatment phase and the OLE

	Marstacimab prophylaxis during BASIS trial ATP ^a (N=83)	Marstacimab prophylaxis during OLE ^b (N=58)
ABR_{treat}		
Mean (SD)	5.17 (8.041)	2.12 (3.929)
Median (range)	2.02 (0.00, 35.51)	0.00 (0.00, 20.39)
Model-derived ABR_{treat}		
Estimate ^c (95% CI)	5.08 (3.40, 6.77)	2.27 (1.40, 3.67)

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^a 17th April 2023 data cut-off, mITT analysis set; ^b 10th March 2023 data cut-off, safety analysis set; ^c Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: Modified intention to treat; OLE: open label extension; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023, Pfizer marstacimab Phase 3 OLE CSR, 2023^{104, 107}

Secondary endpoints

The long-term efficacy of marstacimab was maintained when administered beyond 12 months in the OLE as demonstrated by the trials secondary endpoints: AJBR_{treat}, ABR_{spontaneous}, ABR_{target joint}, and ABR_{total}. A summary of OLE secondary endpoint results are presented in Table 28.

Table 28: Summary of AJBR_{treat}, ABR_{spontaneous}, ABR_{target joint}, and ABR_{total} after 12 months of marstacimab prophylaxis in the BASIS trial active treatment phase and the OLE

	Marstacimab prophylaxis during BASIS trial ATP ^a (N=83)	Marstacimab prophylaxis during OLE ^b (N=58)
AJBR_{treat}		
Mean (SD)	4.20 (7.304)	1.67 (3.440)
Median (range)	1.02 (0.00, 33.48)	0.00 (0.00, 20.39)
Model-derived AJBR_{treat}		
Estimate ^c (95% CI)	4.13 (2.59, 5.67)	1.87 (1.14, 3.08)
ABR_{spontaneous}		
Mean (SD)	3.85 (7.262)	1.44 (3.049)
Median (range)	0.00 (35.51)	0.00 (0.00, 16.69)
Model-derived ABR_{spontaneous}		
Estimate ^c (95% CI)	3.78 (2.25, 5.31)	1.62 (0.96, 2.73)
ABR_{target joint}		
Mean (SD)	2.55 (5.954)	0.80 (2.786)
Median (range)	0.00 (0.00, 27.24)	0.00 (0.00, 18.54)
Model-derived ABR_{target joint}		
Estimate ^c (95% CI)	2.51 (1.25, 3.76)	0.91 (0.36, 2.27)
ABR_{total}		
Mean (SD)	6.06 (8.733)	2.55 (5.108)
Median (range)	2.89 (0.00, 37.54)	0.00 (0.00, 28.57)
Model-derived ABR_{total}		
Estimate ^c (95% CI)	5.97 (4.13, 7.81)	2.73 (1.70, 4.38)

^a 17th April 2023 data cut-off, mITT analysis set; ^b 10th March 2023 data cut-off, safety analysis set; ^c Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: Modified intention to treat; OLE: open label extension; SD: standard deviation.

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Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023, Pfizer marstacimab Phase 3 OLE CSR, 2023^{104, 107}

Additionally, marstacimab prophylaxis preserved joint health as assessed by HJHS at Day 180, with a –2.7 mean change from OLE baseline in the prior prophylaxis group (n=24). The mean number of target joints also remained low at 0.10 in the OLE study. The mean total IU (annualised) factor replacement consumption during the OLE was 7528.8 in the prior prophylaxis group.

With regards to PROs, the long-term treatment effect of marstacimab prophylaxis was maintained as measured by the Haem-A-QoL Physical Health domain and Total score. Patients in the prior prophylaxis group (n=24 reporting values at Day 180), the mean change from OLE study baseline was 1.1 in both the Physical Health Domain and the Total score. There were three adolescents in the prior prophylaxis group that reported Haemo-QoL Physical Health Domain and total scores at Day 180. The mean change from OLE study baseline was –4.8 for the Physical Health Domain and –3.5 for the Total score. Additionally, for patients in the prior prophylaxis group the mean change in EQ-5D-5L index score from OLE baseline (of the 29 patients who completed ≥180 days of marstacimab prophylaxis in the OLE, 26 reported values at Day 180) was 0.0, and in EQ VAS (n=27 reporting values at Day 180) it was –2.1.

Safety endpoints

An overview of the safety endpoints for the OLE are presented in Appendix F.2.

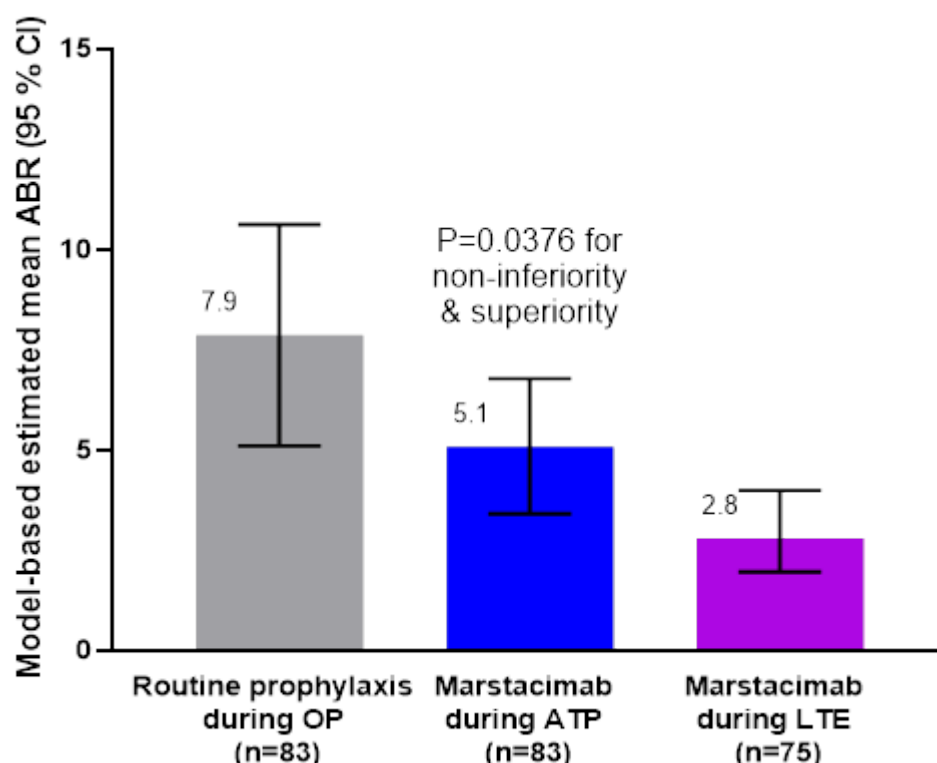
Updated submission – October 2023 data cut

At the interim analysis data cut-off of October 2023, 75 patients with haemophilia A or B, previously treated with prophylaxis in the BASIS trial OP, were treated with marstacimab, with a median treatment duration of 12.5 months (range 1-23 months) beyond the 12 month BASIS trial ATP. Overall, compliance with marstacimab was 98.9% indicating good adherence with study medication administration. As of the interim analysis data cut-off, 11 participants had their dose escalated from 150 mg weekly (QW) to 300 mg QW during the OLE in the prior prophylaxis cohort.¹¹⁰

Primary endpoint – ABR_{treat}

The long-term efficacy of marstacimab was maintained when administered beyond 12 months, up to an additional 23 months, in the OLE as measured by ABR_{treat}. The mean model derived ABR_{treat} was 2.79 (95% CI: 1.95, 3.98) for marstacimab prophylaxis during the OLE, in those previously receiving prophylaxis during the BASIS trial OP (Figure 9, Table 29).

Figure 9: Comparison of model-derived ABR_{treat} after 6 months of routine factor prophylaxis during the OP,^a after 12 months of marstacimab prophylaxis in the ATP^a and after marstacimab prophylaxis therapy during the OLE^b



^a 17th April 2023 data cut-off, mITT analysis set; ^b 9th October 2023 data cut-off, safety analysis set

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; LTE: long-term extension study; mITT: Modified intention to treat; OLE: open label extension; OP: observational phase; RP: routine prophylaxis.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023, Pfizer marstacimab Phase 3 OLE EHA presentation June 2024. ^{104, 110}

Table 29: Comparison of ABR_{treat} after 12 months of marstacimab prophylaxis in the BASIS trial active treatment phase and the OLE

	Marstacimab prophylaxis during BASIS trial ATP ^a (N=83)	Marstacimab prophylaxis during OLE ^b (N=75)
ABR_{treat}		
Mean (SD)	5.17 (8.041)	2.88 (5.50)
Model-derived ABR_{treat}		
Estimate ^c (95% CI)	5.08 (3.40, 6.77)	2.79 (1.95-3.98)

^a 17th April 2023 data cut-off, mITT analysis set; ^b 9th October 2023 data cut-off, safety analysis set; ^c Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: modified intention to treat; OLE: open label extension; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023, Pfizer marstacimab Phase 3 OLE EHA abstract June 2024. ^{104, 110}

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Secondary endpoints

The long-term efficacy of marstacimab was maintained when administered beyond 12 months, up to an additional 23 months, in the OLE as demonstrated by the trials secondary endpoints: $AJBR_{treat}$, $ABR_{spontaneous}$, $ABR_{target\ joint}$, and ABR_{total} . A summary of OLE secondary endpoint results are presented in Table 30.

Table 30: Summary of $AJBR_{treat}$, $ABR_{spontaneous}$, $ABR_{target\ joint}$, and ABR_{total} after 12 months of marstacimab prophylaxis in the BASIS trial active treatment phase and the OLE

	Marstacimab prophylaxis during BASIS trial ATP ^a (N=83)	Marstacimab prophylaxis during OLE ^b (N=75)
$AJBR_{treat}$		
Mean (SD)	4.20 (7.304)	■ (■)
Median (range)	1.02 (0.00, 33.48)	■ (■, ■)
Model-derived $AJBR_{treat}$		
Estimate ^c (95% CI)	4.13 (2.59, 5.67)	■ (■, ■)
$ABR_{spontaneous}$		
Mean (SD)	3.85 (7.262)	■ (■)
Median (range)	0.00 (35.51)	■ (■, ■)
Model-derived $ABR_{spontaneous}$		
Estimate ^c (95% CI)	3.78 (2.25, 5.31)	■ (■, ■)
$ABR_{target\ joint}$		
Mean (SD)	2.55 (5.954)	■ (■)
Median (range)	0.00 (0.00, 27.24)	■ (■, ■)
Model-derived $ABR_{target\ joint}$		
Estimate ^c (95% CI)	2.51 (1.25, 3.76)	■ (■, ■)
ABR_{total}		
Mean (SD)	6.06 (8.733)	■ (■)
Median (range)	2.89 (0.00, 37.54)	■ (■, ■)
Model-derived ABR_{total}		
Estimate ^c (95% CI)	5.97 (4.13, 7.81)	■ (■, ■)

^a 17th April 2023 data cut-off, mITT analysis set; ^bOctober 2023 data cut-off, mITT analysis set; ^c Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; CI: confidence interval; mITT: Modified intention to treat; OLE: open label extension; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023, Pfizer. Data of File. Marstacimab Phase 3 OLE October 2023 data.^{104, 111}

Safety endpoints

No new safety signals have emerged and there have been no reports of there were no reports of thromboembolic events.^{110, 112} An overview of the safety endpoints for the OLE are presented in Appendix F.2.

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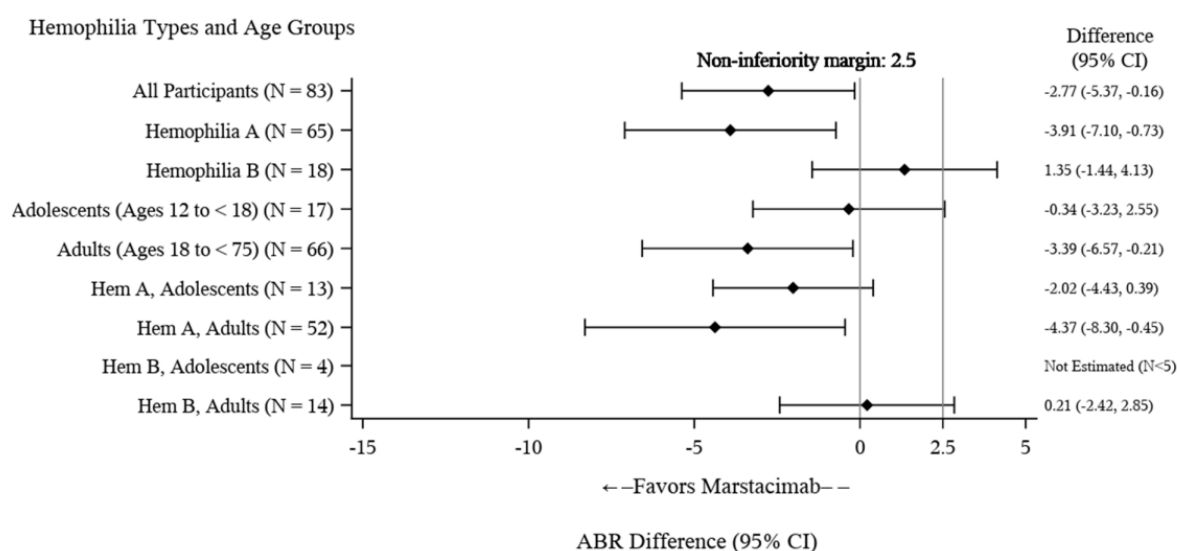
B.2.8 Subgroup analysis

Due to the targeting of marstacimab as a treatment for both haemophilia A and B, the BASIS study was not powered to detect differences within subgroups. Despite this, data are presented for the primary endpoint, ABR_{treat} , split by haemophilia A and B as well as adult and adolescent patients (Figure 10). The efficacy of marstacimab was consistent across subgroups and all point estimates of differences were consistently under 2.5, the non-inferiority margin for the primary analysis.

Mean ABR_{treat} in patients with haemophilia A was 5.30 for marstacimab prophylaxis during the 12 month ATP compared with 9.16 for routine prophylaxis during the 6 month OP. For haemophilia B, mean ABR_{treat} was 4.71 for marstacimab prophylaxis during the 12 month ATP compared with 3.26 for routine prophylaxis during the 6 month OP. Six patients with haemophilia B increased their dose of marstacimab during the ATP; the mean ABR_{treat} for all 18 patients with haemophilia B during the entire ATP including the data following the dose increase was 3.88 indicating similar bleed control compared to routine prophylaxis.

Given the lack of powering and small sample sizes associated with the subgroup analyses by haemophilia type (A or B), in particular for haemophilia B, the primary analysis of treated bleeds in the overall population is considered most relevant to this submission, and informs the base case economic analysis (see Section B.3.2). However, for completeness, scenario analyses have been conducted in which the subgroup analyses by haemophilia type are used to inform the efficacy of marstacimab and factor prophylaxis in the model.

Figure 10: Comparison of ABR_{treat} for haemophilia types and age groups during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; mITT analysis set)



Bleeding records on or after a dose escalation to 300 mg for the eleven patients in the trial who received a dose escalation are censored from these data;

Abbreviations: ABR: annualised bleeding rate; CI: confidence interval; mITT: Modified intention to treat.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

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B.2.9 Post-hoc analyses to inform cost-effectiveness model

Efficacy results from the BASIS trial, presented in Section B.2.6, censored bleeding records on or after a dose escalation to 300 mg during the ATP, as prespecified in the BASIS trial protocol.

Additional post hoc analyses were conducted to inform the data used in the economic model; the structure of the model and rationale for these post hoc analyses is described further in Section B.3.1.2. For factor prophylaxis and marstacimab, ABR_{treat} and $AJBR_{treat}$ reported in the BASIS ATP and OP, respectively, for patients who received routine prophylaxis during the OP, informed the rate of bleed events in the “Bleeds” health state. These were further analysed post hoc in two ways to provide the relevant inputs for the model:

- Firstly, the ABR_{treat} and $AJBR_{treat}$ for the model included data from all patients who received marstacimab during the ATP, including data after dose escalation for those who escalated their marstacimab dose. In comparison, the BASIS trial primary outcome ABR_{treat} and $AJBR_{treat}$ data censored results on or after a dose escalation to 300 mg for the 11 patients who had their marstacimab dose escalated.
- Additionally, ABR_{treat} and $AJBR_{treat}$ for the model were measured amongst those who experienced at least one bleeding event (i.e. excluding those with zero treated bleeding events who enter the “No bleeds” health state at model entry).

Data informing the base case

The proportion of patients with 0 bleeds or ≥ 1 bleed during the OP and ATP of the BASIS trial, which informs the distribution of patients into the bleeds and no bleeds health states of the model base case are presented in Table 31. Efficacy data for factor prophylaxis and marstacimab which informs the base case of the cost effectiveness model are presented in Table 32.

Table 31: The proportion of patients with 0 bleeds and ≥ 1 bleed after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set including patients with dose escalation of marstacimab)

	Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
0 bleeds, n (%)	33 (39.76%)	31 (37.35%)
≥ 1 bleed, n (%)	50 (60.24%)	52 (62.65%)

Abbreviations: ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024¹¹³

Table 32: Comparison of ABR_{treat} and $AJBR_{treat}$ after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set including patients with dose escalation of marstacimab)

	Routine prophylaxis and >0 bleeds during OP (N=50)	Marstacimab prophylaxis and >0 bleeds during ATP (N=52)
ABR_{treat}		
Mean (SD)	13.09 (14.478)	7.53 (8.164)
Median (Range)	7.98 (1.78, 59.51)	4.06 (1.00, 35.51)

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AJBR_{treat}		
Mean (SD)	9.43 (12.758)	6.09 (7.634)
Median (Range)	4.21 (0.00, 55.89)	3.96 (0.00, 33.48)

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024¹¹³

Data informing scenarios

Data from the post hoc analyses informing scenario analyses in the economic model are presented in Appendix N.2.

B.2.10 Meta-analysis

No meta-analysis was conducted as part of this appraisal.

B.2.11 Indirect and mixed treatment comparisons

Results from an unanchored indirect treatment comparison (ITC) of marstacimab and emicizumab suggest that the efficacy of marstacimab is comparable to that of emicizumab with respect to the control of bleeding events among adults or adolescents with severe haemophilia A, without inhibitors, and who received prior prophylaxis

- In the absence of head-to-head evidence between marstacimab and emicizumab, an unanchored simulated treatment comparison (STC) was conducted
- The STC accounted for differences in important prognostic variables and treatment effect modifiers between BASIS and HAVEN 3 (Cohort D), the two studies informing efficacy for marstacimab and emicizumab respectively: prior ABR_{total}, presence of target joints, age, BMI, ethnicity and race were controlled for in the outcome regression models
- Point estimate results from the STC favoured emicizumab, which was associated with lower proportions of patients experiencing total and treated bleeds, and lower rates of treated and total bleeds
- However, none of the results reached statistical significance, and the analysis was associated with limitations which should be acknowledged. Whilst attempts were made to account for confounding, the possibility of residual confounding remains. Additionally, differences treatment of bleeds between BASIS and HAVEN 3 may have led to an underestimation of marstacimab's treatment effect

Whilst the BASIS trial provides a comparison between marstacimab and factor prophylaxis products, no direct comparative evidence between marstacimab and emicizumab exists. Given this absence of direct head-to-head evidence, an indirect treatment comparison (ITC) was conducted to inform the relative efficacy estimates for marstacimab versus emicizumab in patients with haemophilia A; following a feasibility assessment, an STC was identified as the most appropriate approach. The following section provides an overview of the feasibility assessment and the subsequent STC methodology and results, with additional details presented in Appendix D.

B.2.11.1 Identification of comparator data and feasibility assessment

As detailed in Section B.2.1 and Appendix D, a clinical SLR was conducted to identify relevant clinical evidence for adults and adolescents with severe haemophilia A or B, in line with the

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expected indication for marstacimab. A total of 79 unique trials reported in 333 records were included in the SLR, including two trials assessing marstacimab.

Of the 77 comparator trials identified in the SLR, 47 studies were excluded from consideration in an ITC based on a feasibility assessment with respect to data availability, outcome measurement, geography, and trial phase. Of the remaining 30 trials, 28 were excluded because they did not report on a relevant comparator of interest. Since factor replacement therapy was evaluated in the BASIS trial, studies assessing these therapies (n=22) were not considered for inclusion into the ITC analyses. In addition, six trials were excluded because they assessed gene therapies (n=4) or rebalancing agents (n=2) which were not relevant candidate therapies for the target population of this submission. A flow chart demonstrating the initial feasibility assessment of the studies identified in the SLR for use in an ITC is presented in Appendix D, with the list of excluded studies, including reasons for exclusion, presented in Appendix D.1.3.

The remaining two trials, HAVEN 3 and HAVEN 4, both evaluating emicizumab were identified and carried forward to the feasibility assessment (Table 33).

Feasibility assessment

Trial populations

The similarity of the HAVEN 3 and HAVEN 4 study populations to that of the BASIS trial was first assessed. HAVEN 3 and HAVEN 4 trials both exclusively enrolled individuals with haemophilia A whereas the BASIS trial included individuals with haemophilia A and B. In order to minimise any potential heterogeneity and maximise overlap of the two populations, the feasibility assessment and subsequent ITC focused on the subgroup of patients with haemophilia A in the BASIS trial.

HAVEN-3 consisted of multiple treatment cohorts: Cohorts A and B evaluated emicizumab at two different doses in patients who received prior on-demand therapy; Cohort C evaluated no prophylaxis use in patients who received prior on-demand therapy; and Cohort D evaluated emicizumab in patients who received prior prophylaxis. Cohort D was therefore considered the only relevant cohort from the HAVEN 3 trial to the decision problem of this evaluation, and the only cohort of relevance for the feasibility assessment.

Relative to the haemophilia A subgroup of the BASIS trial, Cohort D of the HAVEN 3 trial was found to have a comparable study population in terms of its restriction to individuals who had severe disease and who did not have inhibitors. In contrast, the HAVEN 4 trial included individuals both with or without inhibitors. Although stratified outcome data were available for the HAVEN 4 trial, baseline data were not reported for the without inhibitors subgroup. The HAVEN 4 trial was therefore excluded from the ITC analyses since the overall study population was not comparable to that of the BASIS trial and since baseline characteristics were not reported for the without inhibitor subgroup.

Table 33: Overview of trials included in the ITC feasibility assessment

Trial author, year	Trial name	Study design	Treatments	Severity	Sample size	Outcomes	Results and conclusions	Consideration for ITC
Mahlangu, 2018 ¹¹⁴	NCT02847637, HAVEN 3	Randomised controlled open-label phase 3 trial	Emicizumab (Hemlibra®) Comparator: No prophylaxis (with different dosing compared)	Severe	Total: N=152 Cohort D: N=63	• ABR • AJBR • Zero bleeds • SAEs • Discontinuations due to AEs • Thromboembolic events • Infusion reactions • ALT elevation	ABR_{total} was 1.5 events (95% CI: 0.9, 2.5) in group A and 1.3 (0.8, 2.3) in group B, and 38.2 (22.9, 63.8) in group C. 56% of patients in group A and 60% of group B had no treated bleeding events, vs all patients in group C, had treated bleeding events. Emicizumab prophylaxis administered SC once weekly or every two weeks led to a significantly lower bleeding rate than no prophylaxis among patients with haem A without inhibitors.	Include

Trial author, year	Trial name	Study design	Treatments	Severity	Sample size	Outcomes	Results and conclusions	Consideration for ITC
Pipe, 2019 ¹¹⁵	NCT03020160, HAVEN 4	Non-randomised, open-label phase 3 trial	Emicizumab (Hemlibra®)	Severe	N=48 (with prior prophylaxis)	• ABR • AJBR • any ≥ Grade 3 AEs • dose per infusion • SAEs • treatment-related AEs • treatment-emergent AEs • overall discontinuations • discontinuations due to AEs • thromboembolic events • infusion reactions • low/high titre inhibitors AEs	ABR _{treat} was 2.4 (95% CI: 1.4, 4.3) and 23/41 reported zero bleeds and there were no observed thrombotic events. Emicizumab given once every four weeks showed clinically meaningful bleed control while being well tolerated.	Exclude: The population includes both individuals both with inhibitors and without inhibitors. Baseline data were not available for the without inhibitor subgroup alone. Therefore, this was not comparable to the BASIS trial where those with inhibitors were excluded.

Abbreviations: ABR: annualised bleeding rate; AE: adverse event; AJBR: annualised joint bleeding rate; ALT: alanine transaminase; SAE: serious adverse event.

Assessment of outcomes

Five efficacy outcomes were assessed for the ITC feasibility assessment, which were reported for both BASIS and HAVEN 3 and relevant for use in the economic model. These included ABR_{total} , ABR_{treat} , $AJBR_{treat}$, percentage with zero total bleeding events and percentage with zero treated bleeding events. Although the definitions of these endpoints were comparable, there were notable differences in the proportion of treated versus total bleeds. Specifically, the proportion of bleeding events that were treated was considerably lower in the HAVEN 3 trial (23.9% of all bleeding events were treated) than in the BASIS trial (83.3% [haemophilia A subgroup]). Similarly, the ratio of ABR_{treat} versus ABR_{total} was much lower in the HAVEN 3 prior prophylaxis emicizumab arm (0.48) compared with the corresponding BASIS subgroup (0.84). Clinical experts consulted for this appraisal noted that bleeds are very subjective, and the reporting of bleeds in trials can also be subjective; the experts were unable to rationalise the difference in ratio of treated bleeds to total bleeds in HAVEN 3 compared with BASIS.⁶⁸ Since such differences cannot be controlled for in an unanchored ITC, treated bleeding rates may not be directly comparable between the BASIS and HAVEN 3 trials.

To address this issue, both total and treated bleeding events were considered as outcomes of interest in the ITC analyses. In the economic modelling, whilst the comparative ABR_{treat} rate ratio (RR) is used in the cost-effectiveness analysis (CEA) versus emicizumab, a scenario is conducted using the comparative ABR_{total} RR to explore this uncertainty (see Section B.3.10.3 for further detail).

Assessment of effect modifiers and prognostic factors

The distribution of effect modifiers and prognostic factors was compared between the HAVEN 3 and BASIS trials. Based on published literature,¹¹⁶⁻¹²⁰ input from three clinical experts, and results from regression analyses conducted using individual-level data from the BASIS trial, the following variables were identified as important effect modifiers and/or prognostic factors:

- Prior total ABR (rate)
- Target joints (yes/no)
- Age (years)
- BMI (kg/m^2)
- Race/ethnicity

Among individuals with severe haemophilia A, without inhibitors, and who received prior prophylaxis, there were clinically meaningful imbalances in the distribution of age, prior total ABR, target joints, and race/ethnicity between the HAVEN 3 and BASIS trials. Due to the presence of such imbalances, an unadjusted (naïve) ITC was considered inappropriate.

Further information on the identification of relevant effect modifiers and prognostic variables is presented in Appendix D.1.5.1.

Summary of feasibility assessment

In summary, an ITC of marstacimab (BASIS) relative to emicizumab (HAVEN 3) with respect to total bleeding events among individuals with haemophilia A was deemed feasible. Large

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between-trial differences in the distribution of effect modifiers and prognostic factors were observed which necessitates the use of population-adjustment methods to reduce bias.

B.2.11.2 Methods of the indirect treatment comparison

Choice of methodology

A population-adjusted unanchored ITC was conducted to compare efficacy outcomes for marstacimab relative to emicizumab. Since the Phase 3 BASIS study was a single-arm crossover trial that lacked a randomised control group, methods for anchored ITCs such as a network meta-analysis or network meta-regression were not feasible. An anchored ITC based on inpatient comparisons of the BASIS and HAVEN 3 trials was not considered due to likely differences in disease management during the non-interventional and interventional treatment periods, the reduced sample size of HAVEN 3 Cohort D compared with BASIS haemophilia A subgroup (N=48 versus N=63) and the lack of reporting of key baseline characteristics for the HAVEN 3 Cohort D inpatient comparison. An unadjusted (naïve) unanchored ITC was also not feasible due to large imbalances in the distribution of effect modifiers and prognostic factors as noted in the feasibility assessment.

Population adjustment was therefore necessary and, following consideration of different methods, was performed using a STC:

- A multi-level network meta-regression (ML-NMR) was not considered for these analyses because its implementation within unanchored settings is currently under development and because it is unlikely to provide any meaningful improvements over an STC in this particular two-study setting where there is only one treatment comparison of interest.^{121, 122} Moreover, the same can be said about network meta-interpolation (NMI), where its necessary data requirements also fell short in terms of its lack of development for use within unanchored settings.³⁰
- An STC was selected over a matching adjusted indirect comparison (MAIC) based on recommendations from the 2020 National Institute for Health and Care Excellence Decision Support Unit (NICE-DSU) review of methods for evidence synthesis.¹²² This review notes that unanchored ITCs require all prognostic factors and effect modifiers to be adjusted for, which is unlikely to be achieved in practice but the STC methodology can reduce bias in these unanchored comparisons. Additionally, it recommends that in anchored comparisons, MAICs should not be used under any circumstances and that STCs can be used for two-study scenarios, as there is with the BASIS and HAVEN 3 trials.¹²² Further, a recent publication which presents a novel methodology for the implementation of an unanchored STC states that an STC approach could be more efficient than a MAIC approach because regression-based approaches give more precise estimates.¹²³ Finally, conducting a MAIC was considered inappropriate due to the limited sample size and considerable lack of overlap in the distribution of baseline characteristics, with recent simulation research indicating that a MAIC performs poorly in these settings.¹²¹

Methodology

Study populations

The HAVEN 3 trial included four separate treatment arms for emicizumab. Three of these arms were assessed among individuals who received prior on-demand therapy, which does not reflect

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the current standard of care for haemophilia in the UK. As such, analyses were restricted to individuals who received prior prophylaxis in both trials (Group D of the HAVEN 3 trial). As described above, to reduce heterogeneity, the BASIS trial was also restricted to the subgroup of those with haemophilia A.

Statistical analyses

The STC was implemented in accordance with guidance from the NICE-DSU-Technical Support Document 18 (NICE DSU TSD18) using individual-level data (IPD) from the BASIS trial and aggregate-level data from the HAVEN 3 trial.¹²⁴ Given that aggregate level data for ABR_{treat} and ABR_{total} from the HAVEN 3 trial were reported in the overall population of patients, ABR_{treat} and ABR_{total} results from the BASIS trial in all haemophilia A patients were used (i.e., as opposed to the population of patients who experienced bleeds).

With respect to the effect modifiers and prognostic factors identified in the feasibility assessment, prior total ABR (rate), target joints (yes/no), age (years), body mass index (BMI; kg/m²), percent white, and percent Hispanic/Latino were all controlled for in the outcome regression models. Considering the number of patients included in the analyses, the list of variables can be considered a reasonable number of characteristics to adjust for. Categorical variables were modelled as indicator variables and linearity was assumed with respect to the continuous covariates.

ABR_{total} was modelled using negative binomial regression with log-time included as an offset and zero total bleeding events (Yes/No) was modelled using logistic regression. The conditional outcomes for marstacimab on the linear predictor scale (i.e., the log-rate for ABR_{total} and the log odds for zero total bleeding events) were estimated at the mean values of the covariates from the HAVEN 3 trial. This estimation was accomplished using the intercept and corresponding variance estimates from the outcome regression models after centering the covariates within the BASIS trial to the mean observed values from the HAVEN 3 trial. A non-identity link function was used within the analyses, therefore the marginal and conditional outcomes of each trial may differ.^{125, 126}

Relative treatment effects were estimated on the linear predictor scale and were expressed as RR and odds ratios (OR) for rate and binary outcomes, respectively. Both unadjusted (naïve) and adjusted effects were presented alongside the corresponding 95% confidence intervals (CI) and p-values. All analyses were conducted using R.

B.2.11.3 Results of the indirect treatment comparisons

Population matching results

Table 34 presents the baseline characteristics for individuals in the BASIS trial and HAVEN 3 trial included in the STC analysis. The BASIS trial data were based on the subgroup of patients with haemophilia A, and in line with the primary endpoint from the trial, censored data on or after a dose escalation to 300 mg for the 11 patients that had their dose of marstacimab escalated.

Relative to the HAVEN 3 trial, individuals included in the BASIS trial tended to have more severe disease as indicated by a higher prior total ABR and higher proportion with target joints; this is aligned with clinical expert feedback that considered the BASIS trial to include more phenotypically severe patients than other haemophilia trials.⁶⁸ On average, the BASIS

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participants tended to be younger and have a lower BMI relative to those of the HAVEN 3 trial, additionally, there was a higher proportion of non-white patients.

Table 34: Baseline characteristics in the BASIS and HAVEN 3 trials

Baseline characteristic	BASIS (n=65)	HAVEN 3 (n=63)	ASD
Age, year (mean, SD)	31.63 (14.2)	36.4 (14.4)	0.336
Hispanic/Latino (%)	13.85%	11.1%	0.083
White (%)	52.31%	74.6%	0.476
BMI (mean, SD)	23.91 (4.3)	25.56 ^a (NR)	-
Prior total ABR (mean, SD)	10.26 (14.8)	6.4 ^a (NR)	-
Prior treated ABR (mean, SD)	9.2 (14.3)	NR	-
Target Joint (%)	56.92%	41.3%	0.317

^aPrior total ABR and BMI were not available in the primary HAVEN 3 publication and were instead captured from Astermark et al. (2023) and Kiialainen et al. (2022), respectively.

Abbreviations: ABR: annualised bleeding rate; ASD: absolute standardised difference (a difference greater than 0.1 was used as an indication of a clinical meaningful difference); BMI: body mass index; NR: not reported; SD: standard deviation.

Efficacy results

Results from the STC for ABR_{total}, ABR_{treat}, AJBR_{treat}, proportion of patients with zero bleeding events at six months, and proportion of patients with zero treated bleeding events at six months are presented across Table 35–Table 39.

After adjustment, there were no statistically significant differences between marstacimab and emicizumab with respect to the total ABR (RR: ■■■; 95% CI: ■■■, ■■■; p value = ■■■; Table 35) or the proportion with zero total bleeding events (OR: ■■■; 95% CI: ■■■, ■■■; p value = ■■■; Table 38). Although the point estimates were slightly larger in magnitude, there were also no statistically significant differences between marstacimab and emicizumab with respect to the treated bleed endpoints examined (

Table 36 and Table 39).

Table 35: Marstacimab vs emicizumab - unadjusted and STC for mean ABR_{total}

Source trial	N	Mean ABR _{total} (95% CI)	Rate ratio	95% CI Lower Limit	95% CI Upper Limit	p- value
BASIS: Unadjusted ^a	65	■■■■■	■■■	■■■	■■■	■■■
BASIS: STC	65	■■■■■	■■■	■■■	■■■	■■■
HAVEN 3	63	3.3 (2.2, 4.8)	NA	NA	NA	NA

^a Bleeding records on or after a dose escalation to 300 mg for the five patients who received a dose escalation are censored from these data;

Abbreviations: ABR: annualised bleeding rate; CI: confidence interval; NA: not applicable; STC: simulated treatment comparison.

Table 36: Marstacimab vs emicizumab - unadjusted and STC for mean ABR_{treat}

Source trial	N	Mean ABR _{total} (95% CI)	Rate ratio	95% CI Lower Limit	95% CI Upper Limit	p- value
BASIS: Unadjusted	65	██████████	██	██	██	██
BASIS: STC	65	██████████	██	██	██	██
HAVEN 3	63	1.6 (1.1, 2.4)	NA	NA	NA	NA

^a Bleeding records on or after a dose escalation to 300 mg for the five patients who received a dose escalation are censored from these data;

Abbreviations: ABR: annualised bleeding rate; CI: confidence interval; NA: not applicable; STC: simulated treatment comparison.

Table 37: Marstacimab vs emicizumab - unadjusted and STC for mean AJBR_{treat}

Source trial	N	Mean AJBR _{treat} (95% CI)	Rate ratio	95% CI Lower Limit	95% CI Upper Limit	p- value
BASIS: Unadjusted	65	██████████	██	██	██	██
BASIS: STC	65	██████████	██	██	██	██
HAVEN 3	63	1.2 (0.7 to 2.0)	NA	NA	NA	NA

^a Bleeding records on or after a dose escalation to 300 mg for the five patients who received a dose escalation are censored from these data;

Abbreviations: AJBR: annualised joint bleeding rate; CI: confidence interval; NA: not applicable; STC: simulated treatment comparison.

Table 38: Marstacimab vs emicizumab - unadjusted and STC for the proportion of patients with zero bleeding events (total bleeds) at 6-months

Source trial	N	Proportion with zero bleeds (95% CI)	Odds ratio	95% CI Lower Limit	95% CI Upper Limit	p- value
BASIS: Unadjusted	65	██████████	██	██	██	██
BASIS: STC	65	██████████	██	██	██	██
HAVEN 3	63	44.4% (31.9%, 57.5%)	NA	NA	NA	NA

Abbreviations: CI: confidence interval; NA: not applicable; STC: simulated treatment comparison.

Table 39: Marstacimab vs emicizumab - unadjusted and STC for the proportion of patients with zero bleeding events (treated bleeds) at 6-months

Source trial	N	Proportion with zero bleeds (95% CI)	Odds ratio	95% CI Lower Limit	95% CI Upper Limit	p-value
BASIS: Unadjusted	65	██████████	██	██	██	██
BASIS: STC	65	██████████	██	██	██	██
HAVEN 3	63	55.6% (42.5, 68.1)	NA	NA	NA	NA

Abbreviations: CI: confidence interval; NA: not applicable; STC: simulated treatment comparison.

B.2.11.4 Uncertainties in the indirect and mixed treatment comparisons

Strengths and weaknesses of the analyses

In alignment with NICE DSU TSD 18, the effect modifiers and prognostic variables to be included for adjustment were carefully considered;¹²⁴ the variables chosen to be accounted for in the analyses were identified based on an evidence-based process. The comprehensive assessment of the between study heterogeneity and potential sources of bias through the feasibility assessment represents a key strength of these analyses.

Unanchored ITCs rely on the assumption that all prognostic variables and effect modifiers are known, observed and fully accounted for. In reality, bias due to residual confounding and unaccounted unobserved residual bias cannot be excluded from the analyses. Whilst differences such as how BASIS included patients with more severe disease at baseline than those in the HAVEN 3 trial were controlled for in the analyses there remains a risk of bias due to residual imbalances. In contrast, some geographic and temporal differences could not be fully accounted for: for example, the data cut-off of the HAVEN 3 trial was September 2017, whereas enrolment for the BASIS trial began in March 2020. Additionally, some baseline characteristics were not reported in the primary publication of the HAVEN 3 trial.

The implementation of the STC analyses resulted in a comparison of marginal and conditional outcomes which may have introduced bias. Specifically, the outcomes from the HAVEN 3 trial corresponded to marginal outcomes whereas the STC-adjusted outcomes of the BASIS trial corresponded to conditional outcomes.¹²⁵ Since a non-identity link function was used within the analyses, the marginal and conditional outcomes of each trial may differ.^{125, 126} Due to the current implementation of the STC, there is therefore a risk of bias due to potential differences between the marginal and conditional outcomes.

In order to reduce heterogeneity in the analyses, the BASIS trial population was restricted to those with haemophilia A, without inhibitors and having previously receiving FVIII prophylaxis only, to align with the HAVEN 3 trial Cohort D. The BASIS trial however was not designed to detect subgroup differences based on haemophilia type, and the reduced sample size resulted in wide confidence intervals.

Finally, as noted in Section B.2.11.1, there were notable differences in terms of the ratio between ABR_{total} and ABR_{treat} between the BASIS and HAVEN 3 trials, with substantially fewer bleeds being treated in the HAVEN 3 trial. This indicates that there are important trial differences in the

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clinical management of bleeding events, and as such, the comparative results from the ABR_{treat} STC may not be reflective of the true comparative efficacy of marstacimab and emicizumab; the comparison of ABR_{total} may therefore provide a more accurate reflection of the comparative efficacy. To address this uncertainty, scenarios are conducted in the CEA to explore the impact of the different ORs (see Section B.3.10.3 for further detail).

Summary of results of the ITCs

Overall, the results of the ITC presented above show emicizumab being associated with numerical improvements in ABRs (total and treated) and numerically lower proportions of patients experiencing bleeds (total and treated). However, no results reached statistical significance, meaning that the true difference in treatment effect between both treatments is associated with important uncertainty. Furthermore, whilst important differences in prognostic variables and effect modifiers were adjusted for, important differences in methodology and treatment practices between trials may exist, which cannot be accounted for within the STC and available data. In particular, treatment of bleeds may have differed between BASIS and HAVEN 3, likely leading to greater differences in treated bleed rates and proportion of patients experiencing treated bleeds, as compared with total bleeds.

B.2.12 Adverse reactions

The BASIS trial safety analysis results showed that marstacimab is well tolerated with no notable safety findings. Marstacimab exhibited an acceptable safety profile when compared with factor prophylaxis.

- Ninety-one participants with prior prophylactic factor treatment entered the study, of whom 84 completed the 6 month OP. Eighty-three participants then entered the ATP of whom 78 completed the 12 month analysis period. One patient discontinued from the ATP due to an adverse event, meningioma, however this was not considered treatment related
- Treatment emergent adverse events (TEAEs) occurred in 22.0% of patients during the 6 month OP and 74.7% of patients during the 12 month marstacimab ATP. TEAEs in the OP were mild or moderate with only one patient reporting a TEAE of Grade 3 severity
- Seven participants reported serious adverse events during the marstacimab ATP, with one (Grade 1 peripheral calf swelling) considered by the investigator to be treatment related
- No thrombosis events or deaths were reported during the BASIS trial
- Forty-six patients reported adverse events of special interest (AESIs) during the 12 month marstacimab ATP. COVID-19 infection was the most common AESI, occurring in 18 (21.7%) patients in the ATP
- The overall safety profile of marstacimab is considered manageable and tolerable in this patient population, with no new safety signals identified

B.2.12.1 Clinical safety results

The safety data presented in this section are based on data reported in the BASIS trial. In the BASIS trial, adverse events (AEs) during the 6 month OP were collected during two clinic visits and three phone calls, whereas AEs during the 12 month ATP were collected during nine clinic visits and five phone calls.

With consideration to the differences in study phase duration, frequency of study visits, opportunities to report AEs and external factors, marstacimab exhibits an acceptable safety profile versus standard of care.

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Patient disposition

Overall, 179 patients were screened for enrolment in the BASIS trial, of whom 50 patients discontinued (47 patients failed at screening, 1 patient withdrew, 1 patient due to AE, and 1 patient was withdrawn by parent/guardian). Among the 129 patients who completed screening, 128 entered the OP (1 patient completed screening but did not enter the OP: At the time of the data cut-off, the inhibitor cohort data was missing because the patient had their enrolment/cohort assignment visit after the data cut-off date).

Ninety-one participants with prior prophylactic factor treatment entered the study, of whom 84 (92.3%) completed the 6 month OP. Eighty-three participants then entered the ATP of whom 78 (94.0%) completed the 12 month analysis period. Full details of disposition events for those on routine prophylaxis during the OP are presented in Table 40.

Table 40: Summary of disposition events during the Phase 3 BASIS trial (17th April 2023 data cut-off; safety analysis set)

	Routine prophylaxis during OP (N=91)	Marstacimab prophylaxis during ATP (N=83)
Number of patients, n (%)		
Discontinued	7 (7.7)	5 (6.0)
AE	0 (0.0)	1 (1.2)
Protocol deviation	2 (2.2)	0 (0.0)
Withdrawal by subject	0 (0.0)	4 (4.8)
No longer meets eligibility criteria	5 (5.5)	0 (0.0)
Completed	84 (92.3)^a	78 (94.0)

^a One patient completed the OP but did not enter the ATP because they did not meet the eligibility criteria.

Abbreviations: AE: adverse event; ATP: active treatment phase; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Summary of adverse events

A summary of all-causality AEs is presented in Table 41. An overview all-causality AEs split by adult and adolescent patients in the BASIS trial are presented in Appendix F.1.

Table 41: Summary of adverse events after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; safety analysis set)

	Routine prophylaxis during OP (N=91)	Marstacimab prophylaxis during ATP (N=83)
Number of patients, n (%)		
Number of AEs	44	262
Patients with AEs	25 (27.5)	66 (79.5)
Patients with serious AEs	2 (2.2)	7 (8.4)
Patients discontinued from the study phase due to AEs ^a	0 (0)	1 (1.2)

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Patients discontinued from the study drug due to AEs ^b	0 (0)	0
Patients with dose reduced or temporary discontinuation due to AEs	0 (0)	14 (16.9)

^a Patients who have an AE record that indicates that the AE caused the patient to be discontinued from the study

^b Patients who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the patient to be discontinued from study

Abbreviations: AE: adverse event; ATP: active treatment phase; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Treatment emergent adverse events

The total incidence of treatment emergent adverse events (TEAEs) during the 6 month OP where patients were receiving SOC factor prophylaxis was 22.0% (20 patients with 31 TEAEs). In comparison, incidence of TEAEs during the 12 month marstacimab ATP was 74.7% (62 patients with 249 TEAEs). In general, TEAEs were mild or moderate with only one patient reporting a TEAE of Grade 3 severity. A summary of all-causality TEAEs (≥5%) are presented in Table 42. An overview TEAEs split by adult and adolescent patients in the BASIS trial are presented in Appendix F.1.

Table 42: Summary of TEAEs after 6 months of routine factor prophylaxis during the observational phase and after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; safety analysis set; >5% patients in either treatment phase)

	Routine prophylaxis during OP (N=91)	Marstacimab prophylaxis during ATP (N=83)
Number of patients, n (%)		
With any AE	20 (22.0)	62 (74.7)
COVID-19	3 (3.3)	18 (21.7)
Headache	0 (0)	6 (7.2)
Contusion	0 (0)	5 (6.0)

Abbreviations: AE: adverse event; ATP: active treatment phase; OP: observational phase; TEAE: treatment emergent adverse event.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Treatment related TEAEs

The BASIS trial collected “study treatment-related AEs” where the study treatment was defined as marstacimab prophylaxis during the ATP, therefore there were no treatment-related TEAEs in the OP by design.

For patients with prior routine prophylaxis, the most frequently reported treatment-related TEAEs in the marstacimab ATP were injection site pruritis (4 [4.8%] patients), injection site erythema (3 [3.6%] patients), and prothrombin fragment 1.2 increased (3 [3.6%] patients). All treatment related TEAEs were mild or moderate in severity, with a full breakdown presented in Table 43. An overview treatment related TEAEs split by adult and adolescent patients in the BASIS trial are presented in Appendix F.1.

Table 43: Summary of treatment related TEAEs after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; safety analysis set)

	Marstacimab prophylaxis during ATP (N=83)
Number of patients, n (%)	
With any AE	19 (22.9)
General Disorders and Administration Site Conditions	11 (13.3)
Fatigue	1 (1.2)
Injection site bruising	1 (1.2)
Injection site erythema	3 (3.6)
Injection site induration	1 (1.2)
Injection site oedema	1 (1.2)
Injection site pain	1 (1.2)
Injection site pruritus	4 (4.8)
Injection site swelling	2 (2.4)
Peripheral swelling	1 (1.2)
Injury, Poisoning and Procedural Complications	1 (1.2)
Contusion	1 (1.2)
Investigations	3 (3.6)
Fibrin D dimer increased	2 (2.4)
Prothrombin fragment 1.2 increased	3 (3.6)
Musculoskeletal and Connective Tissue Disorders	1 (1.2)
Arthralgia	1 (1.2)
Nervous System Disorders	1 (1.2)
Headache	1 (1.2)
Skin and Subcutaneous Tissue	2 (2.4)
Pruritus	2 (2.4)

Abbreviations: AE: adverse event; ATP: active treatment phase; TEAE: treatment emergent adverse event.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Serious adverse events

Two (2.2%) serious adverse events (SAEs) were reported during the OP and 7 (8.4%) during the ATP, with one (Grade 1 peripheral calf swelling) considered by the investigator to be treatment related. Additionally, 1 (1.1%) patient reported a SAE during screening.¹⁰⁴

A full breakdown of SAEs in the ATP and OP, across both adolescent and adult populations, is presented in Appendix F.1.

Deaths

There were no deaths reported as of the data cut-off in the BASIS study.¹⁰⁴

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Discontinuations from trial interventions in BASIS study due to adverse events

Data regarding permanent and temporary discontinuations of marstacimab due to AEs are presented in Table 44. Additionally, no dose modifications due to AEs were made for patients during the OP or ATP.¹⁰⁴

A summary of BASIS trial discontinuations, split by adults and adolescents, is presented in Appendix F.1.

Table 44: Summary of study drug temporary discontinuations due to adverse events after 12 months of marstacimab prophylaxis in the active treatment phase (17th April 2023 data cut-off; safety analysis set)

	Marstacimab prophylaxis during ATP (N=83)
Number of patients, n (%)	
Permanent discontinuation with any AE	1 (1.2)
Meningioma ^a	1 (1.2)
Temporary discontinuation with any AE	14 (16.9)
COVID-19	10 (12.0)
SARS-CoV-2 positive test	1 (1.2)
Tympanic membrane perforation	1 (1.2)
Dental caries	1 (1.2)
Peripheral swelling	1 (1.2)

^a The meningioma SAE was not considered related to the study intervention

Abbreviations: AE: adverse event; ATP: active treatment phase.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Adverse events of special interest

The adverse events of special interest (AESIs) in the BASIS study included injection site reactions, thrombotic events, AEs requiring continuous monitoring (e.g. additional lab testing) and AEs requiring treatment modification (e.g. delay or discontinuation of study intervention). Additionally, COVID-19 was designated as an AESI due to its potential to increase the risk of thrombotic events.

More patients reported AESIs during the 12 month marstacimab ATP compared to the 6 month OP; 46 (55.4%) versus 15 (16.5%) respectively. COVID-19 infection was a notable AESI, occurring in 3 (3.3%) patients in the OP compared to 18 (21.7%) patients in the ATP. It should be noted that many patients entered the ATP as COVID-19 rates were rising in early 2022. Injection site reactions occurred in 9 (10.8%) patients during the ATP, however reactions were generally mild and did not cause patient discontinuation. A full breakdown of AESIs are presented in Table 45.

One (1.1%) participant reported a thromboembolic event of device occlusion (blocked port-a-cath) during the OP, which required hospitalisation for the device to be successfully restored and the participant allowed to continue the study. No participants reported thromboembolic events during the marstacimab ATP.

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Table 45: Summary of AESIs after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; safety analysis set; >5% patients in either treatment phase)

	Routine prophylaxis during OP (N=91)	Marstacimab prophylaxis during ATP (N=83)
Number of patients, n (%)		
With any AESI	15 (16.5)	46 (55.5)
COVID-19	3 (3.3)	18 (21.7)
Haemorrhages	5 (5.5)	13 (15.7)
Hypersensitivity	2 (2.2)	6 (7.2)
Hypertension	2 (2.2)	5 (6.0)
Injection site reactions	0 (0.0)	9 (10.8)

Abbreviations: AE: adverse event; AESI: adverse event of special interest; ATP: active treatment phase; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹⁰⁴

Subgroup analysis – AEs in patients with dose escalation

Eleven patients had a dose escalation from 150 mg QW marstacimab to 300 mg QW marstacimab during the ATP. Of these individuals, none experienced an SAE or TEAE that led to discontinuation of the study intervention. TEAEs while on 300 mg QW marstacimab for patients who increased their marstacimab dose from 150 mg to 300 mg are presented in Table 46.

Table 46: Summary of TEAEs in patients who increased marstacimab dose from 150 mg to 300 mg during the active treatment phase (17th April 2023 data cut-off; safety analysis set)

	Dose adjusted marstacimab prophylaxis during ATP (N=11)
Number of patients, n (%)	
With any TEAE	4 (36.4)
Infections and Infestations	2 (18.2)
Laryngitis	1 (9.1)
Rhinitis	1 (9.1)
Musculoskeletal and Connective Tissue Disorders	2 (18.2)
Arthralgia	2 (18.2)
Joint range of motion decreased	0 (0)

Abbreviations: ATP: active treatment phase; mg: milligram; TEAE: treatment emergent adverse event.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023.¹⁰⁴

Clinical laboratory values

Data for relevant clinical laboratory value endpoints, including the incidence of anti-drug (marstacimab) antibodies, are presented in Appendix F.1.

B.2.13 Ongoing studies

Both the Phase 3 BASIS trial and its OLE are ongoing. Interim efficacy data from the OLE study, in which patients had been followed for a mean duration of 12.5 months, were recently presented in a presentation to the European Haematology Association (EHA) congress.¹²⁷

B.2.14 Interpretation of clinical effectiveness and safety evidence

Clinical efficacy for marstacimab

The clinical efficacy and safety evidence for marstacimab as a treatment for severe haemophilia is derived from the BASIS trial. In BASIS, patients received treatment with routine factor prophylaxis during the 6 month OP, followed by treatment with marstacimab in the 12 month ATP. Results from the BASIS trial showed marstacimab to be effective at controlling patient bleeding. Marstacimab demonstrated non-inferiority and superiority over routine prophylaxis as measured by ABR_{treat} , the primary endpoint of the BASIS trial. The mean model-based estimated ABR_{treat} for marstacimab prophylaxis during the ATP was 5.08 (95% CI: 3.40, 6.77) compared with 7.85 (95% CI: 5.09, 10.61) for routine prophylaxis during the OP, equating to a 35.2% (95% CI: 5.6, 55.6) decrease.

Marstacimab also demonstrated non-inferiority to factor prophylaxis in all bleed-related secondary efficacy outcomes, reducing the incidence of $AJBR_{treat}$, $ABR_{target\ joint}$, $ABR_{spontaneous}$ and ABR_{total} from the OP to the ATP. Importantly, reductions in joint bleeds following treatment with marstacimab were reflected in improved HJHS reported by patients completing the ATP, with an estimated median difference between marstacimab and routine factor prophylaxis of -2.2 (95% CI: -4.8, 0.3). The efficacy of marstacimab was consistent across subgroups and all point estimates of differences were consistently under 2.5, the non-inferiority margin for the primary analysis. These results provide strong evidence for marstacimab's ability to maintain or improve patients' joint health, an important treatment goal in haemophilia (see Section B.1.3.1.4).

The improvements in measured efficacy outcomes associated with marstacimab were accompanied with numerically improved HRQoL measures across a variety of patient surveys, both general and specific to haemophilia.

Comparative efficacy for marstacimab

The BASIS trial provides direct, inpatient comparative efficacy evidence for marstacimab versus factor prophylaxis in patients with severe haemophilia without inhibitors. As described above, results from the OP and ATP of the BASIS trial show marstacimab to be associated with statistically significant reductions in treated bleed rates, the primary outcome in the BASIS trial. This was accompanied by numerical improvements in total bleeds, joint bleeds, and HRQoL outcomes.

In the absence of direct comparative efficacy evidence for marstacimab versus emicizumab in patients with severe haemophilia A, an unanchored STC was conducted to estimate relative efficacy of each treatment. The STC adjusted for differences in a number of important prognostic variables and treatment effect modifiers between BASIS and HAVEN 3 (Cohort D), the two trials which informed the comparison. Results from an unanchored ITC of marstacimab and emicizumab suggest that the efficacy of marstacimab is comparable to that of emicizumab with respect to the control of bleeding events among adults or adolescents with severe haemophilia

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A, without inhibitors, and who received prior prophylaxis. Residual confounding post-adjustment cannot be ruled out, and the analyses were subject to limitations which could not be overcome. As such, the STC provides a plausible but uncertain estimate of relative treatment efficacy between marstacimab and emicizumab. The STC informs the comparison between marstacimab and emicizumab in the economic model (see Sections B.3.2.2 and B.3.2.3), however scenario analyses have been conducted exploring different assumptions around the relative efficacy of each treatment.

Safety evidence for marstacimab

The BASIS safety analysis results showed that marstacimab is well tolerated with no notable safety findings. Marstacimab exhibited an acceptable safety profile when compared with factor prophylaxis. The most frequently observed treatment-emergent adverse events (TEAEs) ($\geq 5\%$) during the 12 month marstacimab ATP were pruritus, upper respiratory tract infection, joint range of motion decreased, headache, contusion, and events related to COVID-19. There were no thrombosis events or deaths in patients without inhibitors, with only one SAE deemed to be treatment related.

B.2.14.1 Conclusions

BASIS is a methodologically robust and well-reported trial, and the results reported demonstrate that marstacimab provides significant improvements in ABR_{treat} , and clinically meaningful improvements in ABR_{total} and $AJBR_{treat}$ for adults and adolescents with severe haemophilia compared with currently available factor prophylaxis treatments. These benefits have been demonstrated to continue in the OLE of the BASIS trial. Furthermore, marstacimab has a tolerable and manageable safety profile and does not present any additional safety signals compared with currently available treatment options.

Data for marstacimab from the BASIS trial provide strong evidence to suggest it would be a valuable addition to the treatment pathway for individuals with severe haemophilia without inhibitors, offering a conveniently administered prophylaxis therapy to patients with a high existing treatment burden.

B.3 Cost effectiveness

Model structure and approach

- A cost-effectiveness model was developed to assess the cost-effectiveness of marstacimab for the treatment of severe haemophilia
- The model adopted a Markov approach with three health states (“Bleeds” [consisting of treated bleeds, both joint and non-joint], “No bleeds” and an absorbing “Dead” state), over a lifetime time horizon
- Separate analyses are presented for patients with severe haemophilia A and those with severe haemophilia B, given the different comparator treatments used in each subpopulation. The base case analysis assumes a common treatment effect across haemophilia A and B for marstacimab and factor prophylaxis, in line with the evidence base from the BASIS trial.
- Three comparators were modelled: emicizumab and a basket of FVIII prophylaxis therapies in haemophilia A; and a basket of FIX prophylaxis therapies in haemophilia B. The two baskets of FVIII and FIX therapies were weighted according to real-world market share data in the UK in haemophilia A and B, respectively.
- Efficacy for factor prophylaxis treatments and marstacimab was informed by data collected following the OP and ATP of the Phase 3 BASIS trial (Section B.2.3), respectively. The efficacy of emicizumab was informed by a simulated treatment comparison (STC), using BASIS and relevant clinical trials
- Health state utility values (HSUVs) were the same in the “Bleeds” and “No Bleeds” health states, derived from EQ-5D data collected at baseline in the ATP of the BASIS trial. Differentiation in utility between treatments was derived from disutility reported in external sources applied to bleed events experienced by patients in the “Bleeds” health state and treatment administration-related utility decrements for each IV and SC injection.
- Costs included in the model comprised drug acquisition costs and treatment management costs of acute bleed events

Cost-effectiveness analysis results

- Marstacimab was found to be more effective and less costly than both FVIII and FIX prophylaxis comparator baskets (i.e. dominant) across analyses conducted; in the base case, marstacimab (with PAS) was associated with positive deterministic NHB versus FVIII and FIX prophylaxis of [REDACTED] and [REDACTED], respectively, at a WTP of £30,000 per QALY gained
- Versus emicizumab, marstacimab resulted in fewer QALYs but was less costly, resulting in a positive deterministic NHB of [REDACTED] at a WTP of £30,000 saved per QALY forgone
- In probabilistic sensitivity analyses, marstacimab had a 100% probability of being cost-effective against all comparators, and the deterministic sensitivity analyses demonstrated that the model was largely robust to individual parameter uncertainty
- Conducted scenario analyses additionally demonstrated that marstacimab remained cost-effective versus all comparators

Overall, marstacimab for the treatment of severe haemophilia, can be considered a cost-effective use of NHS resources, whilst also expanding the choice of therapies available to both patients with haemophilia and their clinicians, offering a convenient, easy-to-administer prophylaxis therapy.

B.3.1 Published cost-effectiveness studies

An SLR was conducted in August 2020 and updated in May 2024 in order to identify economic evidence in the field of haemophilia. Literature searches were conducted for cost-effectiveness studies (Appendix G), utility studies (Appendix H) and HCRU studies (Appendix I), with each record identified assessed for eligibility for inclusion on the SLR.

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Across all three evidence streams in the original SLR, a total of 5,519 records were retrieved from the electronic databases, of which 2,611 were duplicates, resulting in 2,908 novel records that were screened at the title/abstract review stage. Subsequently, 663 full publications were screened against the eligibility criteria for all 3 SLRs at full-text review. Following this, 387 publications were excluded. 276 publications were included in total, comprising of 151 haemophilia A studies, 58 haemophilia B studies and 67 studies reporting on non-separable haemophilia.

A total of 192 publications did not report relevant economic outcomes, resulting in 84 publications being included in the review. To prioritise evidence most relevant to this submission, included records were prioritised for extraction if they were key studies informing the structure of the economic model in this submission, or informed utilities or costs in the economic model. This resulted in prioritisation of data extraction of four articles from the original SLR. Following pooling of records across all three evidence streams, a total of 2,831 records were retrieved from the electronic databases, of which 1,495 were duplicates (including duplicates against the original SLR searches), resulting in 1,336 novel records that were screened at the title/abstract review stage. Subsequently, 284 full publications were screened against the eligibility criteria for all three evidence streams at full-text review.

In total, 134 articles reporting included in the SLR. A full list of these studies is presented in Appendix G. No prior economic evaluations were identified for marstacimab in the population of relevance to this submission. Therefore, a *de novo* health economic analysis was conducted for the purpose of this appraisal.

In line with the NICE reference case, the analysis of costs was conducted from the perspective of the NHS and Personal Social Services (PSS) in the UK and included direct medical costs over a lifetime horizon.¹²

B.3.1.1 Patient population

In line with the decision problem addressed in this submission (Section B.1.1), and the anticipated licensed indication for marstacimab, the modelled population included patients aged 12 and above, with documented severe haemophilia (defined as <1% circulating factor level) without factor inhibitors.

The model considers two populations, differentiated by haemophilia type, A and B. Marstacimab is the intervention of interest in both populations, whilst different comparators are considered in each population: emicizumab and FVIII prophylaxis in haemophilia A, and FIX prophylaxis in haemophilia B (see Section B.3.1.3). Given clinical feedback indicating that no differences in marstacimab treatment effect would be expected between haemophilia A and B, a common marstacimab treatment effect is assumed across both populations in the base case analysis, in line with the evidence base from the BASIS trial. Similarly, clinical advisors consulted for this appraisal agreed that it is appropriate to assume all factor replacement products are equal in efficacy.⁶⁸ Therefore the same treatment effect is assumed for all FVIII and FIX prophylaxes in haemophilia A and B respectively, derived from the BASIS trial (see Section B.3.2). A number of scenario analyses around the efficacy assumptions for marstacimab and the comparators, including separate efficacy inputs for haemophilia A and B and across SHLs and EHLs, were also explored (see Section B.3.2.4).

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B.3.1.2 Model structure

A cohort disease state transition model was built in Microsoft Excel® and followed a Markov structure.

Justification of model structure

The use of a state transition model structure (Markov or semi-Markov) is consistent with previous cost-effectiveness models in haemophilia, which have followed either a cohort approach^{128, 129} or microsimulation^{130, 131} (where individual patients are simulated through the health states). Justifications provided for the use of a more complex microsimulation approach included incorporating patient heterogeneity and patient history into the disease course.^{130, 131} A cohort Markov state transition model was deemed sufficient to capture relevant outcomes over time and thus was used in this appraisal, in line with the NICE haemophilia appraisals of etranacogene dezaparvovec (ID3812), fidanacogene elaparvovec (ID4032) and efanescotocog alfa (ID6170).^{9, 10, 84}

There is no set consensus on the structure of cost-effectiveness models to assess interventions in haemophilia across previously published literature.^{128, 129, 131-133} However, the occurrence of bleeds remains a consistent factor in the models identified, as well as forming the primary endpoint of the BASIS trial and comparator trials, leading to its selection as the focus of this model. The economic model for marstacimab was composed of three health states: two defined by the presence or absence of bleeds (“Bleeds” and “No bleeds”), and an absorbing “Dead” state, as described below. This model structure is similar to a model submitted to Canada’s Drug and Health Technology Agency (CADTH) for emicizumab, which utilised a simple approach in which the only health states were “Alive” and “Dead”, accounting for the occurrence of bleeds within the “Alive” state.¹³⁴

The model structure is aligned with that used in the ongoing appraisals for fidanacogene elaparvovec as a treatment for haemophilia B (ID4032) and efanescotocog alfa as a treatment for haemophilia A (ID6170).^{9, 84} Both the fidanacogene elaparvovec and efanescotocog alfa models also consisted of “Bleeds” and “No bleeds” health states, with patients able to transition between the bleeds and no bleeds health states.

The economic model submitted in the prior NICE appraisal of etranacogene dezaparvovec (ID3812) included health states according to the occurrence of bleeds, with transition to the separate bleed health states being determined by annual (joint) bleed rates: “No bleed”, “Bleed (joint)”, “Bleed (not joint)” and “Death”.¹⁰ This means that joint and non-joint bleeds are assumed to be mutually exclusive, with a steady-state distribution modelled across the “Bleed (joint)” and “Bleed (not joint)” health states.¹⁰

The *de novo* model mirrors that of fidanacogene elaparvovec (ID4032) and efanescotocog alfa (ID6170), using the single “Bleeds” health state (see Section B.3.2.3).

Prior models in haemophilia have used ABR_{total} to inform the various “Bleeds” and “No Bleeds” health states in their structures.^{9, 10, 84} The marstacimab model however utilises ABR_{treat} in the efficacy analysis. The choice of modelling treated rather than total bleeds in this evaluation instead, was made to align with the primary outcome in the BASIS trial, and to reflect the fact that

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bleed events in the model incur treatment costs (see Section B.3.4.2). Furthermore, treated bleeds are likely to have a greater impact on patients' lives than those not requiring treatment, and were therefore considered a more meaningful outcome, better able to reflect treatment impact on patients' QoL.

Joint health and its progression have also been incorporated in previous cost-effectiveness models in haemophilia, by tracking target joint status,¹³² Pettersson score,¹²⁹ or joint surgery and joint damage as health states.¹³⁰ In this model, any impact associated with joint pain is assumed to be implicitly included in the utility values. This is similar to the approach taken in the models submitted as part of the NICE evaluations for etranacogene dezaparvovec (ID3812),¹⁰ fidanacogene elaparvovec (ID4032)⁸⁴ and efanescotocog alfa (ID6170)⁹ where the benefit of preventing joint damage and associated joint replacement surgeries was excluded due to data limitations. As marstacimab has been shown to reduce AJBR compared with prophylactic factor replacement in the BASIS trial (Section B.2.6) and maintain these improvements when continuing marstacimab up to an additional 16 months (Section B.2.7.2), it is therefore expected that patients may receive additional long-term benefit by the reduction of joint damage not captured in the economic model. Improvements in joint health in the short term may translate to long-term reductions in joint pain, improved mobility, and better quality of life. Additionally, if patients experienced fewer joint surgeries, this could be expected to provide cost-savings for the health system. Therefore, the decision to not include the occurrence of, or costs associated with, joint damage in the model could be considered a conservative assessment of the cost-effectiveness of marstacimab.

Model health states and patient flow

At model entry, patients receiving factor prophylaxis or marstacimab are distributed among the “No bleeds” and “Bleeds” health states, based on the BASIS OP and ATP trial results, respectively, for the proportion of patients with zero *treated* bleeding events. For emicizumab, health state occupation was derived by applying an odds ratio to the health state distribution of marstacimab patients (see B.3.2.2). The odds ratio was derived from the STC using IPD from BASIS and cohort-level data from HAVEN 3 (see Section B.2.11). In the factor prophylaxis and emicizumab arms, distribution across the “No bleeds” and “Bleeds” health states is unchanged across the model time horizon, and patients are assumed to remain on treatment whilst alive. In the marstacimab arm of the model, health state distribution is assumed to remain constant over time whilst on treatment; subsequent redistribution across these health states occurs to reflect discontinuation, as described in Section B.2.12.1.

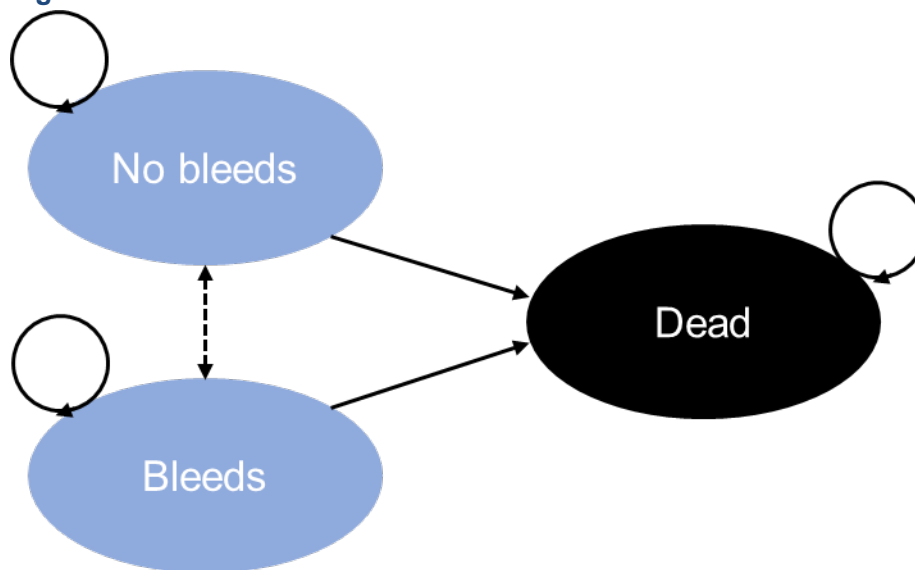
Within the “Bleeds” health state, both joint and non-joint treated bleeds are considered. ABR_{treat} and $AJBR_{treat}$ were estimated from post-hoc analyses of the BASIS trial for marstacimab and factor prophylaxis, and from the ITC for emicizumab (see Section B.3.2). An overview of the model health states is provided below and in Figure 11:

- **No bleeds:** Patients with no bleeding events.
- **Bleeds:** Patients are assumed to experience an average number of bleeds annually within this state. The average number of bleeds per annual cycle is assumed to remain constant, with no natural increase in bleed likelihood. Within this state, ABR_{treat} and $AJBR_{treat}$ were modelled separately to inform corresponding costs and utility decrements per bleed event, as described in Section B.3.2.3. The model applies costs and disutilities associated with these acute bleed events.

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- **Death:** All patients were subject to a risk of death in each model cycle and could transition to the absorbing death state from either of the bleed health states (Section B.3.2.7).

Figure 11: Markov model structure



Within the “Bleeds” health state, patients experience treated non-joint or joint bleeds based on ABR_{treat} and $AJBR_{treat}$ outcomes. Arrows represent permissible transitions between states while loops represent no transition. Death is possible from any health state. The dotted arrow represents the redistribution of patients across bleed health states in the marstacimab arm of the model following discontinuation. In the factor prophylaxis and emicizumab arms of the model, no such transitions occur.

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate.

Features of the cost-effectiveness analysis

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. The analysis was conducted from the perspective of the NHS in England, including direct medical costs and PSS costs over a lifetime horizon of the patient cohort from the initiation of treatment, in line with the ongoing etranacogene dezaparvovec (ID3812) and fidanacogene elaparvovec (ID4032) evaluations, and the NICE reference case.^{10, 12} A one-year cycle length was selected to align with the period of time over which the primary endpoint of the Phase 3 BASIS trial was assessed and to align with the unit of measurement defining health states, ABR_{treat} , which is also the principal outcome of interest in clinical trials in haemophilia. Whilst the one-year cycle length is not aligned with the administration schedule of products used for prophylaxis, patients receiving prophylaxis are not modelled as being able to alter their administration schedule and are assumed to receive continuous treatment throughout the model time horizon. Within this model framework, a one-week model cycle is not necessary to model prophylaxis administration; this would yield the same costs as with a one-year model cycle, whilst adding additional modelling complexity. Costs and utilities associated with short-term events, i.e., a single acute treated bleed event, are therefore accumulated over a year based on the number of events per year, rather than modelled explicitly as one-off events. A half-cycle correction was applied to account for the fact that clinical events can occur at any point during the cycle, not necessarily at the start or end of each cycle. An annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case.¹² The key features of the economic analysis are summarised in Table 47.

Table 47: Features of the economic analysis

Factor	Etranacogene dezaparvovec (ID3812) ¹⁰		Efanesoctocog alfa (ID6170) ⁹	Current evaluation	
				Chosen values	Justification
Model structure	Cohort Markov state transition model		Markov Model	Cohort Markov state transition model	Aligned with prior cost-effectiveness models in haemophilia, ^{128, 129} including ID3812 ¹⁰
Perspective	NHS and PSS (base case)		NHS and PSS	NHS and PSS	As per NICE reference case ¹²
Time horizon	Lifetime		Lifetime	Lifetime	A lifetime horizon was chosen to capture the long-term expected benefits of a gene therapy in line with the NICE reference case, in alignment with ID3812 ¹⁰
Cycle length	1 week		6 months	1 year	The cycle length was aligned with the primary endpoint of the Phase 3 BASIS trial (annualised bleeding rate for treated bleeds), ¹⁰⁴ which in turn informs health state definitions, as well as improving computational efficiency as a result of the overall fewer

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Factor	Etranacogene dezaparvovec (ID3812) ¹⁰		Efanesoctocog alfa (ID6170) ⁹	Current evaluation	
				Chosen values	Justification
					number of cycles in the model
Annual discount rate	3.5% for costs and effects		3.5% for costs and effects	3.5% for costs and effects	As per NICE reference case ¹²
Long-term durability and waning of treatment effect	Treatment effect durability of etranacogene dezaparvovec based on changes in FIX levels as reported in Shah <i>et al.</i> (2022) ¹³⁵		Waning of treatment effect was not included in the model	Waning of treatment effect has not been included in the model.	Given the mechanism of action of marstacimab as a TFPI, and its weekly dosing regimen, a waning of treatment effect is not expected, as confirmed by clinical expert opinion ⁶⁸
Source of utilities	HOPE-B trial, ¹³⁶ US-ICER (2022) ¹²⁹		XTEND-1 clinical trial ¹³⁷	BASIS trial, US-ICER (2022) ¹²⁹	EQ-5D data from BASIS provide the most appropriate source of QoL data for the “Bleeds” and “No bleeds” health states. Additional disutility for individual bleed events are informed by literature, in alignment with prior appraisals
Source of costs	- Intervention costs were based on the UK list price including a confidential discount - Comparator costs		- NHS Business Services Authority (NHS BSA) - National Schedule of NHS Costs	Intervention costs were based on the UK list price including a confidential discount	These are established sources of drug costs within the NHS and in alignment with prior appraisals

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Factor	Etranacogene dezaparvovec (ID3812) ¹⁰		Efanesoctocog alfa (ID6170) ⁹	Current evaluation	
				Chosen values	Justification
	(drug and administration) were taken from the BNF and MIMS National Schedule of NHS Costs (2019/2020)	•	(2019/2020) PSSRU 2023¹⁴²	- Comparator acquisition costs were taken from the BNF (2024)¹³⁸ and MIMS¹³⁹ - Treatment administration and follow up costs were sourced from National Schedule of NHS Costs (2021/2022)¹⁴⁰ and PSSRU 2023¹⁴²	
Health effects measure	QALYs; ICERS		QALYs; ICERS	QALYs; ICERS	As per NICE reference case ¹²

Abbreviations: BNF: British National Formulary; BSA: Business Services Authority; ICER: incremental cost-effectiveness ratio; LTFU: long term follow up; MIMS: Monthly Index of Medical Specialities; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; QALY: quality-adjusted life years; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit.

B.3.1.3 Intervention technology and comparators

Marstacimab

The intervention considered in the cost effectiveness analysis was marstacimab. The model included the recommended marstacimab dose, administered as a weekly 150 mg SC injection following an initial one-off loading dose of 300 mg, in line with the dosing regimen included in the Phase 3 BASIS trial and the draft SmPC.^{5, 104}

In line with the BASIS trial protocol and draft SmPC, the model base case also included a proportion of patients receiving 300 mg weekly to account for patients who had their dose of marstacimab escalated. Dose escalation was determined by clinician discretion, with criteria including patients experiencing two or more spontaneous bleeds (joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of FVIII or FIX over a 6 month period. Eleven patients (13%) in the BASIS trial ATP had their marstacimab dose escalated from 150 mg to 300 mg weekly.

Efficacy data in the model for marstacimab were derived from post-hoc analyses of the BASIS Phase 3 trial, inclusive of data from eleven patients who received dose escalation, as presented in Section B.2.9. A scenario analysis was also conducted in which no marstacimab dose escalation was modelled; in this scenario, efficacy data in the model were informed by post hoc analyses of the BASIS trial, in which bleeding records on or after a dose escalation to 300 mg during the ATP were censored. Efficacy data informing this scenario are presented in Appendix N.1.

Comparators

Factor prophylaxis

As detailed in Section B.1.3.2.2, prophylactic factor therapy represents an important treatment option in haemophilia in the UK. The basket comparators consisting of FVIII and FIX treatments reflect this established clinical management for people with severe haemophilia A and B, respectively, in the UK. This approach was taken to align with the requested analysis from the committee in the ongoing evaluation of etranacogene dezaparvovec (ID3812),¹⁰ in which a comparison versus a comparator basket was requested. The committee considered that using a basket of prophylaxis treatments weighted by NHS market share was the most appropriate comparator for the economic modelling and best reflects the most commonly used treatments in clinical practice.¹¹ This approach was further validated by clinicians consulted as part of this appraisal, who agreed that assuming equal efficacy across factor treatments was an appropriate approach.⁶⁸ The treatments included are in line with UK clinical recommendations developed by the BSH, expert clinical opinion, and real-world treatment sales data derived from the IQVIA MIDAS database. As described in Section B.1.3.2.2, currently available recombinant factor therapies include SHL products and EHL products.^{13, 14} In haemophilia A, SHL products require administration 3 to 4 times a week, while EHL products are typically administered twice weekly.⁶⁹⁻⁷⁵ In haemophilia B, SHL products can require administration twice per week, whilst EHL products are typically administered at frequencies from once a week to once every two weeks for those whose bleeding is well controlled.⁷⁶⁻⁷⁹

Each factor basket comparator includes SHL and EHL products relevant to UK clinical practice, as presented in Table 48. The FVIII basket includes four SHL products and three EHL products.

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The FIX basket includes one SHL product and three EHL products. Clinical experts noted that the use of SHL products and their relevance as a comparator is likely to continue declining over time in patients with haemophilia B. [REDACTED]

Dosing schedules for prophylactic factor replacement therapies are summarised in Table 48, derived from their respective SmPCs.

Table 48: Recommended dose regimens for factor prophylaxis therapies

Comparator	Comparator Type	Licensed dose and dosing frequency
<i>FVIII prophylaxis</i>		
Advate® (octocog alfa)	SHL	• 20–40 IU/kg every 2–3 days
ReFacto AF® (moroctocog alfa)		• 20–40 IU/kg every 2–3 days
NovoEight® (turoctocog alfa)		• 20–40 IU/kg every second day or 20–50 IU/kg thrice weekly
Nuwiq® (simoctocog alfa)		• 20–40 IU/kg every 2–3 days
Esperoct® (turoctocog alfa pegol)	EHL	• 50 IU/kg every 4 days
Elocta® (efmoroctocog alfa)		• 50 IU/kg every 3–5 days
Adynovi® (rurioctocog alfa pegol)		• 40–50 IU/kg every 3–4 days
<i>FIX prophylaxis</i>		
BeneFIX® (nonacog alfa)	SHL	• 40 IU/kg every 3–4 days ^a
Alprolix® (eftrenonacog alfa)	EHL	• 50 IU/kg once weekly ^b • 100 IU/kg every 10 days (well-controlled patients can be treated every 14 days or longer)
Idelvion® (albutrepenonacog alfa)		• 35–50 IU/kg once weekly ^c • 75 IU/kg every 10–14 days
Refixia® (nonacog beta pegol)		• 40 IU/kg once weekly

^aAssumed to be twice weekly due to being SHL product. ^bFor Alprolix®, all patients were assumed to receive 50 IU/kg weekly. ^cApplied as 42.5 IU/kg weekly (the midpoint of 35–50 IU/kg). All patients were assumed to receive 35–50 IU/kg dose.

Abbreviations: EHL: extended half-life; FIX: factor IX; FVIII: factor VIII; IU/kg: international unit per kilogram; SHL: standard half-life; SmPC: summary of product characteristics.

Sources: Advate® SmPC;⁶⁹ ReFacto AF® SmPC;⁷⁰ NovoEight® SmPC;⁷¹ Nuwiq® SmPC;⁷² Esperoct® SmPC;⁷³ Elocta® SmPC;⁷⁴ Adynovi® SmPC;⁷⁵ BeneFIX® SmPC;⁷⁶ Alprolix® SmPC;⁷⁷ Idelvion® SmPC;⁷⁸ Refixia® SmPC.⁷⁹

Treatments included in the basket comparators were weighted to reflect real-world usage of each product in UK clinical practice. In the base case analysis, market share weights were based on IQVIA sales volume data from April 2023 to April 2024, as shown in Table 49 and Table 50. As described in Section B.1.3.2.5, IU volumes reported for each factor prophylaxis treatment were converted to DOT to account for the higher daily dose required for SHL products. The

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proportions shown below inform both weighted costs and efficacy for the comparator arm for the entirety of the model time horizon.

Whilst providing a robust method of estimating relative usage of each treatment included in the basket comparator, some uncertainty exists as to the exact share of treatments used in UK clinical practice. An alternative source of market share data was therefore explored as a scenario. The UKHCDO 2023 report provides additional real-world treatment usage data derived from the National Haemophilia Database, with the proportions of each factor treatment shown in Table 49 and Table 50. The distribution of treatments were similar in both cases, indicating that these market share values are likely to be broadly correct. The IQVIA market share data are more recent, capturing treatment patterns from 2023 and 2024, and were therefore selected as the base case. Factor prophylaxis therapies with <1% market share in both IQVIA 2023/24 sales data and UKHCDO 2022/23 data were not considered in this submission; therefore Rixubis®, a FIX treatment, has not been included in the comparator FIX basket.

Table 49: Distribution across prophylactic FVIII replacement therapies

FVIII basket	Distribution	
	IQVIA 2023/2024 sales data (base case)	UKHCDO 2022/2023 usage data (scenario)
Advate®	████	28.13%
ReFacto AF®	████	16.50%
NovoEight®	████	7.78%
Nuwiq®	████	2.68%
Esperoct®	████	23.40%
Elocta®	████	19.66%
Adynovi®	████	1.85%

Proportions based on DOT, rather than IU. See Section B.1.3.2.5 for further detail.

Abbreviations: FVIII: factor VIII; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation.

Source: IQVIA market share analysis for haemophilia A and B, 2024;⁸⁰ UKHCDO Annual Report 2023 and Bleeding Disorder Statistics for the Financial Year 2022/23⁴

Table 50: Distribution across prophylactic FIX replacement therapies

FIX basket	Distribution	
	IQVIA 2023/2024 sales data (base case)	UKHCDO 2022/2023 usage data (scenario)
BeneFIX®	████	23.40%
Alprolix®	████	46.70%
Idelvion®	████	15.10%
Refixia®	████	14.80%

Proportions based on DOT, rather than IU. See Section B.1.3.2.5 for further detail.

Abbreviations: FIX: factor IX; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation.

Source: IQVIA market share analysis for haemophilia A and B, 2024;⁸⁰ UKHCDO Annual Report 2023 and Bleeding Disorder Statistics for the Financial Year 2022/23⁴

As described in Section B.1.3.2.3, management of haemophilia in the UK may also involve on-demand administration of factor replacement products, either on its own or in addition to factor prophylaxis, with the aim of stopping bleeding once it has occurred, as may be required following trauma or surgery.⁸¹ On-demand treatment on its own is therefore not recommended for use in severe haemophilia, as per WFH and BSH guidelines.^{13, 14} The low usage of on-demand factor treatment in UK clinical practice was confirmed by clinicians.⁶⁸ In addition, patients enrolled in the BASIS trial had received at least six months of treatment with prophylaxis (the lead-in period) before marstacimab administration. Therefore, on-demand factor therapy was not included as a standalone comparator in this submission, in line with the etranacogene dezaparvovec and fidanacogene elaparvovec NICE appraisals (ID3812, ID4032).^{10 84} On-demand factor therapy alongside marstacimab and comparator therapies has been included in the model in the form of acute bleed event management costs, as described in Section B.3.4.2.

Emicizumab

As detailed in Section B.1.3.2.4, emicizumab, administered as a SC prophylactic therapy, also represents a key comparator in the population of patients with haemophilia A. Based on the previously mentioned IQVIA sales data, emicizumab makes up █████ of prophylactic therapies administered to patients with haemophilia A in the UK.⁸⁰ Emicizumab is given as a 3 mg/kg dose once weekly for the first four weeks (loading dose), followed by a maintenance dose from Week 5, of either 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks, with all doses administered as a SC injection.

B.3.2 Clinical parameters and variables

B.3.2.1 Baseline characteristics

The baseline characteristics for the modelled population in terms of age and weight were derived from UKHCDO analysis and can be found in Table 51. Patients enrolled in the BASIS trial were younger and had a lower mean body weight compared with UKHCDO data. Therefore, to ensure the baseline characteristics in the model are most aligned with the UK clinical population, the baseline characteristics of patients studied in the UKHCDO analysis were used.⁴⁰ Clinical experts consulted as part of this submission agreed that the average body weight derived from the UKHCDO of █████ kg was more representative of their patients’ weight than that in the BASIS study.⁶⁸ The mean age in the UKHCDO and BASIS trial were very similar (█████ and 33.0 years, respectively), however a scenario analysis was conducted in which the age in the BASIS trial was used instead. All patients were modelled as male, in line with the population enrolled in the BASIS trial. However, as noted in Sections B.1.1 and B.1.4, this evaluation is not expected to exclude the small number of female patients living with haemophilia.

Table 51: Baseline characteristics of modelled cohort

Characteristic	Parameter	Source
Mean age, years	█████	Pfizer bespoke UKHCDO analysis ^a
Mean body weight, kg	█████	

^a Patients registered with the UK National Haemophilia Database throughout October 2022 – September 2023. Data on weight only includes those patients with recent weight measurement, defined as one year prior to study start data (i.e., October 2021).
Abbreviations: kg: kilogram; UKHCDO: United Kingdom Haemophilia Centres Doctors’ Organisation.
Source: Pfizer Bespoke UKHCDO Analysis, 2024.⁴⁰

B.3.2.2 Health state distributions

Starting model health state distributions

Marstacimab and factor prophylaxis

At model entry, patients are distributed among the “No bleeds” and “Bleeds” health states. In the intervention arm, the starting proportion of patients in each health state is informed by the proportion of patients who reported no treated bleed events following treatment with marstacimab during the ATP in the BASIS trial. As noted in Section B.3.1.2, this analysis includes data from all patients who received marstacimab in the ATP, including data for those who received a dose escalation. Whilst differing from the primary analysis of treated bleeds in the BASIS trial, which censored data for patients after they received dose escalation, this analysis was chosen to inform bleed rates in the model to reflect the efficacy of dose escalation observed in the trial, and detailed in the draft SmPC for marstacimab.⁵ This aligns with the approach taken to marstacimab costs, which reflect the dose escalation seen in the trial (Section B.3.4.1). [REDACTED]

[REDACTED]

The proportion of patients experiencing no treated bleed events in those receiving marstacimab and factor prophylaxis is shown in Table 52.

It should also be noted that a discrepancy exists between the timepoints of assessments informing the proportion of patients experiencing zero bleeds at model entry for factor treatments and marstacimab. For factor prophylaxis, this was measured following six months of treatment in the BASIS OP, as opposed to 12 months in the BASIS ATP for marstacimab. Therefore, patients in the BASIS OP may have subsequently experienced a bleed(s) had the OP lasted 12 months, prior to initiating treatment with marstacimab. Consequently, the proportion of patients experiencing zero bleeds with factor prophylaxis in the model may be an underestimate. Whilst this represents an inherent limitation of the available data, the use of a shorter period of assessment for factor prophylaxis to inform the model health state distribution should be considered a conservative approach.

Emicizumab

In the absence of direct comparative evidence for emicizumab, the proportion of patients entering the “No bleeds” health state for this comparator therapy is informed by the STC analysis comparing marstacimab and emicizumab (see Section B.2.11). The emicizumab health state distributions were derived in the following way:

Odds of experiencing no treated bleeding events for marstacimab were calculated as:

$$\text{Odds No Treated Bleeds}_{(\text{intervention})} = \frac{\% \text{ Experiencing No Treated Bleeds}}{1 - \% \text{ Experiencing No Treated Bleeds}}$$

The inverse of simulated odds ratios for the proportion of patients experiencing zero treated bleeding events (see Section B.2.6) were applied to the odds of no treated bleeding events for the intervention to derive an odds of no bleeding for emicizumab:

$$\text{Odds No Treated Bleeds}_{(\text{emicizumab})} = \frac{\text{Odds No Treated Bleeds}_{(\text{intervention})}}{\text{Odds Ratio}}$$

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This method of deriving comparator treatment effect for emicizumab ensures that the relative effects of the treatments, adjusted for differences in confounding variables, are maintained and applied to the population informing the model. However, certain limitations of this method should be recognised.

The unanchored STC method used to derive relative treatment effect assumes that all effect modifiers and prognostic variables have been accounted for. Whilst the analysis adjusted for important differences between the BASIS and HAVEN 3 populations, residual confounding cannot be ruled out. Furthermore, the ITC analyses of the proportion of treated bleeds did not reach statistical significance following adjustment, meaning a high degree of uncertainty exists surrounding the true treatment effect of marstacimab relative to emicizumab.

The resulting odds of experiencing no treated bleed events were used to derive the proportion of patients experiencing no treated bleed events of emicizumab, which are shown alongside the intervention in Table 52.

Table 52: Health state distributions at model entry

	Bleeds	No bleeds
Intervention		
Marstacimab	62.65%	37.35%
Comparators		
FVIII prophylaxis	60.24%	39.76%
FIX prophylaxis	60.24%	39.76%
Emicizumab		

The proportion of patients with bleeds was measured following 12 months for marstacimab, in contrast to six months for factor prophylaxis.

Abbreviations: FIX: factor IX; FVIII: factor VIII.

In order to align with the chosen model structure based on treated bleeds, the relative efficacy of treated bleeds from the STC was used to inform the relative proportion of emicizumab patients in the “Bleeds” and “No Bleeds” health states at model entry. The ITC predicted a lower odds ratio of treated bleeds compared with total bleeds (see Section B.2.11.3), indicating fewer bleeds were treated in HAVEN 3 compared with BASIS. Clinical experts consulted for this appraisal noted that bleeds are very subjective, and the reporting of bleeds in trials can also be subjective; the experts were unable to rationalise the difference in ratio of treated bleeds to total bleeds in HAVEN 3 compared with BASIS.⁶⁸ An alternative source of comparative efficacy was therefore explored in a scenario analysis, where the odds ratio for the proportion of patients experiencing no total bleeds was instead used to inform the starting distributions for patients receiving emicizumab in the model (see Section B.3.10.3). Considering the non-significance of the ITC results, an additional scenario was also conducted in which no difference in efficacy between marstacimab and emicizumab was assumed.

Health state transitions

As noted in the description of the model structure in Section B.3.1.2 above, the model allows for patients in the intervention arm to transition between health states, in order to account for discontinuation of treatment. In the intervention arm, 6.02% of marstacimab patients are modelled as discontinuing from treatment and returning to factor prophylaxis as a one-off event in the first model cycle. This was derived from marstacimab discontinuation rates during the year-

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long ATP of the BASIS trial.¹⁰⁴ In the comparisons versus haemophilia A comparators (FVIII prophylaxis and emicizumab), patients who discontinue are then assumed to experience the bleed rate and costs associated with FVIII prophylaxis, supported by clinical feedback that haemophilia A patients would most likely return to factor prophylaxis upon discontinuation.⁶⁸ In the comparison versus the haemophilia B comparator (FIX prophylaxis), discontinuing patients experience the bleed rate and costs associated with FIX prophylaxis. Clinical feedback indicated that any discontinuation from marstacimab is likely to occur early on, therefore the base case approach does not consider subsequent discontinuation from marstacimab following the first model cycle.⁶⁸ Scenario analyses exploring this assumption were conducted and are described in Section B.3.2.5.

To model discontinuation, the proportion of patients discontinuing marstacimab is redistributed between the "Bleeds" and "No Bleeds" health states to match the health state distribution in the factor prophylaxis comparator arms (FVIII and FIX prophylaxis in the haemophilia A and B comparisons, respectively). The proportion of discontinuing patients experiencing treated bleeds experience ABR_{treat} associated with the factor prophylaxis basket they discontinue on to. Clinical expert opinion received as part of this submission indicated that very few patients receiving emicizumab would be expected to discontinue treatment in clinical practice,⁶⁸ therefore no discontinuation is modelled from emicizumab in the model, with all patients receiving treatment throughout the model time horizon.

The distribution amongst health states in the model of patients receiving factor prophylaxis is assumed to remain constant over the model time horizon. This is in line with the assumption that patients receiving factor prophylaxis experience constant bleed rates throughout the model time horizon, the rationale for which is detailed further in Section B.3.2.3 below.

B.3.2.3 Annualised bleeding rates and annualised joint bleeding rates

Marstacimab and factor prophylaxis

As described in Section B.3.1.2, patients are assumed to experience an average number of treated bleeds annually within the "Bleeds" health state. Within this state, joint and non-joint bleed rates were modelled separately to inform corresponding costs and utility decrements per joint and non-joint bleed events.

Within each health state, treated bleed rates were modelled as treatment-specific. For factor prophylaxis and marstacimab, post hoc analyses of ABR_{treat} and $AJBR_{treat}$ in the BASIS ATP and OP respectively informed the rate of bleed events in the "Bleeds" health state. As presented in Section B.2.9, the post hoc analyses included all patients who received marstacimab during the ATP, i.e. including those who received dose escalation of marstacimab. Additionally, ABR_{treat} was measured amongst those who experienced at least one bleeding event (i.e. excluding those with zero treated bleeding events who enter the "No bleeds" health state at model entry, see Section B.3.1.2).

The rate of non-joint events was calculated by subtracting the post hoc analysed $AJBR_{treat}$ from ABR_{treat} . Annual joint and non-joint bleed rates were then multiplied by the respective costs and disutilities for each treated bleed event type to inform per-cycle costs and QALYs as reported in later sections of this submission. ABR_{treat} and $AJBR_{treat}$ input bleeding rates for marstacimab and the factor comparator baskets are presented in Table 53.

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Emicizumab

For modelling emicizumab, the simulated rate ratios for ABR_{treat} and $AJBR_{treat}$ derived from the STC reported in Section B.2.11 were applied to the marstacimab ABR_{treat} and $AJBR_{treat}$ (adjusted for patients experiencing no bleeds) to derive ABR_{treat} and $AJBR_{treat}$ for emicizumab. As with marstacimab and factor prophylaxis, the derived $AJBR_{treat}$ informed joint-bleed events in the model, whilst the rate of non-joint bleed was calculated by subtracting the derived $AJBR_{treat}$ from the ABR_{treat} . ABR_{treat} and $AJBR_{treat}$ input bleeding rates for emicizumab are presented in Table 53.

Table 53: Annualised bleeding rates and annualised joint bleeding rates applied within the “Bleeds” health state (adjusted for the exclusion of patients with zero bleeds)

Bleeding rates	ABR_{treat}	$AJBR_{treat}$	Non-Joint ABR_{treat}
Intervention			
Marstacimab	7.53	6.09	1.44
Comparators			
FVIII prophylaxis	13.09	9.43	3.66
FIX prophylaxis	13.09	9.43	3.66
Emicizumab	■	■	■

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; FIX: factor IX; FVIII: factor VIII.

As with the odds ratio of treated bleeds, the ratio of ABR_{treat} between marstacimab and emicizumab may be overestimated, due to differences in treatment of bleeds in the BASIS and HAVEN 3 trials informing the ITC analysis (see Section B.2.11.4). In the scenario analysis described in Section B.3.2.2, in which the odds ratio of the proportion of patients with no total (rather than treated bleeds) is used, the same approach is used to derive ABRs associated with emicizumab, using the rate ratio of total rather than treated bleeds (scenario number 12 in Table 76).

The average number of bleeds per cycle is assumed to remain constant in each treatment arm, with no natural increase in bleed likelihood. The rationale for this approach is as follows. The bleed rates of patients have historically improved, likely due to an increased uptake of prophylaxis and improvement in management generally and individualised treatment optimisation strategies, which have helped patients better manage their disease.^{47, 143, 144} Recent studies reporting longitudinal data of patients with haemophilia A suggest that bleed rates do not further improve with the current SOC prophylaxis.^{145, 146} Furthermore, a constant bleed distribution approach is consistent with previous cost-effectiveness models in haemophilia, which did not consider a change in the ABR over time for patients receiving prophylaxis.¹²⁹⁻¹³¹

B.3.2.4 Scenario efficacy analyses

As described in Sections B.2.9, B.3.2.2 and B.3.2.3, additional post hoc analyses from the BASIS trial are used to inform the efficacy of marstacimab and factor prophylaxis in the base case cost-effectiveness analyses. ABR_{treat} and $AJBR_{treat}$ reported in the BASIS ATP and OP, respectively, for patients who received routine prophylaxis during the OP, informed the rate of bleed events in the “Bleeds” health state. These were further analysed post hoc in two ways to provide the relevant inputs for the model:

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- Firstly, the ABR_{treat} and $AJBR_{treat}$ for the model included all patients who received marstacimab during the ATP, including the 11 patients who escalated their marstacimab dose.
- Additionally, ABR_{treat} and $AJBR_{treat}$ for the model were measured amongst those who experienced at least one bleeding event (i.e. excluding those with zero treated bleeding events who enter the “No bleeds” health state at model entry).

In line with the primary outcomes from the BASIS trial, these data include patients with both haemophilia A and B, providing one pooled efficacy regardless of haemophilia type. This approach is aligned with clinical feedback indicating that no differences in marstacimab treatment effect would be expected between haemophilia A and B, and that it is appropriate to assume all factor replacement products are equal in efficacy.⁶⁸

A number of scenarios were conducted to explore the uncertainty in key assumptions related to the efficacy estimates in the model. Each of these are described below, with the data informing these scenarios presented in Appendix N.

Scenario analysis excluding dose escalation

To align with the primary outcome of the BASIS trial, a scenario was conducted using post hoc efficacy data excluding those who escalated their marstacimab dose. The costs of marstacimab treatment are also updated in this scenario, with all patients receiving the 150 mg dose.

Scenario analyses by type of haemophilia

It is acknowledged that differences in point estimates of marstacimab's treatment effect relative to factor prophylaxis were seen in subgroup analyses of the BASIS trial across haemophilia A and B (see Section B.2.8 above). The results of these subgroup analyses should be interpreted with caution for the following two reasons: 1) these are informed by very small patient numbers (particularly in the haemophilia B subgroup [n=18]) and were not powered to detect statistically significant differences between marstacimab and factor prophylaxis; 2) clinical feedback received as part of this submission indicated that there was no biological reason identified which could explain the different point estimates seen in each haemophilia type subgroup, and that these could most likely be attributed to the small sample sizes at play leading to random variation in observed efficacy.⁶⁸

The overall efficacy estimates derived from the trial are considered to be most appropriate to model treatment efficacy for marstacimab, and FVIII and FIX prophylaxis. Clinical experts also agreed that using the overall clinical trial data to inform efficacy for factor prophylaxis products was appropriate for this submission.⁶⁸ Nonetheless, scenario analyses have been conducted in which these treatments' efficacy in the model is derived from the equivalent post-hoc subgroup analysis of the BASIS trial used in the base case, for the subgroups of haemophilia A and haemophilia B separately. These data are analogous to the that of overall population, and include the [REDACTED] and [REDACTED] of patients who received an escalated dose of marstacimab in the haemophilia A and B subgroups, respectively, which is also captured within the treatment costs in the model. As above, these data are based on increasingly small sample sizes, and the BASIS trial was not powered to detect differences between the two types of haemophilia. Additional scenario analyses are also presented in which dose-escalated patients are excluded from the post hoc subgroup analyses.

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Scenario analyses by EHL and SHL products

No inherent differences in treatment effectiveness may be expected between EHL and SHL factor products given their identical mechanisms of action. However, the less demanding administration schedule of EHL products has been associated with improved adherence and clinical outcomes, including ABR, when switching from SHL products.^{147, 148} To explore any uncertainty around potential differences in EHL and SHL efficacy, scenario analyses were conducted in which separate efficacy estimates were applied for EHL and SHL products in both the FVIII and FIX baskets for haemophilia A and B, respectively. Due to the small sample sizes, it was not possible to explore the subgroups of patients receiving EHL and SHL products within the subgroups of haemophilia type, and an overall efficacy of EHL and SHL products across haemophilia is used in this scenario.

B.3.2.5 Treatment discontinuation

As reported in Section B.2.12.1, 6.02% (n=5) of patients who received marstacimab during the BASIS trial ATP discontinued the weekly treatment.¹⁰⁴ To reflect the BASIS trial results, a one-off discontinuation rate of 6.02% is applied in the first model cycle for patients receiving marstacimab. No discontinuation is modelled for patients receiving emicizumab or factor prophylaxis.

Patients discontinuing marstacimab in the BASIS trial returned to the factor prophylaxis treatment they were receiving in the prior OP. This reflects expected clinical practice, as indicated by clinical feedback received. As such, all patients discontinuing marstacimab in the model base case are assumed to receive FVIII in the case of patients with haemophilia A, and FIX in the case of patients with haemophilia B, and are assumed to then remain on these treatments indefinitely. Upon discontinuation, patients are redistributed between the “Bleeds” and “No Bleeds” health state based on the starting health state distributions for factor prophylaxis (see Table 52 above).

As noted in Section B.3.2.2 above, clinicians consulted as part of this submission indicated that any discontinuation from marstacimab is likely to occur early on following treatment initiation. As such, no discontinuation from marstacimab was modelled past the first model cycle. However, in the absence of long-term data on discontinuation from marstacimab, uncertainty exists around the best approach to modelling long-term discontinuation from marstacimab. Two scenario analyses relating to the long-term rate of marstacimab discontinuation were therefore conducted, one optimistic and one conservative. In the optimistic scenario, no discontinuation is modelled at all (either in the first model cycle or subsequently), and in the conservative scenario the 6.02% rate is applied annually, rather than as a one-off event (see Section B.3.11).

B.3.2.6 Adverse events

In the base case analysis, no AEs were modelled. This is because, as reported in Section B.2.12.1, SAEs (Grade 3+) were reported in 8.4% of patients in the BASIS trial, with each SAE occurring in a single patient (1.2% of the trial population). The 5% threshold for severe AEs is commonly used for inclusion in economic models, representing AEs likely to incur meaningful decrements in utility and costs to the healthcare system.¹⁴⁹ As such, AEs reported in BASIS are unlikely to materially impact estimates of cost-effectiveness, and were therefore not included in the base case, either for the intervention or comparator.

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For completeness, a scenario analysis has been conducted in which severe treatment-related AEs reported by at least one patient in BASIS were included in the analysis. These are presented in Table 54 below. Details of the events' durations and associated utility decrements are presented in Table 57, and associated costs are presented in Table 68. One-off costs and utility decrements were applied at the start of the model. In the absence of reliable AE data and a lack of comparative follow-up and AE definitions for the factor prophylaxis comparators, no AEs were modelled for factor prophylaxis in this scenario, which represents a conservative assumption. A previous economic evaluation of emicizumab in haemophilia A by CADTH did however include a proportion of patients experiencing epistaxis,¹³⁴ based on results from the HAVEN 3 study.¹¹⁴ This was therefore included in the scenario analysis in which the impact of AEs were considered.

Table 54: Incidence of treatment-related AEs included in the economic model (scenario analysis)

Adverse Events	Marstacimab (BASIS) ¹⁰⁴	Emicizumab (HAVEN 3) ¹¹⁴
Tympanic membrane perforation	1.2%	0%
Chest pain	1.2%	0%
Peripheral swelling	1.2%	0%
Tonsillitis	1.2%	0%
Traumatic haemorrhage	1.2%	0%
Haemarthrosis	1.2%	0%
Meningioma	1.2%	0%
Haemorrhage	1.2%	0%
Epistaxis	0%	2.9%

Abbreviations: AEs: adverse events.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023.¹⁰⁴

B.3.2.7 Mortality

In the base case, transition probabilities from all health states to the 'Death' health state are informed by age- and sex-matched general population mortality statistics from the Office for National Statistics 2018–2020.¹⁵⁰ No additional haemophilia-specific mortality was modelled, in line with the etranacogene dezaparvovec NICE appraisal (ID3812).¹⁰ Due to a lack of evidence, no direct treatment effect on mortality is considered in the base case analysis.

However, some evidence suggests that people with haemophilia have a higher mortality risk than the general population.^{52, 53} A recent meta-analysis showed that people with severe haemophilia have a standardised mortality ratio (SMR) of 4.1 (95% CI: 2.5–6.7) compared with the general population. However, three of the five studies included in the meta-analysis were published between the 1980s and 1990s, and one study was published in 2006; therefore, this SMR is likely an overestimation. In the fifth included study, which used data from 2001–2018 (N=1,031), an SMR of 2.4 (95% CI: 1.8, 3.0) was reported for Dutch people with severe haemophilia compared with the general Dutch population, which is more likely reflective of current clinical practice. The primary causes of death were intracranial bleeding and malignancies.⁵² Additionally, as noted above in Section B.1.3.1.4, the UKHCDO 2023 report suggest that patients with moderate and severe haemophilia have a lower life expectancy than those with mild haemophilia.^{4, 150} Therefore, a scenario analysis was conducted where the death risk for patients in the "Bleed" health state of the model was calculated by applying a disease-specific SMR of 2.4

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relative to the general population. This was justified because intracranial bleeding is the leading cause of death among people with haemophilia, and a patient with zero bleeds can be assumed to have the same risk of intracranial bleeding as the general population.

B.3.3 Measurement and valuation of health effects

B.3.3.1 Health-related quality-of-life data from clinical trials

Health-state utility values

HRQoL outcomes were measured using EQ-5D-5L, Haem-A-QoL and HAL in the BASIS trial (Section B.2.6). For use in the model, data on the EQ-5D-5L descriptive system collected in BASIS were mapped to the 3L value set in accordance with the NICE reference-case. The mapping function used to generate utility values was based on the mapping function developed by the NICE Decision Support Unit using the ‘EEPRU’ dataset, as specified in the NICE process and methods guide (PMG36).¹²

The treatment-independent health state utility values (HSUVs) used in the economic analysis are shown in Table 55. HRQoL data from the BASIS trial showed numerical but non-significant improvement in EQ-5D-5L and ED-VAS scores in patients receiving 12 months of marstacimab during the ATP, compared to 6 months of factor prophylaxis in the OP. Additionally, there were numerical but non-significant improvements in Haem-A-QoL and Haemo-QoL values for adults and adolescents, respectively. Given that differences between PROs were not significant between marstacimab and factor prophylaxis groups, it was assumed that treatment-independent HSUVs would be used for both marstacimab and factor prophylaxis. In the absence of comparative utility evidence versus emicizumab, the same HSUV taken from the BASIS trial was applied in this comparison.

The EQ-5D-5L data reported in the BASIS trial reflected the HRQoL of patients experiencing both bleeds and no bleeds, as a single utility value. Both health states in the model are therefore associated with the same utility value, as shown in Table 55 above. Differential QoL between treatments is instead captured in the model via short-term utility decrements associated with acute treated bleeds, which occur at different rates in each treatment arm (see Table 53 above).

Table 55: Health-state utility values used in the economic analysis

State	Utility value
No Bleeds	0.73
Bleeds	
Source	BASIS EQ-5D data at ATP baseline

Abbreviations: ATP: active treatment phase.
Source: Table 14.2.2.3.11, Pfizer marstacimab Phase 3 BASIS trial CSR, 2023.¹⁰⁴

Bleed-related utility decrements

As shown in Table 55 above, no differences in HSUVs were explicitly modelled in the economic analysis. Differences in quality of life between the “Bleeds” and “No bleeds” health states were instead derived via utility decrements applied to acute joint and non-joint bleed events, which only occur in the “Bleeds” state. This approach of separating acute treated bleed events from

health state HRQoL allows for the occurrence of multiple, relatively short bleed events to be more accurately captured within the year-long cycle length.

EQ-5D patient scores were collected at pre-specified timepoints within the BASIS trial which, depending on the timing of EQ-5D measurements compared with timings of a bleed, may not have been reflective of change in QoL related to acute bleed events. It was therefore considered unfeasible to use EQ-5D data from the BASIS trial to derive utility values associated with bleeds in the model. As such, utility values for joint and non-joint events were sourced from the literature instead. The joint bleed utility decrement was based on a study by Mazza *et al.* (2016), whilst those for non-joint bleeds were sourced from Neufeld *et al.* (2012). Both utility decrements were assumed to last 4.5 days, in line with the previous CEA published by ICER,¹²⁹ and NICE's evaluations of etranacogene dezaparvovec and fidanacogene elaparvovec.^{10, 84} The disutility, duration and resulting annual decrement applied to joint and non-joint bleed events in the model are shown in Table 56 below.

Table 56: Disutility decrement associated with bleed events in the model

Clinical Events	Disutility	Source	Duration (Days)	Source	Annual utility decrement
Non-Joint Bleeds	0.16	Neufeld <i>et al.</i> (2012) ¹⁵¹	4.50	Neufeld <i>et al.</i> (2012) ¹⁵¹	0.0020
Joint Bleeds	0.28	Mazza <i>et al.</i> (2016) ²⁶			0.0034

Age-related utility decrements

The model considered additional age-related decrements as the modelled population became older over the time horizon. The decrements were derived from Health Survey for England (HSE) 2014, as recommended by the NICE DSU.¹⁵² Adjustments were calculated for each age range to reflect the impact associated with age on utility. For each given age, the same adjustment was applied to all utility inputs regardless of health states.

It should be noted that the age-related utility decrements derived from HSE 2014 begin at age 16. Given the anticipated marketing authorisation for marstacimab includes adolescents (aged 12 to 18), a scenario analysis was conducted where the starting age was set to age 12. An assumption was made that the utility decrement for those aged 16 was the same as the utility decrement for those aged 12 to 16.

Administration-related utility decrements

An important difference between marstacimab and factor prophylaxis relates to the administration of both therapies. Marstacimab is given as a flat-dose subcutaneous injection by pre-filled pen, and therefore represents a more convenient and less burdensome method of administration compared to factor prophylaxis treatments, which are administered via IV infusion. Furthermore, clinical feedback indicated that the ease of marstacimab SC administration via a flat-dosed, pre-filled pen represented an important benefit, which should be reflected in the economic modelling.¹⁰¹ Given this difference in administration, and the potential impact on patients as a result, the base case analysis considered treatment administration-related utility decrements. The decrements were derived from Johnson *et al.*, 2021, a vignette-based time

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trade-off utilities elicitation conducted in Canadian adults with haemophilia A.¹⁵³ The per-administration disutilities applied were 0.0003 for each intravenous infusion, applied to factor prophylaxis, and 0.0002 for each subcutaneous injection, applied to marstacimab and emicizumab. A scenario analysis was conducted in which administration-related utility decrements are not included in the CEA.

B.3.3.2 Mapping

Mapping was not used within this economic analysis.

B.3.3.3 Health-related quality-of-life studies

As described in Section B.3.1, an SLR was conducted in August 2020 and updated in May 2024 in order to identify clinical and economic evidence in the field of haemophilia. Simultaneous literature searches were conducted for cost-effectiveness studies (Appendix G), utility studies (Appendix H) and healthcare resource use studies (Appendix I). In total, seven articles reporting on six unique studies were included in the SLR of HRQoL studies.

B.3.3.4 Adverse reactions

As outlined in Section B.3.2.6, decrements in utility for AEs associated with treatment with marstacimab were captured in a scenario analysis via the application of disutility values and estimated AE duration. The magnitude of disutilities associated with each AE was sourced for the literature, or estimated, as shown in Table 57. All AEs were assumed to last 7 days which is in line with the durations reported in the NICE evaluations of etranacogene dezaparvovec (ID3812) and fidanacogene elaparvovec (ID4032).^{10, 84}

Table 57: AE disutilities applied in the economic model

Adverse Events	Disutility	Duration (Days)	Source
Chest Pain	0.070	7 days	Doyle et al. 2008 (pain) ¹⁵⁴
Epistaxis	0.003	7 days	Doble et al. 2018 (minor bleed) ¹⁵⁵
Haemarthrosis	0.030	7 days	Doble et al. 2018 (major bleed) ¹⁵⁵
Haemorrhage (vascular disorder)	0.030	7 days	Doble et al. 2018 (major bleed) ¹⁵⁵
Meningioma	0.100	7 days	Assumption
Peripheral Swelling	0.033	7 days	Sullivan et al. 2016 (peripheral oedema) ¹⁵⁶
Tonsillitis	0.050	7 days	Assumption
Traumatic Haemorrhage	0.030	7 days	Doble et al. 2018 (major) ¹⁵⁵
Tympanic Membrane Perforation	0.020	7 days	Ontario Health (complication during hearing impact procedure) ¹⁵⁷

Abbreviations: AE: adverse event.

B.3.3.5 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the utility values used in the model is provided in Table 58 below.

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Table 58: Summary of utility values used in the base case cost-effectiveness analysis

State	Utility value: mean	Interquartile Range	Reference in submission	Justification
Health state utilities				
No bleeds	0.73	0.61, 0.99	Section B.3.3.1	In the BASIS trial, numerical but non-significant improvements in patient QoL (including EQ-5D) were observed during the ATP where patients received marstacimab prophylaxis, compared with the OP where patients were receiving factor prophylaxis. Treatment-independent utility values have therefore been assumed.
Bleeds				
Bleed events				
Non-joint bleeds	−0.16 (0.03)	-	Section B.3.3.1	Utility decrements associated with bleed events were sourced from previous CEAs, published by ICER ¹²⁹ and in the ongoing NICE evaluation of etranacogene dezaparvovec. ¹⁰
Joint bleeds	−0.28 (0.06)	-		
AE disutilities ^a				
Chest Pain	0.070	-	Section B.3.3.4	No severe (Grade 3+) AEs were reported by more than 5% of patients in the BASIS trial, therefore no associated utility decrements were modelled in the base case. A scenario was presented in which utility decrements sourced from the literature were applied for severe treatment-related AEs reported in the BASIS trial, for a duration of seven days.
Epistaxis	0.003	-		
Haemarthrosis	0.030	-		
Haemorrhage (vascular disorder)	0.030	-		
Meningioma	0.100	-		
Peripheral Swelling	0.033	-		
Tonsillitis	0.050	-		
Traumatic Haemorrhage	0.030	-		
Tympanic Membrane Perforation	0.020	-		

^aOnly applied as part of a scenario analysis.

Abbreviations: AE: adverse event; ATP: active treatment phase; CEA: cost-effectiveness analysis; CI: confidence interval; ICER: Institute for Clinical and Economic Review; NICE: National Institute for Health and Care Excellence; OP: observational phase; QoL: quality of life.

B.3.4 Cost and healthcare resource use identification, measurement and valuation

As described in Section B.3.1, a SLR was conducted in August 2020 and updated in May 2024 in order to identify clinical and economic evidence in the field of haemophilia. Simultaneous literature searches were conducted for utility studies (Appendix H) and healthcare resource use studies (Appendix I). In total, 13 articles reporting on 10 unique healthcare resource use studies were included in the SLR.

The following cost categories were included in the model base case:

- Drug acquisition costs
- Management costs of acute bleed events (including acquisition costs for on-demand factor replacement therapy)

The economic analysis was conducted from an NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS. Cost inputs were based on British National Formulary (BNF) 2024, Monthly Index of Medical Specialities (MIMS) and National Schedule of NHS costs (2021/2022).¹³⁸⁻¹⁴⁰

B.3.4.1 Intervention and comparators' costs and resource use

Acquisition and administration costs for marstacimab

The drug acquisition costs of marstacimab, which is administered as 150 mg once weekly following a one-off 300 mg loading dose, were applied in the model as a weekly cost. 13% (n=11) of patients in the BASIS trial had their dose escalated to 300 mg weekly; these additional costs of the increased dose are also considered in the model. In the scenarios in which efficacy is modelled using haemophilia A and B subgroups from the BASIS trial, dose escalation rates specific to each subgroup were used (■ and ■ respectively). Patients receiving the escalated dose in the model are assumed to do so from the first model cycle onwards. The resulting weekly and annual treatments costs for the 300 mg loading dose and the 150 mg and 300 mg maintenance doses are presented in Table 59.

Table 59: Marstacimab drug acquisition costs

Drug	Quantity (number of pens)	Treatment dose	Price per administration	Weekly treatment cost	Annual treatment cost
Marstacimab maintenance dose, SC	1	150 mg per week	List: £■ With PAS: £■	List: £■ With PAS: £■	List: £■ With PAS: £■
	2	300 mg (2 x 150 mg) per week	List: £■ With PAS: £■	List: £■ With PAS: £■	List: £■ With PAS: £■
Marstacimab loading dose, SC	2	300 mg (2 x 150 mg dose one-off)	List: £■ With PAS: £■	-	-

Abbreviations: mg: milligram; PAS: patient access scheme; SC: subcutaneous.

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As a weekly, SC injection administered by the haemophilia patient themselves, marstacimab was modelled as not being associated with any administration costs.

Acquisition costs for factor prophylaxis

Drug acquisition costs of prophylactic factor replacement therapies were informed by the BNF and MIMS.^{138, 139} Information on dosing (IU/kg and frequency of dose) was informed by respective SmPCs (as reported in Table 60). Vial sharing was not modelled in the base case, and wastage is assumed. This is based on recommendations in respective SmPCs that factor treatments should be used within hours of reconstitution. Once the factor is drawn up into the syringe, the vial and adapter are recommended to be discarded. A scenario analysis was conducted in which vial sharing was modelled, with no wastage assumed (see Section B.3.10.3). Factor prophylaxis unit costs are presented in Table 60, and the resulting annual acquisition costs are presented in Table 61 for FVIII products and Table 62 for FIX products. Factor prophylactic treatments are administered via IV and assumed to be self-administered. It is possible that some patients may require nurse support to administer their treatment, however a conservative assumption was made that no administration costs were applied for the comparator.

Dosing regimens were sourced from each treatment's respective SmPC, as detailed in Table 48. Dose per administration was derived using the modelled patient weight () presented in Table 51. The weighted factor prophylaxis cost was calculated based on the market shares presented in Table 49 and Table 50.

Table 60: Factor prophylaxis unit costs

Treatment	Units per pack	Cost per vial	Cost per unit	Source
Haemophilia A				
Advate®	250 IU	£177.50	£0.71	BNF (2024) ¹³⁸
	500 IU	£355.00	£0.71	
	1,000 IU	£710.00	£0.71	
	2,000 IU	£1,420.00	£0.71	
ReFacto AF®	250 IU	£125.55	£0.50	
	500 IU	£251.10	£0.50	
	1,000 IU	£502.20	£0.50	
	2,000 IU	£1,004.40	£0.50	
	3,000 IU	£1,506.60	£0.50	
NovoEight®	250 IU	£138.59	£0.55	
	500 IU	£277.18	£0.55	
	1,000 IU	£554.37	£0.55	
	1,500 IU	£831.55	£0.55	
	2,000 IU	£1,108.74	£0.55	
	3,000 IU	£1,663.11	£0.55	
Nuwiq®	250 IU	£190.00	£0.76	
	500 IU	£380.00	£0.76	
	1,000 IU	£760.00	£0.76	
	1,500 IU	£1,140.00	£0.76	
	2,000 IU	£1,520.00	£0.76	

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Esperoct®	500 IU	£425.00	£0.85	
	1,000 IU	£850.00	£0.85	
	1,500 IU	£1,275.00	£0.85	
	2,000 IU	£1,700.00	£0.85	
	3,000 IU	£2,550.00	£0.85	
Elocta®	250 IU	£212.50	£0.85	
	500 IU	£425.00	£0.85	
	750 IU	£637.50	£0.85	
	1,000 IU	£850.00	£0.85	
	1,500 IU	£1,275.00	£0.85	
	2,000 IU	£1,700.00	£0.85	
	3,000 IU	£2,550.00	£0.85	
Adynovi®	250 IU	£212.50	£0.85	
	1,000 IU	£850.00	£0.85	
	2,000 IU	£1,700.00	£0.85	
Haemophilia B				
BeneFIX®	3,000 IU	£1,821.60	£0.61	BNF (2024) ¹³⁸
	2,000 IU	£1,214.40	£0.61	
	1,000 IU	£607.20	£0.61	
	500 IU	£303.60	£0.61	
	250 IU	£151.80	£0.61	
Alprolix®	3,000 IU	£3,600.00	£1.20	MIMS (2024) ¹³⁹
	2,000 IU	£2,400.00	£1.20	
	1,000 IU	£1,200.00	£1.20	
	500 IU	£600.00	£1.20	
	250 IU	£300.00	£1.20	
Idelvion®	2,000 IU	£4,180.00	£2.09	MIMS (2024) ¹³⁹
	1,000 IU	£2,090.00	£2.09	
	500 IU	£1,045.00	£2.09	
	250 IU	£522.50	£2.09	
Refixia®	2,000 IU	£4,886.00	£2.44	MIMS (2024) ¹³⁹
	1,000 IU	£2,443.00	£2.44	
	500 IU	£1,221.50	£2.44	

Abbreviations: BNF: British National Formulary; IU: international units; MIMS: Monthly Index of Medical Specialities.

Table 61: FVIII prophylaxis unit costs

Treatment	Average dose per administration (IU/kg)	Dose per administration	Acquisition cost per administration	Administration per week	Annual acquisition cost
Advate®	30.0	██████	██████	2.8	██████
ReFacto AF®	30.0	██████	██████	2.8	██████
NovoEight®	30.0	██████	██████	3.5	██████
Nuwiq®	30.0	██████	██████	2.8	██████
Esperoct®	50.0	██████	██████	1.8	██████
Elocta®	50.0	██████	██████	1.8	██████
Adynovi®	45.0	██████	██████	2.0	██████
Weighted FVIII prophylaxis					██████

Dose per administration was derived using the modelled patient weight (██████) presented in Table 51.

Abbreviations: FVIII: factor VIII; IU: international units; kg: kilogram.

Table 62: FIX prophylaxis drug acquisition costs

Treatment	Average dose per administration (IU/kg)	Dose per administration	Acquisition cost per administration	Administration per week	Annual acquisition cost
BeneFIX®	40.0	██████	██████	2	██████
Alprolix®	50.0	██████	██████	1	██████
Idelvion®	42.5	██████	██████	1	██████
Refixia®	40.0	██████	██████	1	██████
Weighted FIX prophylaxis					██████

Dose per administration was derived using the modelled patient weight (██████) presented in Table 51.

Abbreviations: FIX: factor IX; IU: international units; kg: kilogram.

Acquisition costs for emicizumab

Drug acquisition costs for emicizumab were informed by the BNF and MIMS.^{138, 139} Information on dosing (IU/kg and frequency of dose) was informed by the SmPCs (as reported in Table 48). The maintenance dose of 3.0 mg/kg every two weeks was chosen, in line with clinician feedback and with the approach taken in the NICE evaluation of efanesoctocog alfa (ID6170).⁹ Clinical expert feedback indicated that UKHCDO guidelines can be used in UK clinical practice to determine the dose of emicizumab to be administered.⁶⁸ These guidelines group weight ranges together, assigning a single fixed dose to each weight range.¹⁵⁸ As such, a scenario analysis was explored in which the dose (240 mg) corresponding to the mean weight reported in the UKHCDO analysis (██████ kg) was used.

Vial sharing was not modelled in the base case, with wastage assumed. This is based on the recommendation in the emicizumab SmPC that states the pierced vial should be used immediately.¹⁵⁹ Once the treatment is drawn up into the syringe, the vial and adapter are recommended to be discarded. A scenario analysis was conducted in which vial sharing was modelled, with no wastage assumed (see Section B.3.10.3).

Emicizumab unit costs are presented in Table 63, with the resulting annual acquisition costs presented in Table 64. Emicizumab is administered via self-administered SC injection, therefore

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while it is possible that some patients may require nurse support to administer their treatment, an assumption was made that no administration costs were applied for the comparator.

Table 63: Emicizumab unit costs

Treatment	Units per pack	Cost per vial	Cost per unit	Source
Emicizumab (Hemlibra®)	30 IU	£2,415.30	£80.51	BNF 2024 ¹⁶⁰
	60 IU	£4,830.60	£80.51	
	105 IU	£8,453.55	£80.51	
	150 IU	£12,076.50	£80.51	

Abbreviations: BNF: British National Formulary; IU: international units.

Table 64: Emicizumab drug acquisition costs

Treatment	Average dose per administration (IU/kg)	Dose per administration	Acquisition cost per administration	Administration per week	Annual acquisition cost
Emicizumab (Hemlibra®) maintenance dose	3.0	████	██████	0.5	██████
Emicizumab (Hemlibra®) loading dose	3.0	████	██████	1.0	██████

Dosing regimens were sourced from the Hemlibra® SmPC. Dose per administration was derived using the modelled patient weight (████) presented in Table 51.

Abbreviations: FIX: factor IX.

Source: Hemlibra® SmPC.¹⁵⁹

B.3.4.2 Health-state unit costs and resource use

Management of acute bleed events

Disease management costs were assumed to be entirely related to the management of acute bleed events. The health care interaction costs associated with managing acute bleeds in the model is shown in Table 65. The treatment acquisition costs for the use of on-demand factor prophylaxis therapy was calculated as a weighted average of the distribution of prophylactic factor replacement therapies, as reported in Table 66 and Table 67.

UK clinical expert feedback indicated that acute bleeds are treated with one additional dose of factor prophylaxis. Feedback also indicated that joint and non-joint bleeds are typically treated in a similar manner, with the same doses of factor treatment.⁶⁸ As such, the base case assumes that joint and non-joint bleeds are associated with the same management costs, with patients receiving one additional dose of factor prophylaxis per acute bleed.

However, some publications provide different estimates of factor prophylaxis doses to be used to treat joint and non-joint bleeds, and previous submissions to NICE have assumed that joint bleeds are associated with higher management costs.¹⁰ Additionally, as part of consultations with clinical experts for this appraisal, one advisor stated that they might recommend for a patient to take a second dose for a joint bleed.⁶⁸ As such, a scenario analysis was conducted in which joint

bleeds were assumed to be associated with a higher dose of additional factor prophylaxis, equivalent to double the doses of FVIII and FIX prophylaxis (see Table 66 and Table 67).

Table 65: Costs associated with the management of acute bleed events

Average Annual Costs (by Category)	Unit Cost	Resource Use per Bleed	Total Cost	Source
Haematologist Visit	£209.41	0.97	£203.13	Cost: NHS reference costs 21/22, currency code WF01A, Consultant Led Clinical Haematology Service, Non-Admitted Face-to-Face Attendance, Follow-up Resource use: O'Hara <i>et al.</i> (2018)¹⁶¹
Orthopaedist Visit	£132.88	0.97	£128.90	Cost: NHS reference costs 21/22, currency code WF01A, Consultant Led Clinical Haematology Service, Non-Admitted Face-to-Face Attendance, Follow-up Resource use: O'Hara <i>et al.</i> (2018)¹⁶¹
A&E Visit	£309.86	0.18	£55.78	Cost: NHS reference costs 21/22, Emergency Medicine, weighted average of VB01Z:VB09Z Resource use: O'Hara <i>et al.</i> (2018)¹⁶¹
Inpatient Hospital Stay	£542.77	0.29	£157.40	Cost: NHS reference costs 21/22, weighted average of SA08G:SA08J Resource use: O'Hara <i>et al.</i> (2018)¹⁶¹
Total			£545.21	

Abbreviations: A&E: accident and emergency; NHS: National Health Service.

Table 66: FVIII prophylaxis costs to treat acute bleed events

Distribution of FVIII Products to Treat Bleeds	Average Dose (IU/kg) per Bleed Event		
	Non-Joint Bleeds	Joint Bleeds (base case)	Joint Bleeds (scenario)
Advate®	30.0		60.0
ReFacto AF®	30.0		60.0
NovoEight®	30.0		60.0
Nuwiq®	30.0		60.0
Esperoct®	50.0		100.0
Elocta®	50.0		100.0
Adynovi®	45.0		90.0
Weighted Dose per Bleed Event	41.9		83.8
Weighted Cost per Bleed Event	[REDACTED]		[REDACTED]

Abbreviations: FVIII: factor VIII; IU: international unit; kg: kilogram.

Table 67: FIX prophylaxis costs to treat acute bleed events

Distribution of FIX Products to Treat Bleeds	Average Dose (IU/kg) per Bleed Event		
	Non-Joint Bleeds	Joint Bleeds (base case)	Joint Bleeds (scenario)
BeneFIX®	40.0		80.0
Alprolix®	50.0		100.0
Idelvion®	42.5		85.0
Refixia®	40.0		80.0
Weighted Dose per Bleed Event	45.8		91.5
Weighted Cost per Bleed Event	[REDACTED]		[REDACTED]

Abbreviations: FIX: factor IX; IU: international unit; kg: kilogram.

B.3.4.3 Adverse reaction unit costs and resource use

As noted in Section B.3.2.6 above, no AEs were included in the base case analysis, however a scenario analysis including AEs for marstacimab was explored. Unit costs associated with AEs included in the scenario analysis are presented in Table 68. The same unit cost was assumed for all AEs included in the scenario analysis, based on nurse attendance.

Table 68: AE unit costs included in the economic model

Adverse Events	Unit cost	Source/assumption
Chest Pain	£53.74	Community Health Services, District Nurse, Adult, Face-to-face (Currency code N02AF); National Schedule for NHS 2021/2022 ¹⁶²
Epistaxis		
Haemarthrosis		
Haemorrhage (vascular disorder)		
Meningioma		
Peripheral Swelling		
Tonsillitis		
Traumatic Haemorrhage		
Tympanic Membrane Perforation		

Abbreviations: AE: adverse event; NHS: National Health Service.

B.3.4.4 Miscellaneous unit costs and resource use

No additional costs were considered in the base case of the economic model. Haemophilia patients are likely to incur costs for ongoing standard disease management which may include orthopaedist visits, physiotherapist appointments, and standard laboratory tests. However, these costs are assumed to be incurred by all haemophilia patients, regardless of treatment. As a result, these costs are not expected to substantially impact the estimate of marstacimab's cost-effectiveness, and were therefore not included in the model. Additionally, previous research has revealed that factor treatment acquisition costs comprise almost all (99%) of total annual haemophilia-related direct medical costs in haemophilia patients.^{45, 58} Therefore, it was considered appropriate to not include other miscellaneous costs for the factor prophylaxis treatment arm, though this can be considered a conservative approach.

A scenario analysis was carried out, in which direct (such as transportation) and indirect (such as lost productivity) non-medical costs for patients were included in the economic analysis. Indirect costs were assumed to be £3,290.09 for all haemophilia A and B patients with and without bleeds. This cost was sourced from Burke et al. 2021,⁵⁸ which reported the mean annual indirect cost for patients with haemophilia B in the UK. Since costs were reported in Euros, a conversion of 1 Euro = 0.88 GBP was assumed. The cost was also inflated to 2022 GBP, with the resulting costs shown in Table 69 below.

Table 69: Indirect non-medical costs of disease

Annual Indirect Cost	No Bleeds	Bleeds
Factor prophylaxis	£3,290.09	
Emicizumab	£3,290.09	
Marstacimab	£3,290.09	

Like indirect costs, direct non-medical costs were modelled as an aggregated annual cost, stratified by with and without bleeds and type of therapy (factor prophylaxis, emicizumab or marstacimab), sourced from Chowdary *et al.* (2022).⁵⁹ In the Chowdary study, direct non-medical costs are reported stratified by severity (moderate, severe) and if patients have 0, 1, or greater than or equal to 2 problem joints. First, it was assumed that all patients in the model have 1

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problem joint, and it was assumed that patients with no bleeds are considered to be equivalent to “moderate” haemophilia. A conversion of 1 Euro = 0.88 GBP was assumed. Direct medical costs modelled in this scenario are presented in Table 70 below.

Table 70: Direct Non-medical Costs – Annual Aggregate

	Without Bleeds	With Bleeds
Factor prophylaxis	£874.72	£1,497.76
Emicizumab	£874.72	£1,497.76
Marstacimab	£874.72	£1,497.76

B.3.5 Severity

The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by McNamara *et al.* (2023).¹⁶³ The total life expectancy for the modelled population was calculated using population mortality data from the Office for National Statistics for 2018–2020.¹⁵⁰ The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava *et al.* (2022) through the NICE DSU.¹⁵²

The total discounted QALYs for the current population of patients with severe haemophilia receiving existing treatments were calculated from the economic model (Table 71). The absolute QALY shortfall and proportional QALY shortfall compared to the population receiving treatment with existing treatments (baseline characteristics reported in Section B.3.2.1) were below the threshold, therefore, no severity weights were used in the present analysis. All patients in the model were assumed to be male; the mean starting age of patients, contributing to the QALY shortfall analysis, can be found in Table 51.

Table 71: Summary of QALY shortfall analysis

Treatment	Expected total discounted QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment	Absolute Shortfall (AS)	Proportional Shortfall (PS)	Severity modifier vs comparator
FVIII Basket	19.36	■	■	■	1.00
Emicizumab		■	■	■	1.00
FIX Basket		■	■	■	1.00

Abbreviations: AS: absolute shortfall; FIX: factor IX; FVIII: factor VIII; PS: proportional shortfall; QALY: quality-adjusted life year.

B.3.6 Uncertainty

Given that severe haemophilia A and B are rare diseases, the number of patients able to be recruited for a clinical trial is low. The BASIS trial investigating marstacimab recruited 91 patients who received factor prophylaxis during the OP, with 83 progressing to the ATP. This small population size meant that the trial was not powered to detect differences in subgroups. Only 18 patients with haemophilia B and receiving prior factor prophylaxis participated in the ATP of the trial. Haemophilia A and B are largely indistinguishable with regards to clinical outcomes, and clinical expert feedback has indicated that no differences in marstacimab treatment effect would

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be expected between haemophilia A and B.^{2, 68} As such, the model base case used a single efficacy value for marstacimab across both haemophilia A and B, in line with the efficacy data from the BASIS trial. To explore uncertainty around this assumption, marstacimab was also compared to factor prophylaxis for haemophilia A and B in scenario analyses which utilised specific subgroup post hoc efficacy data, however the efficacy data informing this were not powered for significance.

Another source of uncertainty was the lack of data available to inform the long-term impact on joint health for patients with haemophilia. Joint health is an important factor for patients with haemophilia and can have a significant impact on their quality of life, as explained in Section B.1.3.1.5. However, data evaluating the long-term impact of marstacimab on joint damage is lacking. Therefore, improvements in joint health and reductions in joint pain following treatment with marstacimab, compared with factor prophylaxis, seen in the BASIS trial ATP and OLE may therefore not be fully captured in the model. As a result, the model likely underestimates the potential health and cost benefits that marstacimab may offer through reduction of long-term joint damage as a result of the observed improvements in joint bleed rates and joint health.

B.3.7 Managed access proposal

No managed access proposal is planned for marstacimab.

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

B.3.8.1 Summary of base-case analysis inputs

A summary of inputs utilised in the deterministic sensitivity analyses (DSA) or Probabilistic sensitivity analysis (PSA) for the base case analysis is presented in Table 72.

Table 72: Summary of variables applied in the economic model

Variable	Value	DSA Input measurement of uncertainty (lower bound) ^a	DSA Input measurement of uncertainty (higher bound) ^a	PSA Input measurement of uncertainty: distribution (SE)	Reference to section in submission
Baseline Age of Patients	██████	██████	██████	██████████	Section B.3.2.1
Baseline Weight of Patients	██████	██████	██████	██████████	
Odds Ratio, Zero Bleed Events - Hemlibra	██	██	██	██████████	Section B.3.2.2 and B.3.2.3
Rate Ratio, ABR Treat - Hemlibra	██	██	██	██████████	
Rate Ratio, ABR Joint - Hemlibra	██	██	██	██████████	
Marstacimab - % in 'No Bleeds' State	37.35%	32.04%	42.66%	Beta (2.71%)	
BeneFix - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Alprolix - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Idelvion - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	

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Refixia - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Advate - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Refacto AF - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
NovoEight - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Nuwiq - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Esperoct - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Elocta - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Adynovi - % in 'No Bleeds' State	39.76%	34.39%	45.13%	Beta (2.74%)	
Marstacimab - Joint Bleed Rate	6.09	2.00	6.49	Lognormal (3.33)	
BeneFix - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Alprolix - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Idelvion - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Refixia - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Advate - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Refacto AF - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
NovoEight - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Nuwiq - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Esperoct - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Elocta - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
Adynovi - Joint Bleed Rate	9.43	1.96	9.43	Lognormal (5.53)	
One-off marstacimab discontinuation (onto FIX prophylaxis)	6.02%	3.41%	8.64%	Beta (1.33%)	Section B.3.2.5
One-off marstacimab discontinuation (onto FVIII prophylaxis)	6.02%	3.41%	8.64%	Beta (1.33%)	
% Receiving Higher Marstacimab Dose after 6 Months	13.25%	10.60%	15.90%	Beta (2.65%)	Section B.3.4.1
Average Dose - Non-Joint Bleeds - BeneFIX	40.00 IU	Not varied		Gamma (8.00 IU)	Section B.3.4.1
Average Dose - Joint Bleeds - BeneFIX	40.00 IU	Not varied		Gamma (8.00 IU)	

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Average Dose - Non-Joint Bleeds - Alprolix	50.00 IU	Not varied		Gamma (10.00 IU)	
Average Dose - Non-Joint Bleeds - Idelvion	42.50 IU	Not varied		Gamma (8.50 IU)	
Average Dose - Non-Joint Bleeds - Refixia	40.00 IU	Not varied		Gamma (8.00 IU)	
Average Dose - Joint Bleeds - Alprolix	50.00 IU	Not varied		Gamma (10.00 IU)	
Average Dose - Joint Bleeds - Idelvion	42.50 IU	Not varied		Gamma (8.50 IU)	
Average Dose - Joint Bleeds - Refixia	40.00 IU	Not varied		Gamma (8.00 IU)	
Average Dose - Joint Bleeds - Advate	30.00 IU	Not varied		Gamma (6.00 IU)	
Average Dose - Joint Bleeds - Refacto AF	30.00 IU	Not varied		Gamma (6.00 IU)	
Average Dose - Joint Bleeds - NovoEight	30.00 IU	Not varied		Gamma (6.00 IU)	
Average Dose - Joint Bleeds - Nuwiq	30.00 IU	Not varied		Gamma (6.00 IU)	
Average Dose - Joint Bleeds - Esperoct	50.00 IU	Not varied		Gamma (10.00 IU)	
Average Dose - Joint Bleeds - Elocta	50.00 IU	Not varied		Gamma (10.00 IU)	
Average Dose - Joint Bleeds - Adynovi	45.00 IU	Not varied		Gamma (9.00 IU)	
Average Dose - Non-Joint Bleeds - Advate	30.00 IU	Not varied		Gamma (6.00 IU)	
Average Dose - Non-Joint Bleeds - Refacto AF	30.00 IU	Not varied		Gamma (6.00 IU)	
Average Dose - Non-Joint Bleeds - NovoEight	30.00 IU	Not varied		Gamma (6.00 IU)	
Average Dose - Non-Joint Bleeds – Nuwiq)	30.00 IU	Not varied		Gamma (6.00 IU)	
Average Dose - Non-Joint Bleeds - Esperoct	50.00 IU	Not varied		Gamma (10.00 IU)	
Average Dose - Non-Joint Bleeds - Elocta	50.00 IU	Not varied		Gamma (10.00 IU)	
Average Dose - Non-Joint Bleeds - Adynovi	45.00 IU	Not varied		Gamma (9.00 IU)	
Haematologist Visit RU Cost	£203.13	£162.50	£243.75	Not varied	Section B.3.4.2
Orthopaedist Visit RU Cost	£128.90	£103.12	£154.68	Not varied	
A&E Visit RU Cost	£55.78	£44.62	£ 66.93	Not varied	
Inpatient Hospital Stay RU Cost	£157.40	£125.92	£188.89	Not varied	
Baseline Utility	0.7256	0.6100	0.9867	Beta(0.026)	Section B.3.3.5
Utility Decrement - Non-Joint Bleeds	0.16	0.13	0.19	Beta(0.03)	
Utility Decrement - Joint Bleeds	0.28	0.22	0.34	Beta(0.06)	

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Utility Decrement Duration - Non- Joint Bleeds	4.5 days	3.6 days	5.4 days	Gamma(0.9 days)	
Utility Decrement Duration - Joint Bleeds	4.5 days	3.6 days	5.4 days	Gamma(0.9 days)	
Utility Decrement - IV Administration	0.0003	0.0002	0.0004	Beta(0.00006)	
Utility Decrement - SC Administration	0.0002	0.00016	0.00024	Beta(0.00004)	

*±20% used in cases where no CI were available.

Abbreviations: ABR: annualised bleed rate; AE: adverse events; CI: confidence interval; DSA: deterministic sensitivity analysis; PSA: probabilistic sensitivity analysis; RU: resource use; SE: standard error; SMR: standardised mortality ratio; Tx: treatment.

B.3.8.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 73.

Table 73: Modelling assumptions

Assumption	Justification	Addressed in scenario analysis
The comparators in this analysis are modelled as a basket of individual FVIII prophylaxis treatments and an individual comparison with emicizumab in patients with haemophilia A. For haemophilia B patients, a basket of individual FIX prophylaxis treatments forms the comparator.	FVIII therapy and emicizumab form the two prophylaxis options for patients with haemophilia A, while FIX prophylaxis represents the mainstay of current treatment for haemophilia B, in the UK. In line with the committee's request in the ongoing evaluation of etranacogene dezaparvovec, ¹⁰ a basket comparator of the most widely used factor treatments, separately for haemophilia A and B has been modelled. Additionally, a comparison with emicizumab, which makes up over 50% of the market share in haemophilia A, was also performed to best enable the committee in evaluating the cost-effectiveness of marstacimab in UK clinical practice.	Fully incremental and pairwise comparisons to individual treatments included in the comparator baskets have been presented in Appendix O.
The makeup of the comparator baskets is derived from real-world sales data.	Clinical expert feedback received as part of this submission suggested that the treatments included in the comparator baskets were an accurate representation of current treatment for haemophilia in the UK. ⁶⁸ Use of real-world sales data provides the most accurate representation of treatment usage in NHS clinical practice.	A scenario analysis has been carried out in which the proportions of each treatment making up the comparator baskets are informed by real-world usage data derived from the UKHCDO 2023 report. ⁴
Efficacy data for marstacimab and the two separate basket comparators of FVIII and FIX are informed by	FVIII prophylaxis is a treatment option for haemophilia A patients only, and similarly FIX prophylaxis for haemophilia B patients only. However, the BASIS trial was not	Scenario analyses have been presented in which efficacy data for marstacimab and each factor basket are informed by haemophilia A

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Assumption	Justification	Addressed in scenario analysis
BASIS trial data including patients with haemophilia A and haemophilia B.	powered to detect differences in treated bleed rates between marstacimab and factor prophylaxis in each population. It was therefore considered more appropriate to use the same overall population efficacy data from the trial for both FVIII and FIX basket comparators. This assumes that the overall data for factor prophylaxis are generalisable to FVIII and FIX efficacy. The same approach was taken for marstacimab to use one overall set of haemophilia efficacy data across both haemophilia A and B comparisons. ⁶⁸	and haemophilia B subgroup analyses from the BASIS trial.
For emicizumab, comparator efficacy data are informed by an indirect treatment comparison.	In the absence of direct comparative trial data, efficacy data for emicizumab are derived from STC analyses, in which IPD from the BASIS trial were matched to cohort-level data from the HAVEN 3 trial. The resulting odds ratios ABR_{treat} , $AJBR_{treat}$ and odds of experiencing no treated bleeds were applied to marstacimab outcomes to derive emicizumab's relative treatment effect in the model. This assumes that all confounding variables are accounted for in the STC analysis, and that the relative treatment effect is generalisable to the unadjusted BASIS trial population informing the model.	NA
HSUVs are assumed to be the same between intervention and comparators.	While some numerical improvements in patient QoL were seen following injection with marstacimab in the BASIS trial ATP, compared with when receiving factor prophylaxis only in the OP, differences were not statistically significant. Therefore, the HSUVs derived from ATP baseline were conservatively assumed to reflect the QoL in both patient groups.	NA
HSUV are assumed to be the same between "Bleeds" and "No bleeds" health states. Utility decrements are applied to acute joint and non-joint bleeds per bleeding event	The approach of separating acute treated bleed events from health state HRQoL allows for the occurrence of multiple, relatively short bleed events to be more accurately captured within the year-long cycle length.	A scenario analysis has been carried out which assumes non-joint bleeds and joint bleeds have the same disutility per bleed event (-0.28 over 4.5 days).
Administration-related utility decrements are applied with differing	An important difference between marstacimab and factor prophylaxis relates to the administration of both	A scenario analysis has been carried out in which

Assumption	Justification	Addressed in scenario analysis
values for SC and IV administration	therapies. Marstacimab is given as a flat-dose SC injection by pre-filled pen, and therefore represents a more convenient and less burdensome method of administration compared to factor prophylaxis treatments, which are administered via IV infusion. Additionally, clinical feedback indicated that the ease of marstacimab administration represented an important benefit, which should be reflected in the economic modelling. ¹⁰¹	administration-related disutilities are excluded.
No waning effect of treatment efficacy was modelled.	Waning of treatment effect has not been included in the model. Given the mechanism of action of marstacimab as a TFPI, and its weekly dosing regimen, a waning of treatment effect is not expected, which was confirmed by clinicians consulted as part of this submission. ⁶⁸	NA
Haemophilia A patients who discontinue from marstacimab are assumed to return to FVIII prophylaxis, as per current UK market share. Haemophilia B patients who discontinue from marstacimab are assumed to return to FIX prophylaxis as per current UK market share.	Results from the BASIS trial indicate that 6% of patients receiving marstacimab prophylaxis discontinued over the 12 month ATP. Patients in the BASIS trial discontinuing marstacimab treatment returned to the factor prophylaxis they were originally receiving in the OP. To reflect this, in the model patients were assumed to discontinue onto treatments reflective of current UK clinical practice for haemophilia.	NA
Patients discontinuing marstacimab are assumed to do so in the first year of treatment only. No subsequent discontinuation is modelled.	Only 12-month discontinuation data are available from the BASIS trial ATP, showing 6% of patients discontinued treatment with marstacimab. Clinicians consulted as part of this submission indicated that any discontinuation from marstacimab is likely to occur early on. ⁶⁸ As such, the base case analysis assumes no discontinuation from marstacimab past the first model cycle.	The long-term discontinuation rate of marstacimab is uncertain. As such, two scenario analyses were explored. One applies the one-year rate reported in the BASIS trial annually for the whole model horizon. The other assumes no discontinuation from marstacimab at all.
No disease-specific mortality is modelled.	The impact of haemophilia on mortality has not been established, therefore no additional mortality beyond general population mortality has been modelled in the base case analysis.	Given some evidence exists suggesting patients with severe haemophilia have shorter life expectancy than patients with mild haemophilia (see Section B.3.2.7), a scenario analysis was

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Assumption	Justification	Addressed in scenario analysis
		conducted accounting for additional mortality. In this scenario, a disease-specific SMR of 2.4 was applied to all patients in the "Bleeds" health state.
Modelling of AEs is not included in the base case.	No single severe AEs (i.e. AEs likely to materially impact estimates of cost-effectiveness) were reported by more than 5% of patients in the BASIS trial, as such it was deemed appropriate to exclude these from the base case analysis (see Section B.3.2.6).	A scenario analysis included costs and disutilities associated with severe treatment-related AEs reported by at least one patient in BASIS.

Abbreviations: AE: adverse event; ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; FIX: factor IX; FVIII: factor VIII HSUVs: health state utility values; OP: observational phase; QoL: quality of life; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation; SMR: standardised mortality ratio; STC: simulated treatment comparison; TFPI: tissue factor pathway inhibitor.

B.3.9 Base-case results

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

Table 74 presents the *deterministic* base case results of the economic evaluation of marstacimab versus FVIII prophylaxis, emicizumab and FIX prophylaxis. These show marstacimab to be a cost-effective alternative to all three comparator therapies, with net health benefit (NHBs) of █████, █████ and █████ versus FVIII prophylaxis, emicizumab, and FIX prophylaxis, respectively, at a willingness-to-pay (WTP) threshold of £30,000. In the comparison versus FVIII and FIX prophylaxis (in patients with haemophilia A and B, respectively), marstacimab was dominant, being associated with both lower costs and greater health benefits (i.e., higher total QALYs). In the comparison versus emicizumab, marstacimab resulted in fewer overall QALYs, however resulted in cost savings large enough to be considered cost-effective at a WTP threshold of £30,000 saved per QALY forgone.

Table 75 presents the *probabilistic* base case results of the economic evaluation of marstacimab versus FVIII prophylaxis, emicizumab and FIX prophylaxis. These show concordant results to the deterministic results, with all NHB results within 1% of the deterministic model results, indicating that cost-effectiveness results are largely insensitive to joint parameter uncertainty.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J. Fully incremental and pairwise comparisons to individual treatments included in the comparator baskets have been presented in Appendix O.

Table 74: Deterministic base-case results for marstacimab versus comparators (with PAS)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Marstacimab versus haemophilia A comparators									
Marstacimab	██████	21.52	██████	-	-	-	-	-	-
FVIII prophylaxis	██████	21.52	██████	██████	-	██████	Marstacimab is dominant	██████	██████
Emicizumab	██████	21.52	██████	██████	-	██████	£23,107,095 ^a	██████	██████
Marstacimab versus haemophilia B comparator									
Marstacimab	██████	21.52	██████	-	-	-	-	-	-
FIX prophylaxis	██████	21.52	██████	██████	-	██████	Marstacimab is dominant	██████	██████

^aICER in the south west (SW) quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: FIX: Factor IX; FVIII: factor VIII; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; SW: south west; QALYs: quality-adjusted life years.

Table 75: Probabilistic base-case results for marstacimab versus comparators (with PAS)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Marstacimab versus haemophilia A comparators									
Marstacimab	██████	21.63	████	-	-	-	-	-	-
FVIII prophylaxis	██████	21.63	████	██████	-	████	Marstacimab is dominant	████	████
Emicizumab	██████	21.63	████	██████	-	████	£24,196,182	████	████
Marstacimab versus haemophilia B comparator									
Marstacimab	██████	21.64	████						
FIX prophylaxis	██████	21.64	████	██████	-	████	Marstacimab is dominant	████	████

^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: FIX: Factor IX; FVIII: factor VIII; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; SW: south west; QALYs: quality-adjusted life years.

B.3.10 Exploring uncertainty

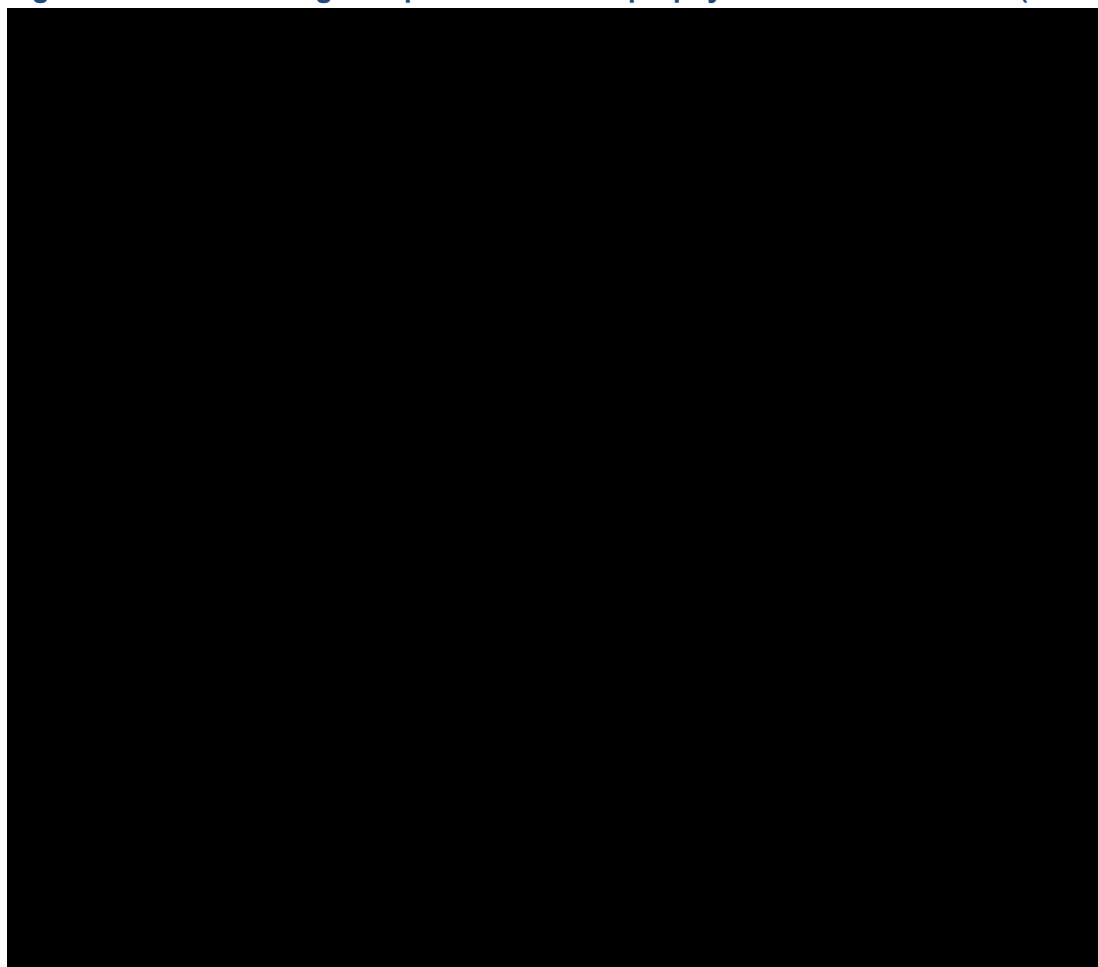
Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses the results of which are presented in Sections B.3.10.1 and B.3.10.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.3.10.3. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.10.1 Probabilistic sensitivity analysis

A PSA was conducted in order to assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. A Monte-Carlo simulation with 1,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions. The values of the inputs were determined by random variation with statistical distributions as outlined in Table 72.

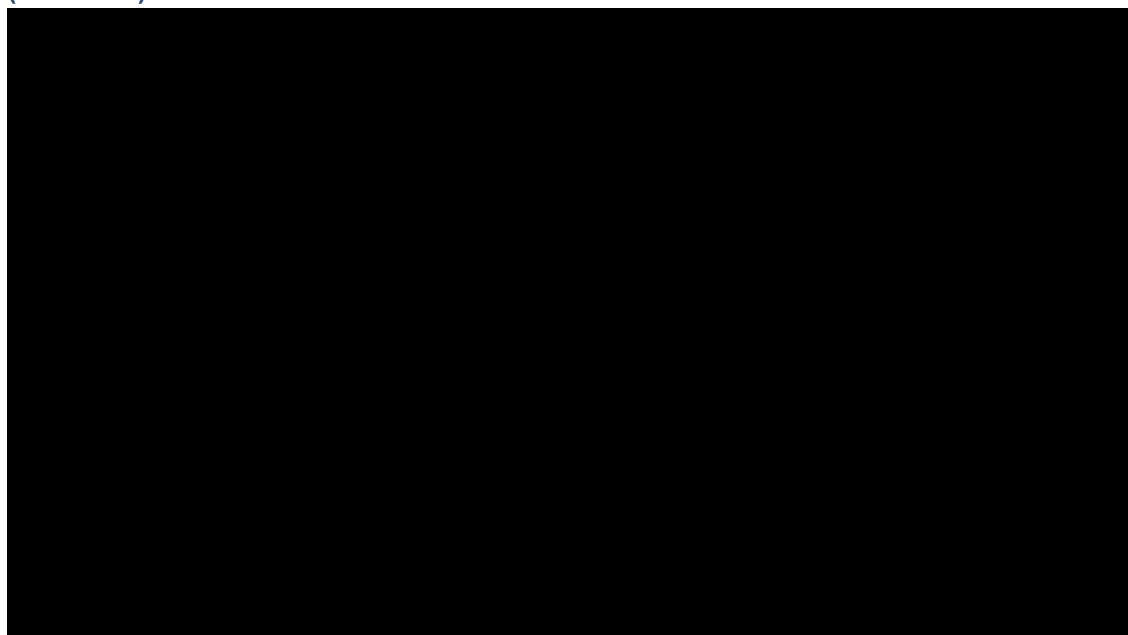
An ICER convergence plot and probabilistic cost-effectiveness place versus FVIII prophylaxis and emicizumab (haemophilia A) are shown in Figure 12 and Figure 13. An ICER convergence plot and probabilistic cost-effectiveness place versus FIX prophylaxis (haemophilia B) are shown in Figure 14 and Figure 15.

Figure 12: ICER convergence plot versus FVIII prophylaxis and emicizumab (with PAS)



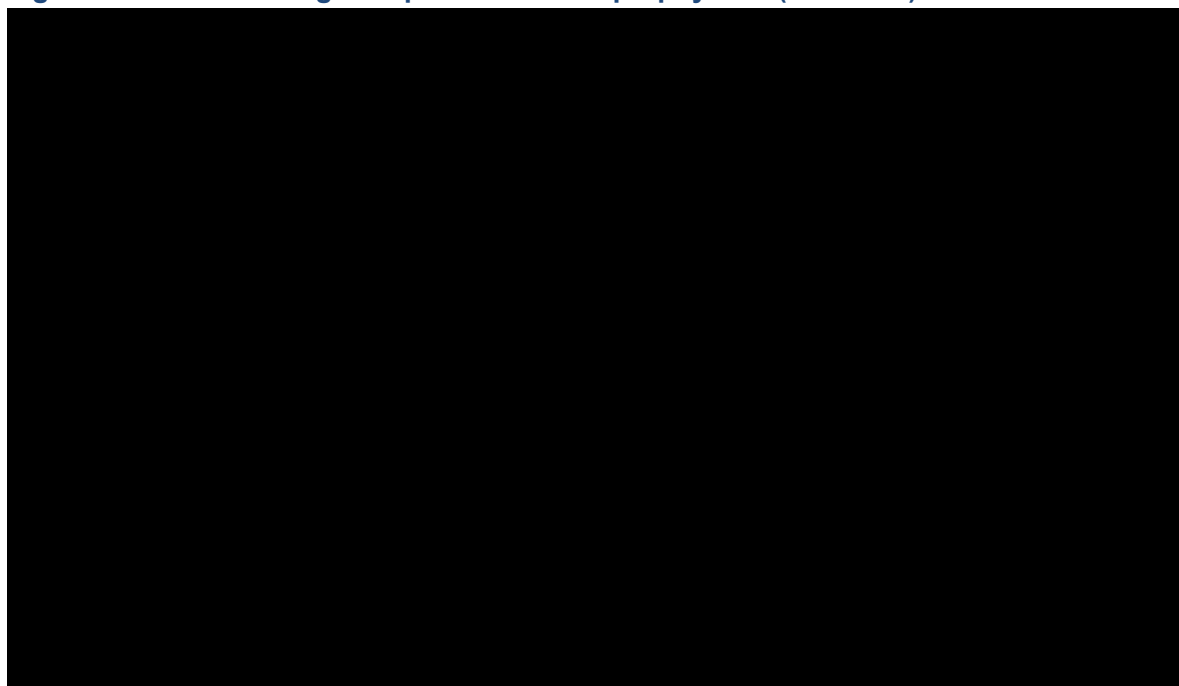
Abbreviations: FVIII: factor VIII; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme.

Figure 13: Probabilistic cost-effectiveness plane versus FVIII prophylaxis and emicizumab (with PAS)



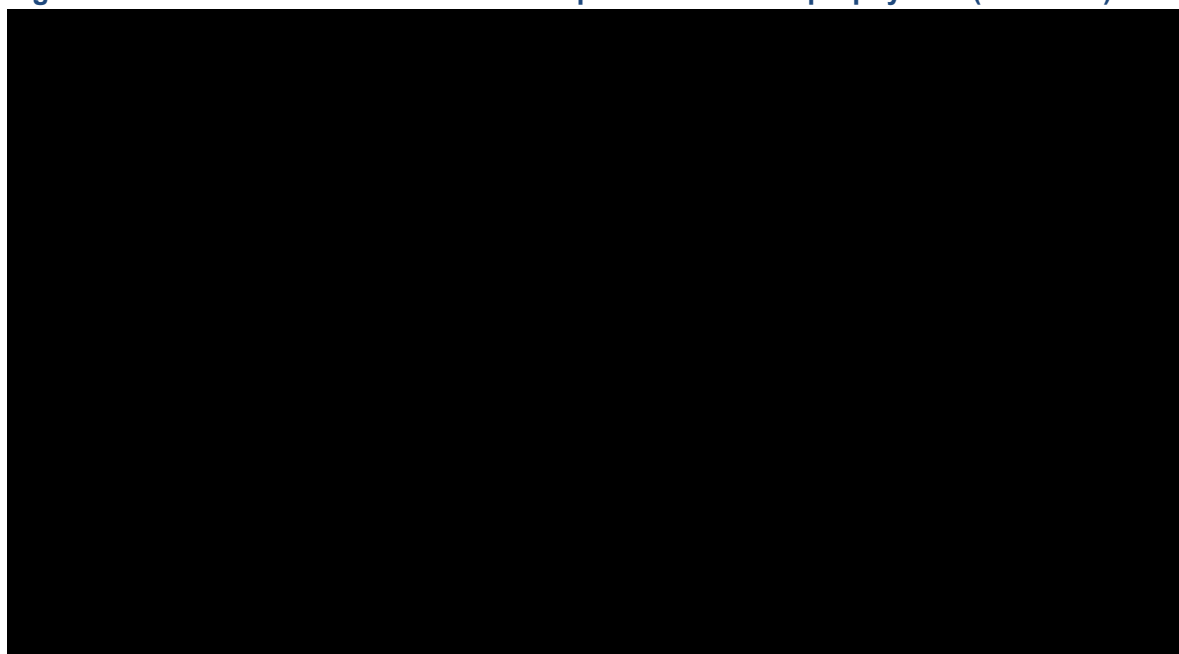
Abbreviations: FVIII: factor VIII; PAS: patient access scheme; QALYs: quality-adjusted life years.

Figure 14: ICER convergence plot versus FIX prophylaxis (with PAS)



Abbreviations: FIX: factor IX; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme.

Figure 15: Probabilistic cost-effectiveness plane versus FIX prophylaxis (with PAS)



Abbreviations: FIX: factor IX; PAS: patient access scheme; QALYs: quality-adjusted life years.

B.3.10.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, DSA were conducted, in which individual inputs (Table 72, Section B.3.8.1) were varied whilst keeping all other model inputs constant. The impact of varying individual inputs on the NHB associated with marstacimab compared to FVIII prophylaxis, emicizumab, and FIX prophylaxis is shown in the form of tornado diagrams in Figure 16, Figure 17, and Figure 18, respectively.

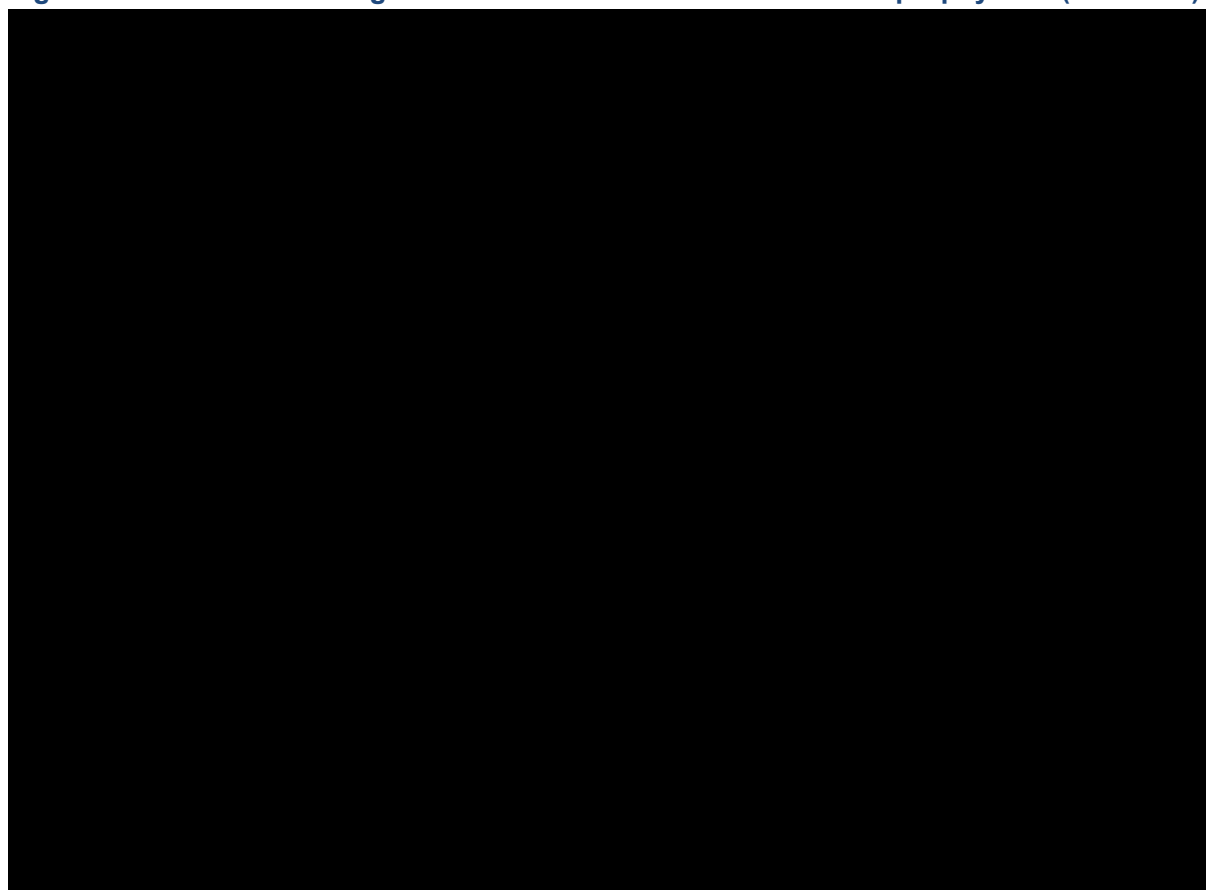
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In all comparisons, the input with the greatest impact on cost-effectiveness estimates was the starting weight of patients in the model, with a higher weight resulting in greater NHB associated with marstacimab. This can be rationalised by the fact that marstacimab is administered as a flat dose, whilst all comparator treatment doses are based on patient weight, with a higher weight requiring higher doses, and therefore incurring greater costs in the model.

The other model input with an appreciable impact on cost-effectiveness estimates is patient starting age, which is to be expected given the relatively young starting age, the lifetime model horizon, and the lifetime costs incurred by patients in all treatment arms.

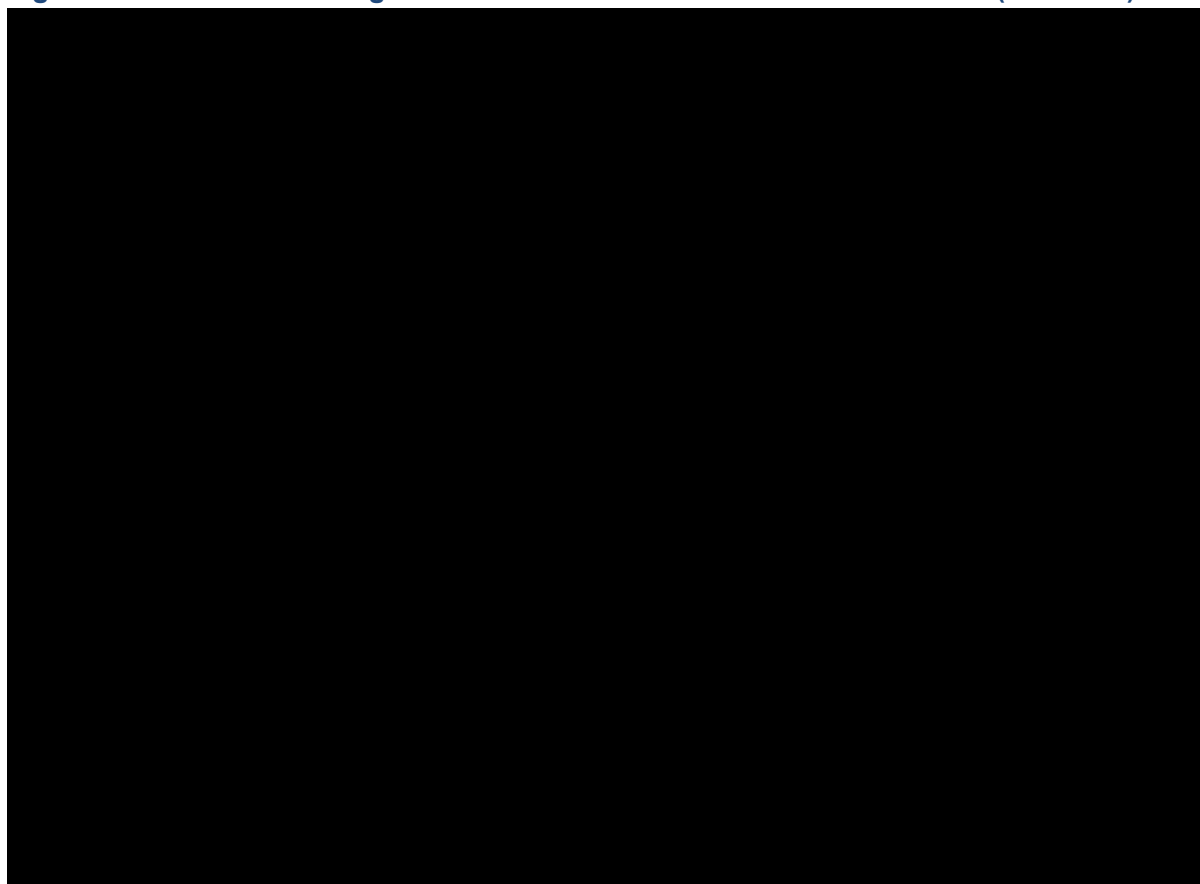
With the exception of patients' starting weight and age, no variation of individual inputs had any substantial impact on cost-effectiveness estimates, showing the model to be largely robust to individual parameter uncertainty. It should be further noted that, whilst weight and age have large impacts on numerical model results, the conclusions of marstacimab's cost-effectiveness against each comparator remain unchanged, with input variation still resulting in large NHB across all comparisons.

Figure 16: DSA tornado diagram for net health benefit versus FVIII prophylaxis (with PAS)



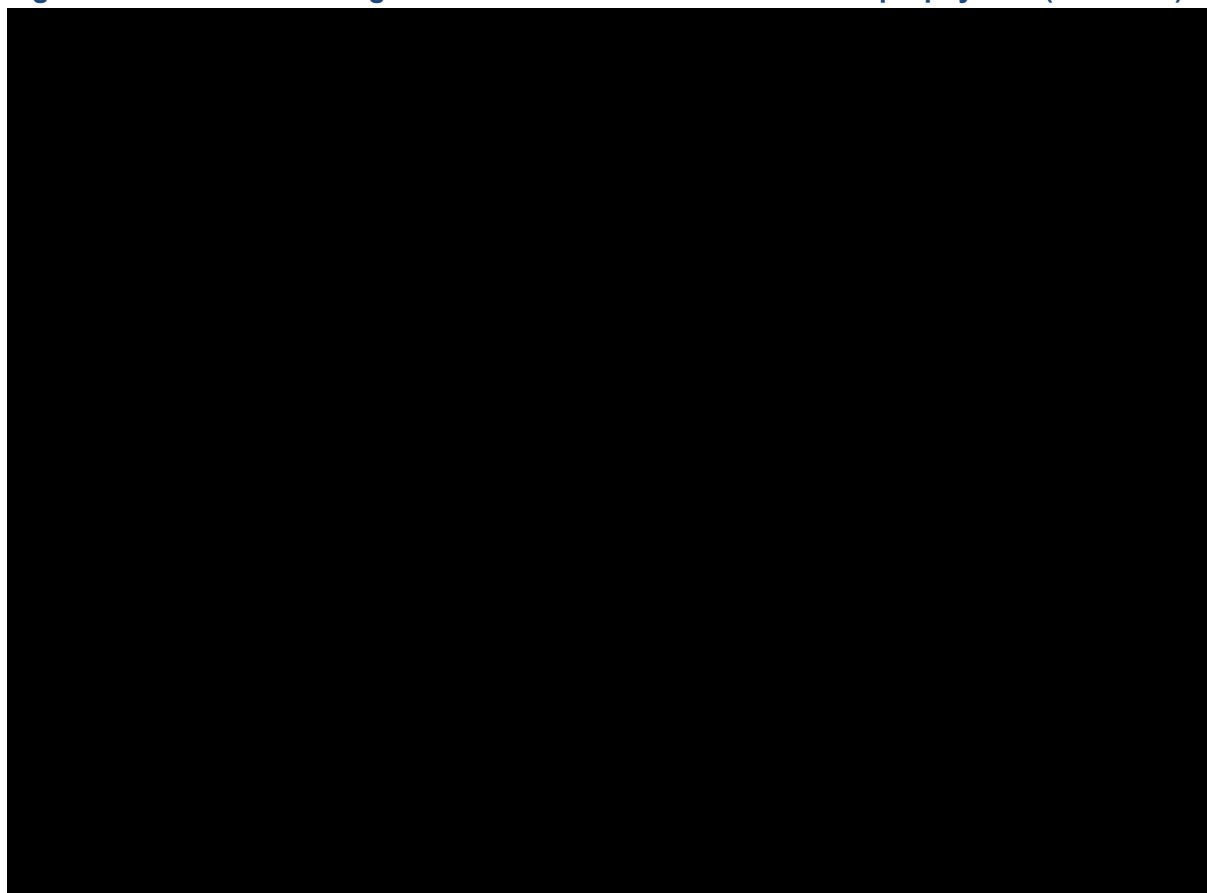
Abbreviations: DSA: deterministic sensitivity analysis; FVIII: factor VIII; IV: intravenous; NHB: net health benefit; PAS: patient access scheme; RU: resource use.

Figure 17: DSA tornado diagram for net health benefit versus emicizumab (with PAS)



Abbreviations: ABR: annualised bleeding rate; DSA: deterministic sensitivity analysis; FVIII: factor VIII; NHB: net health benefit; PAS: patient access scheme; RU: resource use.

Figure 18: DSA tornado diagram for net health benefit versus FIX prophylaxis (with PAS)



Abbreviations: DSA: deterministic sensitivity analysis; FIX: factor IX; IV: intravenous; NHB: net health benefit; PAS: patient access scheme; RU: resource use; SC: subcutaneous.

B.3.10.3 Scenario analysis

Several probabilistic scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the economic model, as detailed in Table 73. Results of these scenario analyses in the haemophilia A and B analyses are presented in Table 76 and Table 77, respectively. Some variation may exist in the interpretation of these results relative to the base case results due to the probabilistic nature of the analyses.

The majority of scenarios had a limited impact on cost-effectiveness results, and marstacimab remained consistently dominant versus both FVIII and FIX prophylaxes across all tested scenarios, and cost-effective against emicizumab. The scenario in which the discontinuation rate of 6.02% is applied annually to marstacimab patients had the largest impact on results, resulting in the lowest NHB against each comparator, however this result remained above the accepted cost-effectiveness thresholds set by NICE.

Table 76: Results of the scenario analyses for patients with haemophilia A (with PAS; probabilistic)

Scenario		Marstacimab vs FVIII prophylaxis				Marstacimab vs emicizumab			
		Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (£30,000)	Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (£30,000)
Base case		██████	██	Dominant	██	██████	██	£24,196,182 ^a	██
Patient age									
1	Starting age set to the minimum age as per draft SmPC (12 years)	██████	██	Dominant	██	██████	██	██████	██
2	Starting age set to the average age from the BASIS trial (33 years)	██████	██	Dominant	██	██████	██	██████	██
Comparator basket composition									
3	Factor prophylaxis basket composition informed by UKHCDO 2023 Annual Report	██████	██	Dominant	██	██████	██	██████	██
Dosing									
4	Assume alternative emicizumab dosing (240 mg) corresponding to UKHCDO advice	██████	██	Dominant	██	██████	██	██████	██
Vial sharing									
5	Vial sharing included (for factor prophylaxis)	██████	██	Dominant	██	██████	██	██████	██
Treatment efficacy									
6	Assume same efficacy across all treatments (regarding occurrence of zero bleed events, ABR and AJBR)	██████	██	Dominant	██	██████	██	██████	██

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7	Assume no patients receive marstacimab dose escalation. Efficacy data for patients with marstacimab dose escalation during the BASIS trial ATP excluded in overall ABR _{treat} and AJBR results			Dominant					
8	Use BASIS trial haemophilia A subgroup analysis efficacy data (including dose escalation)			Dominant					
9	Use BASIS trial haemophilia A subgroup analysis efficacy data (excluding dose escalation)			Dominant					
10	SHL and EHL efficacy informed by BASIS subgroup analyses			Dominant					
11	Emicizumab relative efficacy (odds and rate ratios) are based on total bleed-based analyses			Dominant					
Discontinuation									
12	No discontinuation from marstacimab			Dominant					
13	Include an annual discontinuation of 6.02% (per year) from marstacimab to factor prophylaxis			Dominant					
Adverse events									

14	Include adverse events	██████	██	Dominant	██	██████	██	██████	██
Medical Costs									
15	Assume no resource use per bleed	██████	██	Dominant	██	██████	██	██████	██
16	Assume acute bleed dosing per joint bleed is higher than for non-joint bleed.	██████	██	Dominant	██	██████	██	██████	██
Non-medical costs									
17	Include indirect and direct non-medical costs	██████	██	Dominant	██	██████	██	██████	██
Disutility									
18	Assume non-joint bleeds and joint bleeds have the same disutility per bleed event (−0.28 over 4.5 days)	██████	██	Dominant	██	██████	██	██████	██
19	Exclude administration based disutilities	██████	██	Dominant	██	██████	██	██████	██
Mortality									
20	Assume patients with treated bleeds have a SMR of 2.4 (versus the general population)	██████	██	Dominant	██	██████	██	██████	██

Some variation may exist in the interpretation of these results relative to the base case results due to the probabilistic nature of the analyses.

^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; EHL: extended half-life; FVIII: factor VIII; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; SHL: standard half-life; SmPC: summary of product characteristics; SMR: standardised mortality ratio; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation.

Table 77: Results of the scenario analyses for patients with haemophilia B (with PAS; probabilistic)

Scenario	Marstacimab vs FIX prophylaxis

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		Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (£30,000)
Base case		██████	██	Dominant	████
Patient age					
1	Starting age set to the minimum age as per SmPC (12 years)	██████	██	Dominant	████
2	Starting age set to the average age from the BASIS trial (33 years)	██████	██	Dominant	████
Comparator basket composition					
3	Factor prophylaxis basket composition informed by UKHCDO 2023 Annual Report	██████	██	Dominant	████
Dosing					
4	Assuming alternative dosing regimen for Alprolix and Idelvion	██████	██	Dominant	████
Vial sharing					
5	Vial sharing included (for factor prophylaxis)	██████	██	Dominant	████
Treatment efficacy					
6	Assume same efficacy across all treatments (regarding occurrence of zero bleed events, ABR and AJBR)	██████	██	Dominant	████
7	Assume no patients receive marstacimab dose escalation. Efficacy data for patients with marstacimab dose escalation during the BASIS trial ATP excluded in overall ABR _{treat} and AJBR results	██████	██	Dominant	████
8	Use BASIS trial haemophilia B subgroup analysis efficacy data (including dose escalation)	██████	██	Dominant	████
9	Use BASIS trial haemophilia B subgroup analysis efficacy data (excluding dose escalation)	██████	██	Dominant	████

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10	SHL and EHL efficacy informed by BASIS subgroup analyses	██████	██	Dominant	██
Discontinuation					
11	No discontinuation from marstacimab	██████	██	Dominant	██
12	Include an annual discontinuation of 6.02% (per year) from marstacimab to factor prophylaxis	██████	██	Dominant	██
Adverse events					
13	Include adverse events	██████	██	Dominant	██
Medical Costs					
14	Assume no resource use per bleed	██████	██	Dominant	██
15	Assume acute bleed dosing per joint bleed is higher than for non-joint bleed.	██████	██	Dominant	██
Non-medical costs					
16	Include indirect and direct non-medical costs	██████	██	Dominant	██
Disutility					
17	Assume non-joint bleeds and joint bleeds have the same disutility per bleed event (−0.28 over 4.5 days)	██████	██	Dominant	██
18	Exclude administration based disutilities	██████	██	Dominant	██
Mortality					
19	Assume patients with haemophilia have a SMR of 2.4 (versus the general population)	██████	██	Dominant	██

Some variation may exist in the interpretation of these results relative to the base case results due to the probabilistic nature of the analyses.

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Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; EHL: extended half-life; FIX: factor IX; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; SHL: standard half-life; SmPC: summary of product characteristics; SMR: standardised mortality ratio; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation.

B.3.11 Subgroup analysis

The base case considers separate analyses for haemophilia A and B, and their relevant comparator products, however efficacy data used are the same for both populations, in line with the BASIS trial. Scenario analyses present results using post-hoc data from the BASIS trial which considers specific and distinct efficacy of FVIII, FIX and marstacimab in haemophilia A and B populations.

B.3.12 Benefits not captured in the QALY calculation

The economic model presented in this submission captures the key benefit of marstacimab compared with current therapy options, the observed reductions in bleeding rates from the BASIS trial compared with individuals receiving factor prophylaxis. Whilst this represents an important aspect of treatment with marstacimab, there are additional benefits that are not able to be captured in the model.

Impact of long-term joint damage on HRQoL and costs

As outlined in Section B.1.3.1.4, long-term damage to joints represents a substantial burden associated with haemophilia bleeds. Due to limited availability of data from comparator trials and a lack of long-term studies evaluating the impact of marstacimab on joint damage, the *de novo* model structure in this submission does not explicitly capture long-term joint damage or future surgery as part of the health state definitions. The improvements in joint health and reductions in joint pain following treatment with marstacimab, compared with factor prophylaxis, seen in the BASIS trial ATP and OLE may therefore not be fully captured in the model. For example, improvements in joint health in the short term may translate to long-term reductions in the development of joint arthropathy, improved mobility, reduced chronic pain, and reduced chronic disability. Additionally, if patients experience fewer joint surgeries in the long term, this could be expected to provide cost-savings to the NHS. In summary, the model likely underestimates the potential health and cost benefits that marstacimab may offer through reduction of long-term joint damage as a result of the observed improvements in joint bleed rates and joint health.

Psychological benefits of reduced treatment burden and increased simplicity of administration

Beyond the physical and psychological aspects of the condition, haemophilia is associated with a substantial treatment burden as highlighted in Section B.1.3.1.5. Factor prophylaxis treatment for both haemophilia A and B requires frequent IV infusions which are strenuous and time consuming. This can interfere with an individual's daily life, employment and travel. While emicizumab is administered as a SC injection, issues remain due to its complex weight based dosing schedule and the fact patients have to draw up their own vials. Additionally, there is no SC treatment option available for patients with haemophilia B. Treatment with marstacimab as a fixed-dose, pre-filled SC pen has the potential to free patients from the burden of regular factor infusions, allowing patients to live life more freely, and reducing the amount that haemophilia is on their mind. In the model, the baseline HRQoL utility was assumed to be the same for patients receiving marstacimab or factor prophylaxis. This could be seen as a conservative assumption as it does not capture the benefits highlighted above.

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

Clinical expert opinion

Expert clinical opinion was sought during the development of this evaluation to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice. In order to obtain this expert opinion, Pfizer obtained partnership agreements with 5 clinical experts (4 NHS haemophilia specialists and one haemophilia scientist) experienced in the treatment of haemophilia in the UK. The objective of the partnerships were to obtain the experts' opinion on key assumptions and/or inputs which included:

- The use of a basket comparator of FVIII and FIX products
- The pooling of BASIS trial efficacy
- The disutility applied for administration of treatment
- The rate of discontinuation from marstacimab and the products patients discontinue onto
- The absence of marstacimab treatment waning over time

Outputs from these discussions are detailed throughout the submission alongside the descriptions of the relevant assumptions and approaches.

Technical validation

In alignment with best practice, a number of technical and internal consistency checks were completed by an independent health economist prior to submission to ensure that the model functioned as intended and generated accurate results which were consistent with input data and robust to extreme analyses. This model quality control check was conducted in line with the published TECH-VER checklist.¹⁶⁴

The validation process also aimed to ensure that a high degree of transparency was maintained throughout the model and adaptations were carried out where necessary to ensure the validity of the model.

B.3.14 Interpretation and conclusions of economic evidence

Summary of cost-effectiveness evidence

In order to assess the cost-effectiveness of marstacimab in severe haemophilia in patients in the UK, a *de novo* cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in the UK. The model considered a population in line with the anticipated market authorisation for marstacimab: people aged 12 or over with severe haemophilia A (without inhibitors) or severe haemophilia B (without inhibitors). This reflects the population in BASIS, the pivotal Phase 3 trial for marstacimab, which also informed the modelled efficacy of marstacimab. The comparators in haemophilia A consisted of a basket of FVIII prophylaxis treatment and emicizumab, and the comparator in haemophilia B consisted of a basket comparator of FIX prophylaxis treatment. Clinical expert feedback considered these comparators to be reflective of current treatment options for haemophilia B in the UK. The relative efficacy of comparator factor

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prophylaxis (FVIII and FIX) was derived from a direct inpatient comparison of the percentage of patients experiencing treated bleeds and the rate of treated bleeds in the OP and ATP phases of the BASIS trial. In the absence of direct comparative efficacy data for emicizumab versus marstacimab, the treatment efficacy of emicizumab relative to marstacimab was derived from STC analysis using data from the BASIS and HAVEN trials.

Marstacimab was found to be more effective and less costly than both FVIII and FIX prophylaxis comparator baskets (i.e. dominant) across all analyses conducted. In the base case, marstacimab (with PAS) was associated with positive deterministic NHB versus FVIII and FIX prophylaxis of [REDACTED] and [REDACTED] QALYs, respectively, at a WTP of £30,000 per QALY gained. Marstacimab resulted in fewer QALYs but was less costly than emicizumab, resulting in a positive deterministic NHB of [REDACTED] at a WTP of £30,000 saved per QALY forgone. The probabilistic base case analysis showed very similar results, with marstacimab resulting in positive NHBs versus FVIII prophylaxis, emicizumab, and FIX prophylaxis of [REDACTED], [REDACTED], and [REDACTED] QALYs at a WTP of £30,000 per QALY, respectively, indicating the base case results to be robust to uncertainty in parameter estimates. Marstacimab had a 100% probability of being cost-effective against all comparators, across all 1,000 probabilistic simulations.

The DSA results identified two influential parameters (patient age and weight), however the model was largely robust to individual parameter uncertainty and marstacimab remained cost-effective across all extreme variables. Scenario analyses were conducted to explore the impact of certain assumptions within the model, all of which showed similarly cost-effective results for marstacimab in the comparison against each comparator, with minimum NHBs of [REDACTED], [REDACTED] and [REDACTED] against QALYs at a WTP threshold of £30,000 per QALY against FVIII prophylaxis, emicizumab, and FIX prophylaxis, respectively. These minimum NHBs were all in the scenario in which an annual discontinuation rate of 6.02% is applied to marstacimab, which, as per expert clinician feedback, can be considered highly conservative.⁶⁸

Overall, all analyses demonstrated marstacimab to be a cost-effective treatment option at the WTP threshold of £30,000 per QALY.

Strengths

The clinical evidence base for marstacimab and comparators in this submission has been derived from a robust SLR of clinical trials investigating treatments for severe haemophilia. Results from the marstacimab trial demonstrate that marstacimab is associated with a reduced risk of bleeds and treated bleeds compared with routine factor prophylaxis. The promising early results observed in the BASIS trial ATP are supported by its OLE study, showing sustained reductions in bleed rates compared with treatment with routine factor prophylaxis in the trial OP. The results of the BASIS trial in the overall population of patients with severe haemophilia (both A and B) informed the efficacy of marstacimab, and both FVIII and FIX prophylaxis. Scenario analyses were conducted in which subgroup analyses from the BASIS trial by haemophilia type (A or B) were instead used to inform efficacy of these three treatments.

Unlike the comparison with factor prophylaxis treatments, no direct comparative evidence existed between marstacimab and emicizumab. In the absence of any such direct evidence, an unanchored STC was conducted to compare marstacimab to emicizumab in patients with severe haemophilia A, informed by data from the BASIS and HAVEN 3 trials. Emicizumab was found to be associated with a slight reduction in treated joint and non-joint bleed rates compared with marstacimab, however none of the results reached statistical significance (Section B.2.11).

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A cost-utility analysis was selected to assess the cost-effectiveness of marstacimab in severe haemophilia A and severe haemophilia B. The model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to fully capture all costs and QALY gains associated with modelled treatments, and discount rates for costs and benefits of 3.5%. As discussed in Section B.3.13, the model underwent rigorous internal validation, and clinical expert feedback was sought to validate many of the assumptions and inputs used in the model.

Limitations

A key limitation of the clinical evidence base was the lack of appropriate head-to-head trial evidence for marstacimab versus emicizumab. An unanchored STC was conducted in order to obtain relative efficacy estimates to inform the economic analysis, which are subject to inherent uncertainty. Whilst clinically important covariates were adjusted to better match populations across included studies, it is unlikely that all confounding was accounted for, an assumption and limitation inherent to all unanchored ITCs. Furthermore, results did not reach statistical significance, therefore the true difference in treatment effect is uncertain. Despite these limitations, the STC analysis represents a rigorous method of accounting for confounding, using the best available comparator trial data.

As noted in Section B.3.12, whilst the model attempted to capture the health and HRQoL outcomes of most relevance to patients with moderately severe to severe haemophilia B, a lack of appropriate data meant that not all important aspects of the disease could be explicitly captured.

Finally, whilst BASIS provides robust evidence for the efficacy of marstacimab for a year, and the BASIS OLE for a further six months, the model extends over a lifetime horizon. This therefore necessitated long-term extrapolation of treatment effect, and assumptions around the long-term rate of discontinuation from marstacimab. Uncertainty therefore exists in the long-term treatment efficacy of marstacimab, as well as the three comparators, whose efficacy is informed by the BASIS trial (directly or indirectly). Long-term efficacy, in particular the long-term rate of marstacimab discontinuation, represents the principal source of uncertainty which has a large impact on the cost-effectiveness estimates of marstacimab. Scenario analyses were conducted using different sources of efficacy, and different assumptions around long-term marstacimab discontinuation. These show marstacimab to be cost-effective under all analyses conducted, against all comparators.

Conclusion

Patients with severe haemophilia face a serious unmet need for a treatment with a simple method of administration, which is able to maintain low bleed rates and improve patient QoL. Marstacimab represents a convenient, efficacious and well tolerated treatment, with an acceptable safety profile and novel mechanism of action, offering less burdensome administration requirements for patients. Results from the BASIS trial show improvements in ABR_{treat} compared with factor prophylaxis, supported by numerical improvements in EQ-5D-5L scores.

In the cost-effectiveness analysis, marstacimab was shown to be associated with a greater number of QALYs and fewer costs than the FVIII and FIX basket comparators, and associated with substantial cost savings against emicizumab. This led to cost-effective economic model

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results against all three comparators, across all analyses conducted. Marstacimab therefore represents a cost-effective treatment option at a WTP threshold of £30,000 per QALY, and its reimbursement for the treatment of severe haemophilia can be considered a cost-effective use of NHS resources, whilst also expanding the choice of therapies available to both patients with haemophilia and their clinicians.

B.4 References

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Company evidence submission template for marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Summary of Information for Patients (SIP)

July 2024

File name	Version	Contains confidential information	Date
ID6342_Marstaci mab_SIP_17Jul20 24_[NoCON]	V1.0	No [NoCON]	17th July 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Marstacimab

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Marstacimab has been developed to treat severe haemophilia A and severe haemophilia B in people 12 years and over. This submission focuses on people **without inhibitors** to align with the anticipated initial marketing authorisation. Please note, the exact intended population for Marstacimab is confidential until regulatory approval is granted. For details, please see Document B, Section B.1.1.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marstacimab is currently being assessed by regulatory authorities including the European Medicines Agency (EMA). In the United Kingdom, Marstacimab will be assessed by the Medicines and Healthcare products Regulatory Agency (MHRA). Marketing authorisation is pending. Please see Document B, Section B.1.2, Table 2 for confidential anticipated dates of marketing authorisation approval.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

In England, the key patient organisation is The Haemophilia Society. As defined by the Association of the British Pharmaceutical Agency (ABPI) 2021 Code of Practice, donations and grants may be

provided for the purpose of supporting healthcare, scientific research or education, with no consequent obligation on the recipient organisation, institution and the like to provide goods or services to the benefit of the pharmaceutical company in return.¹ Additionally, collaborative working between the pharmaceutical industry and patient organisations may involve contracted services. Payments are publicly disclosed via Pfizer's UK company website here: [Patient Organisation funding and support | Pfizer UK](#) and via Disclosure UK. Details for the previous 4 years are provided below:

2024:

- The Haemophilia Society: Grant of £5,000
- The Haemophilia Society: Grant of £5,000

2023:

- The Haemophilia Society: Grant of £10,000

2022:

- The Haemophilia Society: Grant of £10,000
- The Haemophilia Society: Grant of £10,000

2021:

- The Haemophilia Society: Contracted service of £500

2020:

- The Haemophilia Society: Grant of £15,000
- The Haemophilia Society: Sponsorship of £5,000
- The Haemophilia Society: Sponsorship of £53,957.50

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

Haemophilia is a lifelong, rare genetic condition that affects the blood's ability to clot.^{2,3} Typically, if a person bleeds, substances in the blood known as clotting factors mix with blood cells called platelets to make the blood sticky and form a clot, ensuring the bleeding stops.^{2,3} People with haemophilia have less clotting factors in their blood meaning they bleed for longer than usual.²

There are two main types of the condition, haemophilia A and haemophilia B, and both are caused by defects in the genes responsible for producing proteins that help the blood clot. These proteins are known as clotting factors and the type of haemophilia is defined by which clotting factor is affected.

Individuals with Haemophilia A have a defect in the gene responsible for producing factor VIII (eight), referred to as FVIII.⁴ In contrast, individuals with haemophilia B have a defect in the gene responsible for producing factor IX (nine), known as FIX.⁴ Haemophilia B is rarer than haemophilia

A, and both conditions mostly impact males.^{6,9} In 2022/23 in the UK, 2,128 people were treated for severe haemophilia A and 329 people were treated for severe haemophilia B.⁵

FVIII and FIX are important proteins within the blood clotting process; and an absence or reduced amount of either causes a delay in clot formation once bleeding has occurred.^{6,7} Consequently, people with haemophilia A or B can experience prolonged bleeding events. Depending on how severe the disease is, these bleeding events can occur either spontaneously or following trauma (e.g., after an injury or surgery).^{8,9} Bleeding episodes most commonly occur in joints, but can also occur in other locations including muscles, soft tissue, the gastrointestinal (digestive) system, and the brain or spinal cord.⁸ Repeated bleeding into joints can cause considerable pain, reduced range of motion and poor mobility, all of which reduce quality of life. These challenges can limit the ability of those with haemophilia to do daily activities or to live spontaneously.

The severity of haemophilia A or B depends on the level of FVIII or FIX in the blood compared to normal levels and are classified as mild (>5% to <40% of normal), moderate (1–5% of normal) or severe (<1% of normal). This submission focusses on severe haemophilia A or B (FVIII or FIX activity levels of <1% of normal).^{8,10,11}

Haemophilia has a large impact on patients and carers due to the symptoms and treatments, with reduced quality of life arising from pain, functional impairment, anxiety and depression due to unpredictability of bleeding events and frustration with treatment burden, a reduction in work productivity, and an increase in healthcare spending.^{10,12-15}

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

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

Haemophilia can be diagnosed before birth if there is a family history of haemophilia.^{2,16} There are several tests for genetic conditions, such as chorionic villus sampling (CVS) in early pregnancy.¹⁶ An alternative is free-foetal DNA testing – this does not diagnose haemophilia but it can identify the sex of the baby in the womb, which is particularly helpful in what are known as X-linked disorders, like haemophilia, that mainly affect males.¹⁶

After birth, a diagnosis of haemophilia will often be made after unexplained bleeding in an otherwise healthy infant.¹⁷ Haemophilia can then be diagnosed using a sample of blood for testing in a laboratory.¹⁶ A test to measure how long a sample takes to clot may suggest a clotting disorder, which would then be investigated further for specific clotting factors.¹⁶ Doctors will try to identify the gene mutation as well, as this can be helpful in planning for future children.¹⁶

2c) Current treatment options:

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Haemophilia A and B are life-long conditions and there is currently no treatment that provides a cure. Given that recurrent bleeding episodes can lead to irreversible joint damage, the main treatment goal is to reduce or prevent bleeding while allowing patients to lead active lives and achieve a quality of life comparable to individuals not affected by the condition.¹⁸

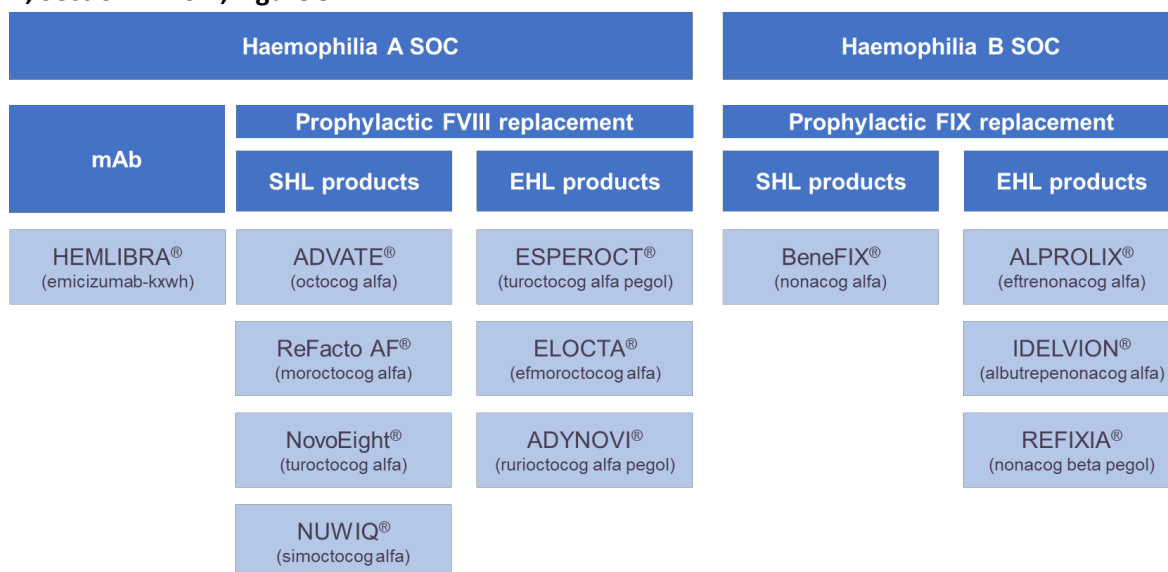
Most medicines for haemophilia A and B focus on replacing the missing clotting protein (FVIII or FIX). The standard of care, as recommended by the World Federation of Hemophilia (WFH), is regular injections of FVIII or FIX into the vein (intravenous injections) to raise the level of FVIII or FIX in the blood and therefore prevent bleeding.⁸ This is known as a prophylactic (or preventative) treatment and is how the majority of individuals with severe haemophilia are managed. Following a bleeding episode, FVIII or FIX injections can also be administered “on-demand” with the aim of stopping bleeding once it has occurred.¹⁹

FVIII or FIX replacement medicines are available in two forms: standard half-life (SHL) products, which require administration multiple times per week, and extended half-life (EHL) products, which are typically administered at frequencies from once a week to once every two weeks for those whose bleeding is well controlled.²⁰⁻³⁰ Due to their reduced frequency of administration and therefore reduced treatment burden, EHL products tend to be favoured over SHL products.

For people with haemophilia A there is also an alternative treatment option called emicizumab (brand name Hemlibra®) which is the most commonly used treatment for severe haemophilia A in the UK⁵. Emicizumab is a monoclonal antibody (MAb) and is administered every 1-4 weeks.³¹ Unlike medicines that focus on replacing the missing factor, emicizumab is administered subcutaneously (injection into fatty tissue, just under the skin) rather than intravenously. However, self-administration of emicizumab requires the individual to first determine their correct dose (based on their body weight) and then draw this up into the syringe, prior to administration.³¹

Medicines used for current clinical management of severe haemophilia A and B in the UK is presented in Figure 1 (described further in Document B, Section B1.3.2).

Figure 1: Current clinical management of severe haemophilia in UK clinical practice – Document B, Section B.1.3.2, Figure 5



Only SHL and EHL products with a market share of >1% in the UK are included in the diagram and as relevant comparators in this appraisal.

Some individuals may also administer factor replacement therapy on an on-demand basis to stop bleeding when it arises, as may occur following injury or local trauma, for example, following surgery.

Abbreviations: EHL: extended half-life; FIX: factor IX; FVIII: Factor VIII; mAb: monoclonal antibody; SHL: standard half-life; SOC: standard of care.

Source: IQVIA for Pfizer. Data on File. UK - Market Share Analysis in DOT & IU for Haemophilia A & B. 2024 ³²

FVIII and FIX prophylaxis treatments have a high treatment burden, as the need for frequent self-administered intravenous infusions disrupts day-to-day activities that others without the condition may take for granted.^{15,33} Additionally, despite regular FVIII and FIX prophylaxis, people with severe haemophilia A or B can still experience bleeds. As mentioned previously, frequent bleeds into single or multiple joints has a negative impact on quality of life and can lead to joint damage.³⁴

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

Context:

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

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

Severe haemophilia A and B both have a substantial physical, psychological, and economic impact on patients with the condition. Additionally, a substantial treatment burden exists due to the regular IV injections associated with FVIII and FIX prophylaxis.

Bleeding, joint damage and pain

The recurrent bleeding episodes patients experience with severe haemophilia A and B can lead to progressive joint damage (arthropathy) and pain, resulting in physical impairment and negatively impacting quality of life.^{12,35-38} Recent discussions with patients with severe haemophilia B attending a workshop (n=5), and interviews (n=4) conducted by a specialist organisation called Haemnet on behalf of Pfizer revealed that bleeding rates are a key driver of reduced quality of life in this population.³⁹

“Having so many bleeds, it was so disruptive to my work, just to life in general.”

The development of joint damage as a result of repeated bleeding episodes represents one of the most debilitating consequences of haemophilia A and B. Evidence for this comes from the CHES (Cost of Haemophilia across Europe – a Socioeconomic Survey) study in which individuals with haemophilia and physicians from five European countries (including the UK) completed questionnaires between 2014 and 2015.³⁷ Analysis of these questionnaires revealed there is a strong association between the number of damaged joints and worsening quality of life.¹³ Participants with severe haemophilia interviewed in the Haemnet study also raised the issue of joint health and the frustrations this causes on multiple occasions.³⁹

“Speaking as somebody who has long-term joint damage and, you know, really painful long-term joint damage, it really affects my mobility and so I can’t be as spontaneous as I would like to be.”

Pain is another factor that can have a high impact on individuals with haemophilia A or B. Evidence for this comes from the CHES II study which collected data between 2019 and 2020 and aimed to build on the original CHES study.⁴⁰ Data from CHES II reported that 76% of participants with severe haemophilia B had mild or moderate chronic pain, and 5% endured chronic pain, which consequently resulted in low quality of life scores.⁴⁰ Similar experiences were found in the United States in the pain, functional impairment and quality of life (P-FiQ) study, an observational study on 381 adults with haemophilia A or B.¹² In this study, pain due to haemophilia caused substantial interference across many aspects of the patients’ lives, including the ability to enjoy life, work normally, sleep and walk, all of which are areas that individuals without the disease may take for granted. Finally, UK participants in the recent workshop and interviews by Haemnet raised the issue of pain and associated frustrations, including having to manage it constantly. The indifferent attitude of people with haemophilia may often mask the true impact of the disease, as revealed by one UK participant in the recent interviews conducted by Haemnet:³⁹

“You get pain whatever, don’t you, really, so you just deal with it.”

Impact on daily living

The physical impairments that can develop as a result of bleeding are closely linked with challenges in performing routine activities of daily living, including physical activity and household tasks.^{12,13} Education, employment, and physical leisure activities can also be affected in individuals with haemophilia. During the Haemnet patient discussions, one participant noted:³⁹

“My earliest memory of a consultant was [them saying] ‘you will not play football, you will not play cricket, you will not play rugby, you will not play basketball, you will not do PE at school’ and I was bored, and I got fed up.”

Psychological impacts

Beyond the physical aspects of the condition, anxiety and depression are commonly reported in people with haemophilia A or B, highlighting how aspects of living with the condition can result in an additional psychological (mental) burden.^{13-15,41} Psychological well-being was also explored within a study involving members of The Haemophilia Society.¹⁴ The inability to participate in activities that individuals valued, along with a lack of independence, were reported as reasons for depression. Feelings of anger and frustration were also raised as described by one individual:

“I think there are a lot of us who are angry and haemophilia is definitely frustrating, it can bring on an awful lot of anxiety”; “I sometimes feel ... why me and I do get angry because it’s not my fault that I’ve got this thing which now I have to live with every day because I know it’s not going to ever go away.”

Impact on employment

Severe haemophilia A and B are also associated with significant social and financial burden resulting from reduced work productivity and a negative impact on education. People with haemophilia A or B are up to four times more likely to be unemployed among people of working age and to experience restrictions in performing their job due to pain and frequent absences.^{42,43} Participants discussed the impact of haemophilia on employment:³⁹

“It [bleeding] was basically every month and I was having to have, like, a week off work and then come in in a wheelchair the next week, and it was just like ... it was crap.”

Treatment burden associated current therapies

FVIII and FIX prophylaxis requires time-consuming and frequent intravenous injections over the lifetime of an individual to try and prevent bleeding. As individuals are primarily responsible for their administration of FIX prophylaxis, such frequent infusions can substantially interfere with opportunities to take part in day-to-day activities. The effect of treatment burden interfering with daily life was identified in the Hemo-TEM study, where participants reported that travel and social activities were often impacted and that they had to stop activities to treat bleeds.¹⁵ In the Haemnet workshop and interviews with people with haemophilia B, current treatment burden and its impact on the ability to travel was also mentioned;³⁹

“I’d love to go exploring, I’d love to do stuff like that, that’s one of the reasons why I wanted to join the Forces. I’d love to go hiking, I’d love to try all these different things, but not if I’ve got to take factor with me because it’s limiting.”

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

Marstacimab belongs to a group of medicines called monoclonal antibodies. Monoclonal antibodies are a type of protein that recognize and bind to a target in the body. Discovered by Pfizer scientists, marstacimab works differently to FVIII and FIX replacement treatments⁴⁴. Instead of replacing missing or insufficient clotting factors, marstacimab works by targeting a protein called tissue factor pathway inhibitor (TFPI) that is naturally produced in the body. TFPI prevents blood clot formation, known as an anticoagulation protein. Marstacimab works to block TFPI, enhancing the body's ability to form clots, therefore reducing excessive and spontaneous bleeds.

Marstacimab can be taken once weekly by the patient giving themselves an injection under the skin (subcutaneous) using a pre-filled pen. This offers patients a practical alternative to current treatments. With its subcutaneous administration, marstacimab aims to free patients from the requirement for regular intravenous injections, thereby reducing treatment burden and its associated impact on daily living. Additionally, as marstacimab is given as pre-filled pen, it eliminates the need for complicated weight-based dosing calculations and the requirement for patients to prepare and draw up their own dose.

3b) Combinations with other medicines

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

- Yes / No

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

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

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

No, marstacimab is not intended to be used in combination with other medicines for the routine prophylaxis of bleeding episodes.

3c) Administration and dosing

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

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

Treatment with marstacimab will be started under the supervision of a healthcare professional experienced in the treatment of haemophilia. It can then be self-administered by patients or caregivers after a doctor, nurse or pharmacist has shown the patient how to administer it using the pre-filled pen.

The recommended dose for patients 12 years of age and older, weighing at least 35 kg, is an initial dose of 300 mg as a loading dose, given by subcutaneous injection by an experienced healthcare professional in the treatment of haemophilia. Thereafter, this will be followed by 150 mg by subcutaneous injection once weekly which can be self-administered by the patient.

Dosing may be increased to 300 mg weekly in patients weighing ≥ 50 kg if bleeding is still considered uncontrolled by the healthcare professional. Marstacimab can be administered at any time of day. The recommended injection sites are the abdomen and thigh with recommendation for injection site rotation.

3d) Current clinical trials

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

Marstacimab's Phase 3 clinical trial programme consists of the pivotal trial, called BASIS, described in Table 1 below, and its open-label extension (OLE) study. More details on the OLE study can be found here: <https://clinicaltrials.gov/study/NCT05145127>.

In the BASIS trial, 91 adult male patients aged 12 years and older with severe haemophilia A or B, without inhibitors, received their standard factor prophylaxis treatment (standard of care, SoC) for 6 months, known as the observational phase (OP) of the trial; 83 of those patients then went on to receive weekly SC marstacimab prophylaxis for 12 months, known as the active treatment phase (ATP) of the trial. Several outcomes were measured during each phase of the trial, with the main outcome being the annualised bleeding rate (ABR). Each patient is able to act as their own control between the OP and ATP phases of the BASIS trial.

Please see Document B, Section B.2.3, Table 8 for more detail on the BASIS trial. Additionally, there were several inclusion and exclusion criteria for the trial, therefore, links for the detailed inclusion and exclusion information have been provided below.

Table 1. BASIS Phase 3 Clinical Trial

Study	BASIS (Phase 3 study, NCT03938792)
Title^a	An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor Activity <1%) Haemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Haemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis
Location	Multi-centre
Population^a	Adult or adolescent male participants (12 to <75 years of age) with a diagnosis of severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively)
Comparators	Participants were assigned to treatment with marstacimab after a 6 month Observation Phase (OP) on their current haemophilia regimen.
Completion dates	Estimated study completion date: 16 th June 2025
Key inclusion / exclusion criteria (and further trial information)	Please see the following web page for details of the inclusion and exclusion criteria and further trial information: https://classic.clinicaltrials.gov/ct2/show/study/NCT03938792
^a Please note that, although the trial enrolment protocol included patients with moderately severe haemophilia B, ultimately only patients with severe disease enrolled in the trial.	

3e) Efficacy

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

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Efficacy results from the BASIS trial

The efficacy and safety of marstacimab compared with prior routine prophylaxis was demonstrated in the BASIS Phase 3 trial, described in Document B, Section B.2.6.

Primary endpoint – Annualised bleeding rate for treated bleeds (ABR_{treat}):

This was the primary endpoint of the trial and represents the average number of treated bleeds per year experienced by patients. There was a statistically significant and clinically relevant reduction (35.2%) in ABR_{treat} after 12 months of marstacimab prophylaxis in the ATP compared with 6 months of factor prophylaxis in the OP.

Secondary endpoints:

Marstacimab also demonstrated numerically similar results to factor prophylaxis in other bleed-related outcomes, with non-significant reductions in ABR_{joint} , $ABR_{target\ joint}$, $ABR_{spontaneous}$ and ABR_{total} observed between the OP and the ATP. Finally, the BASIS trial measured patients' Haemophilia Joint Health Score (HJHS) which provides a measure of joint health for the knees, ankles, and elbows. Results at 6 months of the ATP revealed a numerical but non-significant improvement in joint health following marstacimab prophylaxis, compared to the 6 month OP value.

Indirect treatment comparison (ITC)

Whilst the BASIS trial provides a comparison between marstacimab and factor prophylaxis products, there is no trial comparing marstacimab and emicizumab for patients with haemophilia A. Therefore, a statistical method was used to indirectly compare the marstacimab and emicizumab clinical trials to determine how their efficacy compare. The statistical method is known as an indirect treatment comparison (ITC), and the particular type of ITC used was a simulated treatment comparison (STC).

Two clinical trials were used to provide clinical data on marstacimab (BASIS trial) and emicizumab (HAVEN3 trial). When the STC was used to indirectly compare the two drugs, overall, the results showed that the efficacy of marstacimab was similar to that of emicizumab for the prevention of bleeding events, with no statistically significant differences between results.

Summary

The lack of direct head-to-head comparator trials and the limitations associated with conducting an indirect treatment comparison against emicizumab means there is some uncertainty associated with the efficacy results. However, the results from the BASIS trial demonstrate that marstacimab could provide a clinical benefit to patients, compared with current factor products used for prophylaxis, and the indirect treatment comparison revealed no statistically significant differences when marstacimab was compared to emicizumab.

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

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

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

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

Phase 3 BASIS trial ⁴⁵

In the BASIS trial, several health-related quality of life (HRQoL) questionnaires were used to understand the impact of haemophilia disease and treatment options on a patients' quality of life. Descriptions of these questionnaires are presented below. Full results are presented in Document B, Section B 2.6.3.

EuroQol 5-dimension 5-level (EQ-5D-5L)

The EQ-5D-5L questionnaire measures 5 areas of health on a 5-point scale: Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. EQ-5D results can be used to generate utility values, where 1.0 represents perfect health and 0.0 represents death, which can then be applied in an economic analysis. Results showed that the change in quality of life from baseline for participants following marstacimab prophylaxis in the ATP was greater than the change from baseline for participants following routine prophylaxis in the OP, but this difference was statistically non-significant.

Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)

This is a disease specific measure of HRQoL intended for adults with haemophilia. It assesses 10 areas of health: Physical Health, Feelings, View of Self, Sport/Leisure, Work/school, Dealing with Haemophilia, Treatment, Future, Family Planning, and Partnership and Sexuality. Results showed marstacimab prophylaxis maintained the benefit of prior routine prophylaxis, as measured by the change from baseline to 6 months for the Haem-A-QoL physical health domain and total score.

Patients Global Impression of Change Haemophilia (PGIC-H)

Patients Global Impression of Change Haemophilia (PGIC-H) is a Haemophilia focused 7-point scale representing a patient's rating of overall improvement in their life. Patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse". Marstacimab prophylaxis during the BASIS study improved patient global impression of change in health state as assessed by the PGIC-H compared with prior routine prophylaxis.

Haemophilia Activities List (HAL)

This is a measure of the impact of haemophilia on a patient's ability to function. It assesses 7 domains: lying/sitting/kneeling/standing, lower (leg) functioning, upper (arm) functioning, transportation, self-care, household tasks, and sports/Leisure. Results showed treatment with

marstacimab was comparable to routine prophylaxis in improving a haemophilia patients' ability to function.

Haemophilia Life Impacts Questionnaire (HLIQ)

This is a 9-item assessment of the life impacts associated with living with and receiving treatment for haemophilia. With treatment with marstacimab, improvements in most HLIQ domains related to life impacts associated with living with and receiving treatment for haemophilia were observed. For example, from baseline to Year 1, the number of patients reporting that haemophilia was not on their mind at all increased from 16% to 26.7%. Detailed results of the haemophilia life impact questionnaire (HLIQ) are presented in Appendix M.2.4.

Summary

Overall, marstacimab is comparable to routine prophylactic factor treatments with respect to disease specific and general patient reported HRQoL outcomes.

3g) Safety of the medicine and side effects

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

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

Marstacimab was generally well tolerated in the clinical trial with no notable safety findings when compared with factor prophylaxis, as demonstrated in the BASIS trial. No deaths were reported and there have been no thrombotic (when a blood clots forms in an artery or vein) or embolic (a block in an artery caused by a blood clot or other substances) adverse events (AEs) recorded by patients treated with marstacimab during the BASIS trial. Marstacimab exhibits an acceptable safety profile versus factor prophylaxis.

The majority of treatment emergent adverse event (an adverse event that starts or worsens after starting the medicine) were mild to moderate in severity. The most frequently observed treatment emergent adverse event (TEAEs) occurring in 5% or more patients during the 12-months of marstacimab treatment were: COVID-19-related, itching, upper respiratory tract infection (infection affecting the nose, throat and airways), joint range of motion decreased, headache, and bruising. Furthermore, the overall occurrence and severity of TEAEs was generally similar across age subgroups (12 to <18 and ≥18 years).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

Overall, data for marstacimab show strong evidence to suggest it would be a valuable addition to the treatment pathway for patients with severe haemophilia A or B, without inhibitors. It offers an effective and conveniently administered prophylaxis therapy to patients, especially for haemophilia B patients for whom there is currently no subcutaneous treatment option available.

Reduced treatment burden for patients:

As a once-weekly, subcutaneous injection, marstacimab has the potential to reduce the burden of current treatment with FVIII and FIX prophylaxis products which require frequent intravenous injections. This is particularly true in haemophilia B where there are currently no subcutaneous treatment options available to NHS patients. A subcutaneous option is also likely to be desirable for patients who currently struggle with venous access, required for intravenous products.

Prevention of bleeding events:

Clinical evidence results from the BASIS trial showed marstacimab to be effective at controlling patient bleeding. Patients reported significant reductions in treated bleeds during the ATP compared with routine factor prophylaxis treatment in the OP. Marstacimab also showed improvements compared to routine factor prophylaxis in other bleed related end points, such as joint bleeds, spontaneous bleeds and total bleeds (treated and untreated), though these improvements were not significant. In summary, marstacimab has the potential to reduce the risk of bleeding episodes that are associated with pain, long-term joint damage, and anxiety and depression.

In an indirect treatment comparison against emicizumab, the results showed that the efficacy of marstacimab was similar to that of emicizumab for the prevention of bleeding events, with no statistically significant differences between results.

Acceptable safety profile:

The BASIS safety analysis results showed that marstacimab is well tolerated with no notable safety findings compared with factor prophylaxis.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?

- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Though marstacimab is generally well tolerated, in the BASIS clinical trial a small number of patients experienced a serious AE (SAE). However, only one of those SAEs (Grade 1 peripheral calf swelling) were considered to be related to the treatment marstacimab. Overall, marstacimab is well tolerated with no notable safety findings.

3j) Value and economic considerations

Introduction for patients:

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

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

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects severe haemophilia A and B

A health economic model has been developed to assess the value of the drug marstacimab to the NHS. The model is split into three health states which is designed to reflect the condition of patients. The three health states are:

- Bleeds (consisting of both joint and non-joint bleeds)
- No bleeds
- Dead

The model estimated the total costs of treating a patient with marstacimab across their lifetime. As mentioned, the main treatment options for patients with severe haemophilia A or B are emicizumab, FVIII and FIX prophylaxis. As such, the model aimed to compare the cost of managing a patient with marstacimab against the cost of managing a patient with each of the three current treatment options (comparators).

Modelling how marstacimab extends life

There is no scientific evidence that marstacimab extends life compared to current treatments and therefore no effect on mortality is considered in the model.

Modelling how marstacimab improves quality of life

Marstacimab is able to improve quality of life via two routes. The first route is by reducing the number of bleeding events experienced by a patient. In the model, each individual bleeding event results in a short-term reduction in quality of life. To inform bleeding rates in the model, efficacy data for factor prophylaxis treatments and marstacimab was informed by data collected from the Phase 3 BASIS trial. The efficacy of emicizumab was informed by the results of the ITC mentioned previously. The second route intends to capture the impact of treatment administration on quality of life. Clinical experts consulted as part of this appraisal agreed that both the route of administration (SC vs IV) and the frequency of administration would have an impact on a patient's quality of life. Therefore, in the model, each injection results in a short-term reduction in quality of life. Consequently, an intervention that reduces bleeding, has a subcutaneous administration, and is administered less frequently, will result in a better quality of life for patients.

Modelling the costs for different treatments

Research has shown that drug costs account for the majority (99%) of direct medical costs for patients with haemophilia⁴⁰. In the model, drug costs for prophylaxis are included for each treatment. Additionally, drug costs associated with "on-demand" treatment of bleeding are included for each individual bleeding event. Beyond drug costs, the model also includes costs of managing bleeding events such as the cost of hospital stays, orthopaedist visits, haematologist visits and visits to A&E. The cost of managing adverse events was also included in the model in a scenario analysis.

Uncertainty

The model made several assumptions including the use of the overall BASIS trial data to inform efficacy for both FVIII and FIX products and the use of an ITC to inform the efficacy of emicizumab. These assumptions are further described in Section B3.9.2. In order to explore the uncertainty in the assumptions made, alternative model scenarios were also calculated to see if the results changed significantly.

Cost-effectiveness results

Marstacimab was found to be more effective and less costly than both FVIII and FIX prophylaxis. Compared to emicizumab, marstacimab resulted in fewer quality adjusted life years (QALYs) but was less costly, resulting in cost-savings for the NHS. Alternative model scenarios demonstrated that marstacimab consistently remained cost-effective against all comparators, even when different assumptions were used. Overall, marstacimab can be considered a cost-effective use of NHS resources, whilst also expanding the choice of therapies available to both patients with haemophilia and their clinicians, offering a convenient, easy to use prophylaxis therapy.

Limitations of the cost-effectiveness analysis:

A key limitation was the lack of data available to inform the long-term impact on joint health for patients with haemophilia. Joint health is an important factor for patients with haemophilia and can have a significant impact on their quality of life, as explained in Section B.1.3.1.5 of

Document B. However, data on the long-term impact of marstacimab on joint damage is lacking. Therefore, any long-term improvements in joint health and reductions in joint pain following treatment with marstacimab, compared with factor prophylaxis, may not be fully captured in the model. As a result, the model could underestimate the potential health and cost benefits that marstacimab may offer through reduction of long-term joint damage as a result of the observed improvements in joint bleed rates. Other limitations include the lack of direct trial evidence comparing marstacimab to emicizumab and the lack of long-term data for marstacimab beyond the open-label extension (OLE) data from BASIS.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Factor prophylaxis treatment is associated with substantial administration burden; the need for frequent self-administered intravenous infusions greatly interferes with an individual's ability to take part in day-to-day activities that others without the condition may take for granted.^{8,15,33} Additionally, although emicizumab offers a subcutaneous option for individuals with haemophilia A, self-administration of emicizumab still requires the individual to first determine their correct dose (based on their body weight) and then draw this up into the syringe, prior to administration.³¹

Therefore, a substantial unmet need exists for an efficacious therapy with a novel mechanism of action and a convenient and simple method of administration, especially for individuals with haemophilia B where there are currently no subcutaneous treatment options available to NHS patients. Marstacimab is an innovative therapy that offers a practical pre-filled subcutaneous, self-administered, prophylactic option for individuals with severe haemophilia A or B. Treatment with marstacimab has the potential to free patients from the burden of regular factor infusions, allowing patients to live life more freely.

3l) Equalities

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

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

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There are a couple of equality considerations that should be taken into account by NICE. Whilst the BASIS trial only recruited male participants, a very small number of females may also be living with severe haemophilia A and B. It is expected that this appraisal will not exclude any people

protected by equality legislation or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Separately, it is worth noting that individuals who are human immunodeficiency virus (HIV) positive (evidenced by CD4 cell count $\leq 200/\mu\text{L}$) at the time of enrolment were ineligible for the marstacimab trials, which may present an equality consideration for NICE.

SECTION 4: Further information, glossary and references

4a) Further information

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

Further information related to marstacimab:

- ClinicalTrials.gov. BASIS. <https://clinicaltrials.gov/study/NCT03938792>
- ClinicalTrials.gov. BASIS OLE. <https://clinicaltrials.gov/study/NCT05145127>
- Published results from Phase 3 study (NCT03938792). Matino, D., Acharya, S., Palladino, A., Hwang, E., McDonald, R., Taylor, C. T., & Teeter, J. (2023). Efficacy and Safety of the Anti-Tissue Factor Pathway Inhibitor Marstacimab in Participants with Severe Hemophilia without Inhibitors: Results from the Phase 3 Basis Trial. *Blood*, 142, 285.
<https://www.sciencedirect.com/science/article/pii/S0006497123048899>
- Pfizer Press Release: [Pfizer Announces Positive Marstacimab Results from Pivotal Phase 3 Hemophilia A and B Trial | Pfizer](#)

Further information on NICE and the role of patients:

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

4b) Glossary of terms

Annualised bleeding rate (ABR): The number of bleeding events a person experiences each year.

ABR_{treat}: annualised bleeding rate of treated bleeds.

ABR_{joint}: annual bleed rate of treated joint bleeds.

ABR_{target joint}: annualised bleeding rate of treated target joint bleeds.

ABR_{spontaneous}: annualised bleeding rate of spontaneous bleeds.

ABR_{total}: annualised bleeding rate of total (treated and untreated) bleeds.

Factor VIII: A protein that helps the blood to clot. Individuals with haemophilia A have a defect in the gene responsible for producing factor VIII.

Factor IX (FIX): A protein that helps the blood to clot. Individuals with haemophilia B have a defect in the gene responsible for producing factor IX, known as FIX.

Indirect treatment comparison (ITC): In the absence of direct evidence (e.g., a single trial comparing different treatments), indirect treatment comparisons can estimate the relative treatment effects of two or more treatments.

Quality adjusted life year (QALY): The number of additional years patients spend alive; however this measure also takes into account the quality of these additional years.

On-demand treatment: Following a bleeding episode, administration of Factor VIII/IX can also be given “on-demand” with the aim of stopping bleeding once it has occurred.

Prophylaxis treatment: Regular injections of Factor VIII/IX into the vein to raise the factor levels in the blood with the aim of preventing bleeding.

Standard half-life (SHL) products: Drugs which require administration multiple times per week.

Extended half-life (EHL) products: Drugs which are typically administered once weekly.

Health-related quality of life (HRQoL): A broad concept commonly used to examine the impact of health status on quality of life. Simply, it narrows quality of life to aspects relevant to health.

Infusion: Medication is administered via a needle into a vein.

4c) References

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Clarification questions

August 2024

File name	Version	Contains confidential information	Date
ID6342_Marstacimab_Haemophilia A and B_NICE Clarification Questions Response_27AUG24_[NoCON]	Final	No	27 th August 2024

Notes for company

Highlighting in the template

Square brackets and [REDACTED] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [REDACTED] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Clarification response summary from the company

There are a number of questions requesting additional data analysis for haemophilia A and B subtypes. However, due to the targeting of marstacimab as a treatment for both haemophilia A and B, the BASIS study was not powered to detect differences within subgroups. Given the lack of powering and small sample sizes associated with the subgroup analyses by haemophilia type (A or B, particularly for haemophilia B), the company has provided the information requested for completeness in response to questions (e.g. A25, A26, A27, A28, A37, A40, B5). However, we recommend that these data are interpreted with caution.

Additionally, there were a number of requests for data for other subgroups including with and without censoring for dose escalation (e.g. A26, A27, A28, A39, A40), factor prophylaxis therapy type (e.g. A23, B2, B3, B4) and weight and age (e.g. B6). The company has provided the information requested for completeness in response to these questions however, given the small sample sizes, the company recommend that these data are interpreted with caution.

The original company submission presented data from a March 2023 data cut of the open label extension (OLE) study. A more recent analysis comprising of a 4-month safety update was conducted in October 2023 and presented at the European Haematology Association conference in June 2024. The October 2023 data cut was a limited data cut primarily assessing safety for regulatory commitments and no study report is available. However, main trial endpoints were also analysed and this October 2023 data-cut has been used to respond to the majority of the OLE requests in these clarification questions. However, not all trial endpoints were assessed as part of this interim analysis (e.g., patient reported outcomes) and therefore, for some clarification question responses, data from the original March 2023 data cut has been presented.

For clarity, a summary of the different data sources used to respond to each clarification question related to the marstacimab clinical trials is provided in Table 1 below. The company have also clarified in the individual questions responses which OLE data set has been used. An updated company submission document (Document B) including the topline results from the October 2023 data cut will also be provided.

Table 1: Summary of data used to respond to clarification questions

CQ number	BASIS	OLE March 2023 data cut	OLE October 2023 data cut
A1	x	n/a	n/a
A2	x	n/a	n/a
A3	x	n/a	n/a
A4	n/a	x	-
A5	x	n/a	n/a
A6	x	-	x
A7	x	n/a	n/a
A8	x	x	n/a
A9	x	n/a	n/a
A10	x	-	x
A11	x	n/a	n/a
A12	x	n/a	n/a
A13	n/a	n/a	n/a
A14	n/a	-	x
A15	x	n/a	n/a
A16	n/a	n/a	n/a
A17	x	n/a	n/a
A18	x	n/a	n/a
A19	n/a	n/a	n/a
A20	n/a	n/a	n/a
A21	x	n/a	x
A22	n/a	n/a	n/a
A23	x	n/a	n/a
A24	x	n/a	n/a
A25	x	-	x
A26	x	n/a	n/a
A27	x	n/a	x
A28	x	n/a	x
A29	n/a	n/a	n/a
A30	x	n/a	x
A31	n/a	n/a	n/a
A32	n/a	n/a	n/a
A33	x	n/a	n/a
A34			
A35			
A36			
A37	x	-	x
A38	x	n/a	n/a
A39	n/a	-	x
A40	x	-	x
A41	n/a	n/a	n/a

A42	n/a	n/a	n/a
A43	n/a	n/a	n/a
A44	n/a	n/a	n/a
A45	n/a	n/a	n/a
A46	n/a	n/a	n/a
A47	n/a	n/a	n/a
A48	n/a	n/a	n/a
A49	n/a	n/a	n/a
B1	n/a	n/a	n/a
B2	x	n/a	n/a
B3	x	n/a	n/a
B4	x	n/a	n/a
B5	x	x	-
B6	x	n/a	n/a
B7	n/a	n/a	n/a

Section A: Clarification on effectiveness data

BASIS Patient Flow

A1. The BASIS Trial Protocol, p. 68 inclusion criteria stated participants must demonstrate at least 80% compliance with the scheduled prophylaxis regimen during 6 months prior to enrolment. Please clarify: how many patients were excluded for not demonstrating 80% compliance, how compliance was assessed, and during what stage of the BASIS trial were participants not demonstrating 80% compliance removed? Please provide information on mean, median and IQR of compliance for those included in the relevant trial population (mITT).

Compliance to routine prophylaxis in the 6 months prior to enrolment (i.e. prior to screening and observational phase [OP]) was confirmed by the investigator as part of the inclusion criteria. Compliance to prescribed treatment regimen during the OP was monitored by sites and study teams. The investigator (or designee) was responsible for regular monitoring of the compliance of the participants via the eDiary during the study.

- One patient did not meet inclusion criterion #3 due to compliance <80%.
- No participants discontinued for compliance <80% during the OP.
- One participant completed the OP but did not enter the active treatment phase (ATP) because their compliance was <80%.

Two protocol deviations were recorded for <80% compliance in OP.

The mean compliance was 99.40% (SD 1.347) and median compliance was 98.72% (IQR 13.70).

A2. Please explain the withdrawal of each person from the All Safety dataset (n=91) to the mITT dataset (n=83).

A complete listing of withdrawals is available in the enclosed document labelled [REDACTED]. In summary:

- 7 participants did not complete the OP:
 - 5 participants no longer met eligibility criteria.
 - 2 participants had protocol deviations.
- 1 participant completed OP but did not meet criteria for the ATP.

A3. Table 3 of the BASIS Trial Clinical Study Report. p. 47 states [REDACTED] discontinued from the Active Treatment Phase (ATP) due to “Withdrawal by Subject” What were the reasons for these withdrawals? Please also provide details on the two protocol deviations as per Figure 3 of the Company Appendices?

All [REDACTED] participants who discontinued due to ‘Withdrawal by Subject’ had haemophilia A. The reasons for their withdrawal are summarised below. All [REDACTED] participants were included in the primary and subgroup analyses, including data up to the date of discontinuation.¹

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Details of the two identified protocol deviations are summarised below:

- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]

The BASIS CSR states that overall, there was no observed impact to safety or efficacy due to protocol deviations.¹

A4. Section 4.1 of the Open-Label Extension Clinical Study Report, p.28 states that [REDACTED] discontinued the study due to *withdrawal by participant*. Please clarify the circumstances of these withdrawals?

Please find below a summary of the reasons for the withdrawal for these [REDACTED]

• [REDACTED]

• [REDACTED]

A5. Please provide a breakdown of all discontinuations of marstacimab occurring at any point, by haemophilia type and marstacimab dose?

5 participants discontinued marstacimab during the BASIS trial, all of whom had haemophilia A and were receiving the 150 mg marstacimab dose. The reasons for discontinuation are provided below.

• [REDACTED]

• [REDACTED]

• [REDACTED]

• [REDACTED]

• [REDACTED]

A6. How many patients changed from the non-inhibitor cohort to an inhibitor cohort on or before the ATP Day -7 testing? Was there any subsequent testing for inhibitors in ATP or OLE? If so please provide details on the number of subsequent newly detected people with inhibitors and what phase this was in. How does testing of inhibitors during the BASIS trial compare to routine UK practice?

During the BASIS trial, there were 1 participants in the prior routine prophylaxis cohort who experienced a change in inhibitor status (defined by a Nijmegen-modified Bethesda Inhibitor assay result of >0.6 Bethesda Units, BU). Details of these participants are provided below:

• [REDACTED]

[REDACTED]

• [REDACTED]

[REDACTED]

• [REDACTED]

[REDACTED]

While there were modest changes in BU titres in a small number of patients, these elevations were considered transient and, in all cases, returned to levels below the ≤ 0.6 BU threshold.

As per the BASIS trial protocol inhibitor testing was conducted in the ATP phase at the Day 180 visit and the Day 360 study completion/termination visit (see BASIS protocol Page 34 Section 1.3 Schedule of Activities).² During the OLE inhibitor testing took place on Day 180 visit and Day 360/Study completion termination visit of each year of the OLE.

Based on UK expert clinical feedback routine inhibitor screening is typically conducted every 6 months for severe haemophilia patients in the UK.³ This is comparable to the inhibitor testing conducted in BASIS and the OLE.

A7. Please provide reasons for failing screening for entry into the BASIS trial, presented separately for those with prior on-demand therapy and those with prior routine prophylaxis.

A summary of the 47 participants and captured reasons for screen failure prior to enrolment are summarised in the enclosed document labelled [REDACTED].

Of note, the 47 participants listed includes both inhibitor and non-inhibitor cohort participants who discontinued at screening. As cohort assignment occurred upon entering the observational phase, the company are not able to provide a separation of cohorts based on inhibitor status or baseline treatment.

For clarity, there is a small typo in Figure 3 of the Company Submission Appendices where the wording states “179 patients without inhibitors screened for entry into the BASIS study”; this is incorrect and should instead state “179 patients screened for entry into the BASIS study”.

A8. 111 patients completed the ATP phase but 4 are not planning to enter the OLE. What are the reasons for each not continuing to the OLE? Will they continue to receive marstacimab? Of the 108 who completed BASIS and planned to enter the OLE phase, only 88 had done so by 10 March 2023. What was happening to the other 20 patients in the interim? Did they continue with marstacimab treatment regardless and is it only a break in their trial follow-up that occurred, or something else?

2 of the 4 participants not planning to enter the open-label extension (OLE) are located in Russia and unable to continue due to evolving geopolitical-induced limitations. Reasons for discontinuation were captured per the case report forms; however, as the remaining 2 participants completed the study, they were not required to provide rationale for completing but choosing to not enter the OLE. Only participants who chose to continue in the OLE study were eligible to receive marstacimab.

The discrepancy in the OLE enrolment numbers at the 10 March 2023 interim analysis is attributable to a data collection lag time. A more recent analysis comprising of a 4-month safety update was recently presented at the European Haematology Association meeting (June 13-16 2024) where data for 107 of 116 (92.2%) of BASIS non-inhibitor participants had enrolled as of October 2023.⁴ The results of this update are discussed in greater detail in response to question A14.

Trial Conduct

A9. Please present adherence information relating to the ATP phase of BASIS for marstacimab. It is currently only reported for BASIS OLE.

Compliance for weekly marstacimab SC treatment during the ATP was $\geq 80\%$ in 98.8% (82 of 83) prior prophylaxis cohort participants. For the one participant whose compliance was $< 80\%$, their compliance was between 70 and $< 80\%$.¹

A10. Section 6.4 of the BASIS Trial Protocol, p. 75 states that

[REDACTED]

How often did this occur in BASIS, both during the ATP phase and OLE phase?

For the prior prophylaxis cohort during the ATP study, a missed dose occurred a total of 7 times. During the OLE study, a missed dose occurred a total of 2 times.

A11. Table 8 of the Company Evidence Submission Document B, p. 40 states the locations and sites of the BASIS trial. Please provide the breakdown of the number of participants recruited in each country, by each site.

A summary of BASIS trial sites, investigators, and recruitment are provided in the enclosed document labelled: [REDACTED]

A12. The draft SpC states

[REDACTED]

[REDACTED] Please provide details (number of participants, number of episodes, treatments used) of breakthrough bleeds during each treatment period of the BASIS trial.

Please find below a summary of the information requested in Table 2.

Table 2: Summary of bleeding events and treatments in the Non-Inhibitor Cohort

	OP (n=83)	ATP (n=83)
Number of participants with bleeds n (%)	[REDACTED]	[REDACTED]
Number of bleeds	[REDACTED]	[REDACTED]
Number of treated bleeds	[REDACTED]	[REDACTED]
<i>Treatments used</i>		
Blood coagulation factors	[REDACTED]	[REDACTED]
Damoctocog alfa pegol	[REDACTED]	[REDACTED]
Efmoroctocog alfa	[REDACTED]	[REDACTED]
Eftrenonacog alfa	[REDACTED]	[REDACTED]

Moroctocog alfa	████	████
Nonacog alfa	████	████
Octocog alfa	████	████
Rurioctocog alfa pegol	████	████
Turoctocog alfa	████	████

A13. Annualised Bleeding Rate (ABR) is measured as either total bleeds, treated bleeds, joint bleeds, or non-joint bleeds. Please provide additional details on the definition of a bleed and how it was measured, providing evidence from the literature on standardised methods to measure bleeding. What guidance was given to participants about recording and seeking treatment for their bleeds? Please confirm how simultaneous (or near simultaneous) bleeds on multiple joints were classified? Is there the potential for overcounting when these rates are applied in the economic model?

As a result of the treatment shift from on-demand to prophylactic management of haemophilia, bleeds, rather than factor activity levels, have become the primary outcome to evaluate new therapies.⁵ However, it is recognised that not all bleeds are the same and the need to subdivide this parameter has evolved. For instance, as the goal of prophylactic treatment is primarily driven by the preservation of joint health, joint-specific ABR is commonly included as a secondary outcome. Moreover, the concept of breakthrough bleeding has originally been proposed to reflect the overall haemostatic efficacy of a treatment that has historically been characterised by peaks and troughs of factor activity, resulting in the further delineation of treated and total bleeding events across all contemporary clinical programs.⁶⁻⁸

The strengths of ABR as a primary efficacy endpoint are two-fold: first, it is a meaningful, singular clinical event that patients associate with their haemophilia management. Second, ABR is also strongly associated with joint function and serves as a surrogate for long-term joint health. While other assessment modalities for joint function exist (like the Haemophilia Joint Health Score [HJHS]), they require a much longer observation period.⁹⁻¹¹

ABR is not without limitations. The subjective nature of patient-reported bleeding, especially joint bleeding, limits its reliability, as joint pain and swelling may indicate arthritis and inflammation rather than bleeding.¹² Clinically, patients are instructed to treat any suspected bleeding, as under-treatment or delayed treatment may accelerate joint deterioration, and thus may result in over-reporting of bleeding to prevent long-term complications. Therefore, haemophilia providers acknowledge the possibility of over-treatment, especially in patients with established joint disease.¹³

The identification of a bleeding episode is clarified in the Protocol Appendix 10.10.² Any sign or symptom of a bleed, regardless of whether or not medication/treatment is administered, was reported as a “bleed” or “bleeding episode”. Bleeds related to a procedure/surgery such as haematomas/bruising resulting from any surgeries or invasive procedures (e.g., tooth extractions, venipuncture, or subcutaneous drug administrations) or invasive diagnostic procedures (e.g., lumbar puncture, endoscopy with biopsy) were not counted as bleeds. All data during the

preventative treatment for medical/dental procedures, sport activity, or physical therapy (plus 72 hours) were not included in the derivation of the ABR.

A treated bleed from the same location occurring >72 hours after stopping treatment from the original bleed for which treatment was initiated, or a treated bleed occurring at a different site regardless of the time of the bleed, was considered a new treated bleed. In addition, the determination of whether a bleed is treated needed to satisfy two conditions: 1) the participant reported the bleed as “treated” in the Bleed Diary, and 2) an infusion AFTER the bleed was reported in the Infusion Diary.²

Multiple concurrent bleeds (spontaneous or traumatic) on the same date and time but in different locations were recorded as 1 bleed for that participant. However, the bleed was counted towards all attributable locations in summaries of bleeds of specific site. If concurrent bleeds occurred on the same day but different times and different locations, they were counted as independent bleeds. On the other hand, if concurrent bleeds occurred on the same day but different times at the SAME location, they were counted as 1 bleed. Overall, the company believe the potential for overcounting simultaneous bleeds in the economic model is negligible.

Teaching materials were not provided as part of BASIS prior to study initiation, however, instruction on how to recognise bleeds is standard care for patients with haemophilia and their caregivers.¹⁴ At enrolment in BASIS, participants were provided Bleeding/Treatment Diary training (including the timing and nature of the information to be entered). At each study visit following Enrolment, the participant’s diary was reviewed to ensure compliance with prescribed haemophilia treatments (including those used to treat breakthrough bleeding) and assessment of bleeds (including bleeding site and if bleeds were “spontaneous” or “traumatic”) as outlined in Protocol Amendment 7 Section 1.3.² Additionally, within the eTouch device under the Bleed Log, the definitions of Spontaneous, Traumatic and Medical/Dental Procedure were available to participants. Considering a participant’s prior knowledge of bleed recognition, assessment, and discussion of bleed type at every visit and the definitions provided by the eTouch device, the company is confident that participants were competent to distinguish between the different bleeding types.

A14. The results available for BASIS OLE are from an interim analysis from March 2023, when do you anticipate publication of these (or subsequent data cuts) of BASIS?

Additional follow-up data (4-month safety update; cut-off October 2023) was recently presented at the European Haematology Association (EHA, June 13-16 2024).⁴ The October 2023 data cut was a limited data cut primarily assessing safety for regulatory commitments and no study report is available. However, main trial endpoints were also analysed and this October 2023 data-cut has been used to respond to the majority of the OLE requests in these clarification questions. However, not all trial endpoints were assessed as part of this interim analysis (e.g., patient reported outcomes) and therefore, for some clarification question responses, data from the original March 2023 data cut has been presented. For clarity, a summary of the different data cuts used to respond to each clarification question related to the marstacimab clinical trials is provided in Table 1 at the start of this response document.

At the time of this analysis, 107 of 116 (92.2%) of non-inhibitor participants from the pivotal study had enrolled in the OLE study (32 from the prior on-demand group and 75 from the prior prophylaxis group). Participants on marstacimab prophylaxis demonstrated sustained reductions

in treated ABR (OD: 3.70 [95% CI: 2.19, 6.26]; RP: 2.79 [95% CI: 1.95, 3.98]). The next interim analysis is planned for the OLE cohort when 12 months of follow-up data is available for all non-inhibitor participants (estimated date of data availability October 2024).

The primary completion date (Last Subject Last Visit) for the OLE is currently anticipated as Q3 2030 but this is potentially subject to change. The final Clinical Study Report will be available within ~4 months of the primary completion date, i.e., it is anticipated Q4 2030, assuming no change to the primary completion date.

A15. Please provide baseline characteristics for the people who started but did not complete the OP phase (n=8), e.g. Tables 9-10

A summary of baseline characteristics for these participants are provided in the BASIS CSR (pages 186-189), Table 14.1.2.1.1.¹

A16. Please clarify the definition of “ATP Day -7 testing”

ATP Day -7 is also defined as Visit 6. The ATP-7 Visit occurs after the end of the OP and 7 days before the first dose of the investigational product.

A17. Disease control for a small number of people in BASIS got worse when beginning marstacimab. Please share any known or hypothesised reasons for why this happened. Please provide the exact number of participants who experienced zero ABR during OP, but experience at least one bleed during ATP.

For the non-inhibitor cohort with routine prophylaxis at OP, ■ participants experienced zero ABR during OP (6-month time period) but experienced at least one bleed during the ATP phase of BASIS (12-month time period). Please note that the OP phase was 6 months whereas the ATP phase was 12 months. Therefore, the longer follow-up period during the ATP may explain why some participants did not achieve zero bleeds during the ATP and this may not necessarily be due to a worsening of disease control. Of these participants:

- [REDACTED]
- [REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]

The pharmacokinetic properties of marstacimab were found to include a mean steady-state accumulation ratio of approximately 3 to 4, relative to the first dose exposure following weekly subcutaneous dosing of 150 mg and 300 mg. Steady-state concentrations of marstacimab are expected to be achieved by approximately 60 days, i.e. by the 8th or 9th subcutaneous dose when administered once weekly.¹⁵

On average, bleeding rates for participants receiving marstacimab have continued to improve with longer follow-up as demonstrated by lower bleeding rates for ABR_{treat} and AJBR_{treat} during the OLE phase compared to the ATP phase of BASIS. This data is presented in Table 4 of this document. In the OLE phase, a higher proportion of participants also experienced zero bleeding events.

A18. Table 4 of the BASIS Trial Clinical Study Report, p. 50 states 22 participants (17.2%) experienced an “investigational product dosing/administration error”. Please clarify the circumstances surrounding these dosing/administration errors. Have measures been put in place to ensure this do not continue to occur?

Participants with dosing/administration errors reported a variety of different deviations including missed dose, incorrect dose administered, additional dose administered, delayed dose administration, missed dose administration, incorrect loading dose administered, incorrect dose prescribed and no rotation of administration site. The BASIS CSR reports that they typically were one-time errors and had no impact on overall efficacy or safety.¹ For every error, the clinical trial research associate would address it with the site and re-educate them on the protocol.

A19. The IQVIA IU FVIII market shares of Document B Tables 5 does not sum to 100%. Please provide an account of this. Please outline how the DoT of Document B Tables 5 and 6 has been calculated, also supplying the data that underlies these calculations including both the IU data for Factor VIII/IX and the mg data for emicizumab as well as the data underlying the calculation of the days of therapy. If it is easier please feel free to supply this in an excel spreadsheet.

Market share data from IQVIA were provided in both international unit (IU) and days of therapy (DOT) formats. The method of calculating market shares from both IU and DOT data are presented in the accompanying Excel document, A19 ID6342 Market Share Calculations. Briefly, products with a market share <1% were excluded in the reweighted market share calculation. It should be noted that Nuwiq® was included in the table because its market share was >1% in the UKHCDO data.

The IQVIA sales volume data presented in Document B, Table 5 for FVIII market share by IU sums to ■■■%. The remaining ■■■% market share is made up of haemophilia A patients receiving the anti-inhibitor coagulant complex (FEIBA®). Given this therapy is not a FVIII replacement, it was excluded from this table, however the market share percentages were incorrectly not re-weighted to reflect this. Whilst this error was present in Document B Table 5, the IQVIA market shares applied in the economic model base case were correctly accounting for the exclusion of FEIBA®. For completeness, data presented in the accompanying Excel have been updated to correctly re-calculate market shares excluding FEIBA®.

The UKHCDO report published the number of people receiving each therapy and the total units (IU) administered in 2022/2023. Market share by IU was calculated directly from the IU values. DOT was calculated using the following method:

$$DoT = \frac{Total\ IU}{(average\ weekly\ dose \div 7)}$$

Each product's summary of product characteristic (SmPC) was used to inform the average weekly dosing in IU. For emicizumab, doses measured in mg, not IU, were used to calculate DOT. These calculations can be found in the accompanying Excel document. The company notes that there appears to be a small discrepancy between the results for haemophilia product market shares based on UKHCDO data (by DOT) presented in Document B (Table 5 and Table 6), the economic model and the accompanying Excel; this is due to small rounding errors. The economic model provided with this response has been updated to correct for these rounding errors, however, due to the immaterial impact on the model outcomes, and this falling below the probabilistic variation, no updated results for the scenario analyses based on using UKHCDO shares have been provided at this stage.

A20. Table 4 of the BASIS Trial Clinical Study Report, p.50 states several incorrect/incomplete patient-reported outcomes (PROs). Please detail how these were accounted for in the analysis.

For the physical health domain and the total score of Haem-A-QoL, as well as EQ-5D-5L index score and EQ-VAS score, the superiority and non-inferiority testing was conducted as outlined in Sections 5.1.2 and 5.1.3 of the BASIS statistical analysis plan (SAP), based on the Wilcoxon signed rank test.¹⁶ In summary, missing observations for these endpoints were handled via multiple imputation approach under the 'missing at random' assumption for the main analyses. Sensitivity tipping point analyses were also conducted via successively applying pessimistic assumptions for missingness due to withdrawals due to AE or lack of efficacy. More detail is provided below.

For the Wilcoxon signed rank test used to analyse physical health domain and the total score of Haem-A-QoL, as well as EQ-5D-5L index score and EQ-VAS scores, a multiple imputation approach with 10 imputations was applied via monotone or fully conditional specification (FCS) regression approach utilising the 'missing at random' assumption. The same approach was used for the following endpoints: HJHS total score, Haemo-QoL total score, HAL/pedHAL total score, and PGIC. For the domain or component scores (9 in Haem-A-QoL, 12 in Haemo-QoL, 10 in HAL, and 7 in pedHAL), a single imputation procedure using the month 6 OP value was used for the Wilcoxon signed rank test. Further information regarding missing data is detailed in Section 5.3.5.3 Methods to Manage Missing Data of the BASIS statistical analysis plan.¹⁶ Appendix 5 of the SAP includes example SAS and R codes for multiple imputation, analysis of each imputed data set, and the final combined testing and inferences.

The BASIS CSR states PRO questionnaires not completed resulted in missing PRO data, however, the impact of the missing data was minimal on the overall analysis of the PRO data.¹

A21. Document B Table 14 states that during the ATP phase, 42 mITT patients had at least two treated bleeds. Please split this data by Haemophilia A patients and Haemophilia B patients. How many of these patients, split by Haemophilia A patients and Haemophilia B patients, satisfied the formal dose escalation criteria of the CSR for the non-inhibitor cohort of two of these

bleeds being within 6 months and inhibitor free. Were the dose escalation criteria for the non-inhibitor cohort the same for the OLE phase and how many patients, split by Haemophilia A patients and Haemophilia B patients, satisfied the formal dose escalation criteria during the OLE phase?

The requested tables, split by haemophilia subtype, are available in the enclosed document labelled: A21: Primary Analysis of the ABR for Treated Bleeds for Non-Inhibitor Cohort with Routine Prophylaxis at OP by Haemophilia Type. Data from the latest OLE data cut (October 2023) was used for the OLE analyses.

Participants in the non-inhibitor factor prophylaxis and on-demand haemophilia A and haemophilia B study populations were evaluated in BASIS if they met criteria for dose escalation and whether or not they dose escalated. In the routine prophylaxis group █% (█) of haemophilia A participants compared to █% (█) of haemophilia B participants met dose escalation criteria, however, only █ (█%) of the factor prophylaxis haemophilia A participants that met dose escalation criteria were dose escalated while █ (█) of the factor prophylaxis haemophilia B participants that met criteria were dose escalated.

According to the protocol (Protocol Amendment 7 Section 6.6) “modification of study intervention dose is not required, but under certain circumstances, is allowed”.² The same guidance was used for both the primary study as well as the OLE. Following 6 months of active treatment with marstacimab and at any time after completion of Visit 14, the dose may be escalated from 150 mg SC QW to 300 mg SC QW if the following criterion is met:

- The participant must weigh at least 50 kg in order to escalate to the 300 mg SC QW dose
- The participant must have two or more spontaneous bleeds (consisting of joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusions of FVIII or FIX over a 6-month period in the absence of a confirmed FVIII or FIX inhibitor, respectively.

The choice to escalate a participant’s dose was at the discretion of the investigator and the decision not to increase did not need to be discussed with the sponsor.

By the data cut of October 2023, █ additional participants in the prior prophylaxis cohort have had their dose escalated (█) at the discretion of their physician.⁴ During the OLE study period, in the routine prophylaxis group █% (█) of haemophilia A participants compared to █% (█) of haemophilia B participants met dose escalation criteria.

Further analyses and documentation

A22. Please provide a copy of the original version of the BASIS protocol.

The ‘10.13. Appendix 13: Protocol Amendment History’ section of the protocol, provided with the Company Submission (pages 160-241), details all of the protocol amendments from the original version to the current version (version 7 dated March 2022).²

A23. Please provide a breakdown of factor therapies used in OP phase of BASIS by patients in the non-inhibitor prophylaxis cohort?

Factor therapies used in the BASIS trial OP are presented in Table 3.

Table 3: Factor therapies used during OP phase of BASIS by patients in the non-inhibitor prophylaxis cohort (17th April 2023 data cut-off; mITT analysis set)

	Routine prophylaxis during OP (N=83)
■	■
Antihaemophilic factor (recombinant), pegylated AUCL	■
Jivi®	■
Elocta®	■
Alprolix®	■
Adynovi®	■
■	■
FIX	■
FIX Human	■
FVIII (Antihemophilic factor)	■
FVIII (Antihemophilic factor); Von Willebrand factor	■
FVIII, recombinant	■
ReFacto AF®	■
BeneFIX®	■
Advate®	■
NovoEight®	■

Abbreviations: EHL: extended half-life; mITT: modified intention to treat; OP: observational phase; SHL: standard half-life.

Please refer to Figure 5 in Document B of the Company Submission for a summary of the current treatments used for the management of severe haemophilia in UK clinical practice.

Please note that, compared with the EHL/SHL scenario presented in the Company's original Submission (Appendix N.2.3), a minor error regarding the classification of one participant's prophylactic regimen has been identified. This has since been corrected and is reflected in Table 3 above. This has not been updated in the economic model; as this misclassification only involves one patient it is anticipated to have a very minor impact on the results of the EHL/SHL scenario.

A24. Please confirm how pausing of marstacimab for COVID-19 impacted patients in BASIS and how this was factored into data-collection and analyses (i.e. duration of discontinuation, alternative therapies received, how key trial data were collected and analysed).

The study began on 09 March 2020 and was ongoing at the time of last patient last visit for the non-inhibitor cohort, which included the period during which the COVID-19 pandemic was occurring globally. The study was safely conducted, despite the impact of the pandemic, and the objectives of the primary analysis for the non-inhibitor cohort were achieved. The overall COVID-19 impact on the study was minimal.

No sites were closed due to the COVID-19 pandemic. Protocol deviations related to COVID-19 were reported during the study (as described in Section 4.2 of the BASIS CSR).¹

No participants discontinued study intervention due to COVID-19 related events. No SAEs or deaths due to COVID-19 occurred during the study.

Treatment with marstacimab was suspended for any participant with presumed or confirmed symptomatic COVID-19 infection (see amendment to Protocol Section 7.1).² These patients were discussed with the Pfizer Medical Monitor to determine next steps prior to resumption of treatment with the study intervention. Management was individualised and varied; however, the majority of patients required no change in treatment and recommenced marstacimab once the COVID-19 infection had resolved. 3 patients required factor replacement during the time they had COVID-19 infection.

Please find enclosed documents summarising:

- [Dose modifications due to COVID-19 \(see document labelled \[REDACTED\]\)](#).
- [Protocol deviations related to COVID-19 \(see document labelled \[REDACTED\]\)](#).
- [AE's related to COVID-19 that occurred during BASIS \(see document labelled \[REDACTED\]\)](#).

A25. Please split Tables 9 (N=83) and M.1.2 Table 99 (N=58) by Haemophilia A and Haemophilia B, and extend these tables to show the baseline proportions receiving each individual FVIII/FIX treatment. Please also provide the equivalent of these extended tables for those in the All Safety (N=91) set.

The requested data, split by haemophilia type, is available in the enclosed document labelled 'A25 Baseline and Demographic Characteristics by haemophilia type'.

Data from the latest OLE data cut (October 2023) was used for the OLE analyses.

A26. Please re-perform analyses without censoring for dose-escalation, where this has been applied, (Tables 15-18, Figure 9, Table 33), both pooled and separately by haemophilia type.

The requested analyses are provided in the enclosed folder labelled 'A26, A27 A28'. For clarity, the table below explains how the enclosed tables and figures correspond to the following tables and figures within Document B of the Company Submission:

Table or Figure within Document B of Company Submission	Enclosed Table or Figure <u>with</u> censoring for dose-escalation	Enclosed Table or Figure <u>without</u> censoring for dose-escalation
Table 15	A26 A27 A28 Table 38a_2.1	A26 A27 A28 Table 38a_3.1
Table 16	A26 A27 A28 Table 38a_2.3	A26 A27 A28 Table 38a_3.3
Table 17	A26 A27 A28 Table 38a_2.2	A26 A27 A28 Table 38a_3.2
Table 18	A26 A27 A28 Table 38a_2.4	A26 A27 A28 Table 38a_3.4
Figure 9	A26 A27 A28 Figure 38a_2.5	A26 A27 A28 Figure 38a_2.6

A27. Please re-perform analyses with and without censoring for dose-escalation and including data from both ATP and OLE (n=58) for marstacimab, (Tables 15-18, Figure 9, Table 33), both pooled and separately by haemophilia type.

The requested analyses are provided in the enclosed folder labelled 'A26, A27 A28'. Data from the latest OLE data cut (October 2023) was used for the OLE analyses. For clarity, the table below explains how the enclosed tables and figures correspond to the following tables and figures within Document B of the Company Submission:

Table or Figure within Document B of the Company Submission	Enclosed Table or Figure <u>with</u> censoring for dose-escalation	Enclosed Table or Figure <u>without</u> censoring for dose-escalation
Table 15	A26 A27 A28 Table 38a_2.1	A26 A27 A28 Table 38a_3.1
Table 16	A26 A27 A28 Table 38a_2.3	A26 A27 A28 Table 38a_3.3
Table 17	A26 A27 A28 Table 38a_2.2	A26 A27 A28 Table 38a_3.2
Table 18	A26 A27 A28 Table 38a_2.4	A26 A27 A28 Table 38a_3.4
Figure 9	A26 A27 A28 Figure 38a_2.5 A27 A28 Figure 38a_3.6	A26 A27 A28 Figure 38a_2.6 A27 A28 Figure 38a_3.5

A28. Please re-perform analyses without censoring for dose-escalation and including data from OLE (n=58) for marstacimab. (Tables 15-18, Figure 9, Table 33), both pooled and separately by haemophilia type.

The requested analyses are provided in the enclosed folder labelled 'A26, A27 A28'. Data from the latest OLE data cut (October 2023) was used for the OLE analyses. For clarity, the table below explains how the enclosed tables and figures correspond to the following tables and figures within Document B of the Company Submission:

Table or Figure within Document B of the Company Submission	Enclosed Table or Figure <u>with</u> censoring for dose-escalation	Enclosed Table or Figure <u>without</u> censoring for dose-escalation
Table 15	A26 A27 A28 Table 38a_2.1	A26 A27 A28 Table 38a_3.1
Table 16	A26 A27 A28 Table 38a_2.3	A26 A27 A28 Table 38a_3.3
Table 17	A26 A27 A28 Table 38a_2.2	A26 A27 A28 Table 38a_3.2
Table 18	A26 A27 A28 Table 38a_2.4	A26 A27 A28 Table 38a_3.4
Figure 9	A26 A27 A28 Figure 38a_2.5 A27 A28 Figure 38a_3.6	A26 A27 A28 Figure 38a_2.6 A27 A28 Figure 38a_3.5

A29. Please provide results separately for Haemophilia A and Haemophilia B patients from the BASIS trial, including people with inhibitors to increase sample size. (Tables 15-18, Figure 9, Table 33)

The proposed marketing authorisation for marstacimab is for the non-inhibitor population only. The study for the inhibitor population is ongoing. Therefore, data for this population is not yet

available for analysis. The results by haemophilia type for the non-inhibitor population are provided in A26.

A30. Please expand Appendix M Tables 102, 105, 106, 108, 109, with a column for the OLE phase.

Please find enclosed the data requested in the enclosed document labelled 'A30: OLE data'.

Data from the latest OLE data cut (October 2023) was used for these analyses.

A31. Please share details of what information was requested from the UKHCDO as this is not clear from the output provided.

The information requested from the UKHCDO was the average (mean, median, IQR) body weight and age in completed years (mean, median, IQR) for patients aged ≥ 12 years and above with severe haemophilia A or severe haemophilia B without inhibitors as this is aligned with the anticipated licence age recommendation for marstacimab. The annual UKHCDO report does not provide this information for this specific age and severity cohort.

A32. Please provide the most recent copy of the BASIS trial manuscript being submitted to a peer-reviewed journal

The company are unable to provide a copy of the draft manuscript at this time. However, the company can confirm that the publication will not contain any data that has not already been provided to you as part of this submission. Timely updates regarding the status of the publication will be provided during the appraisal.

A33. PRIORITY QUESTION: Please perform an analysis of the BASIS trial data comparing 0-6 months of follow-up in the ATP period to the 6 month OP phase. Please include results for the (1) proportion with no bleeds (s.e.), (2) ABR_{TOTAL} (s.e.), (3) $ABR_{TREATED}$ (s.e.) and (4) $AJBR_{TREATED}$ (s.e.), and the ABRs excluding people with zero bleeds for each respective outcome. If possible, please also perform the analyses using data from months 1-7 of the ATP period, and with/without censoring for dose escalation.

Although participants receiving routine prophylaxis during the OP were only followed for 6 months, routine prophylaxis is considered standard of care and it is likely these participants were receiving prophylactic treatment for a period of time before enrolment in the OP. In contrast, participants receiving marstacimab in the ATP were new to marstacimab and therefore follow-up is required to observe clinical outcomes once steady-state concentrations are reached. Additionally, except for the endpoint 'proportion with no bleed', the other endpoints are annualised bleeding rates and therefore are already adjusted for the follow-up time period. Therefore, the company believe that utilising the entirety of the 12 month ATP follow-up for analysis is most appropriate.

However, for completeness, please find enclosed the requested data for 0-6 months from BASIS ATP and OP in the enclosed document labelled 'A33: Summary of ABR Including and Excluding Zero Bleeds for Non-Inhibitor Cohort with Routine Prophylaxis at OP'.

A34. PRIORITY QUESTION: Please produce an unanchored STC comparing emicizumab in HAVEN 4 and the non-inhibitor haemophilia A cohort of BASIS marstacimab, using references below. Please account for the covariates: age (% under 18), race (% white), mean number of bleeds in prior 24 weeks, % participants with target joints, and percentage of participants with a record of one or more CV risk factors (see below). Please assess the outcomes: ABR treated, ABR joint treated and ABR total (all bleeds). Please perform this the first 24 weeks of the active trial phase (ATP) of BASIS and the defined data of the HAVEN 4 1-24 follow-up period, separately for the 25-48 weeks follow-up of each trial. Mahlangu, J. *et al.* (2024) 'Long-term outcomes with emicizumab in hemophilia a without inhibitors: Results from the haven 3 and 4 studies', *Research and Practice in Thrombosis and Haemostasis*, 8(2), p. 102364. doi:10.1016/j.rpth.2024.102364. <https://doi.org/10.1016/j.rpth.2024.102364> ,

As agreed with NICE, responses to this request will be provided separately.

A35. PRIORITY QUESTION: Please reperform the STC using the following target variables:

Age = 36.4, White = 74.6%, BMI = 25.56, Mean ABR 6.4, <9 bleeds in 24 weeks prior = 84.1%, standard half-life FVIII = 84.1%, in alignment with the MAIC conducted by Astermark et al. 2023; using data from only the first 33 weeks of BASIS ATP phase for each participant.

As agreed with NICE, responses to this request will be provided separately.

A36. PRIORITY QUESTION: Please perform a MAIC using the following matching variables:

Mean Age = 36.4, White = 74.6%, BMI = 25.56, Mean ABR 6.4, <9 bleeds in 24 weeks prior = 84.1%, standard half-life FVIII = 84.1%; and using data from only the first 33 weeks of BASIS ATP phase for each participant.

As agreed with NICE, responses to this request will be provided separately.

A37. Please provide the following data for those within the mITT (N=83), not censoring ABR for dose escalation.

Please find the data requested in Table 4. Please note that the OLE data is for the October 2023 data cut. As shown in the table below, both mean ABR_{treat} and mean AJBR_{treat} improved for participants receiving marstacimab between the ATP phase of BASIS and the OLE study with a higher proportion of participants also experiencing zero bleeding events. This trend was consistent for both haemophilia A and haemophilia B groups.

Table 4: Number of treated bleeds for mITT patients, not censoring for dose escalation

N patients	Haemophilia A			Haemophilia B		
	OP	ATP	OLE	OP	ATP	OLE
	N=65		N=58	N=18		N=17
Mean ABR _{treat} , (SD)						
N 0 bleed _{treat}						
N 1 bleed _{treat}						
N 2 bleeds _{treat}						
N ≥ 3 bleeds _{treat}						
Mean AJBR _{treat} , (SD)						
N 0 joint bleed _{treat}						
N 1 joint bleed _{treat}						
N 2 joint bleeds _{treat}						
N ≥ joint 3 bleeds _{treat}						
N Discontinued						

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; OLE: open label extension; OP: observational phase; SD: standard deviation.

A38. Please present Appendix Section N.2.3, the analysis split by SHL and EHL, restricted to those with Haemophilia A. It would be much appreciated if this could also be presented for those with Haemophilia B though the EAG notes the small patient numbers and the possible difficulties of inference that may arise from this.

Data informing the distribution of haemophilia A patients receiving SHL or EHL factor prophylaxis into the bleeds and no bleeds health states are presented in Table 5, with efficacy data for factor prophylaxis, grouped by haemophilia A patients receiving either SHL or EHL products are presented in Table 6.

Table 5: The proportion of haemophilia A patients with 0 bleeds and ≥ 1 bleed after 6 months of routine SHL or EHL factor prophylaxis during the OP (17th April 2023 data cut-off; mITT analysis set)

	Routine SHL prophylaxis during OP	Routine EHL prophylaxis during OP
0 bleeds, n (%)		
≥ 1 bleed, n (%)		

Abbreviations: EHL: extended half-life; mITT: modified intention to treat; OP: observational phase; SD: standard deviation; SHL: standard half-life.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024, Tables 22a_11.9a and 22a_11.9b¹⁷

Table 6: ABR_{treat} and AJBR_{treat} in patients with haemophilia A after 6 months of routine SHL or EHL factor prophylaxis during the OP (17th April 2023 data cut-off; mITT analysis set)

	Routine SHL prophylaxis and >0 bleeds during OP	Routine EHL prophylaxis and >0 bleeds during OP
ABR _{treat}		
Mean (SD)		
AJBR _{treat}		
Mean (SD)		

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; EHL: extended half-life; mITT: modified intention to treat; OP: observational phase; SHL: standard half-life.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024, Tables 22a_11.9a, 22a_11.9b, 22a_12.9a, 22a_12.9b¹⁷

Data informing the distribution of haemophilia B patients receiving SHL or EHL factor prophylaxis into the bleeds and no bleeds health states are presented in Table 7, with efficacy data for factor prophylaxis, grouped by haemophilia B patients receiving either SHL or EHL products are presented in Table 8. The results of these subgroup analyses should be interpreted with caution for the following two reasons: 1) these are informed by very small patient numbers (particularly in the haemophilia B subgroup, as noted by the EAG) and 2) the BASIS trial was not powered to detect statistically significant differences between marstacimab and factor prophylaxis within subgroups.

Table 7: The proportion of haemophilia B patients with 0 bleeds and ≥ 1 bleed after 6 months of routine SHL or EHL factor prophylaxis during the OP (17th April 2023 data cut-off; mITT analysis set)

	Routine SHL prophylaxis during OP	Routine EHL prophylaxis during OP
0 bleeds, n (%)		
≥ 1 bleed, n (%)		

Abbreviations: EHL: extended half-life; mITT: modified intention to treat; OP: observational phase; SD: standard deviation; SHL: standard half-life.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024, Tables 22a_11.9a and 22a_11.9b¹⁷

Table 8: ABR_{treat} and AJBR_{treat} in patients with haemophilia B after 6 months of routine SHL or EHL factor prophylaxis during the OP (17th April 2023 data cut-off; mITT analysis set)

	Routine SHL prophylaxis and >0 bleeds during OP	Routine EHL prophylaxis and >0 bleeds during OP
ABR_{treat}		
Mean (SD)		
AJBR_{treat}		
Mean (SD)		

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; EHL: extended half-life; mITT: modified intention to treat; OP: observational phase; SHL: standard half-life.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024, Tables 22a_11.9a, 22a_11.9b, 22a_12.9a, 22a_12.9b ¹⁷

A39. Please provide the equivalent of Appendix M Table 101 for those with dose escalation during the OLE phase with treatment duration based upon the OLE phase.

Please find the requested data below in Table 9.

Table 9: Comparison of ABR_{treat} and treatment duration before and after the dose increase for participants with a dose increase during the OLE (October 2023 data cut-off)

	Before dose increase	On or after dose increase
Treatment duration (Days)		
Mean (SD)		
Median (Range)		
ABR_{treat}		
Mean (SD)		
Median (Range)		

If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.

Abbreviations: ABR: annualised bleeding rate; SD: standard deviation.

A40. For the mITT (N=83) set 11 patients dose escalating during the ATP phase and the 4 patients dose escalating during the OLE phase. Please provide information on their haemophilia type, days on 150mg and days on 300mg during the ATP phase and corresponding ATP ABR_{TREAT} and days on 150mg and days on 300mg during the OLE phase and corresponding OLE ABR_{TREAT} could be presented as per the following table. Please also outline which if any of the 14 ATP dose escalations who went forward to the OLE phase and the 4 OLE dose escalations subsequently discontinued during the OLE.

Please find the data requested in Table 10.

Table 10: Treatment information for individuals who received marstacimab dose escalation during the BASIS trial ATP phase

ATP phase dose escalators: ATP phase data								
150 mg					300 mg			
Haem	Number	Days (SD)	ABR _{treat}	Disc	Number	Days (SD)	ABR _{treat}	Disc
A	■	■	■	■	■	■	■	■
B	■	■	■	■	■	■	■	■

ATP phase dose escalators: OLE phase data								
150 mg					300 mg			
Haem	Number	Days (SD)	ABR _{treat}	Disc	Number	Days (SD)	ABR _{treat}	Disc
A	■	■	■	■	■	■	■	■
B	■	■	■	■	■	■	■	■

OLE phase dose escalators: OLE phase data								
150 mg					300 mg			
Haem	Number	Days (SD)	ABR _{treat}	Disc	Number	Days (SD)	ABR _{treat}	Disc
A	■	■	■	■	■	■	■	■
B	■	■	■	■	■	■	■	■

*A subject with haemophilia A dose escalated in the ATP phase and completed the BASIS study but not entered into OLE.**A subject with haemophilia B did not escalate in BASIS study but escalated on the same day of treatment start date of OLE due to which the subject is not having 150 mg data in the OLE.

Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; Disc: discontinued; OLE: open label extension; SD: standard deviation

SLR

A41. Please provide a list of relevant ongoing studies that would otherwise meet the eligibility criteria.

Ongoing studies that would otherwise potentially meet eligibility are listed below:

- Explorer 8 (NCT04082429)
- FRONTIER 2 (NCT05053139): This study did not specify disease severity for haemophilia A at the time of the SLR so this additional detail is required to determine eligibility.

A42. The CS states the criteria are presented according to the Population, Intervention, Comparators, Outcomes, Timing, and Study design (PICOTS) format. Table 15 does not list criteria for Timing – what was this and was it specified *a priori*?

The timing information was incorrectly included in the 'Language and temporal limits' row on Table 15 instead of a standalone 'Timings' row. The timing criteria was for publications published in 2000 or later and was specified *a priori*.

A43. Please provide clarification on the numbers of search results for the clinical SLR. The numbers of records identified via database searches recorded in Appendix D.1.3 and the PRISMA diagram (Fig. 1) do not match those in the search strategy tables (Tables 1-12) in Appendix D.1.1. For example, for Embase:

2023 update (Table 1):	407
2024 update (table 1):	1,498
original search; haemophilia A (table 2):	1,200
original search; haemophilia B (Table 3):	453
Total Embase results:	3,588 (not 4,524 as recorded in Appendix D.1.3 text and Fig. 1)

Additionally, results from EconLit and NHS EED are recorded in the PRISMA diagram (Appendix D.1.3 Fig. 1) but not elsewhere for the clinical SLR.

Initially, the scope for both clinical and economics SLRs were covered in a single search strategy and screening process. In 2023 the SLRs were split out, each with separate search strategies, methods and reporting. The results in the search strategy tables provides the results related to the clinical SLR only. In contrast, the PRISMA diagram included results from the original SLR, including both the clinical and economic SLR, which explains this discrepancy.

As noted in Appendix section G.1.1. NHS Economic Evaluation Database (EED) was searched as part of the original SLR. However, this database was discontinued in 2015, and therefore were not searched as part of the SLR update. EconLIT was also not searched as part of the SLR update.

Results for the search of EconLit in 2020 are presented in Table 29 of the Appendices of the Company Submission and results of the search on NHS EED in 2020 are presented in Table 30 of the Appendices of the Company Submission.

A44. Please provide details of the search strategies used in the clinical trial registries for the original and update searches for the clinical SLR (Appendix D.1.1).

The keywords use for searching clinical trials registries for the original and updated searches were as follows:

Hemophilia A OR Hemophilia B | Interventional studies | Studies with results | Last update posted on or after 08/01/2020

A45. For the SLR of economic evidence, please provide further explanation of the process of excluding additional publications because they “did not report relevant economic outcomes” (Document B.3.1 and Appendix G.1.3). If these publications did not report relevant economic outcomes then presumably they did not meet the SLR eligibility criteria, so why were they included in the review in the first place? Were the eligibility criteria amended between the original and update SLRs?

As described in Appendix G.1, the original SLR was conducted to identify clinical and economic evidence in severe haemophilia A or severe haemophilia B. Of note, within Appendices G, H and I, the company presented the eligibility criteria relevant to the three economic streams of the original SLR (i.e. economic evaluations, HRQoL/utility and HCRU); eligibility criteria specific to the clinical stream of the original SLR were not presented in Appendices G, H and I. The clinical stream was not updated as part of the SLR update.

The 123 articles that did not report on economic outcomes were included in the original SLR as they reported on clinical outcomes only and were therefore not relevant to the economic streams of the SLR.

A46. Please explain the following discrepancies in numbers of included studies for the economic SLR (all three evidence streams):

- Regarding the original (2020) SLR, Document B.3.1 states: “A total of 192 publications did not report relevant economic outcomes, resulting in 84 publications being included in the review” whilst Appendix G.1.3 reports : “A total of 123 publications did not report relevant economic outcomes, resulting in 153 publications being included in the review.”

This is a slight error in the Company Submission, the company can confirm that the sentence and numbers in Appendix G.1.3 are correct.

- Document B.3.1 states: “In total, 134 articles reporting [?missing text] included in the SLR. A full list of these studies is presented in Appendix G.” It is not clear whether this refers to the original SLR only, or the original and

updates and an overall list of the included studies/publications for all 3 evidence streams is not provided in Appendix G.

This text applies to the updates only. In terms of the overall list of included studies/publications, Tables 75 and 76 (Appendix G), 82 and 83 (Appendix H) and 86 and 87 (Appendix I), when considered together, list out all studies which met the eligibility criteria for the economic streams across the original and update SLRs.

- **Document B.3.3.3 states that: “In total, seven articles reporting on six unique studies were included in the SLR of HRQoL studies”, whereas Appendix H.1.3 and the PRISMA diagram (Appendix G.1.3 Fig. 1) report that 10 publications reporting on 8 unique studies were included.**

The company can confirm that the numbers in the appendices are correct for HRQoL studies.

- **Document B.3.4 states that: “In total, 13 articles reporting on 10 unique healthcare resource use studies were included in the SLR”, whereas Appendix I.1.3 and the PRISMA diagram (Appendix G.1.3 Fig. 1) report that 12 publications reporting on 10 unique studies were included in the costs and healthcare resource use SLR.**

The company can confirm that the numbers in the appendices are correct for HCRU studies.

A47. Please provide clarification on the numbers of search results for the original economic SLR (all three evidence streams). The numbers of records identified recorded in B.3.1 and Appendix G.3.1 (“5,519 records were retrieved from the electronic databases”) do not match those recorded in Tables 26-51, which come to a total of 2,261 records before deduplication.

The database searches for the clinical and economic streams of the original SLR yielded a total of 5,519 hits; however, the EAG is correct in that when considering the database searches relevant only to the economic streams of the original SLR, as presented in Tables 26–51 in Appendix G.3.1, 2,261 hits were identified.

A48. Please provide a list of studies excluded at full-text review during the original (2020) economic SLR (all three evidence streams), including those excluded at a later date because they “did not report relevant economic outcomes.

Please find the list of excluded studies on the “Full Text Excludes” tab of the Excel named ‘2020 SLR Study Listing’.

A49. Please provide the citations for the 79 studies listed in Table 17, indicating the primary and linked publications.

Please find enclosed a folder of the citations for these 79 studies listed in Table 17. These 79 studies are all the primary publications.

Section B: Clarification on cost-effectiveness data

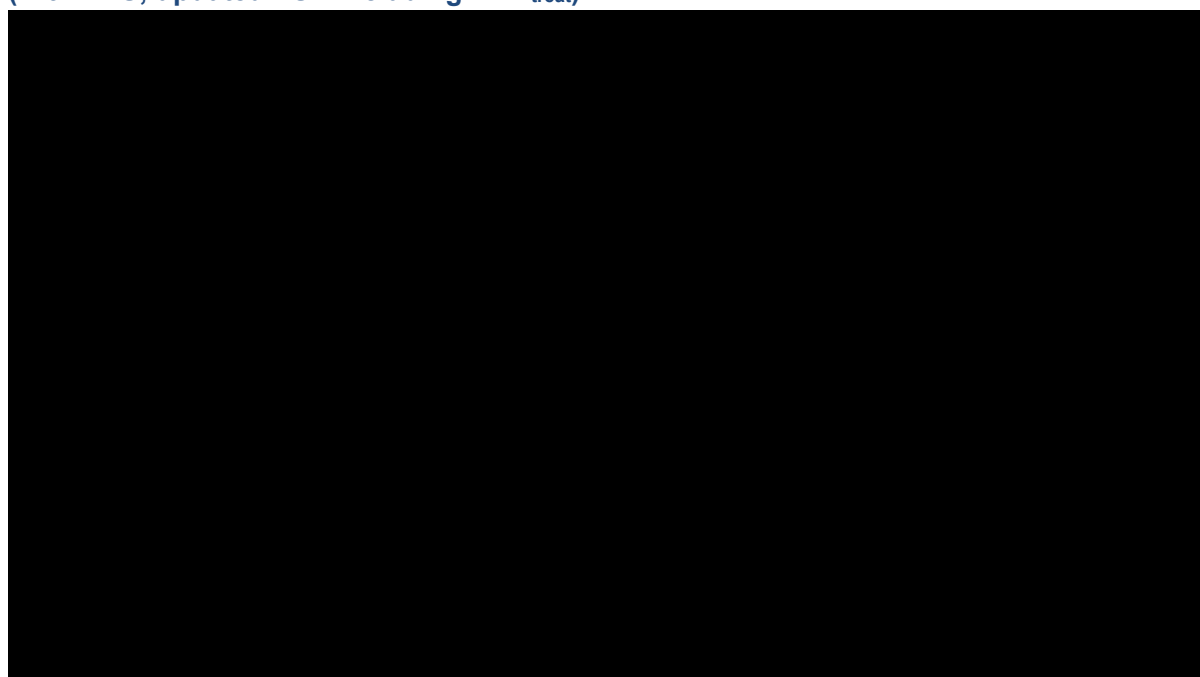
B1. Within the PSA it appears that the treated ABR is sampled but the treated AJBR is not. Is this the case and if so why? Is there a condition that imposes $ABR \geq AJBR$?

The company can confirm that within the PSA of the originally submitted economic model, the treated AJBR was sampled but the treated ABR was not (n.b. this is slightly different from what has been stated in the question above). However, the company agrees that both treated ABR and treated AJBR should ideally be sampled within the PSA (and DSA, for completeness) and that there should also be a condition imposing $ABR \geq AJBR$ in this case.

This has now been included within the updated model version provided with this response (with corresponding changes in the Parameters, DSA Inputs and PSA Inputs sheets indicated via green highlighting).

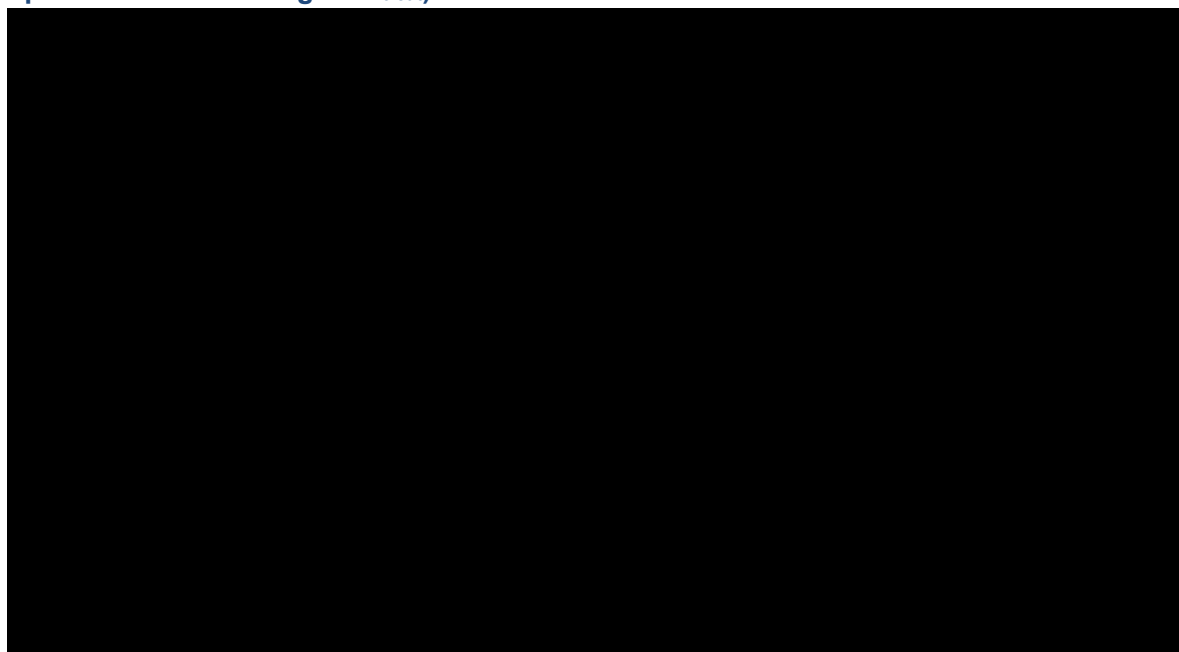
Whilst the inclusion of treated ABR leads to an overall slightly larger spread of the probabilistic results (Figure 1 and Figure 2), which is to be expected based on introducing additional uncertainty to the PSA by adding new parameters to it, the probabilistic average results are essentially unchanged from the originally submitted analyses (Table 11).

Figure 1: Probabilistic cost-effectiveness plane versus FVIII prophylaxis and emicizumab (with PAS; updated PSA including ABR_{treat})



Abbreviations: FVIII: factor VIII; PAS: patient access scheme; QALYs: quality-adjusted life years.

Figure 2: Probabilistic cost-effectiveness plane versus FIX prophylaxis (with PAS; updated PSA including ABR_{treat})



Abbreviations: FIX: factor IX; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 11: Probabilistic base-case results for marstacimab versus comparators (with PAS; updated PSA including ABR_{treat})

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Marstacimab versus haemophilia A comparators									
Marstacimab	██████	21.61	████	-	-	-	-	-	-
FVIII prophylaxis	██████	21.61	████	██████	-	████	Marstacimab is dominant	████	████
Emicizumab	██████	21.61	████	██████	-	████	£24,882,997 ^a	████	████
Marstacimab versus haemophilia B comparator									
Marstacimab	██████	21.60	████	-	-	-	-	-	-
FIX prophylaxis	██████	21.60	████	██████	-	████	Marstacimab is dominant	████	████

^a ICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: FIX: Factor IX; FVIII: factor VIII; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

B2. Please provide the mean (s.d.) IU/kg for the All safety (N=91) and the mITT (N=83) separately for each FVIII/FIX during the OP phase.

Please find the requested data in the enclosed document labelled 'B2 FVIII/FIX During the OP Phase for Non-Inhibitor Cohort with Prophylaxis at OP'. Data is presented in the unit of IU/kg per year for both the All Safety Set (N=91) and the mITT set (N=83). Due to the small sample sizes, the company recommend that this data is interpreted with caution.

B3. Please provide the mean time on treatment (s.d.) for the All Safety (N=91) and the mITT (N=83) during the OP phase, separately for SHL FVIII, EHL FVIII, SHL FIX and EHL FIX or if possible for each individual FVIII/FIX.

Please find the requested data in the enclosed document labelled 'B3 Duration of SHL FVIII/FIX and EHL FVIII/FIX During the OP Phase for Non-Inhibitor Cohort with Prophylaxis at OP'. Data is presented for days on treatment for both the All Safety Set (N=91) and the mITT set (N=83). Due to the small sample sizes, the company recommend that this data is interpreted with caution.

B4. Please present the mean (s.d.) IU/kg per treated bleed during the ATP phase split by SHL FVIII, EHL FVIII, SHL FIX and EHL FIX or if possible for each individual FVIII/FIX. Please also present this for the mean (s.d.) IU/kg per treated joint bleed.

Please find the requested data in the enclosed document labelled 'B4 SHL FVIII/FIX and EHL FVIII/FIX for Treated Bleeds and Treated Joint Bleeds During the ATP Phase for Non-Inhibitor Cohort with Prophylaxis at OP'. Data is presented in the unit of IU/kg per year for both the All Safety Set (N=91) and the mITT set (N=83). Due to the small sample sizes, the company recommend that this data is interpreted with caution.

B5. It appears that the EQ-5D was collected on a 6 monthly basis during BASIS, including during the OLE phase. Please provide the numbers eligible to report, numbers completing the EQ-5D, the median (IQR) tariff value and the mean (s.d.) EQ-5D tariff value, split by Haemophilia A and Haemophilia B and pooled across all patients for (1) the prophylaxis non-inhibitor cohort and (2) the mITT cohort. If the EAG has misinterpreted the EQ-5D collection points please amend the table accordingly.

Please find below the data requested. Data from the March 2023 data cut was used for the OLE analyses as patient reported outcomes were not analysed as part of the October 2023 OLE analysis. The numbers reporting EQ-5D values, the median (IQR) EQ-5D index score and the mean (SD) EQ-5D index score are presented for the ATP and OLE in Table 12 and Table 13, respectively, below. Please note the numbers *eligible* to report were not reported.

ATP

Table 12: EQ-5D data reported in the BASIS ATP

	Reporting	Median (IQR)	Mean (SD)
Haemophilia A			
Baseline	■	■	■
6 months	■	■	■
12 months	■	■	■
Haemophilia B			
Baseline	■	■	■
6 months	■	■	■
12 months (if applicable)	■	■	■
Haemophilia A+B			
Baseline	■	■	■
6 months	■	■	■
12 months	■	■	■

Please note that the EQ-5D data is the same for the all-safety and mITT cohorts as EQ-5D measurements reported in this table started in the ATP.

Abbreviations: ATP: active treatment phase; mITT; modified intention to treat; IQR: interquartile range; SD: standard deviation.

OLE

Table 13: EQ-5D data reported in the BASIS OLE

	Reporting	Median (IQR)	Mean (SD)
Haemophilia A			
Baseline	■	■	■
6 months	■	■	■
12 months	■	■	■
Haemophilia B			
Baseline	■	■	■
6 months	■	■	■
12 months	■	■	■
Haemophilia A+B			
Baseline	■	■	■
6 months	■	■	■
12 months	■	■	■

Abbreviations: IQR: interquartile range; OLE: open-label extension; SD: standard deviation.

B6. Please provide the BASIS mITT (N=83) patient weights split by Haemophilia type, pooled into those aged 12-14, 15-18, 19-29 and 30+. What proportions of the mITT (1) Haemophilia A adult patients, (2) Haemophilia A adolescent

patients, (3) Haemophilia B adult patients and (4) Haemophilia B adolescent patients were above 50kg at baseline?

Patients enrolled in the BASIS trial were younger and had a lower mean body weight compared with UKHCDO data (UK registry data). Therefore, to ensure the baseline characteristics in the model are most aligned with the UK clinical population, the baseline characteristics of patients studied in the UKHCDO analysis were used in the company's submission. Clinical experts consulted as part of this submission agreed that the average body weight derived from the UKHCDO of █ kg was more representative of their patients' weight than that in the BASIS study. In summary, the company believe the body weight data from the UKHCDO is most appropriate and representative of a UK population.

However, for completeness, please find the requested data from BASIS in Table 14. The proportion of each age group who were equal to or above 50 kg at baseline are as follows: Haemophilia A adult patients (█%), Haemophilia A adolescent patients (█%), Haemophilia B adult patients (█%) and Haemophilia B adolescent patients (█%).

Table 14: BASIS trial patient weights split by haemophilia type

Age	Haemophilia A patients (N=65)			Haemophilia B patients (N=18)		
	N	Weight (kg) Mean (min, max)	SD	N	Weight (kg) Mean (min, max)	SD
12-14	█	█	█	█	█	█
15-18	█	█	█	█	█	█
19-29	█	█	█	█	█	█
30+	█	█	█	█	█	█

Abbreviations: kg: kilogram; SD: standard deviation.

B7. Please confirm whether the various ABRs used in the economic model have come from fitting a GEE model or not (e.g. Table 30). Please provide ABR estimates from whichever approach is currently omitted.

All ABRs used within the economic analysis have been directly derived from BASIS trial observations and did not include any additional fitting (see Document B, Table 30 of the Company Submission for the values used in the model base case). These were deemed the most appropriate choice for the purpose of the model given they lead to consistent results between subgroups, which may not be the case for independently fitted subgroup ABR sets and represent the actual rates of bleeds seen in the BASIS trial.

As demonstrated in Table 15 for the model base case-relevant parameters, GEE model-fitted ABR_{treat} and $AJBR_{treat}$ estimates do not significantly differ from the trial-observed equivalent values, it would therefore not be expected that their possible inclusion would change the results and conclusion of the economic analysis.

Table 15: Comparison of trial-observed and model derived ABR values

	Routine prophylaxis and >0 bleeds during OP	Marstacimab prophylaxis and >0 bleeds during ATP

	(N=50)	(N=52)
<i>Trial-observed values (used in the economic analysis)</i>		
ABR_{treat}		
Mean (SD)	13.09 (14.478)	7.53 (8.164)
AJBR_{treat}		
Mean (SD)	9.43 (12.758)	6.09 (7.634)
<i>Values using the GEE model fit^a</i>		
ABR_{treat}		
Estimate (95% CI)	13.02 (9.06, 16.98)	7.37 (5.23, 9.51)
AJBR_{treat}		
Estimate (95% CI)	9.39 (5.90, 12.88)	5.96 (3.95, 7.98)

^a Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; CI: confidence interval; GEE: generalise estimating equation; OP: observational phase; SD: standard deviation.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Company evidence submission

Appendices

August 2024

File name	Version	Contains confidential information	Date
ID6342_Marstacimab_Haemophilia A and B_NICE Appendices_28AUG2024_[NoCON]	Final	No	28 th August 2024

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

C.1 SmPC

A draft summary of product characteristics (SmPC) for marstacimab is provided as part of the reference pack for this submission.

C.2 UK public assessment report

The marketing authorisation for marstacimab is anticipated to be granted by the Medicines and Healthcare products Regulatory Agency (MHRA) in [REDACTED]. Therefore, the public assessment report is not yet available to be included in this submission. This will be provided by Pfizer once available.

Appendix D Identification, selection and synthesis of clinical evidence

D.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted on the 4th August 2020 (original SLR) and subsequently updated on the 21st August 2023 and 17th May 2024. The objective of the SLR was to identify all relevant clinical efficacy and safety evidence for marstacimab and relevant comparator therapies for the treatment of severe haemophilia A and moderately severe to severe haemophilia B without a history of factor VIII or IX inhibitors. The SLR was wider in scope than the proposed indication in this submission, as it additionally included patients with moderately severe haemophilia B. This reflects the enrolment protocol for the BASIS trial, however, the trial ultimately did not enrol any patients with moderately severe haemophilia B.

The SLR was performed in accordance with the methodological principles of conduct for SLRs as detailed in the Cochrane Handbook for Systematic Reviews of Interventions¹ and guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the National Institute for Health and Care Excellence (NICE).^{2, 3}

D.1.1. Search strategy

Electronic database searches

Across the original SLR and the 2023 and 2024 SLR updates, the following electronic databases were searched via the OvidSP® platform:

- MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts of Reviews of Effects (DARE)

The original SLR was limited to records published after 2000 to capture the most relevant and recent evidence reflecting current treatments that have become available during the last decade. DARE was discontinued in 2015; therefore, only the archived databases (until 2015) were searched.

Search terms used for the electronic database searches are presented below (Table 1–Table 14). The search terms for each database included a combination of free-text search terms and controlled vocabulary terms. Searches were restricted to studies conducted in humans and published in English.

The 2024 update used the same strategy as 2023, however the following amendments were made to the search strategy between the 2020 SLR and the first update in 2023.

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- The searches were modified from the 4th August 2020 search strategy to combine the terms for haemophilia A and haemophilia B together and to remove terms for economic and observational studies
- The Embase search strategy was expanded to include any conference indexed in the database
- Terms related to publication type that were not relevant to the Cochrane Central Register of Controlled Trials were removed (i.e., terms to limit to clinical trials or exclude review articles are not needed as only records of clinical trials are included in this database)
- The DARE database was not searched in 2023 or 2024 as the database has been discontinued in 2015

Table 1: Search terms used for EMBASE in the clinical SLR updates

#	Searches	Results (2023 SLR update) Date searched: 21 st August 2023	Results (2024 SLR update) Date searched: 17 th May 2024
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab. or hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	35,456	44,733
2	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 ((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))).tw. or Placebos/ or Placebo\$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or single-arm).tw. or (non-random* or single group assign*).tw.	4,925,574	5,180,250
3	1 and 2	7,442	9,202
4	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,915,325	4,045,040
5	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,956,596	3,057,987
6	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	11,706,947	12,165,127

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

#	Searches	Results (2023 SLR update) Date searched: 21 st August 2023	Results (2024 SLR update) Date searched: 17 th May 2024
7	4 or 5 or 6	17,310,329	17,945,765
8	3 not 7	4,347	5,458
9	limit 8 to english language	4,211	1,498
10	limit 9 to (yr="2020 -Current" and (article or article in press))	383	
11	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,593	N/A
12	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691	N/A
13	Annual Meeting of the American Society of Hematology.cf,cg.	58,296	N/A
14	World Federation of Hemophilia.cf,cg.	3,737	N/A
15	european hematology association.cf,cg.	27,516	N/A
16	or/11-15	101,833	N/A
17	limit 16 to yr="2020 -Current"	6,528	N/A
18	9 and 17	24	N/A
19	10 or 18	407	N/A

Abbreviations: SLR: systematic literature review.

Table 2: Search terms used for EMBASE in the 2020 original clinical SLR (clinical outcomes for haemophilia A)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	25,601
2	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 ((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))).tw. or Placebos/ or Placebo\$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or single-arm).tw. or (non-random* or single group assign*).tw.	4,031,923
3	1 and 2	4,800
4	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,281,678

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
5	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,510,361
6	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	9,880,877
7	4 or 5 or 6	14,666,932
8	3 not 7	2,973
9	limit 8 to english language	2,864
10	limit 9 to (yr="2000 -Current" and (article or article in press))	1,006
11	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,587
12	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691
13	Annual Meeting of the American Society of Hematology.cf,cg.	58,296
14	World Federation of Hemophilia.cf,cg.	3,478
15	european hematology association.cf,cg.	23,576
16	or/11-15	97,628
17	limit 16 to yr="2018 -Current"	18,754
18	9 and 17	194
19	10 or 18	1,200

Abbreviations: SLR: systematic literature review.

Table 3: Search terms used for EMBASE in the 2020 original clinical SLR (clinical outcomes for haemophilia B)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	9,169
2	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 ((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))).tw. or Placebos/ or	4,031,923

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
	Placebo\$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or singlearm).tw. or (non-random* or single group assign*).tw.	
3	1 and 2	2,219
4	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,281,678
5	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,510,361
6	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	9,880,877
7	4 or 5 or 6	14,666,932
8	3 not 7	1,115
9	limit 8 to english language	1,076
10	limit 9 to (yr="2000 -Current" and (article or article in press))	398
11	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,587
12	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691
13	Annual Meeting of the American Society of Hematology.cf,cg.	58,296
14	World Federation of Hemophilia.cf,cg.	3,478
15	european hematology association.cf,cg.	23,576
16	or/11-15	97,628
17	limit 16 to yr="2018 -Current"	18,754
18	9 and 17	55
19	10 or 18	453

Abbreviations: SLR: systematic literature review.

Table 4: Search terms used in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conducted on the 21st August 2023 and 17th May 2024 (clinical outcomes for haemophilia A and B)

#	Searches	Results (2023 SLR update) Date searched: 21 st August 2023	Results (2024 SLR update) Date searched: 17 th May 2024
1	hemophilia a/ or (hemophilia or haemophilia or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab. or hemophilia b/ or (hemophilia or haemophilia or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	27,971	30,440
2	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 ((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))) .tw. or Placebos/ or Placebo\$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or single-arm).tw. or (phase adj3 trial).tw.	3,569,469	3,719,063
3	1 and 2	3,311	3,712
4	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,952,572	6,082,828
5	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,052,216	3,166,374
6	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	1,229,255	1,247,890
7	4 or 5 or 6	8,946,773	9,195,924
8	3 not 7	2,159	2,429
9	limit 8 to english language and year of last search	415	549

Abbreviations: SLR: systematic literature review.

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Table 5: Search terms used in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conducted on the 4th August 2020 (clinical outcomes for haemophilia A)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	22,991
2	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 ((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))).tw. or Placebos/ or Placebo\$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or singlearm).tw. or (non-random* or single group assign*).tw.	3,008,333
3	1 and 2	2,453
4	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,286,782
5	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,576,474
6	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	1,100,747
7	4 or 5 or 6	7,791,249
8	3 not 7	1,570
9	limit 8 to (english language and yr="2000 -Current")	995

Abbreviations: SLR: systematic literature review.

Table 6: Search terms used in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conducted on the 4th August 2020 (clinical outcomes for haemophilia B)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	5,593

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
2	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 ((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))).tw. or Placebos/ or Placebo\$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or singlearm).tw.	3,008,333
3	1 and 2	873
4	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,286,782
5	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,576,474
6	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	1,100,747
7	4 or 5 or 6	7,791,249
8	3 not 7	551
9	limit 8 to (english language and yr="2000 -Current")	364

Abbreviations: SLR: systematic literature review.

Table 7: Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted on the 21st August 2023 and 17th May 2024 (clinical outcomes for haemophilia A and B)

#	Searches	Results (2023 SLR update) Date searched: 21 st August 2023	Results (2024 SLR update) Date searched: 17 th May 2024
1	hemophilia a/ or (hemophilia or haemophilia or factor viii deficiency\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficiency\$ or ahg deficiency\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficiency\$ or classical hemophilia or classical haemophilia).ti,ab. or hemophilia b/ or (hemophilia or haemophilia or F9 deficiency\$ or christmas disease or factor ix deficiency\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficiency\$).ti,ab.	1,385	1,773
2	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	56,706	58,564

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

#	Searches	Results (2023 SLR update) Date searched: 21 st August 2023	Results (2024 SLR update) Date searched: 17 th May 2024
3	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	113,381	117,427
4	'trial registry record'.pt.	--	511,372
5	2 or 3 or 4	164,566	680,200
6	1 not 5	496	1,119
7	limit 6 to (english language and yr="2020 -Current")	88	215

Abbreviations: SLR: systematic literature review.

Table 8: Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted in the clinical SLR searches conducted on the 4th August 2020 (clinical outcomes for haemophilia A)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	893
2	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 ((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))).tw. or Placebos/ or Placebo\$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or singlearm).tw. or (non-random* or single group assign*).tw.	679,547
3	1 and 2	329
4	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	30,169
5	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,969
6	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or	89,504

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
	exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	
7	4 or 5 or 6	118,998
8	3 not 7	300
9	limit 8 to english language	198
10	limit 9 to yr="2000 -Current"	146

Abbreviations: SLR: systematic literature review.

Table 9: Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted in the clinical SLR searches conducted on the 4th August 2020 (clinical outcomes for haemophilia B)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	371
2	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 ((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or	679,547
3	tripl\$) adj (blind\$3 or mask\$3))).tw. or Placebos/ or Placebo\$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or singlearm).tw. or (non-random* or single group assign*).tw.	
4	1 and 2	141
5	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	30,169
6	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,969
7	animal cell/ or animal cell.mp. or animal experiment/ or animal experiment.mp. or animal model/ or animal model.mp. or cancer cell culture/ or cancer cell culture.mp. or human cell/ or human cell.mp. or human tissue/ or human tissue.mp. or in vitro study.mp. or nonhuman/ or nonhuman.mp. or exp biological model/ or biological model.mp. or exp cell culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	89,504
8	4 or 5 or 6	118,998
9	3 not 7	120

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
10	limit 8 to english language	92

Abbreviations: SLR: systematic literature review.

Table 10: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted on the 21st August 2023 and 17th May 2024 (clinical outcomes for haemophilia A and B)

#	Searches	Results (2023 SLR update) Date searched: 21 st August 2023	Results (2024 SLR update) Date searched: 17 th May 2024
1	(hemophilia or haemophilia or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	19	19
2	limit 1 to yr="2020-Current"	10	3

Abbreviations: SLR: systematic literature review.

Table 11: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted on the 4th August 2020 (clinical outcomes for haemophilia A)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	14
2	((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)) or Placebo\$ or Randomly allocated or (allocated adj2 random) or (single arm trial or singl* or single-arm) or (non-random* or single group assign*)).tw.	9,721
3	1 and 2	14
4	limit 3 to yr="2000-Current"	12

Abbreviations: SLR: systematic literature review.

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Table 12: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted on the 4th August 2020 (clinical outcomes for haemophilia B)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	4
2	((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)) or Placebo\$ or Randomly allocated or (allocated adj2 random) or (single arm trial or singl* or single-arm) or (non-random* or single group assign*)).tw.	9,721
3	1 and 2	4
4	limit 3 to yr="2000-Current"	4

Abbreviations: SLR: systematic literature review.

Table 13: Search terms used for the DARE; searches conducted on the 4th August 2020 (clinical outcomes for haemophilia A; database was discontinued in 2015, searches were not updated in 2023 or 2024)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).af.	13
2	((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)) or Placebo\$ or Randomly allocated or (allocated adj2 random) or (single arm trial or singl* or single-arm) or (non-random* or single group assign*)).tw.	10,573
3	1 and 2	7

Abbreviations: SLR: systematic literature review.

Table 14: Search terms used for the DARE; searches conducted on the 4th August 2020 (clinical outcomes for haemophilia B; database was discontinued in 2015, searches were not updated in 2023 or 2024)

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).af.	3

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

#	Searches	Results (original 2020 SLR) Date searched: 4 th August 2020
2	((clinic\$ adj trial\$1) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)) or Placebo\$ or Randomly allocated or (allocated adj2 random) or (single arm trial or singl* or single-arm) or (non-random* or single group assign*)).tw.	10,573
3	1 and 2	1

Abbreviations: SLR: systematic literature review.

Clinical Trial Registries

Keyword searches were conducted across the following clinical trial registries:

- ClinicalTrials.gov
- WHO ICTRP
- EMA EPARs

Clinical trial registry records were linked to trial publications when possible. Clinical trial registry records that could not be linked to a publication were only included when trial results were available. Ongoing trials with no available results were excluded.

Conferences and Congresses

Embase includes abstracts from many major conferences, dating back to 2009. As there is sometimes a delay in when conference abstracts are indexed in Embase, manual searches were conducted for the most current meeting year after each electronic database search for the following conferences.

- Congress of the International Society on Thrombosis and Haemostasis (ISTH)
- Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD)
- World Congress of the World Federation of Hemophilia (WFH)
- Annual Meeting of the American Society of Hematology (ASH)
- Annual Congress of European Hematology Association (EHA)

Bibliography searches

The bibliographies of relevant published reviews evaluating treatments for haemophilia were reviewed as another method to identify relevant studies.

D.1.2. Study selection

Studies were selected for inclusion in two stages: first, the titles and abstracts of the search results were reviewed for relevance according to the eligibility criteria for the SLR; second, the full texts of potentially relevant articles were screened in order to obtain the final list of included studies.

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The eligibility criteria for the clinical SLR are listed in Table 15. Trials meeting the PICOTS criteria after full-text review were linked (results for the same trial reported in more than one publication, the relevant reports were grouped per trial) and included for data extraction. The screening process for all records and full-text reports was recorded in an Excel file. The file included the full list of reports and the final decision regarding each inclusion or exclusion. In the case of exclusion, the reason based on the PICOTS criteria was also recorded. The criteria are presented according to the Population, Intervention, Comparators, Outcomes, Timing, and Study design (PICOTS) format.⁴

Title/abstract review

The titles and abstracts of all unique records identified from the searches were screened independently by two reviewers with disagreements adjudicated by a third reviewer. Trials meeting the PICOTS criteria after full-text review were linked (results for the same trial reported in more than one publication, the relevant reports were grouped per trial) and included for data extraction. The screening process for all records and full-text reports was recorded in an Excel file. The file included the full list of reports and the final decision regarding each inclusion or exclusion. In the case of exclusion, the reason based on the PICOTS criteria was also recorded.

Furthermore, DistillerSR's artificial intelligence technology was used to re-screen all excluded records and assign each a probability of likelihood for inclusion based on the final inclusion and exclusion decisions of each record. Any reference with a probability ranking over 85% was re-screened by a third reviewer.

Full-text review

Each full-text of relevant records identified from the title and abstract screening was then reviewed against the eligibility criteria by two independent reviewers, with disagreements adjudicated by a third reviewer (Table 15). Trials meeting the PICOTS criteria after full-text review were linked (results for the same trial reported in more than one publication, the relevant reports were grouped per trial) and included for data extraction. The screening process for all records and full-text reports was recorded in an Excel file. The file included the full list of reports and the final decision regarding each inclusion or exclusion. In the case of exclusion, the reason based on the PICOTS criteria was also recorded.

Table 15: Eligibility criteria for the clinical SLR

	Inclusion criteria	Exclusion criteria
Population	- Adult or adolescent male patients (age 12 to 75 years) with inherited severe haemophilia A (defined as FVIII <1%) or moderately severe to severe haemophilia B (defined as FIX activity ≤2%) without a history of FVIII or FIX inhibitors and are undergoing any treatment for haemophilia - For studies that included patients of any age, the trial will be included if data were reported separately for patients 12 years or older - For trials that included populations with any severity of haemophilia, the trial will be included if data were	- Studies on other diseases - Studies on patients with acquired haemophilia - Studies not among patients with severe haemophilia A or moderately severe to severe haemophilia B without history of FVIII or FIX inhibitors, or studies that did not report data separately for these subpopulations - Studies with only subpopulations (e.g., with specific comorbidities or

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	Inclusion criteria	Exclusion criteria
	reported separately for patients with severe haemophilia A or moderately severe to severe haemophilia B ○ For trials that included patients with or without inhibitors, the trial will be included if data were reported separately for patients without inhibitors	undergoing surgery)
Intervention	Any haemostatic agent or conventional treatment, such as replacement therapies for haemophilia A or B, including on-demand and prophylaxis treatment, standard and extended half-life, or nonfactor therapy, such as bispecific antibodies rebalancing agents, or gene therapy. Specific eligible treatments include: • Topical haemostatic agents (e.g., fibrin glue) • Antifibrinolytic agents (e.g., tranexamic acid) • Desmopressin (DDAVP) • Blood products (e.g., cryoprecipitate, fresh frozen plasma, plasma-derived) • Clotting factors (plasma-derived factors concentrates, recombinant factor concentrates) ○ Standard half-life FVIII replacement therapy, including octocog alfa (Advate®), moroctocog alfa (ReFacto AF®), turoctocog alfa (NovoEight®), simoctocog alfa (Nuwiq®) ○ Extended half-life FVIII replacement therapy, including turoctocog alfa pegol (Esperoct®), efmoroctocog alfa (Eloctate®), ruriotocog alfa pegol (Adynovi®), lonoctocog alfa (Afstyla®), efanesoctocog alfa (Altuviio®), damoctocog alfa pegol (Jivi®) ○ Standard half-life FIX replacement therapy, including nonacog alfa (BeneFIX®), nonacog gamma (Rixubis®) ○ Extended half-life FIX replacement therapy, including eftrenonacog alfa (Alprolix®), albutrepenonacog alfa (Idelvion®), nonacog beta pegol (Refixia®), dalcinonacog alfa • Emicizumab (Hemlibra®) • Rebalancing agents ○ Marstacimab ○ Fitusiran ○ Concizumab (Alhemo®)	• Studies on interventions not intended for the treatment of haemophilia (e.g., pre or postsurgery protocols)

	Inclusion criteria	Exclusion criteria
	- Gene therapies - Valoctocogene roxaparvovec (Roctavian®) - Giroctocogene fitelparvovec - Etranacogene dezaparvovec (Hemgenix®) - Fidanacogene elaparvovec (Beqvez®, Durveqtix®)	
Comparator	Any of the above interventions or none (no comparison is required)	NA
Outcomes	Clinical outcomes: - Total annualised bleeding rate (ABR) - Treated ABR - Proportion of patients with zero total bleeds - Proportion of patients with zero treated bleeds - Proportion of patients with spontaneous bleeds - Number of patients with spontaneous bleeds - Proportion of patients with traumatic bleeds - Number of patients with traumatic bleeds - Joint arthropathy - Total annualised joint bleeding rate (AJBR) - Treated AJBR - Pettersson score - Number of patients with target joint bleeds - Hemophilia Joint Health Score (HJHS) - Annualised infusion rate (AIR) - Dose and total factor consumption - Patient-reported outcomes (PROs) - EuroQol 5-Dimension (EQ-5D) score - Haemophilia Quality of Life (Haem A QoL) score - Haemophilia Activities List (HAL) score - Safety outcomes, including toxicity, immune response, liver damage, inhibitor (low titre and high titre), thromboembolic events and infusion related reactions	Publications that only report data on following types of outcomes including: - Laboratory-based studies that report on cellular work (ex vivo) or biomarker analyses that are not correlated with outcomes of interest - Validation/accuracy of diagnostic techniques/tests - Pharmacokinetics/pharmacodynamics
Study Design	Clinical outcomes: Clinical trials (phase II/III RCTs, single-arm, non-RCTs) SLRs are not eligible for inclusion; however, SLRs reporting clinical outcomes will be used to identify articles of importance that	Publications of the following types: - Animal studies - In vitro/ex vivo studies - Gene expression/protein expression studies

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	Inclusion criteria	Exclusion criteria
	may not have been identified during search or screening	• Narrative publications • Non-systematic reviews • Phase I studies • Case studies • Case series • Case reports • Editorials
Geographical limits	• No restrictions	• N/A
Language and temporal limits	• English language reports • Published in 2000 or later	• Reports not available in English • Published before 2000

Abbreviations: ABR: annualised bleeding rate; AIR: annualised infusion rate; AJBR: annualised joint bleeding rate; FIX: Factor IX; FVIII: Factor VIII; Haem A QoL: Haemophilia Quality of Life Questionnaire; HAL: Haemophilia Activities List; HJHS: Haemophilia joint health score; PRO: patient reported outcome; N/A: not applicable; RCT: randomised controlled trial; SD: standard deviation; SLR: systematic literature review.

Study extraction

Data extraction was trial-based (i.e., multiple records of the same trial were linked as one study) and was conducted by one reviewer. A second reviewer verified 100% of the data extraction, and a third reviewer was consulted to resolve disagreements as necessary. The data elements extracted for each study are presented in Table 16.

Table 16: Variables extracted for each study included in the clinical SLR

Topic	Data extracted
Publication details	• Author(s) • Title • Journal • Year • Publication type • Trial name • Trial ID or NCT
Study characteristics	• Study objectives (copy/paste) • Study design ○ Number of groups ○ Crossover (yes/no) ○ Blinding, if yes, explanation of blinding methods • Trial phase • Duration of controlled period • Duration of long-term follow-up • Start date and end date of trial • Multicentre or single centre, if multi-centre, number of centres • Countries • Trial setting • Haemophilia type (A, B, or both) • Definition of severity • Inclusion criteria

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Topic	Data extracted	
	- Exclusion criteria - Subgroup data reported (yes/no) - Intervention, name and description - Comparator, name and description - Outcomes reported - Frequency of evaluation - Statistical analyses methods - Number of patients: screened, randomised, completed, analysed (ITT population, completers, safety population, efficacy population)	
Patient characteristics	- Demographics (gender, race/ethnicity) - Age (unit, mean, median, SD, 95% CI, interquartile range, range, % ≥12 years, % ≥18 years) - Weight (unit, mean, SD, range) - BMI (unit, mean, SD, range) - Factor level (as reported by trial authors) - Disease severity (description, percentage) - Duration since diagnosis (mean, SD, median, range) - Age at diagnosis (mean, SD, median, range) - Previously treated information (yes/no; if yes, description, type and duration) - Prior therapies (mean, SD, percentage) - Prior total bleeds (ABR, number, category) - Prior treated bleeds (ABR, number, category) - Prior target joints (AJBR, number, category) - Neutralising antibodies (percentage) - Inhibitors (percentage) - Comorbidities description (copy/paste)	
Treatment characteristics	- Treatment type - Treatment name - Dose and route of administration - Treatment dose type	
Outcomes*	Safety	Type of outcome
	Proportion of any ≥ grade 3 AEs	Binary
	Proportion of SAEs	Binary
	Proportion of overall discontinuations	Binary
	Proportion of discontinuations due to AEs	Binary
	Proportion of treatment-emergent and treatment-related AEs	Binary
	Proportion of liver damage	Binary
	Proportion of inhibitor development	Binary
	Proportion of low titre inhibitors AE	Binary
	Proportion of high titre inhibitors AE	Binary
	Proportion of thromboembolic events	Binary

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Topic	Data extracted	
	Proportion of infusion reactions	Binary
	Proportion with ALT elevation	Binary
	Proportion requiring steroid use	Binary
	Efficacy	
	Total ABR	Rate
	Treated ABR	Rate
	Proportion of patients with zero total bleeds	Binary
	Proportion of patients with zero treated bleeds	Binary
	Proportion of patients with spontaneous bleeds	Binary
	Number of patients with spontaneous bleeds	Continuous
	Proportion of patients with traumatic bleeds	Binary
	Number of patients with traumatic bleeds	Continuous
	Total AJBR	Rate
	Treated AJBR	Rate
	Pettersson score	Continuous
	Number of patients with target joint bleeds	Continuous
	Haemophilia joint health score (HJHS)	Continuous
	Annualised infusion rate	Rate
	Number of infusions per patient	Continuous
	Dose and total factor consumption; dose per infusion, annual total dose, total consumption timeframe	Continuous
	Patient-reported outcomes (PROs)	
	EQ-5D score	Continuous
	Haem A QoL score	Continuous
	HAL score	Continuous

* The definition, type, number, variance, and timepoint were captured for all outcomes

Abbreviations: ABR: annualised bleeding rate; AE: adverse event; AJBR: annualised joint bleeding rate; ALT: alanine transaminase; CI: confidence interval; ITT: intention to treat; SAE: serious adverse event; SD: standard deviation.

Quality assessment

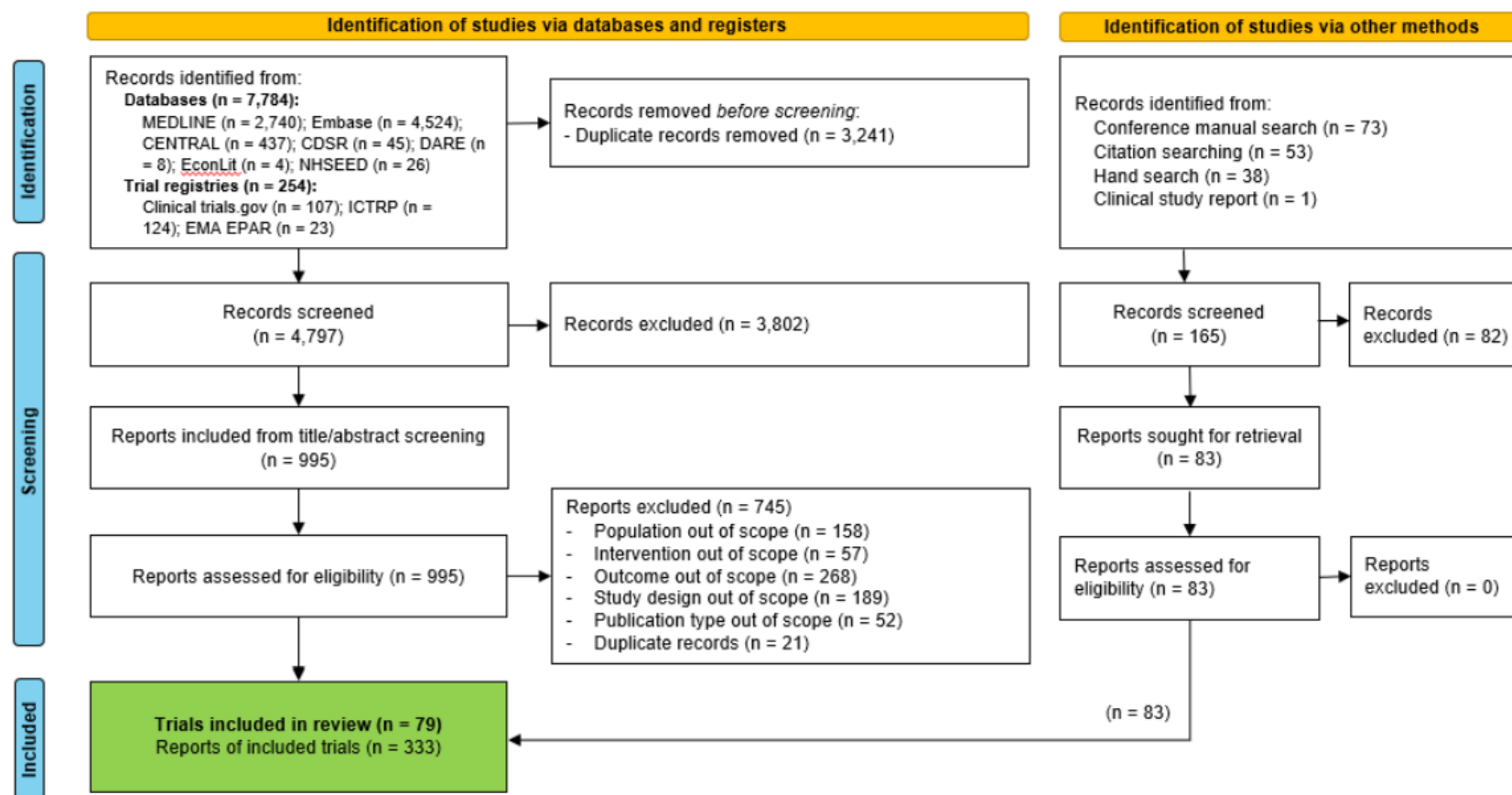
As recommended by NICE, the quality assessment of all included studies was conducted using the Cochrane Risk of Bias Assessment Tool 2 (RoB 2) for RCTs. In addition, non-randomised trials including single-arm trials were assessed using a modified version of the Downs and Black Checklist.

D.1.3. Complete reference lists for included studies and excluded studies

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A total of 8,038 records were identified. After de-duplication, 4,797 records were screened at the title/abstract stage, of which 995 progressed to the full-text review stage. Following the full-text screening and considering the 165 records identified in the grey literature searches, a total of 79 trials, reported in 333 records were included. The PRISMA diagram for the SLR is shown in Figure 1.

Figure 1: PRISMA diagram for the clinical SLR (Original SLR, and 21st August 2023 and 17th May 2024 updates combined)



Abbreviations: SLR: systematic literature review.

Included studies

A full list of the studies included in the clinical SLR, including an overview of these studies, is presented in Table 17.

Table 17: List of studies included in the clinical SLR

	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
1.	BASIS, NCT03938792	Clinical Study Report, 2024	A and B	Phase 3 one-way crossover single-arm trial	Bulgaria, Canada, China, Croatia, France, Hong Kong, India, Italy, Japan, Republic of Korea, Mexico, Oman, Russian Federation, Saudi Arabia, Serbia, South Africa, Spain, Turkey, US	Marstacimab (PF-06741086), Factor replacement (lead-in)	128	Include
2.	NCT03363321	Mahlangu, 2023	A and B	Phase 2 open label, non-RCT	Brazil, Chile, Croatia, Poland, South Africa, Switzerland, US	Marstacimab (PF-06741086), Different dosing	20	Exclude, later phase results available
3.	Atlas-PPX, NCT03549871	Kenet, 2023	A and B	Phase 3 open label, single-arm trial	Australia, China, Denmark, France, Ireland, Israel, Italy, Japan, Korea, Malaysia, Mexico, Turkey, Ukraine, UK, US	Fitusiran (SAR439774), Clotting factor concentrates (lead-in)	80	Exclude, not a relevant comparator
4.	ATLAS-A/B, NCT03417245	Srivastava, 2023	A and B	Phase 3 open label, RCT	Australia, China, Denmark, France, Germany, Hungary, India, Israel, Italy, Japan, South Korea, Malaysia, South Africa, Taiwan, Turkey, Ukraine, UK, US	Fitusiran (SAR439774), Clotting factor concentrates	120	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
5.	Explorer 8, NCT04082429	Chowdary 2023	A and B	Phase 3 open label, RCT	Algeria, Australia, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Denmark, Estonia, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Lithuania, Malaysia, Mexico, Poland, Portugal, Russian Federation, Serbia, Slovakia, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, UK, US	Concizumab (Alhemo™), No prophylaxis	148	Exclude, baseline data not available (trial is ongoing and will be reassessed as more data become available)
6.	NR	Lindvall, 2012	A and B	Crossover RCT (Phase NR)	Sweden	FVIII and FIX products, Different regimens, prophylaxis, on-demand	13	Exclude, not a relevant comparator
7.	Explorer 5, NCT03196297	Shapiro, 2019	A only	Phase 2 open-label, single-arm trial	France, Germany, Italy, Japan, Spain, Sweden, Thailand, Turkey, UK, Ukraine, US	Concizumab (Alhemo™), NA	36	Exclude, later phase results available
8.	GENEr8-1, NCT03370913	Mahlangu, 2023	A only	Phase 3 open-label, single-arm trial	Australia, Belgium, Brazil, France, Germany, Israel, Italy, Korea, South Africa, Spain, Taiwan, UK, US	Valoctocogene roxaparvovec (ROCTAVIAN™), NA	134	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
9.	GENEr8-3, NCT04323098	NA	A only	Phase 3 open-label, single-arm trial	Australia, Brazil, Taiwan, US	Valoctocogene roxaparvovec (ROCTAVIAN™), NA	22	Exclude, not a relevant comparator
10.	BMN 270-201, NCT02576795, EudraCT number, 2014-003880-38	Rangarajan, 2017	A only	Phase 1/2 open-label, dose-escalation, single-arm trial	UK	Valoctocogene roxaparvovec (ROCTAVIAN™), Different dosing	9	Exclude, later phase results available
11.	Alta study, NCT03061201	Leavitt, 2024	A only	Phase 2 open-label, dose ranging, non-RCT	US	Giroctocogene fitelparvovec (PF-07055480), Different dosing	11	Exclude, later phase results available
12.	GO-8, NCT03001830	Chowdary, 2023	A only	Phase 1/2 open-label, single-arm trial	UK, US	Factor VIII variant (AAV-HLP-hFVIII-V3), NA	12	Exclude, baseline data not available
13.	SPK-8011-101/ SPK-8011/8016-LTFU, NCT03003533 / NCT03432520	George, 2021	A only	Phase 1/2 open-label, non-RCT	Australia, Canada, Israel, Thailand, US	SPK-8011, Different dosing	18	Exclude, baseline data not available
14.	NCT03588299	Pipe, 2020	A only	Phase 1/2 open-label, single-arm trial	France, Germany, the Netherlands, Bulgaria, UK, US	Peboctocogene camaparvovec (BAY 2599023; AAVhu37FVIII), NA	2	Exclude, baseline data not available

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
15.	HAVEN 3, NCT02847637	Mahlangu, 2018	A only	Phase 3 open-label, partial RCT	Australia, Costa Rica, France, Germany, Ireland, Italy, Japan, Poland, Republic of Korea, Spain, South Africa, Taiwan, UK, US	Emicizumab (HEMLIBRA®), Dose escalation, no prophylaxis, and dose maintenance	152	Include
16.	HAVEN 4, NCT03020160	Pipe, 2019	A only	Phase 3 open-label, single-arm trial	Australia, Belgium, Japan, Poland, Spain, US	Emicizumab (HEMLIBRA®), NA	48	Include
17.	HAVEN 5, NCT03315455	Yang, 2022	A only	Phase 3 open-label, RCT	China, Malaysia, Thailand	Emicizumab (HEMLIBRA®), Different dosing	70	Exclude, conducted outside of North America, UK, Europe
18.	CTRI/2018/05/013790	Mewada, 2022	A only	Single-arm trial (Phase NR)	India	Antihemophilic factor human (HemoRel-A®), prophylaxis NA	44	Exclude, primary and secondary outcomes from BASIS not reported
19.	CTTQ-NXBYZ-02, NCT04061109	Xi, 2022	A only	Phase 3 open-label, single-arm trial	China	B-domain-deleted recombinant factor VIII (TQG202), prophylaxis NA	81	Exclude, conducted outside of North America, UK, Europe
20.	GC8AIII, NCT01568580	Hyun, 2015	A only	Phase 3 open-label, single-arm trial	Korea	Beractocog Alfa (ALPHANATE®), on-demand NA	88	Exclude, conducted outside of North America, UK, Europe

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
21.	Study 310, NR	Recht, 2009	A only	Study 1: Double blind, RCT crossover study followed by an open-label period Study 2: open-label single-arm trial (Phase NR)	Italy, New Zealand, Poland, UK, US	Moroctocog alfa (Xyntha®), prophylaxis and on-demand Full-length rFVIII concentrate (FLrFVIII, Advate, Baxter), on-demand	204	Exclude, not a relevant comparator
22.	SPINART, NCT00623480	Manco-Johnson, 2013	A only	Phase 3b/4 randomized, controlled, parallel-group, open-label study	Argentina, Bulgaria, Romania, US	Octocog alfa (Kogenate® FS), Prophylaxis and on-demand	84	Exclude, not a relevant comparator
23.	LIPLONG, NR	Powell, 2012	A only	Phase 2 active-controlled, double-blind, RCT	Israel, US	Octocog alfa (Kogenate® FS), prophylaxis rFVIII-FS, prophylaxis	143	Exclude, later phase results available
24.	NR	Collins, 2010	A only	Open-label, single-arm trial (Phase NR)	Europe, US	Octocog alfa (Kogenate® FS), on-demand followed by prophylaxis Different regimen	20	Exclude, primary and secondary outcomes from BASIS not reported
25.	NR	Rothschild, 2002	A only	Single-arm trial (Phase NR)	France, Germany	Octocog alfa (Kogenate® FS), prophylaxis NA	33	Exclude, later phase results available

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
26.	NR	Abshire, 2000	A only	Cross-over RCT (Phase NR)	North America, Europe	Octocog alfa (Kogenate® FS), prophylaxis Different formulation	71	Exclude, primary and secondary outcomes from BASIS not reported
27.	NCT00717626	NA	A only	Phase 2 open-label, single-arm trial	Canada	Octocog alfa (Advate®) or Octocog alfa (Kogenate® FS) or Humate-P, Recombinate, Factor VIII (Helixate FS), prophylaxis	14	Exclude, later phase results available
28.	LEOPOLD I, NCT01029340	Saxena, 2016	A only	Phase 3 cross-over, open-label RCT	Denmark, Germany, Hong Kong, Israel, Italy, Poland, Spain, South Africa, Turkey, UK, US	Octocog alfa (Kovaltry®) twice weekly, prophylaxis Octocog Alfa (Kogenate) thrice weekly, prophylaxis Octocog alfa (Kovaltry®) by Chromogenic Substrate Assay Potency Per European Pharmacopeia Octocog alfa (Kovaltry®) by Chromogenic Substrate Assay/Adjusted to Label Potency	62	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
29.	LEOPOLD II, NCT01233258	Kavakli, 2015	A only	Phase 2/3 cross-over, open-label RCT	Europe, North America, South America, South Africa, Asia (11 countries)	Octocog alfa (Kovaltry®), On-demand Octocog alfa (Kovaltry®), prophylaxis	97	Exclude, not a relevant comparator
30.	SCT800-A401, NCT03947567	Xue, 2022	A only	Phase 4 open-label, single-arm trial	China	Omfiloctocog alfa (Ancain®), prophylaxis and/or on-demand NA	69	Exclude, baseline data not reported
31.	SCT800-A302, NCT03815318	Xue, 2021	A only	Phase 3 open-label, single-arm trial	China	Omfiloctocog alfa (Ancain®), prophylaxis NA	73	Exclude, conducted outside of North America, UK, Europe
32.	NR	Wolf, 2004	A only	Open-label, single-arm trial (Phase NR)	Poland	pdFVIII (Haemoctin® SDH), prophylaxis, on-demand NA	61	Exclude, historical product that is not widely used in clinical practice
33.	NR	Spira J, 2008	A only	Randomized, four-way cross-over, subject-blinded trial (Phase NR)	Russia	PEGLip-rFVIII-FS (sucrose-formulated FVIII that is noncovalently bound to pegylated liposomes), prophylaxis Different dosing	16	Exclude, primary and secondary outcomes from BASIS not reported
34.	NR	Spira, 2006	A only	Controlled, cross-over,	The Netherlands, Russia	PEGylated liposome–	24	Exclude, primary and

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
				patient-blinded trial (Phase NR)		reconstituted rFVIII, prophylaxis Different dosing		secondary outcomes from BASIS not reported
35.	GENA-21b, NCT02256917	Midori, 2023	A only	Phase 3b open-label, single-arm trial	Canada, Croatia, Finland, France, Japan, the Netherlands, North Macedonia, Slovenia, US	Simoctocog alfa (Nuwiq®), prophylaxis NA	58	Exclude, not a relevant comparator
36.	GENA-21, NCT01863758	Dargaud, 2018	A only	Phase 3b open-label, single-arm trial	Austria, Bulgaria, France, Germany, Poland, Romania, Switzerland	Simoctocog alfa (Nuwiq®), prophylaxis Different dosing	66	Exclude, not a relevant comparator
37.	Guardian 1, NCT00840086	Lentz, 2013	A only	Open-label, non-RCT (Phase NR)	Brazil, Croatia, Germany, Israel, Italy, Japan, Malaysia, Russian, Serbia, Spain, Switzerland, Taiwan, Turkey, UK, US	Turoctocog alfa (Novoeight®), prophylaxis NA	150	Exclude, not a relevant comparator
38.	Guardian 2, NCT00984126	Lentz, 2017	A only	Phase 3b open-label, non-RCT	Brazil, Croatia, Germany, Israel, Italy, Japan, Latvia, Lithuania, Macedonia, Malaysia, Poland, Russian Federation, Serbia, Spain, Switzerland, Taiwan, Turkey, UK, US	Turoctocog alfa (Novoeight®), prophylaxis, on-demand Different dosing and regimen	158	Exclude, no outcome data between 6 and 24 months
39.	Guardian 7, NCT02938585	Wu, 2020	A only	Phase 3 open-label, non-RCT	China	Turoctocog alfa (NovoEight®) prophylaxis, on-demand	26	Exclude, conducted outside of North America, UK, Europe

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
40.	NCT04085458	Holme, 2021	A only	Phase 4 open-label, single-arm trial	Bulgaria, Denmark, Greece, Italy, Norway, Poland, Spain	Damoctocog alfa pegol (Jivi®), prophylaxis Different dosing	32	Exclude, not a relevant comparator
41.	PROTECT VIII, NCT01580293	Reding, 2017	A only	Phase 2/3 open-label, RCT	Main trial (Part A): Austria, Belgium, Canada, Colombia, Denmark, France, Germany, Israel, Italy, Japan, the Netherlands, Norway, Poland, Singapore, South Korea, Taiwan, Turkey, UK, US Extension trial: Austria, Belgium, Colombia, Germany, Denmark, France, Israel, Italy, Japan, South Korea, the Netherlands, Norway, Poland, Singapore, Turkey, Taiwan, UK, US	Damoctocog alfa pegol (Jivi®) prophylaxis every 5 or 7 days, On-demand	134	Exclude, not a relevant comparator
42.	XTEND-1, NCT04161495	Drygalski, 2023	A only	Phase 3 open-label, non-RCT	Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, France, Germany, Greece, Hungary, Italy, Japan, Korea, Mexico, the Netherlands, Spain, Taiwan, UK, US	Efanesoctocog alfa (ALTUVIIIIO® or ALTUVOCT®) prophylaxis, On-demand	159	Exclude, not a relevant comparator
43.	ASPIRE, NCT01454739	Nolan, 2016	A only	Open-label, non-RCT (Phase NR)	Europe (Ireland, the Netherlands, Poland, and the United Kingdom), North	Efmoroctocog alfa (Eloctate®),	211	Exclude, no outcome data

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
					America (US), Australia, Hong Kong, South Africa	Prophylaxis, On-demand Different dosing		between 6 and 24 months
44.	A-LONG, NCT01181128	Mahlangu, 2014	A only	Phase 3 open-label, non-RCT	Australia, Belgium, Austria, Canada, France, Brazil, Germany, Hong Kong, India, Israel, Italy, Japan, New Zealand, South Africa, Spain, Sweden, Switzerland, UK, US	Efmoroctocog alfa (Eloctate®), prophylaxis, on-demand	165	Exclude, not a relevant comparator
45.	CSL627_1001, NCT01486927	Mahlangu, 2016	A only	Phase 1/3 open-label, non-RCT	Europe, Japan, US	Lonoctocog alfa (Afstyl®), prophylaxis, on-demand	175	Exclude, not a relevant comparator
46.	CTR20201212 , NCT04456387	Feng, 2023	A only	Phase 3 open-label, non-RCT	China	Recombinant Factor VIII-Fc Fusion Protein (FRSW107), prophylaxis, on-demand	119	Exclude, baseline data not available
47.	PROPEL, NCT02585960 , EudraCT: 2014-005477-37	Klamroth, 2021	A only	Phase 3 open-label, RCT	Australia, Austria, Bulgaria, France, Germany, Hong Kong, Hungary, Israel, Italy, Malaysia, Norway, Poland, Romania, Singapore, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, UK, US	Rurioctocog alfa pegol (Adynovate®/ Adynovi®) FVIII troughs of 1% to 3% or g FVIII troughs of 8% to 12%, prophylaxis	115	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
48.	NCT01945593	Chowdary, 2020	A only	Phase 3b open-label, non-RCT	Australia, Austria, Bulgaria, Czech Republic, Germany, Hong Kong, Israel, Japan, Korea, Lithuania, Malaysia, the Netherlands, Poland, Romania, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Republic of China, Turkey, Ukraine, UK, US	Rurioctocog alfa pegol (Adynovate®/ Adynovi®) prophylaxis, Different dosing	216	Exclude, no outcome data between 6 and 24 months
49.	EXTEN-A, NCT03205163	Konkle, 2020	A only	Phase 1–2a open-label, sequential, non-RCT	Japan, US	Rurioctocog alfa pegol (Adynovate®/ Adynovi®) followed by Efanesoctocog alfa (Altuviiiio; BIVV001), prophylaxis Different dosing	16	Exclude, primary and secondary outcomes from BASIS not reported
50.	PROLONG-ATE, NCT01736475	Konkle, 2015	A only	Phase 2/3 open-label, parallel assignment, non-RCT	Australia, Austria, Bulgaria, Czechia, Germany, Israel, Japan, Korea, Lithuania, Malaysia, the Netherlands, Poland, Romania, Spain, Sweden, Switzerland, Taiwan, Ukraine, UK, US	Rurioctocog alfa pegol (Adynovate®/ Adynovi®) – prophylaxis, On-demand	137	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
51.	Pathfinder 10, NCT05082116	NA	A only	Phase 3 open-label, single-arm trial	China	Turoctocog alfa pegol (Esperoct®) prophylaxis NA	36	Exclude, conducted outside of North America, UK, Europe
52.	Pathfinder 2, NCT01480180	Giangrande , 2020	A only	Phase 3 open-label, non-RCT	Australia, Brazil, Croatia, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Malaysia, the Netherlands, Norway, Russia, Spain, Sweden, Switzerland, Taiwan, Turkey, UK, US	Turoctocog alfa pegol (Esperoct®) prophylaxis, on-demand, Different dosing	186	Exclude, not a relevant comparator
53.	HOPE-B, NCT03569891	Pipe, 2023	B only	Phase 3 open label, single-arm trial	Belgium, Denmark, Germany, Ireland, the Netherlands, Sweden, UK, US	Etranacogene dezaparvovec (HEMGENIX®), FIX prophylaxis (lead-in phase)	54	Exclude, not a relevant comparator
54.	AMT-061, NCT03489291	Von Drygalski, 2019	B only	Phase 2 open label, single-arm trial	Germany, the Netherlands, US	Etranacogene dezaparvovec (HEMGENIX®), NA	3	Exclude, later phase trial available
55.	AMT-060, NCT02396342	Miesbach, 2018	B only	Phase 1/2 open label, non-RCT	Denmark, Germany, the Netherlands	AAV5-hFIX (AMT-060), Different dosing	10	Exclude, manufacturer terminated product development
56.	BENEGENE-2, NCT03861273	Cuker, 2023	B only	Phase 3 open label, single-arm trial	Australia, Brazil, Canada, France, Germany, Greece, Japan, Korea, Republic	Fidanacogene elaparvovec (BEQVEZ),	45	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
					of, Saudi Arabia, Sweden, Taiwan, Turkey, UK, US	FIX prophylaxis (lead-in phase)		
57.	SPK-9001-101, NCT02484092	George, 2017	B only	Phase 1/2a open label, single-arm trial	Australia, US	Fidanacogene elaparvovec (BEQVEZ), NA	15	Exclude, later phase results available
58.	AskBio009-101, NCT01687608	Konkle, 2021	B only	Phase 1/2 open label, non-RCT	US	BAX 335 (AskBio009), Different dosing	8	Exclude, primary and secondary outcomes from BASIS not reported
59.	B-AMAZE, NCT03369444, NCT03641703 EdudraCT: 2017-000852-24, 2017-005080-40	Chowdary, 2022	B only	Phase 1/2 open label, non-RCT	UK	Verbrinacogene setparvovec (FLT180a), Different dosing	10	Exclude, later phase results available
60.	NR	Lissitchkov T, 2010	B only	Open label, single-arm trial (Phase NR)	Bulgaria, Poland, Spain	Factor IX Grifols (AlphaNine® SD), prophylaxis, NA	25	Exclude, primary and secondary outcomes from BASIS not reported
61.	NR	Mauser-Bunschoten, 2011	B only	Phase 3/4 open label, single-arm trial	The Netherlands, Poland	Human coagulation Factor IX (Nonafact®), prophylaxis, on-demand	60	Exclude, no outcome data between 6 and 24 months

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
62.	B1821010, NCT01335061	Kavakli, 2016	B only	Phase 3 open label, non-RCT	Bulgaria, Canada, Croatia, Korea, Malaysia, Mexico, Poland, Singapore, Turkey	Nonacog alfa (BeneFIX®), prophylaxis, on-demand	25	Exclude, not a relevant comparator
63.	B1821059, NCT04286412	Choraria, 2022	B only	Phase 4 open label, single-arm trial	India	Nonacog alfa (BeneFIX®) prophylaxis, NA	25	Exclude, conducted outside of North America, UK, Europe
64.	NR	Korth-Bradley, 2016	B only	Open label, non-RCT (Phase NR)	Spain	Nonacog alfa (BeneFIX®), prophylaxis, on-demand, Different regimen	23	Exclude, primary and secondary outcomes from BASIS not reported
65.	NR	Lambert, 2007	B only	Double-blind crossover RCT (Phase NR)	France, Spain, UK, US	Nonacog alfa (BeneFIX®), prophylaxis, on-demand Different regimen	34	Exclude, later phase results available
66.	NCT01286779	Windyga, 2020	B only	Phase 3 open label, non-RCT	Argentina, Brazil, Bulgaria, Chile, Colombia, Czechia, India, Ireland, Italy, Japan, Poland, Romania, Russian federation, Sweden, Taiwan, Ukraine, UK	Nonacog gamma (RIXUBIS™), prophylaxis, on-demand	117	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
67.	NCT01174446	Windyga, 2014	B only	Phase 1/3 double-blind crossover RCT and open label single-arm trial	Argentina, Brazil, Bulgaria, Chile, Columbia, Czechia, Japan, Poland, Romania, Russian Federation, Spain, Sweden, Ukraine, UK	Nonacog gamma (RIXUBIS™), prophylaxis, on-demand	86	Exclude, not a relevant comparator
68.	NCT01507896	Windyga, 2020	B only	Phase 3 open label, single-arm trial	Bulgaria, Chile, Columbia, Czech Republic, Poland, Romania, Russia, Ukraine	Nonacog gamma (RIXUBIS™), NA	40	Exclude, primary and secondary outcomes from BASIS not reported
69.	KB037, EudraCT: 2005-006186-14	Castaman, 2020	B only	Phase 2 open label, single-arm trial	Italy, Romania, Turkey	Kedrion FIX concentrate (AIMAFIX®), prophylaxis, on-demand, NA	16	Exclude, primary and secondary outcomes from BASIS not reported
70.	NR	Serban, 2012	B only	Open label, single-arm trial (Phase NR)	NR	Plasma-derived FIX concentrate (Haemonine), prophylaxis, on-demand NA	29	Exclude, historical product that is not widely used in clinical practice
71.	IB1001-01, NCT00768287	Collins, 2018	B only	Phase 3 double-blind crossover RCT and open label non-RCT	France, India, Israel, Italy, Poland, UK, US	Trenonacog alfa (Ixinity®), prophylaxis, on-demand	76	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
72.	PROLONG-9FP (primary study), NCT01496274	Santagostino, 2016	B only	Phase 3 open label non-RCT	Austria, Bulgaria, France, Germany, Israel, Italy, Japan, Russia, Spain, US	Albutrepenonacog alfa (Idelvion®) prophylaxis, on-demand with rurioctocog alfa pegol (Adynovate®/Adynovi®)	63	Exclude, not a relevant comparator
73.	PROLONG-9FP (extension), NCT02053792	Mancuso, 2020	B only	Phase 3 open label non-RCT	Austria, France, Germany, Italy, Japan, Malaysia, Philippines, South Africa, Spain, US	Albutrepenonacog alfa (Idelvion®), prophylaxis Different dosing	59	Exclude, no outcome data between 6 and 24 months
74.	DLZ-20, NCT03995784	Mahlangu, 2021	B only	Phase 2 open label single-arm trial	South Africa	Dalcinonacog alfa (DalcA), prophylaxis NA	6	Exclude, primary and secondary outcomes from BASIS not reported
75.	ISU304-001/CB2679d, NCT03186677	You, 2021	B only	Phase 1/2a open label non-RCT	South Korea	Dalcinonacog alfa (DalcA), prophylaxis Different dosing	13	Exclude, primary and secondary outcomes from BASIS not reported
76.	B-LONG, NCT01027364	Powell, 2013	B only	Phase 3 open label non-RCT	Australia, Belgium, Brazil, Canada, People's Republic of China, France, Germany, Hong Kong, India, Italy, Japan, Poland, Russia, South Africa, Sweden, UK, US	Eftrenonacog alfa (Alprolix®) prophylaxis, on-demand Different regimen	123	Exclude, not a relevant comparator

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	Study name, Trial ID	Author, Year	Haemophilia type	Study design	Country	Intervention and comparator	Sample Size	Consideration for ITC assessment
77.	B-YOND, NCT01425723	Pasi, 2017	B only	Phase 3 open label non-RCT	Europe (Belgium, France, Germany, Ireland, Italy, the Netherlands, Poland, Sweden, and the United Kingdom), North America (Canada, US), Australia, Brazil, China, Hong Kong, India, Japan, South Africa	Eftrenonacog alfa (Alprolix®), prophylaxis, on-demand Different dosing and regimen	116	Exclude, no outcome data between 6 and 24 months
78.	Paradigm 2, NCT01333111	Collins, 2014	B only	Phase 3 single blind RCT	France, Germany, Italy, Japan, Macedonia, Malaysia, the Netherlands, Russian Federation, South Africa, Thailand, Turkey, UK, US	Nonacog beta pegol (Rebinyn®) prophylaxis, on-demand	74	Exclude, not a relevant comparator
79.	Paradigm 4, NCT01395810	Young G, 2016	B only	Phase 3 open label non-RCT	France, Germany, Italy, Japan, Macedonia, Malaysia, the Netherlands, Romania, Russia, South Africa, Taiwan, Thailand, Turkey, UK, US	Nonacog beta pegol (Rebinyn®), prophylaxis, on-demand Different regimen	71	Exclude, no outcome data between 6 and 24 months

Studies excluded at the full-text stage

A full list of the studies excluded from the clinical SLR at the full-text stage are available in the reference pack.

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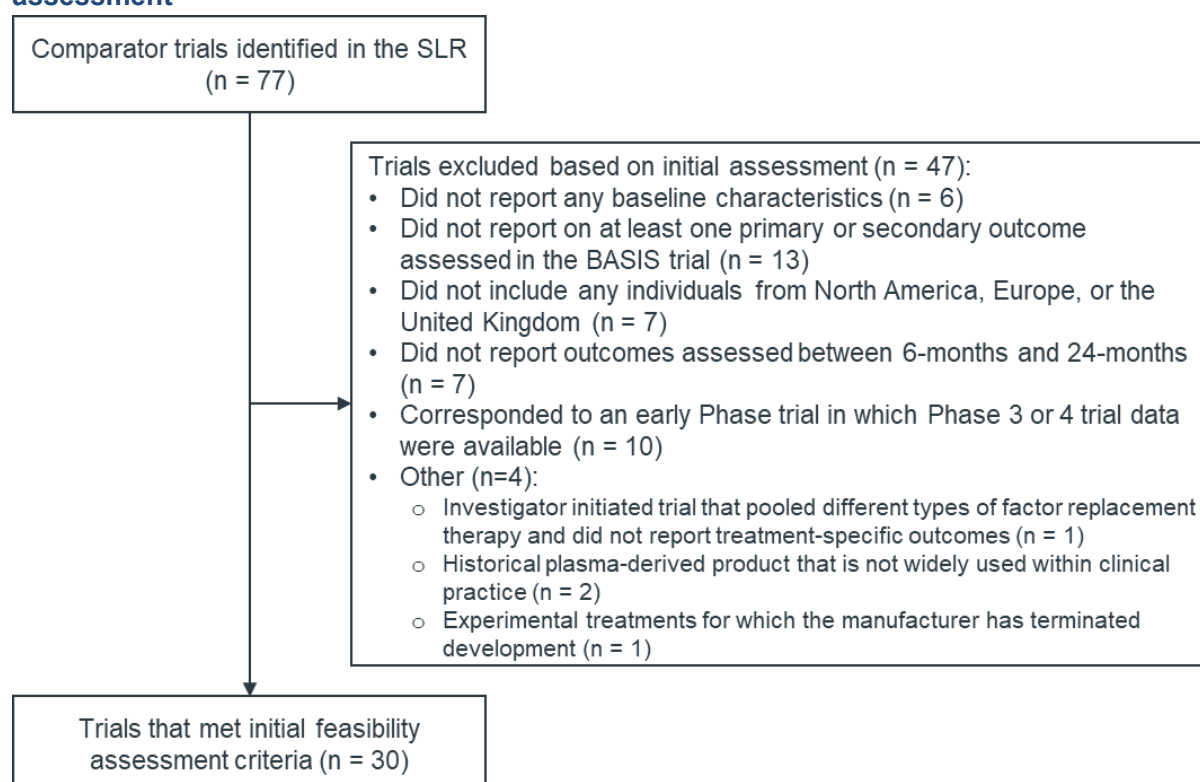
D.1.4. Summary of trials used for indirect or mixed treatment comparisons

Included studies were prioritised for the ITC feasibility assessment. The initial feasibility assessment comprised of the following criteria:

- Were baseline characteristics reported for the target population? (Yes or no); baseline data are important for assessing the comparability of trial populations
- Did the trial report at least one primary or secondary outcome from the BASIS trial? (Yes or no); similar outcome measures are required for conducting ITC analysis
- Did the trial include any individuals from North America, Europe, or the United Kingdom? (Yes or no); settings that may affect health care or patient management should be minimised to reduce differences between trial populations
- Were outcome data available between 6-months and 24-months after treatment initiation? (Yes or no); follow-up time between trials should be comparable
- Were later trial phase data available (e.g., Phase 3 or 4) for treatments evaluated in trials described as Phase 1 or 2? (Yes or no); the ITC should focus on the most relevant data for a given comparator treatment (e.g., recommended dose, regimen, clinical outcomes)
- Other criteria for exclusion:
 - Historical product that is not widely used in clinical practice
 - Experimental treatments for which the manufacturer has terminated development

Among the 79 trials included in the SLR, two investigated marstacimab (BASIS trial and a Phase 2 trial), of which the BASIS trial was selected as the referenced for comparison, and 77 investigated comparator treatments. The prioritisation process to identify trials for inclusion in the ITC feasibility assessment yielded 30 trials to proceed for evaluation within the feasibility assessment. The reasons for deprioritising the excluded 48 comparator studies are presented in Table 17.

Figure 2: Summary of initial feasibility assessment for inclusion in the ITC feasibility assessment



Abbreviations: ITC: indirect treatment comparison; SLR: systematic literature review.

Of the remaining 30 studies, evaluating 22 different interventions, 28 were subsequently excluded because they did not report on a relevant comparator of interest to the decision problem:

- Since factor replacement therapy was evaluated in the BASIS trial, studies assessing these therapies (n=22) were not considered for inclusion into the ITC analyses.
- In addition, six trials were excluded because they assessed gene therapies (n=4) or rebalancing agents (n=2) which were not relevant candidate therapies for the target population of this submission.

The reasons for excluding these remaining 28 studies are presented in Table 17. The remaining two trials, HAVEN-3 and HAVEN-4, both evaluating emicizumab, were identified and carried forward to the feasibility assessment reported in Section B.2.11.1 of Document B.

D.1.5. Methods and outcomes of studies included in indirect or mixed treatment comparisons

Full details of the ITC are presented in Section B.2.11 of Document B, with further supplementary details provided within this appendix.

D.1.5.1. Identification of effect modifiers and prognostic variables

Relevant effect modifiers and/or prognostic variables to include into the unanchored ITCs were identified based on a review of the literature, input from clinical experts, and results of regression

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analyses. First, an initial set of potentially relevant variables was identified based on prior publications which included the following covariates: age, race/ethnicity, body weight or BMI, prior bleeding events (e.g., number of prior bleeds or prior total ABR), target joints, and prior factor product class product (i.e., extended half-life vs. standard half-life).⁵⁻⁹ This initial list of variables was reviewed by clinical experts who confirmed their clinical relevance.

Second, the selected covariates were examined in a series of regression analyses to assess the degree to which they were prognostic using individual-level data from the BASIS trial. Body weight, prior factor product class product, and number of bleeds prior to enrolment were excluded from the analyses due to collinearity with BMI, dose-schedule of prior therapy, and prior total ABR, respectively. Rate ratios were estimated for total ABR using negative binomial regression with log-time as an offset term and odds ratios for zero total bleed events (Yes/No) was modelled using logistic regression. Both univariable and multivariable regression analyses were performed. Given the limited sample size of the BASIS trial, a liberal p-value of 0.1 was used to define statistical significance within the multivariable analyses. A complete case analysis was performed whereby one individual was excluded from the analyses due to missing information on race/ethnicity.

Based on results of the regression analyses, age, race/ethnicity, target joints, and prior total ABR were identified as statistically significant prognostic factors (Table 18). Notably, prior total ABR was the only covariate that remained statistically significant within the multivariable analyses for both outcomes.

Table 18: Results from univariable and multivariable regression analyses assessing potential prognostic factors using individual-level data from the BASIS trial (n=115)

Analysis	Predictor	Point Estimate ^a	95% LCI	95% UCI	p-value
Total ABR: Univariable	Age (per 5-year increase)	████	████	████	████
	White (yes vs. no)	████	████	████	████
	Hispanic/Latino (yes vs. no)	████	████	████	████
	BMI (per 1 unit increase)	████	████	████	████
	Target joint (yes vs. no)	████	████	████	████
	Prior total ABR (per 1 unit increase)	████	████	████	████
Total ABR: Multivariable	Age (per 5-year increase)	████	████	████	████
	White (yes vs. no)	████	████	████	████
	Hispanic/Latino (yes vs. no)	████	████	████	████
	BMI (per 1 unit increase)	████	████	████	████
	Target joint (yes vs. no)	████	████	████	████
	Prior total ABR (per 1 unit increase)	████	████	████	████
Zero bleeding Events: Univariable	Age (per 5-year increase)	████	████	████	████
	White (yes vs. no)	████	████	████	████
	Hispanic/Latino (yes vs. no)	████	████	████	████

	BMI (per 1 unit increase)	■	■	■	■
	Target joint (yes vs. no)	■	■	■	■
	Prior total ABR (per 1 unit increase)	■	■	■	■
Zero bleeding Events: Multivariable	Age (per 5-year increase)	■	■	■	■
	White (yes vs. no)	■	■	■	■
	Hispanic/Latino (yes vs. no)	■	■	■	■
	BMI (per 1 unit increase)	■	■	■	■
	Target joint (yes vs. no)	■	■	■	■
	Prior total ABR (per 1 unit increase)	■	■	■	■

^a Refers to the estimated rate ratio for total ABR and odds ratio for zero total bleeding events

*Denotes statistical significance at the 0.10 threshold

Abbreviations: ABR: annualised bleeding rate; BMI: Body Mass Index; LCI: lower confidence interval; UCI: upper confidence interval.

D.1.6. Methods of analysis of studies included in the indirect or mixed treatment comparison

The methods of the ITCs are presented in Section B.2.11.2 of Document B, with the results for the outcomes, i.e. ABR, AJBR and the proportion of patients with no bleeds, presented in Section B.2.11.3 of Document B.

D.1.7. Programming language for the indirect or mixed treatment comparison

The programming code for the STC is provided in the reference pack.

D.1.8. Risk of bias of studies included in indirect or mixed treatment comparisons

A quality assessment of the HAVEN 3 trial was performed using a modified version of the Downs and Black Checklist.¹⁰ In this checklist, up to one point can be awarded for 26 questions and up to 2 for one question giving a maximum of 28 points per trial. Overall, the HAVEN 3 trial had a score of 13 which falls within the “poor” category (Table 19).

Table 19: Quality assessment of the HAVEN 3 trial

Item		Response	Score
Reporting			
Q1	Hypothesis/aim/objective clearly described	Yes = 1, No = 0	1
Q2	Main outcomes in Introduction or Methods	Yes = 1, No = 0	1
Q3	Patient characteristics clearly described	Yes = 1, No = 0	1
Q4	Interventions of interest clearly described	Yes = 1, No = 0	1
Q5	Principal confounders clearly described	Yes = 2, Partially = 1, No = 0	0
Q6	Main findings clearly described	Yes = 1, No = 0	1
Q7	Estimates of random variability provided for main outcomes	Yes = 1, No = 0	1
Q8	All adverse events of intervention reported	Yes = 1, No = 0	1
Q9	Characteristics of patients lost to follow-up described	Yes = 1, No = 0	0
Q10	Probability values reported for main outcomes	Yes = 1, No = 0	0
External Validity			
Q11	Subjects asked to participate were representative of source population	Yes = 1, No = 0, Unclear = 0	1
Q12	Subjects prepared to participate were representative of source population	Yes = 1, No = 0, Unclear = 0	0
Q13	Location and delivery of study treatment was representative of source population	Yes = 1, No = 0, Unclear = 0	1
Internal Validity – Bias and Confounding			
Q14	Study participants blinded to treatment	Yes = 1, No = 0, Unclear = 0	0
Q15	Blinded outcome assessment	Yes = 1, No = 0, Unclear = 0	0

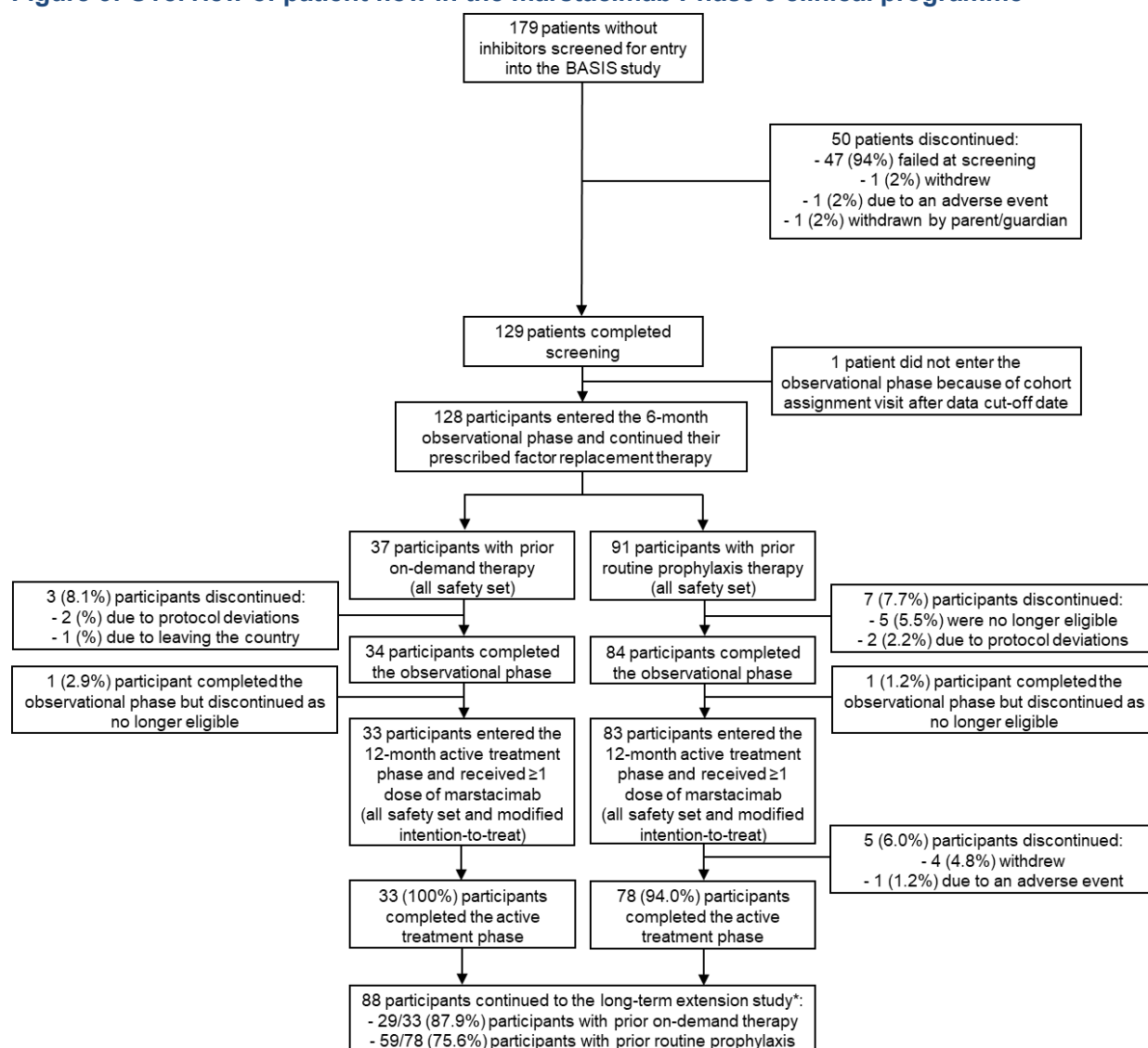
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Item		Response	Score
Q16	Any data dredging clearly described	Yes = 1, No = 0, Unclear = 0	1
Q17	Analyses adjust for differing lengths of follow-up	Yes = 1, No = 0, Unclear = 0	0
Q18	Appropriate statistical tests performed	Yes = 1, No = 0, Unclear = 0	1
Q19	Compliance with interventions was reliable	Yes = 1, No = 0, Unclear = 0	0
Q20	Outcome measures were reliable and valid	Yes = 1, No = 0, Unclear = 0	1
Q21	All participants recruited from the same source population	Yes = 1, No = 0, Unclear = 0	1
Q22	All participants recruited over the same time period	Yes = 1, No = 0, Unclear = 0	0
Q23	Participants randomised to treatment(s)	Yes = 1, No = 0, Unclear = 0	0
Q24	Allocation of treatment concealed from investigators and participants	Yes = 1, No = 0, Unclear = 0	0
Q25	Adequate adjustment for confounding	Yes = 1, No = 0, Unclear = 0	0
Q26	Losses to follow-up taken into account	Yes = 1, No = 0, Unclear = 0	0
Power			
Q27	Sample size calculation was reported	Yes = 1, No = 0, Unclear = 0	0
Total			13

D.2 Participant flow in the relevant randomised control trials

An overview of the patient flow in the marstacimab Phase 3 BASIS clinical trial is provided in Figure 3 below.

Figure 3: Overview of patient flow in the marstacimab Phase 3 clinical programme



Source: Adapted from Pfizer marstacimab Phase 3 BASIS trial CSR, 2023.¹¹

D.3 Critical appraisal for each study

A quality assessment of the BASIS trial can be found in Section B.2.5 of Document B.

Appendix E Subgroup analysis

No pre-specified subgroups were included in the BASIS trial protocol. Subgroup results with efficacy data for patients with haemophilia A or B, and adults or adolescents, are presented in Section B.2.8. Safety data split by the adult and adolescent populations are presented in Appendix F. No additional subgroups were considered of relevance for this appraisal.

Appendix F Adverse reactions

Safety data from the pivotal BASIS trial are presented in Section B.2.12 of Document B. Further safety analyses, including subgroup data for adults and adolescents, are presented in Section F.1.

The Phase 3 open label extension (OLE) also collected safety data which are presented in Section F.2. In the OLE, marstacimab was demonstrated to be well-tolerated in patients with haemophilia without inhibitors aged 12 to <75 years.

F.1 Additional safety endpoints from the BASIS trial

F.1.1. Safety data by adult and adolescent subgroups

Summary of adverse events

A summary of all-causality AEs, split by adults and adolescents, is presented in Table 20.

Table 20: Summary of adverse events after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP for adults and adolescents in the BASIS trial (17th April 2023 data cut-off; safety analysis set)

	Adults (Ages 18 to <75)		Adolescents (Ages 12 to <18)	
	Routine prophylaxis during OP (N=73)	Marstacimab prophylaxis during ATP (N=66)	Routine prophylaxis during OP (N=18)	Marstacimab prophylaxis during ATP (N=17)
Number of patients, n (%)				
Number of AEs	33	226	11	36
Patients with AEs	18 (24.7)	52 (78.8)	7 (38.9)	14 (82.4)
Patients with serious AEs	1 (1.4)	6 (9.1)	1 (5.6)	1 (5.9)
Patients discontinued from the study phase due to AEs ^a	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Patients discontinued from the study drug due to AEs ^b	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with dose reduced or temporary discontinuation due to AEs	0 (0.0)	12 (18.2)	0 (0.0)	2 (11.8)

^a Patients who have an AE record that indicates that the AE caused the patient to be discontinued from the study

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^b Patients who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the patient to be discontinued from study

Abbreviations: AE: adverse event; ATP: active treatment phase; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹¹

Treatment emergent adverse events

A summary of TEAEs, split by adults and adolescents, is presented in Table 21.

Table 21: Summary of TEAEs after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; safety analysis set; >5% patients in overall population in either treatment phase)

	Adults (Ages 18 to <75)		Adolescents (Ages 12 to <18)	
	Routine prophylaxis during OP (N=73)	Marstacimab prophylaxis during ATP (N=66)	Routine prophylaxis during OP (N=18)	Marstacimab prophylaxis during ATP (N=17)
Number of patients, n (%)				
With any AE	13 (17.8)	49 (74.2)	7 (38.9)	13 (76.5)
COVID-19	1 (1.4)	14 (21.2)	2 (11.1)	4 (23.5)
Headache	0 (0.0)	5 (7.6)	0 (0.0)	1 (5.9)
Contusion	0 (0.0)	4 (6.1)	0 (0.0)	1 (5.9)
Dental Caries	0 (0.0)	4 (6.1)	0 (0.0)	0 (0.0)
Pruritus	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	1 (1.5)	1 (5.6)	0 (0.0)

Abbreviations: AE: adverse event; ATP: active treatment phase; OP: observational phase; TEAE: treatment emergent adverse event.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹¹

Treatment related TEAEs

A summary of treatment related TEAEs, split by adults and adolescents, is presented in Table 22.

Table 22: Summary of treatment related TEAEs after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; safety analysis set)

	Adults (Ages 18 to <75) (N=66)	Adolescents (Ages 12 to <18) (N=17)
Number of patients, n (%)		
With any AE	15 (22.7)	4 (23.5)
General Disorders and Administration Site Conditions	7 (10.6)	4 (23.5)
Fatigue	1 (1.5)	0 (0.0)
Injection site bruising	1 (1.5)	0 (0.0)
Injection site erythema	2 (3.0)	1 (5.9)
Injection site induration	1 (1.5)	0 (0.0)

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Injection site oedema	0 (0.0)	1 (5.9)
Injection site pain	1 (1.5)	0 (0.0)
Injection site pruritus	2 (3.0)	2 (11.8)
Injection site swelling	1 (1.5)	1 (5.9)
Peripheral swelling	1 (1.5)	0 (0.0)
Injury, Poisoning and Procedural Complications	1 (1.5)	0 (0.0)
Contusion	1 (1.5)	0 (0.0)
Investigations	3 (4.5)	0 (0.0)
Fibrin D dimer increased	2 (3.0)	0 (0.0)
Prothrombin fragment 1.2 increased	3 (4.5)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	1 (1.5)	0 (0.0)
Arthralgia	1 (1.5)	0 (0.0)
Nervous System Disorders	1 (1.5)	0 (0.0)
Headache	1 (1.5)	0 (0.0)
Skin and Subcutaneous Tissue	2 (3.0)	0 (0.0)
Pruritus	2 (3.0)	0 (0.0)

Abbreviations: AE: adverse event; ATP: active treatment phase; TEAE: treatment emergent adverse event.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹¹

Serious adverse events

A summary of SAEs, split by adults and adolescents, is presented in Table 23. One adolescent individual had a severe adverse event (SAE), haematuria, during the screening phase.

Table 23: Summary of SAEs after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; safety analysis set)

	Adults (Ages 18 to <75)		Adolescents (Ages 12 to <18)	
	Routine prophylaxis during OP (N=73)	Marstacimab prophylaxis during ATP (N=66)	Routine prophylaxis during OP (N=18)	Marstacimab prophylaxis during ATP (N=17)
Number of patients, n (%)				
With any serious AE	1 (1.4)	6 (9.1)	1 (5.6)	1 (5.9)
General Disorders and Administration Site Conditions	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)
Chest Pain	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Peripheral swelling	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Ear and Labyrinth Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)
Tympanic membrane perforation	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)
Gastrointestinal disorders	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Oesophagitis	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and Infestations	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Tonsillitis	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Traumatic haemorrhage	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Haemarthrosis	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Neoplasms	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Meningioma	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Product Issues	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)
Device occlusion	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)
Vascular Disorders	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Haemorrhage	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)

Abbreviations: AE: adverse event; ATP: active treatment phase; OP: observational phase; SAE: severe adverse event.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹¹

Discontinuations from trial interventions in BASIS study due to adverse events

A summary of BASIS trial discontinuations, split by adults and adolescents, is presented in Table 24.

Table 24: Summary of study drug temporary discontinuations due to adverse events after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; safety analysis set)

	Adults (Ages 18 to <75) (N=66)	Adolescents (Ages 12 to <18) (N=17)
Number of patients, n (%)		
Permanent discontinuation with any AE	1 (1.5)	0 (0.0)
Meningioma ^a	1 (1.5)	0 (0.0)
Temporary discontinuation with any AE	12 (18.2)	2 (11.8)
COVID-19	9 (13.6)	1 (5.9)
SARS-CoV-2 positive test	1 (1.5)	0 (0.0)
Tympanic membrane perforation	0 (0.0)	1 (5.9)
Dental caries	1 (1.5)	0 (0.0)
Peripheral swelling	1 (1.5)	0 (0.0)

^a The meningioma SAE was not considered related to the study intervention

Abbreviations: AE: adverse event; ATP: active treatment phase.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹¹

F.1.2. Clinical laboratory values

Overall, clinical laboratory results, as measured by change from baseline, for blood chemistry, haematology and other parameters showed no clinically important findings in the BASIS trial. Parameters indicative of bleeding, such as haemoglobin levels, remained stable or improved during marstacimab treatment in the ATP, compared with the OP.

None of the laboratory test anomalies were considered to be clinically significant or reported as AEs by the investigator.

Anti-drug antibodies

Across both on-demand and prior prophylaxis cohorts, 116 patients were evaluable for anti-drug (marstacimab) antibodies (ADA). Twenty-three patients (19.8%) were ADA positive, with ADAs transient in 14 patients (61%) and persistent in 9 patients (39%). By the end of the study, ADAs were resolved in 22 of the 23 patients (95.7%). Overall, ADA analysis indicated that marstacimab immunogenicity in the study population was of low incidence and mostly transient in nature.

Haemoglobin parameters

Haemoglobin levels in the OP were generally comparable with the marstacimab ATP. Mean change from baseline to last visit on treatment was −0.3 g/L (SD: 10.83) in the OP versus 0.1 g/L (SD: 9.73) in the ATP. Haemoglobin remained within the normal range during the ATP.

Fibrinogen

Fibrinogen values reported during the 6 month OP were compared to values reported during the 12 month ATP. Most fibrinogen values reported were normal in the OP, with small decreases detected during the ATP which is consistent with the known pharmacology of marstacimab. The mean change from baseline to last visit on treatment for fibrinogen during the OP was −0.3 g/L

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(SD: 0.97), compared with -0.2 g/L (SD: 0.64) during the marstacimab ATP. There were no AEs related to decreases in fibrinogen.

F.2 Additional safety data from the OLE

Original submission – March 2023 OLE data cut

Safety data from the OLE indicated that long term administration of marstacimab beyond 12 months in the BASIS trial ATP and up to an average of 16 months was well tolerated in patients with haemophilia. During the OLE, 22 of the 58 patients who had been receiving factor prophylaxis in the BASIS trial OP experienced an adverse event (37.9%). There were two (3.4%) serious adverse events, however neither were considered treatment related.

Treatment-related AEs were reported in 3 participants (5.2%) and included one injection site bruising, one injection site induration and one injection site swelling.

There were no deaths or discontinuations from the OLE due to AEs. Three individuals (5.2%) temporarily discontinued marstacimab prophylaxis; two (3.4%) due to COVID-19 and one (1.7%) due to haemarthrosis, neither of which were deemed to be treatment related. Two participants (3.4%) experienced SAEs however none were considered treatment related by the investigator. Eleven participants (19.0%) experienced an AESI, however only three (5.2%), all injection site reactions, were considered treatment related.

Updated submission – October 2023 OLE data cut

Safety data from the OLE indicated that long term administration of marstacimab beyond 12 months in the BASIS trial ATP and up to 23 months was well tolerated in patients with haemophilia.

Those patients who received routine prophylaxis in the OP and went on to enter the OLE (n=75), 20% (n=15) reported AESIs; four patients (5.3%) had COVID-19, four patients (5.3%) had haemorrhage, four patients (5.3%) had hypersensitivity, two patients (2.7%) had hypertension, six patients (8.0%) had injection site reactions. Five patients (6.7%) experienced a SAE, although none were considered treatment related and no patients discontinued due to SAEs.^{12, 13}

There were no deaths or thromboembolic events reported in the OLE.

Appendix G Published cost-effectiveness studies

G.1. Identification of studies

A SLR was conducted on 4th August 2020 (original SLR) in order to identify clinical efficacy and safety outcomes, as well as novel economic evidence in the form of economic evaluations, utility/health-related quality of life (utility/HRQoL) studies and healthcare cost and resource use (HCRU) studies in people with moderately severe-to-severe haemophilia A or severe haemophilia B. The SLR was updated on 30th May 2024 with a focus on the economic evidence only. The SLR was wider in scope than the proposed indication in this submission, as it additionally included patients with moderately severe disease, to ensure that no relevant information was missed; however, data for subgroups with severe disease were extracted separately where available.

The databases and hand searches were conducted simultaneously for the SLR of economic evaluations (Appendix G), utility/HRQoL studies (Appendix H) and HCRU studies (Appendix I). Each record identified in these searches was assessed for eligibility across all three data streams simultaneously (economic evaluations, utility/HRQoL and HCRU). Each study identified could therefore be included in one or more streams of the SLR. Appendix G.1.1 presents the search strategy across all three streams of the SLR; study selection and extracted data are presented for each stream individually in Appendix G, Appendix H and Appendix I.

The SLR was performed in accordance with a pre-specified protocol. This involved searching electronic databases, manual hand-searching of key conference proceedings from the last two years, manual hand-searching of key HTA body websites and health economics databases, and manual hand-searching of the bibliographies of any relevant systematic reviews, (network) meta-analyses ([N]MAs), economic evaluations or HTAs identified during the review. Full details of the SLR and update are provided below.

G.1.1. Search strategy

The SLR were performed in accordance with the methodological principles of conduct for SLRs as detailed in the University of York Centre for Reviews and Dissemination's "Guidance for Undertaking Reviews in Health Care".¹⁴

For all applicable searches (i.e. of databases with complex search functionality) the search terms to capture economic studies are based on the validated Scottish Intercollegiate Guidelines Network (SIGN) filter set,¹⁵ with the addition of extra terms from other sources.

Electronic databases

Original SLR

The following databases were searched from inception on 4th August 2020:

- MEDLINE, including MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print

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- Embase
- CDSR
- NHS Economic Evaluation Database (NHS EED)
- EconLit
- *DARE [relevant for clinical search only; results not presented]*
- *CENTRAL [relevant for clinical search only; results not presented]*

MEDLINE, Embase, CDSR, CENTRAL, DARE, NHS EED and EconLit were searched separately via the Ovid SP platform. DARE and the NHS EED were discontinued in 2015; therefore, only the archived databases (until 2015) were searched.

An index of search terms tables for the electronic database searches in the original SLR is in Table 25. The search terms used in the original SLR for haemophilia A and B are in Table 26 to Table 51.

SLR update

The following databases were searched on 30th May 2024:

- MEDLINE, including MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print
- Embase
- CDSR
- Health Technology Assessment Database (HTAD) [not searched in the original SLR]

MEDLINE and Embase were searched separately via the Ovid SP platform. CDSR was searched via the Cochrane Library, using the Wiley Online platform. HTAD was searched through the International Network of Agencies for Health Technology Assessment (INAHTA) platform.

Searches of MEDLINE, Embase and CDSR were run with a date limit from 2020 onwards, to identify studies published since the original SLR. DARE and NHS EED were searched as part of the original SLR. These databases were discontinued in 2015, and therefore were not searched as part of the SLR update. EconLIT was not searched as part of the SLR update.

An index of search terms tables for the electronic database searches in the update SLR is in Table 52. The search terms used in the update SLR for haemophilia A and B are in Table 53 to Table 68.

Grey literature sources

Conference proceedings

Original SLR

Conference proceedings from the following conferences held between 2018 and August 2020 were manually searched to identify any relevant abstracts for inclusion:

- Congress of the International Society on Thrombosis and Haemostasis (ISTH)

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- Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD)
- World Congress of the World Federation of Hemophilia (WFH)
- Annual Meeting of the American Society of Hematology (ASH)
- Annual Congress of European Hematology Association (EHA)

SLR update

Conference proceedings from the same conferences searched during the previous SLR were manually searched for the SLR update for the past two years (2022–2024) to identify any relevant abstracts for inclusion. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conference proceedings were additionally searched to identify any additional economic evidence.

The search terms used in the conference searches, retrieved results and number of included results are presented in Table 69.

HTA Websites and economic websites

Original SLR

The Cost-Effectiveness Analysis (CEA) Registry was searched from 2010 to August 2020.

SLR update

Searches of the following HTA body websites were conducted to identify relevant HTAs from the last 10 years (2014–2024):

- National Institute for Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- National Centre for Pharmacoeconomics (NCPE)
- All Wales Medicines Strategy Group (AWMSG)

In line with current best practice guidelines for identifying inputs relevant to cost-effectiveness modelling, the following were also searched:

- The Cost-Effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center (available at <https://cevr.tuftsmedicalcenter.org/databases/cea-registry>)
- The EQ-5D Publications Database (available at <https://eq-5dpublications.euroqol.org/?noheader=true>)

Search terms for each of these sources were based on the terms used for the electronic database searches and the specific requirements and format of each source. The search terms are presented in Table 70 and Table 71, respectively.

Reference list searching

As well as conducting the electronic database and grey literature searches described above, the bibliographies of all relevant SLRs, (N)MAs, HTAs and economic evaluations identified during the

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SLR update were hand-searched, in order to identify any additional, relevant studies for inclusion. A list of these publications searched during the SLR update is shown in Table 72.

In the original SLR, bibliographies were hand-searched for clinical outcomes only.

Search terms of electronic databases

Original SLR

All searches were executed on 4th August 2020. As multiple literature databases were searched, duplicate citations were removed. A list of the search terms used in the electronic databases are provided below.

Table 25. Index of search terms for the original SLR

Haemophilia type	Database	Platform	Economic evaluations	Utilities/ HRQoL	HCRU
Haemophilia A	MEDLINE	Ovid SP	Table 26	Table 36	Table 42
	Embase	Ovid SP	Table 27	Table 37	Table 43
	CDSR	Ovid SP	Table 28	Table 38	Table 44
	EconLit	Ovid SP	Table 29	-	Table 45
	NHS EED	Ovid SP	Table 30	-	Table 46
Haemophilia B	MEDLINE	Ovid SP	Table 31	Table 39	Table 47
	Embase	Ovid SP	Table 32	Table 40	Table 48
	CDSR	Ovid SP	Table 33	Table 41	Table 49
	EconLit	Ovid SP	Table 34	-	Table 50
	NHS EED	Ovid SP	Table 35	-	Table 51

Abbreviations: CDSR: Cochrane Database of Systematic Reviews; HCRU: healthcare cost and resource use; HRQoL: health-related quality of life; NHS EED: NHS Economic Evaluations Database.

Table 26. Search terms used in MEDLINE to search for economic evaluations for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	22,991
2	(economic adj2 model*).mp.	13,094
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).ti,ab,kw.	32,055
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,ab,kw.	325,281
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ab,ti,kw.	35,933
6	(cost or economic*).ti,ab,kw. and (costs or cost-effectiveness or markov).ab,ti,kw.	141,137
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).ti,ab,kw.	35,397
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	163,534
9	exp cost utility analysis/ or exp cost minimization analysis/ or exp economic evaluation/ or exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp Markov chain/ or (cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).ti,ab.	283,470

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Search Number	Search Terms	Results 4 th August 2020
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).ti,ab.	10,829
11	OR/2-10	504,342
12	1 and 11	791
13	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,286,782
14	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,576,474
15	13 or 14	7,544,644
16	12 not 15	464
17	exp Animals/ not exp Humans/	4,722,490
18	16 not 17	462
19	Limit 18 to English language	438
20	limit 19 to yr="2010 -Current"	203

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Versions(R) 1946 to August 2020.

Table 27. Search terms used in Embase to search for economic evaluations for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	25,610
2	(economic adj2 model*).mp.	7,663
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).ti,ab,kw.	51,101
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,ab,kw.	457,995
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ab,ti,kw.	57,474
6	(cost or economic*).ti,ab,kw. and (costs or cost-effectiveness or markov).ab,ti,kw.	212,562
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).ti,ab,kw.	59,440
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ti,ab,kw.	246,771
9	exp cost utility analysis/ or exp cost minimization analysis/ or exp economic evaluation/ or exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp Markov chain/ or (cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).ti,ab.	335,062
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).ti,ab.	18,863
11	OR/2-10	659,589
12	1 and 11	1,375
13	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,281,678
14	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,510,361

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Search Number	Search Terms	Results 4 th August 2020
15	13 or 14	5,785,488
16	12 not 15	1,131
17	exp Animals/ not exp Humans/	4,663,551
18	16 not 17	1,115
19	Limit 18 to English language	1,084
20	limit 19 to (yr="2010 -Current" and (article or article in press))	223
21	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,587
22	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691
23	Annual Meeting of the American Society of Hematology.cf,cg.	58,296
24	World Federation of Hemophilia.cf,cg.	3,478
25	european hematology association.cf,cg.	23,576
26	or/21-25	97,628
27	limit 26 to yr="2018 -Current"	18,754
28	19 and 27	79
29	20 or 28	302

Database(s): Embase (Embase 1974 to August 2020).

Table 28. Search terms used in CDSR to search for economic evaluations for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	14
2	(economic adj2 model*).mp.	71
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).mp.	1,107
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).mp.	4,650
5	(Quality adjusted life year).mp or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ti,ab,kw.	148
6	(cost or economic*).mp. and (costs or cost-effectiveness or markov).ab,ti,kw.	724
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).mp.	700
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).mp.	2,823
9	(cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).mp.	2,256
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).mp.	1,414
11	OR/2-10	4,975
12	1 and 11	10
13	limit 12 to yr="2010 -Current"	9

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2010 to August 2020.

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Table 29. Search terms used in EconLit to search for economic evaluations for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).mp.	4
2	limit 1 to yr="2010 -Current"	2

Database(s): EconLit 1886 to present.

Table 30. Search terms used in NHS EED to search for economic evaluations for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).af.	44
2	(economic adj2 model*).af.	1,516
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).af.	17,397
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).af.	16,082
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).af.	14,749
6	(cost or economic*).af. and (costs or cost-effectiveness or markov).af.	14,429
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).af.	7,634
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).af.	15,538
9	(cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).af.	17,397
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).af.	3,452
11	OR/2-10	17,397
12	1 and 11	44
13	limit 12 to yr="2010 -Current"	19

Database(s): NHS Economic Evaluation Database 1st Quarter 2016.

Table 31. Search terms used in MEDLINE to search for economic evaluations for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	5,593
2	(economic adj2 model*).mp.	13,094

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Search Number	Search Terms	Results 4 th August 2020
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).ti,ab,kw.	32,055
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,ab,kw.	325,281
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ab,ti,kw.	35,933
6	(cost or economic*).ti,ab,kw. and (costs or cost-effectiveness or markov).ab,ti,kw.	141,137
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).ti,ab,kw.	35,397
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	163,534
9	exp cost utility analysis/ or exp cost minimization analysis/ or exp economic evaluation/ or exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp Markov chain/ or (cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).ti,ab.	283,470
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).ti,ab.	10,829
11	OR/2-10	504,342
12	1 and 11	211
13	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,286,782
14	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,576,474
15	13 or 14	7,544,644
16	12 not 15	132
17	exp Animals/ not exp Humans/	4,722,490
18	16 not 17	130
19	Limit 18 to English language	121
20	limit 19 to yr="2010 -Current"	61

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Versions(R) 1946 to August 2020.

Table 32. Search terms used in Embase to search for economic evaluations for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	9,169
2	(economic adj2 model*).mp.	7,663
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).ti,ab,kw.	51,101
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,ab,kw.	457,995
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ab,ti,kw.	57,474

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
6	(cost or economic*).ti,ab,kw. and (costs or cost-effectiveness or markov).ab,ti,kw.	212,562
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).ti,ab,kw.	59,440
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ti,ab,kw.	246,771
9	exp cost utility analysis/ or exp cost minimization analysis/ or exp economic evaluation/ or exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp Markov chain/ or (cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).ti,ab.	335,062
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).ti,ab.	18,863
11	OR/2-10	659,589
12	1 and 11	485
13	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,281,678
14	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,510,361
15	13 or 14	5,785,488
16	12 not 15	368
17	exp Animals/ not exp Humans/	4,663,551
18	16 not 17	364
19	Limit 18 to English language	356
20	limit 19 to (yr="2010 -Current" and (article or article in press))	81
21	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,587
22	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691
23	Annual Meeting of the American Society of Hematology.cf,cg.	58,296
24	World Federation of Hemophilia.cf,cg.	3,478
25	european hematology association.cf,cg.	23,576
26	or/21-25	97,628
27	limit 26 to yr="2018 -Current"	18,754
28	19 and 27	37
29	20 or 28	112

Database(s): Embase (Embase 1974 to August 2020).

Table 33. Search terms used in CDSR to search for economic evaluations for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).af.	4
2	(economic adj2 model*).mp.	71
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).mp.	1,107
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).mp.	4,650

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
5	(Quality adjusted life year).mp or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ti,ab,kw.	148
6	(cost or economic*).mp. and (costs or cost-effectiveness or markov).ab,ti,kw.	724
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).mp.	700
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).mp.	2,823
9	(cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).mp.	2,256
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).mp.	1,414
11	OR/2-10	4,975
12	1 and 11	4
13	limit 12 to yr="2010 -Current"	4

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2010 to August 2020.

Table 34. Search terms used in EconLit to search for economic evaluations for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).mp.	0
2	limit 1 to yr="2010 -Current"	0

Database(s): EconLit 1886 to present.

Table 35. Search terms used in NHS EED to search for economic evaluations for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).af.	11
2	(economic adj2 model*).af.	1,516
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).af.	17,397
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).af.	16,082
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).af.	14,749
6	(cost or economic*).af. and (costs or cost-effectiveness or markov).af.	14,429
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).af.	7,634
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).af.	15,538

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
9	(cost-consequence or cost-minimisation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).af.	17,397
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).af.	3,452
11	OR/2-10	17,397
12	1 and 11	11
13	limit 12 to yr="2010 -Current"	4

Database(s): NHS Economic Evaluation Database 1st Quarter 2016.

Table 36. Search terms used in MEDLINE to search for HRQoL and utilities for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	22,991
2	exp Quality of Life/ or (qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	629,917
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	125,979
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hys or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	88,061
5	or/2-4	777,679
6	1 and 5	1,111
7	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	3,294,267
8	6 and 7	371
9	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,286,782
10	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,576,474
11	9 or 10	7,544,644
12	8 not 11	322
13	exp Animals/ not exp Humans/	4,722,490
14	12 not 13	322

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
15	limit 14 to english language	301
16	limit 15 to (yr="2000-current")	281

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Versions(R) 1946 to August 2020.

Table 37. Search terms used in Embase to search for HRQoL and utilities for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	25,610
2	exp Quality of Life/ or (qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	977,264
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	188,339
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hye or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	126,535
5	or/2-4	1,182,476
6	1 and 5	2,408
7	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	4,165,324
8	6 and 7	842
9	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,281,678
10	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,510,361
11	9 or 10	5,785,488
12	8 not 11	796
13	exp Animals/ not exp Humans/	4,663,551
14	12 not 13	792
15	limit 14 to english language	776
16	limit 15 to (yr="2000-current" and (article or article in press))	239
17	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,587
18	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
19	Annual Meeting of the American Society of Hematology.cf,cg.	58,296
20	World Federation of Hemophilia.cf,cg.	3,478
21	european hematology association.cf,cg.	23,576
22	or/17-21	97,628
23	limit 22 to yr="2018-current"	18,754
24	15 and 23	121
25	16 or 24	360

Database(s): Embase (Embase 1974 to August 2020).

Table 38. Search terms used in CDSR to search for HRQoL and utilities for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	14
2	(qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	2,285
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	128
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hye or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	112
5	or/2-4	2,393
6	1 and 5	2

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2000 to August 2020.

Table 39. Search terms used in MEDLINE to search for HRQoL and utilities for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	5,593
2	exp Quality of Life/ or (qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	629,917
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual	125,979

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
	analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hye or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	88,061
5	or/2-4	777,679
6	1 and 5	349
7	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	3,294,267
8	6 and 7	125
9	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,286,782
10	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,576,474
11	9 or 10	7,544,644
12	8 not 11	112
13	exp Animals/ not exp Humans/	4,722,490
14	12 not 13	112
15	limit 14 to english language	105
16	limit 15 to (yr="2000-current")	100

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Versions(R) 1946 to August 2020.

Table 40. Search terms used in Embase to search for HRQoL and utilities for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	9,169
2	exp Quality of Life/ or (qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	977,264
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	188,339
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hye or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	126,535
5	or/2-4	1,182,476
6	1 and 5	988

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
7	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	4,165,324
8	6 and 7	362
9	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,281,678
10	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,510,361
11	9 or 10	5,785,488
12	8 not 11	343
13	exp Animals/ not exp Humans/	4,663,551
14	12 not 13	342
15	limit 14 to english language	335
16	limit 15 to (yr="2000-current" and (article or article in press))	119
17	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,587
18	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691
19	Annual Meeting of the American Society of Hematology.cf,cg.	58,296
20	World Federation of Hemophilia.cf,cg.	3,478
21	european hematology association.cf,cg.	23,576
22	or/17-21	97,628
23	limit 22 to yr="2018-current"	18,754
24	15 and 23	54
25	16 or 24	173

Database(s): Embase (Embase 1974 to August 2020).

Table 41. Search terms used in CDSR to search for HRQoL and utilities for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	4
2	(qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	2,285
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	128
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hye or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	112
5	or/2-4	2,393
6	1 and 5	1

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Table 42. Search terms used in MEDLINE to search for HCRU for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficiency\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficiency\$ or ahg deficiency\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficiency\$ or classical hemophilia or classical haemophilia).ti,ab.	22,991
2	exp Health Care Costs/ or exp Drug Costs/ or exp "Cost of Illness"/ or exp Hospital Costs/ or exp Economics, Pharmaceutical/ or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	114,515
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	619,107
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	88,378
5	or/2-4	796,410
6	1 and 5	792
7	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	3,294,267
8	exp "Costs and Cost Analysis"/ or (cost-consequence or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab.	237,724
9	7 or 8	3,482,651
10	6 and 9	417
11	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,286,782
12	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,576,474
13	11 or 12	7,544,644
14	10 not 13	294
15	exp Animals/ not exp Humans/	4,722,490
16	14 not 15	294

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
17	limit 16 to (yr="2010 -Current" and english language)	148

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Versions(R) 1946 to August 2020.

Table 43. Search terms used in Embase to search for HCRU for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia a/ or (hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	25,610
2	exp Health Care Costs/ or exp Drug Costs/ or exp "Cost of Illness"/ or exp Hospital Costs/ or exp Economics, Pharmaceutical/ or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	457,767
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	856,623
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	153,794
5	or/2-4	1,412,886
6	1 and 5	1,883
7	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	4,165,324
8	exp "Costs and Cost Analysis"/ or (cost-consequence or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab.	351,261
9	7 or 8	4,456,271
10	6 and 9	1,018
11	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,281,678
12	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,510,361
13	11 or 12	5,785,488
14	10 not 13	813
15	exp Animals/ not exp Humans/	4,663,551
16	14 not 15	809

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
17	limit 16 to (yr="2010 -Current" and english language)	576
18	limit 17 to (article or article in press)	232
19	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,587
20	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691
21	Annual Meeting of the American Society of Hematology.cf,cg.	58,296
22	World Federation of Hemophilia.cf,cg.	3,478
23	european hematology association.cf,cg.	23,576
24	or/19-23	97,628
25	limit 24 to yr="2018-current"	18,754
26	17 and 25	63
27	18 or 26	295

Database(s): Embase (Embase 1974 to August 2020).

Table 44. Search terms used in CDSR to search for HCRU for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	14
2	(Health Care Cost\$ or Drug Cost\$ or "Cost of Illness" or Hospital Cost\$ or Economic\$ or Pharmaceutical\$).mp. or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	5,018
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	903
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	396
5	or/2-4	5,585
6	1 and 5	8
7	limit 6 to yr="2010-current"	7

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2010 to August 2020.

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Table 45. Search terms used in EconLit to search for HCRU for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).mp.	4
2	limit 1 to yr="2010 -Current"	2

Database(s): EconLit 1886 to present.

Table 46. Search terms used in NHS EED to search for HCRU for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).af.	44
2	(treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).af.	8,390
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).af.	6,944
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).af.	2,811
5	or/2-4	8,964
6	1 and 5	21
7	limit 6 to yr="2010-current"	3

Database(s): NHS Economic Evaluation Database 1st Quarter 2016.

Table 47. Search terms used in MEDLINE to search for HCRU for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	5,593
2	exp Health Care Costs/ or exp Drug Costs/ or exp "Cost of Illness"/ or exp Hospital Costs/ or exp Economics, Pharmaceutical/ or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical	114,515

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
	cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	619,107
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	88,378
5	or/2-4	796,410
6	1 and 5	217
7	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	3,294,267
8	exp "Costs and Cost Analysis"/ or (cost-consequence or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab.	237,724
9	7 or 8	3,482,651
10	6 and 9	112
11	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	5,286,782
12	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,576,474
13	11 or 12	7,544,644
14	10 not 13	82
15	exp Animals/ not exp Humans/	4,722,490
16	14 not 15	82
17	limit 16 to (yr="2010 -Current" and english language)	39

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Versions(R) 1946 to August 2020.

Table 48. Search terms used in Embase to search for HCRU for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	9,169
2	exp Health Care Costs/ or exp Drug Costs/ or exp "Cost of Illness"/ or exp Hospital Costs/ or exp Economics, Pharmaceutical/ or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget	457,767

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
	impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	856,623
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	153,794
5	or/2-4	1,412,886
6	1 and 5	727
7	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	4,165,324
8	exp "Costs and Cost Analysis"/ or (cost-consequence or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab.	351,261
9	7 or 8	4,456,271
10	6 and 9	416
11	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	3,281,678
12	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	2,510,361
13	11 or 12	5,785,488
14	10 not 13	302
15	exp Animals/ not exp Humans/	4,663,551
16	14 not 15	302
17	limit 16 to (yr="2010 -Current" and english language)	220
18	limit 17 to (article or article in press)	102
19	(Congress of the International Society on Thrombosis and Haemostasis).cf,cg.	10,587
20	(Annual Congress of the European Association for Haemophilia and Allied Disorders).cf,cg.	1,691
21	Annual Meeting of the American Society of Hematology.cf,cg.	59,296
22	World Federation of Hemophilia.cf,cg.	3,478
23	european hematology association.cf,cg.	23,576
24	or/19-23	97,628
25	limit 24 to yr="2018-current"	18,754
26	17 and 25	29
27	18 or 26	131

Database(s): Embase (Embase 1974 to August 2020).

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Table 49. Search terms used in CDSR to search for HCRU for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	4
2	(Health Care Cost\$ or Drug Cost\$ or "Cost of Illness" or Hospital Cost\$ or Economic\$ or Pharmaceutical\$).mp. or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	5,018
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	903
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	396
5	or/2-4	5,585
6	1 and 5	3
7	limit 6 to yr="2010-current"	3

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2010 to August 2020.

Table 50. Search terms used in EconLit to search for HCRU for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).mp.	0
2	limit 1 to yr="2010 -Current"	0

Database(s): EconLit 1886 to present.

Table 51. Search terms used in NHS EED to search for HCRU for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 4 th August 2020
1	(hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).af.	11
2	(treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).af.	8,390

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 4 th August 2020
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).af.	6,944
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).af.	2,811
5	or/2-4	8,964
6	1 and 5	6
7	limit 6 to yr="2010-current"	0

Database(s): NHS Economic Evaluation Database 1st Quarter 2016.

SLR update

All searches were executed on 30th May 2024. As multiple literature databases were searched, duplicate citations were removed. A list of the search terms used in the electronic databases are provided below.

Table 52. Index of search terms for the SLR update

Haemophilia type	Database	Platform	Economic evaluations	Utilities/ HRQoL	HCRU
Haemophilia A	MEDLINE	Ovid SP	Table 53	Table 61	Table 65
	Embase	Ovid SP	Table 54	Table 62	Table 66
	CDSR	Cochrane Library, Wiley Online	Table 55		
	HTAD	INAHTA	Table 56		
Haemophilia B	MEDLINE	Ovid SP	Table 57	Table 63	Table 67
	Embase	Ovid SP	Table 58	Table 64	Table 68
	CDSR	Cochrane Library, Wiley Online	Table 59		
	HTAD	INAHTA	Table 60		

Abbreviations: CDSR: Cochrane Database of Systematic Reviews; HCRU: healthcare cost and resource use; HRQoL: health-related quality of life; HTAD: Health Technology Assessment Database; INAHTA: international HTA database.

Table 53. Search terms used in MEDLINE to search for economic evaluations for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihaemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	13,327
2	(economic adj2 model*).mp.	15,582
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).ti,ab,kw.	43,736

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 30 th May 2024
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,ab,kw.	438,548
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ab,ti,kw.	49,133
6	(cost or economic*).ti,ab,kw. and (costs or cost-effectiveness or markov).ab,ti,kw.	187,002
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).ti,ab,kw.	51,978
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	225,862
9	exp cost utility analysis/ or exp cost minimization analysis/ or exp economic evaluation/ or exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp Markov chain/ or (cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).ti,ab.	331,937
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).ti,ab.	15,784
11	or/2-10	647,861
12	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	6,091,100
13	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,171,716
14	exp Animals/ not exp Humans/	5,225,513
15	or/12-14	13,436,219
16	1 and 11	647
17	16 not 15	426
18	limit 17 to yr="2020 -Current"	152

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to 29 May 2024.

Table 54. Search terms used in Embase to search for economic evaluations for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	25,847
2	(economic adj2 model*).mp.	10,574
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).ti,ab,kw.	66,396
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,ab,kw.	605,315
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ab,ti,kw.	77,320
6	(cost or economic*).ti,ab,kw. and (costs or cost-effectiveness or markov).ab,ti,kw.	274,361
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).ti,ab,kw.	84,499
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ti,ab,kw.	322,968

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 30 th May 2024
9	exp cost utility analysis/ or exp cost minimization analysis/ or exp economic evaluation/ or exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp Markov chain/ or (cost-consequence or cost-minim?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).ti,ab.	412,167
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).ti,ab.	26,635
11	or/2-10	858,626
12	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	4,051,898
13	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,062,712
14	exp Animals/ not exp Humans/	5,261,339
15	or/12-14	12,110,261
16	1 and 11	1,613
17	16 not 15	1,406
18	limit 17 to yr="2020 -Current"	415

Database(s): Embase 1974 to 29 May 2024.

Table 55. Search terms used in CDSR for haemophilia A (searched via the Cochrane Library, using the Wiley Online platform)

Search Number	Search Terms	Results 30 th May 2024
1	[mh "hemophilia a"]	647
2	(hemophilia a* or haemophilia a* or F8 deficienc* or classic hemophilia* or classic haemophilia* or classical hemophilia* or classical haemophilia* or factor viii deficienc* or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc*).ti,ab	2,391
3	#3 or #4	2,470
4	#4 in Cochrane Reviews, Cochrane Protocols	24
5	Limit #4 to yr="2020 -Current"	7

Database(s): Cochrane Database of Systematic Reviews; Issue 5 of 12, May 2024.

Table 56. Search terms used in HTAD for haemophilia A (searched via the INAHTA platform)

Search Number	Search Terms	Results 30 th May 2024
1	"Hemophilia A"[mh]	44
2	(hemophilia A* or haemophilia A* or hemophilic A* or haemophilic A*)	76
3	("factor VIII deficient" or "factor VIII deficiency" or "factor 8 deficient" or "factor 8 deficiency")	5
4	1 OR 2 OR 3	77

Database(s): International HTA Database, searched May 2024.

Table 57. Search terms used in MEDLINE to search for economic evaluations for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	6,251
2	(economic adj2 model*).mp.	15,582
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).ti,ab,kw.	43,736
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,ab,kw.	438,548

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 30 th May 2024
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ab,ti,kw.	49,133
6	(cost or economic*).ti,ab,kw. and (costs or cost-effectiveness or markov).ab,ti,kw.	187,002
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).ti,ab,kw.	51,978
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	225,862
9	exp cost utility analysis/ or exp cost minimization analysis/ or exp economic evaluation/ or exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp Markov chain/ or (cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).ti,ab.	331,937
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).ti,ab.	15,784
11	or/2-10	647,861
12	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	6,091,100
13	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,171,716
14	exp Animals/ not exp Humans/	5,225,513
15	or/12-14	13,436,219
16	1 and 11	258
17	16 not 15	161
18	limit 17 to yr="2020 -Current"	37

Databases: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to 29 May 2024.

Table 58. Search terms used in Embase to search for economic evaluations for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	11,519
2	(economic adj2 model*).mp.	10,574
3	(cost minimi?ation or cost-utilit\$ or health utilit\$ or economic evaluation\$ or economic review\$ or cost outcome or cost analys?s or economic analys?s or budget\$ impact analys?s).ti,ab,kw.	66,396
4	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,ab,kw.	605,315
5	Quality adjusted life year/ or (life year or life years or qaly\$ or cost-benefit analys?s or cost-effectiveness analys?s).ab,ti,kw.	77,320
6	(cost or economic*).ti,ab,kw. and (costs or cost-effectiveness or markov).ab,ti,kw.	274,361
7	((resource adj2 use*) or (resource adj2 utili*) or ((productivity adj2 loss) or (ICER* or incremental cost))).ti,ab,kw.	84,499
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ti,ab,kw.	322,968
9	exp cost utility analysis/ or exp cost minimization analysis/ or exp economic evaluation/ or exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp Markov chain/ or (cost-consequence or cost-minimi?ation or economic evaluation or economic model or cost benefit or cost analysis or cost effectiveness or cost efficiency analysis).ti,ab.	412,167
10	((cost effectiveness and ratio) or icer or incremental cost effectiveness ratio or incremental cost-effectiveness ratio).ti,ab.	26,635
11	or/2-10	858,626
12	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	4,051,898
13	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,062,712

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 30 th May 2024
14	exp Animals/ not exp Humans/	5,261,339
15	or/12-14	12,110,261
16	1 and 11	660
17	16 not 15	508
18	limit 17 to yr="2020 -Current"	157

Database(s): Embase 1974 to 29 May 2024.

Table 59. Search terms used in CDSR for haemophilia B (searched via the Cochrane Library, using the Wiley Online platform)

Search Number	Search Terms	Results 30 th May 2024
1	[mh "hemophilia b"]	166
2	(hemophilia b* or haemophilia b* or F9 deficienc* or christmas disease or factor ix deficienc* or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc*):ti,ab	2,121
3	#3 or #4	2,139
4	#4 in Cochrane Reviews, Cochrane Protocols	23
5	Limit #4 to yr="2020 -Current"	7

Database(s): Cochrane Database of Systematic Reviews; Issue 5 of 12, May 2024.

Table 60. Search terms used in HTAD for haemophilia B (searched via the INAHTA platform)

Search Number	Search Terms	Results 30 th May 2024
1	"Hemophilia B"[mh]	22
2	(hemophilia B* or haemophilia B* or hemophilic B* or haemophilic B*)	76
3	("factor IX deficient" or "factor IX deficiency" or "factor 9 deficient" or "factor 9 deficiency")	3
4	1 OR 2 OR 3	76

Database(s): International HTA Database, searched May 2024.

Table 61. Search terms used in MEDLINE to search for HRQoL and utilities for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	13,327
2	exp Quality of Life/ or (qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	876,737
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	184,199
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hys or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	118,820
5	or/2-4	1,084,787
6	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	4,456,204

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Search Number	Search Terms	Results 30 th May 2024
7	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	6,091,100
8	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,171,716
9	exp Animals/ not exp Humans/	5,225,513
10	or/7-9	13,436,219
11	1 and 5	1,035
12	6 and 11	386
13	12 not 10	338
14	limit 13 to yr="2020 -Current"	138

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to 29 May 2024.

Table 62. Search terms used in Embase to search for HRQoL and utilities for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	25,847
2	exp Quality of Life/ or (qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	1,369,899
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	270,986
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hye or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	170,532
5	or/2-4	1,656,094
6	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	6,088,872
7	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	4,051,898
8	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,062,712
9	exp Animals/ not exp Humans/	5,261,339
10	or/7-9	12,110,261
11	1 and 5	3,246
12	6 and 11	1,373
13	12 not 10	1,313
14	limit 13 to yr="2020 -Current"	608

Database(s): Embase 1974 to 29 May 2024.

Table 63. Search terms used in MEDLINE to search HRQoL and utilities for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	6,251

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

2	exp Quality of Life/ or (qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	876,737
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	184,199
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hys or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	118,820
5	or/2-4	1,084,787
6	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	4,456,204
7	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	6,091,100
8	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,171,716
9	exp Animals/ not exp Humans/	5,225,513
10	or/7-9	13,436,219
11	1 and 5	442
12	6 and 11	171
13	12 not 10	149
14	limit 13 to yr="2020 -Current"	40

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to 29 May 2024.

Table 64. Search terms used in Embase to search for HRQoL and utilities for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results May 2024	30 th
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	11,519	
2	exp Quality of Life/ or (qol or quality of life or hrql or hrqol or quality adjusted life year or quality adjusted life years or qaly or patient reported outcome or patient reported outcomes or satisfaction or preference* or activities of daily living or adl or assessment of quality of life or aqol or quality of well being scale).ti,ab.	1,369,899	
3	((utilit* and health) or (utilit* and scor*) or (utilit* and valu*) or (disutilit* and health) or (disutilit* and scor*) or (disutilit* and valu*) or daly or dalys or disability adjusted life year or disability adjusted life years or standard gamble or time trade off or time tradeoff or visual analog scale or visual analogue scale or discrete choice experiment or qwb or 15d or health utilities index or hui or hui1 or hui2 or hui3).ti,ab.	270,986	
4	(sf36 or sf 36 or sf6 or sf 6 or short form 6 or sf6d or sf 6d or short form 6d or eq 5d or eq5d or euroqol or euro qol or health status or hys or hyes or health* year* equivalent* or rosser index or quality of wellbeing or qwb).ti,ab.	170,532	
5	or/2-4	1,656,094	
6	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	6,088,872	

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

7	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	4,051,898
8	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,062,712
9	exp Animals/ not exp Humans/	5,261,339
10	or/7-9	12,110,261
11	1 and 5	1,472
12	6 and 11	610
13	12 not 10	578
14	limit 13 to yr="2020 -Current"	256

Database(s): Embase 1974 to 29 May 2024.

Table 65. Search terms used in MEDLINE to search for HCRU for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results May 2024	30 th
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	13,327	
2	exp Health Care Costs/ or exp Drug Costs/ or exp "Cost of Illness"/ or exp Hospital Costs/ or exp Economics, Pharmaceutical/ or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	139,054	
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	832,493	
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	134,945	
5	or/2-4	1,071,560	
6	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	4,456,204	
7	exp "Costs and Cost Analysis"/ or (cost-consequence or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab.	271,415	
8	6 or 7	4,666,007	
9	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	6,091,100	
10	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,171,716	
11	exp Animals/ not exp Humans/	5,225,513	
12	or/9-11	13,436,219	
13	1 and 5	664	
14	8 and 13	366	
15	14 not 12	280	
16	limit 15 to yr="2020 -Current"	100	

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to 29 May 2024.

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Table 66. Search terms used in Embase to search for HCRU for haemophilia A (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	(hemophilia a\$ or haemophilia a\$ or factor viii deficienc\$ or classic hemophilia\$ or classic haemophilia\$ or ahf deficienc\$ or ahg deficienc\$ or antihemophilic factor a or antihemophilic factor a or hemophilic a or haemophilic a or factor 8 deficienc\$ or classical hemophilia or classical haemophilia).ti,ab.	25,847
2	exp Health Care Costs/ or exp Drug Costs/ or exp "Cost of Illness"/ or exp Hospital Costs/ or exp Economics, Pharmaceutical/ or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	560546
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	1151130
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	232400
5	or/2-4	1868499
6	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	6088872
7	exp "Costs and Cost Analysis"/ or (cost-consequence or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab.	420992
8	6 or 7	6421750
9	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	4051898
10	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3062712
11	exp Animals/ not exp Humans/	5261339
12	or/9-11	12110261
13	1 and 5	2416
14	8 and 13	1398
15	14 not 12	1243
16	limit 15 to yr="2020 -Current"	526

Database(s): Embase 1974 to 29 May 2024.

Table 67. Search terms used in MEDLINE to search for HCRU for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	6251
2	exp Health Care Costs/ or exp Drug Costs/ or exp "Cost of Illness"/ or exp Hospital Costs/ or exp Economics, Pharmaceutical/ or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	139054

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	832493
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	134945
5	or/2-4	1071560
6	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	4,456,204
7	exp "Costs and Cost Analysis"/ or (cost-consequence or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab.	271,415
8	6 or 7	4,666,007
9	exp Books/ or exp Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	6,091,100
10	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,171,716
11	exp Animals/ not exp Humans/	5,225,513
12	or/9-11	13,436,219
13	1 and 5	259
14	8 and 13	136
15	14 not 12	101
16	limit 15 to yr="2020 -Current"	20

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to 29 May 2024.

Table 68. Search terms used in Embase to search for HCRU for haemophilia B (searched via the Ovid SP platform)

Search Number	Search Terms	Results 30 th May 2024
1	hemophilia b/ or (hemophilia b\$ or haemophilia b\$ or F9 deficienc\$ or christmas disease or factor ix deficienc\$ or antihemophilic factor b or antihemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc\$).ti,ab.	11,519
2	exp Health Care Costs/ or exp Drug Costs/ or exp "Cost of Illness"/ or exp Hospital Costs/ or exp Economics, Pharmaceutical/ or (treatment cost\$ or direct cost\$ or direct medical cost\$ or nonmedical cost\$ or non-medical cost\$ or total cost or total costs or cost per patient treated or budget impact or cost burden or societal cost\$ or administrative cost\$ or travel cost\$ or travel time or disease cost or cost of drugs).ti,ab.	560,546
3	(indirect cost\$ or disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab.	1,151,130
4	(healthcare resource or healthcare resources or medical resource or medical resources or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitalisation or hospital admission or hospital admissions or icu admission or icu admissions or emergency department visit or emergency department visits or emergency room visit or emergency room visits or er visit or er visits or ed visit or ed visits or inpatient visit or inpatient visits or outpatient visit or outpatient visits or specialist visit or specialist visits or unscheduled doctor visit or unscheduled doctor visits or unscheduled physician visit\$ or general practitioner visit\$).ti,ab.	232,400

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

5	or/2-4	1,868,499
6	exp Longitudinal Studies/ or exp Retrospective Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or exp Cross-Sectional Studies/ or exp Observational Study/ or (longitudinal study or retrospective study or prospective study or cohort\$ or follow up or cross-sectional study or cross sectional study or followup study or observational study or registry or registries or real world or cross sectional).ti,ab.	6,088,872
7	exp "Costs and Cost Analysis"/ or (cost-consequence or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab.	420,992
8	6 or 7	6,421,750
9	exp Books/ or Case Reports/ or exp Models, Theoretical/ or (letter or editorial or erratum or note or short survey).pt.	4,051,898
10	review.pt. not (((systematic or meta) and analy\$) or ((indirect or mixed) and treatment comparison)).ti,ab.	3,062,712
11	exp Animals/ not exp Humans/	5,261,339
12	or/9-11	12,110,261
13	1 and 5	1,094
14	8 and 13	661
15	14 not 12	518
16	limit 15 to yr="2020 -Current"	215

Database(s): Embase 1974 to 29 May 2024.

Search terms of additional sources

Conference proceedings

Original SLR

The search terms used to capture studies from conference searches are detailed in the Embase electronic databases search terms listed above.

SLR update

The search terms used in the conference searches, retrieved results and number of included results and results prioritised for extraction are presented in Table 69. These results therefore cover all three streams of the economic SLR update (results are not presented separately in Appendix H and Appendix I).

Table 69. Search terms used for conference websites

Conference	Link	Search Strategy	Hits (Included Abstracts) <i>Prioritised Abstracts</i>
Annual Meeting of the American Society of Hematology (ASH) - ASH 2022 - ASH 2023	2022 Annual Meeting: https://ashpublications.org/blood/issue/140/Supplement%201 2022 Late Breaking: https://ashpublications.org/blood/issue/140/Supplement%202 2023 Annual Meeting: https://ashpublications.org/blood/issue/142/Supplement%201 2023 Late Breaking:	2022, 2023: Click on the search icon next to "Search within issue" to enter the searching page. Search the following terms: - hemophilia - haemophilia	2022: 208 (1) 0 2023: 244 (1) 0

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Conference	Link	Search Strategy	Hits (Included Abstracts) <i>Prioritised Abstracts</i>
	https://ashpublications.org/blood/issue/142/Supplement%202		
Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) - EAHAD 2022 - EAHAD 2023 - EAHAD 2024	2022: https://onlinelibrary.wiley.com/toc/13652516/2022/28/S1 2023: https://onlinelibrary.wiley.com/toc/13652516/2023/29/S1 2024: https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14915	2022: Download Speaker Abstracts, Oral Presentations, and Poster Presentations 2023: Download Speaker Abstracts, Oral Abstracts, Poster Abstracts, and Publication Only Abstracts 2024: Download AHP Oral Abstracts, Speaker Abstracts, Oral Abstracts, Poster Abstracts, and Publication Only Abstracts 2022, 2023, 2024: In Adobe, use Ctrl+F and click the settings icon and then “Open Full Acrobat Search” Click “Show More Options” and tick “Stemming” and “Case-Sensitive” Under “Return results containing”, select “Match Any of the words” Type in the following search terms in uppercase* and in one line, and click search: Hemophilia, haemophilia, cost, economic, utility, utilities, QoL, resource Click through and highlight the title for each abstract that comes up. Screen the titles and exclude abstracts that are clearly irrelevant. <i>*Because all abstract titles are in capitals, this can help identify relevant abstracts that contain key words in their titles (case sensitivity was unable to be conducted with Abstracts for 2024).</i>	2022: 145 (5) 1 2023: 205 (3) 0 2024: 235 (8) 0
Annual Congress of European Hematology Association (EHA) - EHA 2022 - EHA 2023	2022: https://library.ehaweb.org/eha/#!*menu=6*browsby=3*sortby=2*ce_id=2233*featured=18529*show_banner_in_top_panel=1 2023:	2022, 2023, 2024: In the search bar, type in “hemophilia” and “haemophilia”. Click “Advanced” to expand the drop-down menu, select the corresponding year - EHA2022 Congress - EHA2023 Congress - EHA2024 Hybrid Congress	2022: 12 (0) 2023: 28 (0) 2024: 27 (1) 0

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Conference	Link	Search Strategy	Hits (Included Abstracts) <i>Prioritised Abstracts</i>
EHA 2024	https://library.ehaweb.org/eha/#!*menu=28*browseby=3*sortby=2*ce_id=2489*featured=18528 2024: https://library.ehaweb.org/eha/#!*menu=6*browseby=3*sortby=2*ce_id=2552*featured=18498		
The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International and European Meetings 2022 2023 2024	2022, 2023, 2024: https://www.ispor.org/health-resources/presentations-database/search	2022, 2023, 2024: Conference: select the corresponding conference - ISPOR US 2022 - ISPOR Asia Pacific 2022 - ISPOR Europe 2022 - ISPOR 2023 - ISPOR Europe 2023 - ISPOR Real-World Evidence Summit 2023 - ISPOR US 2024 - ISPOR PCR summit 2024 Keyword: type in "haemophilia" OR "hemophilia" Leave the other items unchanged and click "SEARCH".	2022: ISPOR US 2022: 19 (0) ISPOR Asia Pacific 2022: 0 ISPOR Europe 2022: 30 (1) 0 2023: ISPOR US 2023: 16 (0) ISPOR Europe 2023: 38 (0) ISPOR Real-World Evidence Summit 2023: 0 2024: ISPOR US 2024: 13 (1) 1 ISPOR PCR summit 2024: 0
Congress of the International Society on Thrombosis and Haemostasis (ISTH) - ISTH 2022 - ISTH 2023	2022: https://academy.isth.org/isth/#!*menu=6*browseby=3*sortby=2*ce_id=2251 2023: https://academy.isth.org/isth/#!*menu=6*browseby=3*sortby=2*ce_id=2419	2022: Format: Abstracts, ePosters Topic: "Hemophilia and Rare Bleeding Disorders" Use a multiple highlight plugin to search for "hemophilia B" and "haemophilia B" and "IX" 2023: Format: Abstracts, ePosters Topics: "Bleeding in Neonates and Children", "Hemophilia - Clinical", "Hemophilia Gene Therapy", "Novel biotherapeutics in hemophilia" In these topics, use a multiple highlight plugin to search for "hemophilia" and "haemophilia"	2022: 248 (2) 0 2023: 194 (4) 0
World Congress of the World Federation of Hemophilia (WFH)	2022: https://onlinelibrary.wiley.com/toc/13652516/2022/28/S3	2022: Download Supplement Abstracts and Late Breaking Abstracts	2022: 157 (3) 0 2023:

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Conference	Link	Search Strategy	Hits (Included Abstracts) <i>Prioritised Abstracts</i>
- WFH 2022 - WFH 2023 - WFH 2024	2023: https://onlinelibrary.wiley.com/toc/13652516/2023/29/S2 2024: https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14973	2023: Download CCS_Book of Abstracts 2022, 2023: In Adobe, use Ctrl+F and click the cog icon and then "Open Full Acrobat Search" Click "Show More Options" and tick "Stemming" Under "Return results containing", select "Match Any of the words" Type in the following search terms in one line, and click search: Hemophilia, haemophilia, cost, economic, utility, utilities, QoL, resource Click through and highlight the title for each abstract that comes up. Screen the titles and exclude abstracts that are clearly irrelevant.	58 (1) 0 2024: 179 (6) 1

Abbreviations: ASH: Annual Meeting of the American Society of Hematology; EAHAD: Annual Congress of the European Association for Haemophilia and Allied Disorders; EHA: Annual Congress of European Hematology Association; ISPOR: The International Society for Pharmacoeconomics and Outcomes Research; ISTH: Congress of the International Society on Thrombosis and Haemostasis; WFH: World Congress of the World Federation of Hemophilia; US: United States; QoL: Quality of Life; PCR: Patient-Centered Research.

HTA websites and economic websites

Original SLR

The CEA Registry was searched from 2010 to August 2020 for cost-effectiveness analyses. No further details were provided in the original SLR report.

SLR update

The search terms used in the HTA website searches, retrieved results and number of included results and results prioritised for extraction are presented in Table 70. The search terms used in the economic website searches, retrieved results and number of included results and results prioritised for extraction are presented in Table 71. These results therefore cover all three streams of the economic SLR update (results are not presented separately in Appendix H and Appendix I).

Table 70. Search terms used for HTA website searches

Source	Link	Search Strategy	Results
All Wales Medicines Strategy Group (AWMSG)	https://awmsg.nhs.wales/	Click the search bar on the top right hand side of the page, select "Accessing medicines" and search for the following terms consecutively. Screen titles for relevance. Click on potentially relevant titles and review the "AWMSG Secretariat Appraisal	5 results 0 included

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Source	Link	Search Strategy	Results
		Report (ASAR)" document for relevance. 1) "haemophilia"	
National Centre for Pharmacoeconomics (NCPE)	https://www.ncpe.ie/	Click the search bar on the top right of the screen. Search for each term consecutively. For each potentially relevant hit, select these and review the "Summary" document (where available) for relevance. If no summary document is available, use the information given on the screen (these will therefore always be excluded). 1) "haemophilia" 2) "hemophilia"	0 results
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	Search for the following phrase in the search bar: "haemophilia" Filter results by Type by ticking the "Guidance" and "NICE advice" boxes. Click on relevant results and look for the "History" tab on the right-hand side of the screen. Download the "Final Appraisal Document" and "Committee papers", "ERG/EAG report" (if available) for each relevant result. Within the "Committee papers" document, double click the "Submission from manufacturer" document and screen this for relevance.	16 results 2 included 2 prioritised
Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/	Click on the "Medicines advice" tab and in the search bar search for the following terms consecutively. Expand the advanced search dropdown and review only "Full" and "Resubmission" under submission type. For those which are full and resubmissions, select these and review the "Detailed Advice (PDF)" document for relevance. 1) "haemophilia" 2) "hemophilia"	0 results

Abbreviations: AWMMSG: All Wales Medicines Strategy Group; HTA: Health Technology Assessment; NCPE: National Centre for Pharmacoeconomics; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium.

Table 71. Search terms used for economic website searches

Source	Link	Search Strategy	Results
The Cost-effectiveness Analysis Registry, managed by Tufts	http://healthconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx	Ensure 'Methods' is selected and change the lower limit of the Publication Year range to 2020. Paste the first search term from the list below into the search bar and click search. 1) haemophilia 2) hemophilia	47 results, 0 included

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Source	Link	Search Strategy	Results
Medical Center		Repeat the above with 'Ratios' selected and then with 'Utilities' selected. Then repeat for each subsequent search term in the list.	
The EQ-5D Publications Database	http://eq-5dpublications.euroqol.org/?noheader=true	Ensure the advanced search is presented. In the "type" dropdown, select "abstract" and in the "abstract" box enter the following: 1) haemophilia 2) hemophilia Click the [+] button to the right of the abstract. This will add a new search line. In this search line in the "type" dropdown, select "And" in the operator box and "abstract" in the Type box. Search the following in the "abstract" box: 1) Utility Once the results of [disease] AND utility have been searched, delete "utility" from the abstract box and replace it with the following terms one by one: 1) Utilities 2) Quality of life 3) Cost 4) Economic 5) Resources	0 results

Abbreviations: CEA: cost-effectiveness analysis.

Reference list searching

SLR update

The bibliographies of the following publications were searched during the SLR update (Table 72).

Table 72. SLRs/(N)MAs identified during the SLR update and hand-searched

#	Reference
1	Azeredo-da-Silva AF, Zanotto BS, Kuwabara YS, et al. Quality of life in children and adolescents with hemophilia A: A systematic review and meta-analysis. <i>Research and Practice in Thrombosis and Haemostasis</i> . 2023;7(1).
2	Chapman RH, Kumar VM, Whittington MD, et al. Does Cost-Effectiveness Analysis Overvalue Potential Cures? Exploring Alternative Methods for Applying a "Shared Savings" Approach to Cost Offsets. <i>Value in Health</i> . 2021;24(6):839–845.
3	Chen Y, Cheng SJ, Thornhill T, et al. Health care costs and resource use of managing hemophilia A: A targeted literature review. <i>Journal of Managed Care & Specialty Pharmacy</i> . 2023;29(6):647–658.
4	Kraemmer D, Konigsbrugge O, Moik F, et al. Pharmacokinetic-guided versus standard prophylaxis in hemophilia: a systematic review and meta-analysis. <i>Journal of Thrombosis and Haemostasis</i> . 2023;21(12):3432–3449.
5	McLaughlin P, Hurley M, Chowdary P, et al. Physiotherapy interventions for pain management in haemophilia: A systematic review. <i>Haemophilia</i> . 2020;26(4):667–684.
6	Olasupo OO, Noronha N, Lowe MS, et al. Non-clotting factor therapies for preventing bleeds in people with congenital hemophilia A or B. <i>Cochrane Database of Systematic Reviews</i> . 2024;2024(2):no pagination.
7	Palareti L, Melotti G, Cassis F, et al. Psychological interventions for people with hemophilia. <i>Cochrane Database of Systematic Reviews</i> . 2020;3(3).

G.1.2. Study selection

Studies were selected for inclusion in two stages: first, the abstracts of the search results were reviewed for relevance using the eligibility criteria; second, the full texts of potentially relevant articles were screened in order to obtain the final list of included studies.

The review of abstracts and full texts was performed using predefined eligibility criteria, based on the decision problem for this submission and developed using the Population, Intervention, Comparison, Outcomes and Study design (PICOS) framework. The eligibility of each study captured in the database and hand searching was reviewed for inclusion across all three evidence streams (economic evaluations, utility/HRQoL, and HCRU). The eligibility presented here is specific to the cost-effectiveness evidence stream (Appendix G); eligibility for the other streams is reported in the relevant appendices (utility/HRQoL: Appendix H and HCRU: Appendix I).

Title/abstract review

Each title and abstract were assessed for inclusion by two independent reviewers using the eligibility criteria (Table 73). Where the applicability of the inclusion criteria was unclear, the record was included at this stage to ensure that all potentially relevant studies were captured. The results of the two reviewers were compared and any disagreements were resolved by discussion until a consensus was met. If necessary, a third independent reviewer made the final decision.

Full text review

Each full-text record was then assessed for inclusion by two independent reviewers using the eligibility criteria (Table 73). In cases where the record did not give enough information to be sure that it met the inclusion criteria, the record was excluded to ensure that only relevant records were ultimately included in the SLR. The results of the two reviewers were compared and any disagreements were resolved by discussion until a consensus was met. If necessary, a third independent reviewer made the final decision.

Duplicate and companion publications

Any full duplicates found during the screening phase were excluded. All publications ultimately included in all iterations of the SLR were reviewed, in order to group those reporting on the same study. The primary publication for a study was regarded as the most recent journal article that reported outcomes of interest for the study. Secondary publications were considered as any publications related to the primary study, such as conference abstracts, which reported outcomes of interest. Records reporting on the Cost of Haemophilia in Europe: a Socioeconomic Survey (CHESS; I, II and PAEDS) study were extracted separately and counted as unique studies, except for those published by the same group of authors, which were reference linked.

At subsequent stages of the review (data extraction, quality assessment and write-up), each study was considered as a single unit and only primary publications were extracted.

Evidence prioritisation for data extraction

Due to a large volume of evidence identified as relevant after the full-text review stage, a number of steps were taken to ensure that the most recent and relevant economic evaluations to the decision problem for this submission were prioritised for extraction. Economic evaluations were prioritised for extraction if they:

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- Fulfilled all the following criteria:
 - Cost-utility analyses (CUAs) or CEAs
 - And, conducted in a US, EU4 and/or UK setting
 - And, were identified during the SLR update
- Or, were key studies chosen to inform the structure of the economic model for this submission, based on prior NICE evaluations in haemophilia

Data extraction

Key information from relevant primary publications was extracted into a pre-specified data extraction grid in Microsoft Word. Where more than one publication was identified reporting data on a unique study, each publication was referenced in the table to recognise that more than one publication may have contributed to the entry.

Data extraction was performed in line with guidelines from the University of York CRD,¹⁴ by a single individual for each included study. When the initial extraction was completed, a second individual then independently verified the extracted information and checked that no relevant information had been missed. Any discrepancies or missing information identified by the second individual was discussed by both individuals until a consensus was reached on the information that should be presented in the extraction grid. If necessary, a third individual arbitrated the final decision.

Quality assessment

The quality of economic evaluation studies was assessed using the Drummond checklist,¹⁶ as required by NICE. No quality assessment was performed for utility/HRQoL or HCRU studies. The quality assessments were completed by one individual and verified by another individual.

Eligibility criteria

The eligibility presented here is specific to the economic evaluations evidence stream, eligibility for the other streams are reported in the relevant appendices (utility/HRQoL: Appendix H and HCRU: Appendix I).

Table 73. Eligibility criteria for economic evaluations

Category	Inclusion Criteria	Exclusion Criteria
Population	- Paediatric or adult patients with inherited moderately severe-to-severe haemophilia A or haemophilia B - Subgroups of above target population in studies among mixed haemophilia A/haemophilia B, mixed severity, mixed treatment history or mixed age patient population, if data are separately reported for the target subgroup	- Studies on other diseases - Studies on patients with acquired haemophilia A or haemophilia B - Studies with only subpopulations (e.g. with specific comorbidities)
Intervention	- Any conventional treatment, including replacement therapies and HEMLIBRA® for haemophilia A and replacement therapies for haemophilia B, including all on-demand and prophylaxis treatment, standard and extended half-life. Relevant haemostatic agents, includes: - Topical haemostatic agents (e.g., fibrin glue) - Blood products (e.g., cryoprecipitate, fresh frozen plasma, plasma-derived) - Antifibrinolytic agents (e.g., tranexamic acid) - Desmopressin (DDAVP®) - Clotting factors (e.g., FVIII concentrate, plasma-derived FVIII, rFVIII, FIX concentrate, fibrinogen, recombinant FIX) - Emicizumab (HEMLIBRA®) - Extended half-life FVIII and FIX (e.g., efmoctocog, ruriococog, ruriococog alfa pegol) - Fitusiran, MIM8, concizumab - Gene therapy	Studies with less than 80% of patients or subgroup of patients having received the relevant interventions
Comparators	Any or none	N/A
Outcomes	Model structure	Publications that only reported data on following types of outcomes including:

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Category	Inclusion Criteria	Exclusion Criteria
	ICERs based on QALYs, LYs, budget impact per member per month etc.	- Laboratory based studies that report on cellular work or biomarker analyses that are not correlated with outcomes of interest - Validation/accuracy of diagnostic techniques/tests - Validation of HRQoL or PRO questionnaires - Pharmacokinetics/pharmacodynamics
Study design	- Cost-effectiveness analysis^b - Cost-utility analysis^b - Cost-benefit analysis - Cost-minimisation analysis - Budget-impact analyses - SLRs/(N)MAs (N.B. included for hand-searching at title/abstract stage, but excluded at full-text stage)^a	- Animal studies - In vitro/ex vivo studies - Gene expression/protein expression studies - Narrative publications - Non-systematic reviews - Phase I studies - Case studies - Case series - Case reports - Editorials
Other considerations	- Studies were limited to those conducted within the following regions/countries:^b - North America (United States and Canada) - EU4 + United Kingdom - Japan - Australia - South Korea - International studies - Only English language articles were included Publications from 2020 onwards^b For SLR/(N)MAs, HTAs and economic evaluations reference lists: publications from 2020 onwards	- Countries not of interest - Journal articles not available in English - Articles and abstracts published before the search cut-offs

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Category	Inclusion Criteria	Exclusion Criteria
	Abstracts and other materials from conferences: published from 2022 onwards	

Footnotes: Items in **bold** were added for the SLR update in May 2024. ^aThe reference lists of SLRs/(N)MAs, HTAs and economic evaluations were screened to identify articles of importance that may not have been identified during search or screening. ^bDue to the large volume of evidence identified after the full text review stage, CEA and CUA study designs, publications from 2020 and studies within the US, EU4 and UK were prioritised for extraction.

Abbreviations: CEA: cost-effectiveness analysis; CUA: cost-utility analysis; EU4: France, Germany, Italy and Spain; FVIII: Factor VIII; FIX: Factor IX; HRQoL: health-related quality of life; HTA: health technology assessment; ICER: incremental cost-effectiveness ratio; LY: life years; NA: not applicable; (N)MA: (network) meta-analysis; PRO: patient-reported outcome; QALY: quality-adjusted life years; SLR: systematic literature review; UK: United Kingdom.

G.1.3. Description of identified studies

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the economic SLR is presented in Figure 4, covering all three evidence streams, the original SLR and the SLR update.

Original searches (all evidence streams)

Across all three evidence streams, a total of 5,519 records were retrieved from the electronic databases, of which 2,611 were duplicates, resulting in 2,908 novel records that were screened at the title/abstract review stage. Subsequently, 663 full publications were screened against the eligibility criteria for all three evidence streams at full-text review. Following this, 387 publications were excluded. 276 publications were included in total, comprising of 151 haemophilia A studies, 58 haemophilia B studies and 67 studies reporting on non-separable haemophilia.

A total of 123 publications did not report relevant economic outcomes, resulting in 153 publications being included in the review. To prioritise evidence most relevant to this submission, included records were prioritised for extraction if they were key studies informing the structure of the economic model in this submission, or informed utilities or costs in the economic model. This resulted in prioritisation of data extraction of 4 records from the original SLR.

Update searches (all evidence streams)

Following pooling of records across all three evidence streams, a total of 2,831 records were retrieved from the electronic databases, of which 1,495 were duplicates (including duplicates against the original SLR searches), resulting in 1,336 novel records that were screened at the title/abstract review stage. Subsequently, 284 full publications were screened against the eligibility criteria for all three evidence streams at full-text review. Following this, 190 publications were excluded; these are listed in Table 74 along with the brief rationale for exclusion. This resulted in 94 records being included from the electronic database searches.

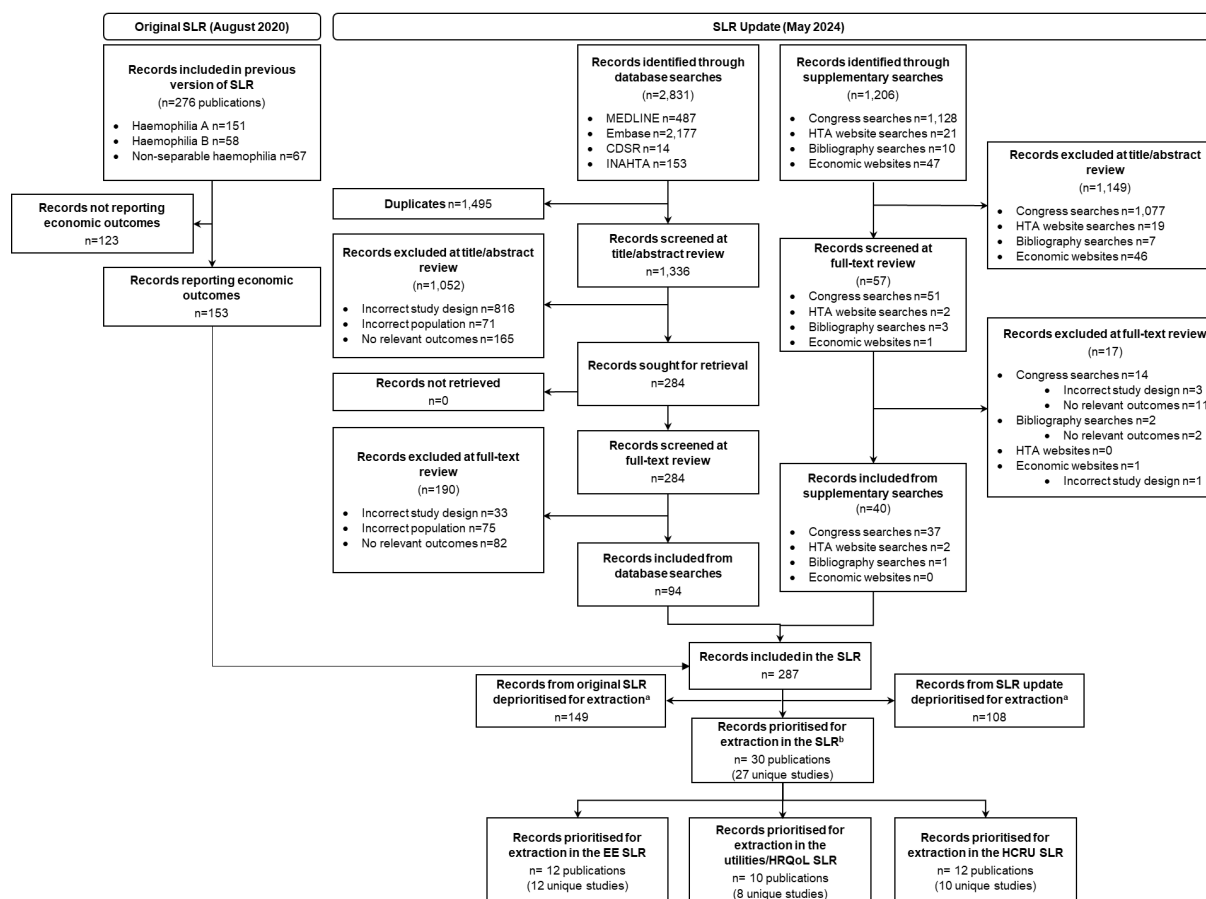
Supplementary searches retrieved an additional 40 records (2 from HTA websites, 1 from reference lists and 37 from conference searches), resulting in a total of 134 records being included in the SLR update, across all three evidence streams. Records were then prioritised for extraction as described in Appendices G.1.2 (economic evaluations), H.1.2 (utility/HRQoL) and I.1.2 (HCRU). This resulted in 26 records being extracted for the submission across all evidence streams in the SLR update.

Lists of the studies deprioritised for data extraction in each evidence stream are presented in Table 75 (economic evaluations), Table 81 (utility/HRQoL) and Table 86 (HCRU).

Total economic evaluations evidence

In total, 12 records reporting on 12 unique studies were prioritised for extraction in the economic evaluations evidence stream of the SLR. A full list of these studies is presented in Table 76. Full details of the prioritised economic evaluations are provided in Table 77 and Table 78.

Figure 4. PRISMA flow diagram of records identified in the original SLR and SLR update (all three evidence streams)



Footnotes: ^aTo prioritise evidence most relevant to this submission, records were prioritised for extraction as described in Appendices G.1.2 (economic evaluations), H.1.2 (utility/HRQoL) and I.1.2 (HCRU). ^bSome records were relevant to multiple streams, therefore the final number of publications does not sum to n=30.

Abbreviations: CDSR: Cochrane Database of Systematic Reviews; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; CRU: cost and resource use; EE: economic evaluation; HCRU: healthcare resource use; HRQoL: health-related quality of life; HTA: Health Technology Assessment; INAHTA: International Network of Agencies for Health Technology Assessment; MEDLINE: Medical Literature Analysis and Retrieval System Online; NHS EED: NHS Economic Evaluation Database; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review; UK: United Kingdom; US: United States.

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Table 74. Publications excluded at the full text review stage in the economic SLR update (economic evaluations, utility/HRQoL and HCRU streams)

#	Reference	Reason for exclusion
1.	Agency for Care, E. Emicizumab prophylaxis for patients with haemophilia A. 2022.	Incorrect publication type
2.	Agency for Care, E. Recombinant blood products for prophylaxis and management of haemophilia A and B. 2022.	Irrelevant population
3.	Aiello A, Mancuso ME, Leone S, et al. Cost analysis of extended half-life recombinant factor IX products in the treatment of haemophilia B in Italy: an update. <i>Global & Regional Health Technology Assessment</i> . 2022;9:Sep-13.	Irrelevant population
4.	Aksu T, Tutar MA, Tan F, et al. Assessment of Joint Health in Patients with Moderate and Severe Hemophilia A and B. <i>Haemophilia</i> . 2023;29(Supplement 1):41.	No relevant outcomes
5.	Alexander WA, Jensen I, Hathway J, et al. Bleeding in patients with hemophilia who have inhibitors: Modeling US medical system utilization and cost avoidance between recombinant factor VIIa products with different clinical dosing requirements. <i>Journal of Managed Care & Specialty Pharmacy</i> . 2022;28(5):518–527.	Irrelevant population
6.	Allard B, Kouakou C, Paré A. Avis: RebinynMC – Prophylaxie de routine chez les enfants et adolescents atteints d'hémophilie de type B. 2023.	No relevant outcomes
7.	Alvarez MT, Castaman G, Janbain M, et al. EE120 Real-World Utilisation of Damoctocog Alfa Pegol in Adults With Haemophilia A: Second Interim Analysis of the HEM-POWR Observational Study. <i>Value in Health</i> . 2022;25(12 Supplement):S76–S77.	Irrelevant population
8.	Alvarez Roman MT, Garcia Dasi M, Entrena Urena L, et al. Anxiety and Depression in Patients with Haemophilia a without Inhibitors and Their Caregivers Included in Hemolife, Non Interventional Study in the Spanish Population. <i>Blood</i> . 2022;140(Supplement 1):11326–11327.	No relevant outcomes
9.	Alvarez-Roman, M., Soto, I., Garcia, M., et al. (2023). Quality of life in patients & caregivers living with hemophilia A without inhibitors in Spain, interim analysis of the HEMOLIFE study. Research and Practice in Thrombosis and Haemostasis, 7(Supplement 2). Conference: ISTH 2023 Congress. Montreal, Canada.	No relevant outcomes
10.	Antonazzo IC, Cortesi PA, Zanoni E, et al. Personalized Prophylaxis with myPKFITCE: A Real-World Cost-Effectiveness Analysis in Haemophilia A Patients. <i>Medicina</i> . 2023;60(1):24.	No relevant outcomes
11.	Arbour S, Jobin N, Nieminen J. Avis: Évaluation de AfstylaMC (rFVIII) – hémophilie de type A. 2022.	Irrelevant population
12.	Astermark J, Al Abbas F, Elliott K, et al. Interim Baseline Data On The 48-Month Prospective, Observational A-More Study Evaluating Long-Term Effectiveness of rFVIIIIFC on Joint Health. <i>Haemophilia</i> . 2022;28(Supplement 1):64–65.	No relevant outcomes
13.	Astermark J, Ljung R, Karlsson E, et al. Trial in Progress: An Open-Label, Multi-Center, First in Human, Phase 1/2a Trial to Evaluate the Safety and Preliminary Efficacy of Autologous Tolerogenic Dendritic Cells Ex Vivo Loaded with Recombinant Factor VIII (FVIII) in Adults with Congenital Hemoph. <i>Blood</i> . 2022;140(Supplement 1):12733–12734.	No relevant outcomes
14.	Ayoub E, Coffin D, Konkle B, et al. WFH World Bleeding Disorders Registry Launches the First Global Data Collection on People with von Willebrand Disease. Research and Practice in Thrombosis and Haemostasis. 2023; Conference: ISTH 2023 Congress. Montreal Canada. 7(Supplement 2).	Irrelevant population
15.	Azeredo-da-Silva AF, Zanotto BS, Kuwabara YS, et al. Quality of life in children and adolescents with hemophilia A: A systematic review and meta-analysis. <i>Research and Practice in Thrombosis and Haemostasis</i> . 2023;7(1).	Incorrect publication type
16.	Bago M, Butkovic A, Kotnik BF, et al. Health-related quality of life in patients with haemophilia and its association with depressive symptoms: A study in Croatia and Slovenia. <i>Psychiatria Danubina</i> . 2021;33(3):334–341.	No relevant outcomes

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#	Reference	Reason for exclusion
17.	Bago M, Butkovic A, Preloznik Zupan I, et al. Association between reported medication adherence and health-related quality of life in adult patients with haemophilia. <i>International Journal of Clinical Pharmacy</i> . 2021;43(6):1500–1507.	No relevant outcomes
18.	Barnett D, Nance D. A Retrospective Analysis and Characterization of Female Patients with Bleeding Disorders Hemophilia B, Hemophilia B and Von Willebrand's Disease and Their Treatment Type at Banner MD Anderson Cancer Center. <i>Blood</i> . 2023;142(Supplement 1):1254.	Irrelevant population
19.	Bartlett C, Miller P, Bracewell J, et al. EE566 Systematic Literature Review for Utility Data in Haemophilia. <i>Value in Health</i> . 2023;26(12 Supplement):S161–S162.	Irrelevant population
20.	Bartlett C, Miller P, Bracewell J, et al. EE719 Systematic Literature Review for Monetary Costs Data in Hemophilia. <i>Value in Health</i> . 2023;26(12 Supplement):S193.	Incorrect publication type
21.	Batt K, Schultz BG, Caicedo J, et al. A real-world study comparing pre-post billed annualized bleed rates and total cost of care among non-inhibitor patients with hemophilia A switching from FVIII prophylaxis to emicizumab. <i>Current Medical Research & Opinion</i> . 2022;38(10):1685–1693.	Irrelevant population
22.	Batt K, Xing S, Kuharic M, et al. Real-world analysis of patients with haemophilia A and haemophilia A carriers in the United States: <i>Demographics, clinical characteristics and costs</i> . <i>Haemophilia</i> . 2023;29(3):809–818.	Irrelevant population
23.	Benton M, Hong D, Skinner M, et al. PCR33 An Updated Analysis of Hemophilia Patient Utility Study of Treatment Administration Impact: A Discrete Choice Experiment (DCE) Using Time Trade-Off (TTO) Methodology. <i>Value in Health</i> . 2023;26(6 Supplement):S318.	Irrelevant population
24.	Benton M, Skinner MW, Garrison LP, et al. A Preliminary Analysis of Hemophilia Patient Utility Study of Treatment Administration Impact: A Discrete Choice Experiment (DCE) Using Time Trade-Off (TTO) Methodology. <i>Haemophilia</i> . 2023;29(Supplement 1):59.	No relevant outcomes
25.	Blenkiron T, Sun SX, O'Hara J, et al. Relationship between Physical Activity Levels and Personalized Care and Clinical Outcomes in Patients with Hemophilia A: Real-World Evidence from the Chess II Study. <i>Haemophilia</i> . 2023;29(Supplement 1):49–50.	No relevant outcomes
26.	Blokzijl J, Pisters MF, Veenhof C, et al. Identifying Persons with Haemophilia at Risk For Functional Decline. <i>Haemophilia</i> . 2022;28(SUPPL 1):17.	Incorrect publication type
27.	Bolous N, Chen Y, Devidas M, et al. The Impact of Different Discounting Rates on Cost-Effectiveness Outcomes in Chronic Disease Populations: Hemophilia A As an Exemplary Disease. <i>Value in Health</i> . 2023;26(6 Supplement):S75–S76.	Irrelevant population
28.	Bolous N, Chen Y, Devidas M, et al. EE203 The Impact of Varying the Target Population on the Outcome of a Cost-Effectiveness Analysis: Hemophilia B As an Exemplary Disease. <i>Value in Health</i> . 2023;26(6 Supplement):S96.	Irrelevant population
29.	Bonanad S, Alvarez MT, Nunez R, et al. Costs of the management of hemophilia A with inhibitors in Spain. <i>Global & Regional Health Technology Assessment</i> . 2021;8:35–42.	No relevant outcomes
30.	Borchiellini A, Castaman G, Feola G, et al. Italian experience with rVIII-single chain: a survey of patients with haemophilia A and their physicians. <i>Journal of Thrombosis and Thrombolysis</i> . 2022;53(4):934–944.	No relevant outcomes
31.	Borhany M, Abid M, Zafar S, et al. Health-related quality-of- lives in hemophilia A patients on prophylactic therapy of Emicizumab (Hemlibra). <i>Research and Practice in Thrombosis and Haemostasis</i> . Conference. 2022;6(Supplement 1):317.	Irrelevant population
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119.	Malacan J, Farej R, Topachevskyi O. EE351 Estimated Annual Treatment Cost of Hemophilia A Prophylaxis in the United States: Comparison of Jivi with the Other Extended Half Life (EHL) Factor VIII Products. <i>Value in Health</i> . 2022;25(7 Supplement):S403–S404.	Irrelevant population
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128.	McLaughlin P, Hurley M, Chowdary P, et al. Physiotherapy interventions for pain management in haemophilia: A systematic review. <i>Haemophilia</i> . 2020;26(4):667–684.	Incorrect publication type
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#	Reference	Reason for exclusion
	to-Severe Haemophilia B in Germany. <i>PharmacoEconomics - Open</i> . 2024;8(3):373–387.	
130.	Miesbach W, Valentino LA, Noone D, et al. Qualitative Research Evaluating Patient Preference For Haemophilia Therapy. <i>Haemophilia</i> . 2022;28(Supplement 1):83.	No relevant outcomes
131.	Nagao A, Ioka A, Nakamura T, et al. Burden of congenital hemophilia A requiring treatment in Japan: The HIKOBOSHI study. <i>Research And Practice In Thrombosis And Haemostasis</i> . 2022;6(7):e12825.	Irrelevant population
132.	Napolitano M, Di Minno M, Calcaterra I, et al. Combined Point of Care Tools Improve Treatment Adherence and Health-Related Quality of Life in Patients with Hemophilia Under Regular Prophylaxis: An Observational Multicenter Prospective Study. <i>Research and Practice in Thrombosis and Haemostasis. Conference: ISTH 2023 Congress. Montreal Canada</i> . 2023;7(Supplement 2):101173.	No relevant outcomes
133.	Olasupo O, Matino D, Iorio A, et al. EE476 Cost-Effectiveness of Emicizumab Prophylaxis in Patients with Hemophilia A without Inhibitors. <i>Value in Health</i> . 2022;25(7 Supplement):S428.	Irrelevant population
134.	Olasupo OO, Noronha N, Lowe MS, et al. Non-clotting factor therapies for preventing bleeds in people with congenital hemophilia A or B. <i>Cochrane Database of Systematic Reviews</i> . 2024;2024(2):no pagination.	Incorrect publication type
135.	Oldenburg J, Halimeh S, Hall GW, et al. Design of a Real-World Observational Study in Previously Untreated and Minimally Treated Hemophilia A Patients: Protect-NOW. <i>TH Open</i> . 2023;7(2):E110–E116.	No relevant outcomes
136.	Oldenburg J, Shima M, Kruse-Jarres R, et al. Outcomes in children with hemophilia A with inhibitors: Results from a noninterventional study. <i>Pediatric Blood & Cancer</i> . 2020;67(10):e28474.	Irrelevant population
137.	Ozelo MC, Brighton S, Ferri Grazzi E, et al. Chronic Disease Outcomes As Predictors of Quality of Life in Patients with Hemophilia A: Data from the Real-World AHEAD International Study. <i>Blood</i> . 2023;142(Supplement 1):5511.	No relevant outcomes
138.	Palareti L, Melotti G, Cassis F, et al. Psychological interventions for people with hemophilia. <i>Cochrane Database of Systematic Reviews</i> . 2020;3(3).	Incorrect publication type
139.	Pan-Petes B, Fouassier M, Guillet B, et al. Real-world use of recombinant factor IX albumin fusion protein (rIX-FP) in patients with hemophilia B: A prospective, multicenter, non-interventional post-marketing surveillance study in France. <i>Research and Practice in Thrombosis and Haemostasis. Conference</i> . 2022;6(Supplement 1):1904.	Irrelevant population
140.	Pathak S, Solanki GS, Aggarwal A, et al. EE261 Economic Burden of Hemophilia B Patients in the United States: A Systematic Literature Review. <i>Value in Health</i> . 2022;25(7 Supplement):S384–S385.	Irrelevant population
141.	Patil R, Shanmukhaiah C, Gogtay NJ, et al. Low-dose emicizumab prophylaxis in patients with severe hemophilia A: a retrospective study bringing new hope for our patients. <i>Journal of Thrombosis & Haemostasis</i> . 2024;22(4):1024–1030.	Incorrect publication type
142.	Pereira FA, Soomro NN, Sulaiman F. Measurement of subjective and objective indices after progressive resistance training compared with aerobic training in Patients with Haemophilia: a study protocol. <i>medRxiv</i> . 2022;30.	Irrelevant population
143.	Perez-Alenda S, Carrasco JJ, Querol-Fuentes F, et al. Benefits of physical activity self-monitoring in patients with haemophilia: a prospective study with one-year follow-up. <i>Haemophilia</i> . 2024;30(3):791–799.	No relevant outcomes
144.	Pochopien M, Tytula A, Toumi M, et al. Cost-Effectiveness of Recombinant Factor IX Fc Prophylaxis and Recombinant Factor IX On-Demand Treatment in Patients with Haemophilia B Without Inhibitors. <i>Advances in Therapy</i> . 2024;41(6):2307–2323.	Irrelevant population
145.	Polack B, Trossaert M, Cousin M, et al. Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France. <i>Haemophilia</i> . 2021;27(1):e1–e11.	Irrelevant population

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#	Reference	Reason for exclusion
146.	Poon MC, Lee A, Germini F, et al. Experience with Emicizumab Among People with Hemophilia A in the Canadian Hemophilia Bleeding Disorders Registry. <i>Blood</i> . 2023;142(Supplement 1):1240.	No relevant outcomes
147.	Prameyllawati D, Lingsma H, Cnossen M, et al. A Systematic Review of Modelling Approaches in Economic Evaluations of Treatments for Inherited Bleeding Disorders. <i>Value in Health</i> . 2023;26(12 Supplement):S201–S202.	Incorrect publication type
148.	Ragni M, Evans M, Croteau S, et al. Improved Quality of Life in People with Hemophilia A Following Gene Therapy with Dirloctocogene Samoparvovec (SPK-8011). Research and Practice in Thrombosis and Haemostasis. Conference: ISTH 2023 Congress. Montreal Canada. 2023;7(Supplement 2):no pagination.	No relevant outcomes
149.	Ragni M, Hu B, Callis J, et al. ATHN 11: Observational Study of Long-Term Outcomes of Liver Transplantation. Research and Practice in Thrombosis and Haemostasis. Conference: ISTH 2023 Congress. Montreal Canada. 2023;7(Supplement 2):no pagination.	No relevant outcomes
150.	Ragni MV, Callis J, Daoud N, et al. Observational cohort study of long-term outcomes of liver transplantation in haemophilia. <i>Haemophilia</i> . 2024;30(1):87–97.	No relevant outcomes
151.	Reding MT, Alvarez Roman MT, Sanabria M, et al. Interim Subgroup Analysis of the Effectiveness and Safety of Damoctocog Alfa Pegol Prophylaxis in Previously Treated Patients with Hemophilia A Treated Every 5 or Every 7 Days: Results from the Real-World Observational HEM-POWR Study. <i>Blood</i> . 2022;140(Supplement 1):5612–5614.	No relevant outcomes
152.	Rosas S, Buller LT, Plate J, et al. Total Knee Arthroplasty among Medicare Beneficiaries with Hemophilia A and B Is Associated with Increased Complications and Higher Costs. <i>The Journal of Knee Surgery</i> . 2021;34(4):372–377.	Irrelevant population
153.	Samelson-Jones BJ, Guelcher C, Kuhn J, et al. Real-world cost estimates of initiating emicizumab in US patients with haemophilia A. <i>Haemophilia</i> . 2021;27(4):591–598.	Irrelevant population
154.	Sarker J, Moradi A, Whittington M, et al. EE555 Cost-Effectiveness of Etranacogene Dezaparvovec for the Treatment of Hemophilia B. <i>Value in Health</i> . 2023;26(6 Supplement):S160–S161.	Irrelevant population
155.	Schwartz CE, Stark RB, Stucky BD, et al. Positive emotions despite substantial burden: The alchemy of haemophilia caregiving. <i>Haemophilia</i> . 2020;26(1):86–96.	No relevant outcomes
156.	Shah S, Waller J, Ibiloye E, et al. Treatment burden and unmet needs in hemophilia patients with inhibitors: Results from a real-world observational study in the United States. Research and Practice in Thrombosis and Haemostasis. Conference: HTRS 2023 Scientific Symposium. Orlando Canada. 2023;7(Supplement 1):100241.	Irrelevant population
157.	Shah S, Waller J, Ibiloye E, et al. EE545 Economic Burden in Patients with Hemophilia with Inhibitors: Results from a Real-World Cohort Study in the United States. <i>Value in Health</i> . 2023;26(6 Supplement):S159. doi:10.2233/vih.2023.159.	Irrelevant population
158.	Sierra Aisa C, Pison C, Garcia-Ruiz J, et al. New Paradigm in the Treatment of Hemophilia B: Spanish Real-Life Experience with rIX-FP. Research and Practice in Thrombosis and Haemostasis. Conference: ISTH 2023 Congress. Montreal Canada. 2023;7(Supplement 2):101237.	No relevant outcomes
159.	Sierra C, Ana M, Garcia-Ruiz JC. New Paradigm in the Treatment of Hemophilia B: Real-Life Experience with Rix-Fp. <i>Haemophilia</i> . 2023;29(Supplement 1):121.	No relevant outcomes
160.	Srichumpuang C, Rakmanotham A, Moonla C, et al. Moderate- to vigorous-intensity physical activities for hemophilia A patients during low-dose pharmacokinetic-guided extended half-life factor VIII prophylaxis. <i>Orphanet Journal Of Rare Diseases</i> . 2024;19(1):135.	Incorrect publication type
161.	Srichumpuang C, Sosothikul D. Impact of Moderate to Vigorous-Intensity Physical Activities on Pharmacokinetic-Guided Extended Half-Life FVIII Concentrates Prophylaxis Severe Hemophilia A Patients. Research and Practice in Thrombosis and Haemostasis. Conference: ISTH 2023 Congress. Montreal Canada. 2023;7(Supplement 2):no pagination.	Incorrect publication type

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#	Reference	Reason for exclusion
162.	Steen Carlsson K, Winding B, Astermark J, et al. High use of pain, depression, and anxiety drugs in hemophilia: more than 3000 people with hemophilia in an 11-year Nordic registry study. <i>Research and Practice in Thrombosis and Haemostasis</i> . 2023;7(2):no pagination.	Irrelevant population
163.	Stonebraker JS, Ducore JM. Modelling future usage and cost of factor and emicizumab to treat haemophilia A for the US Western States Region IX haemophilia treatment centres. <i>Haemophilia</i> . 2021;27(1):e22–e29.	No relevant outcomes
164.	Sun H, Yang M, Poon MC, et al. The impact of extended half-life factor concentrates on patient reported health outcome measures in persons with hemophilia A and hemophilia B. <i>Research and Practice in Thrombosis and Haemostasis</i> . 2021;5(7):no pagination.	No relevant outcomes
165.	Sundaresan PD, Kruger E, Lim M, et al. Dentistry for patients with haemophilia: Trialling a safe and economical change in management. <i>Haemophilia</i> . 2024;30(2):404–409.	No relevant outcomes
166.	Tagliaferri A, Molinari AC, Peyvandi F, et al. IDEAL study: A real-world assessment of pattern of use and clinical outcomes with recombinant coagulation factor IX albumin fusion protein (rIX-FP) in patients with haemophilia B in Italy. <i>Haemophilia</i> . 2023;29(1):135–144.	No relevant outcomes
167.	Taylor S, David J, Partington K, et al. A single centre, open label, pilot study evaluating the effect of intra-articular hyaluronic acid injection on pain and functionality when injected into the ankle (tibio-talar and sub-talar) joint in patients with haemophilic arthropathy. <i>Haemophilia</i> . 2022;28(6):e181–e188.	No relevant outcomes
168.	Teeter J, Charnigo R, Cossons N, Raje S, Hwang E, Le Duigou T. Safety and Efficacy Of Marstacimab For Prevention Of Bleeding Episodes In Paediatric Patients With Severe Haemophilia A Or Moderately Severe To Severe Haemophilia B With Or Without Inhibitors. <i>Haemophilia</i> . 2022; 28(Supplement):88-89.	No relevant outcomes
169.	Thakkar S, Wilcox L, Merla V, et al. RWD58 Impact of Bleeds on the Quality of Life of Patients with Haemophilia: Results from a Multinational Real-World Survey. <i>Value in Health</i> . 2023;26(12 Supplement):S515.	No relevant outcomes
170.	The Federal Joint Committee. Arzneimittel-Richtlinie/Anlage XII: Valoctocogen Roxaparvovec (schwere Hämophilie A). 2023.	Irrelevant population
171.	Thornburg CD, Adamski K, Cook K, et al. Health care costs and resource utilization among commercially insured adult patients with hemophilia A managed with FVIII prophylaxis in the United States. <i>Journal of Managed Care & Specialty Pharmacy</i> . 2022;28(4):449–460.	Irrelevant population
172.	Tran DQ, Ullman MM, Riske B, et al. Adherence to Clotting Factor Treatment and Association with Bleeding and Health-Related Quality of Life in Persons with Hemophilia. <i>Blood</i> . 2023;142(Supplement 1):7334.	No relevant outcomes
173.	Ucero-Lozano R, Lopez-Pina JA, Ortiz-Perez A, et al. Quality of life and its predictors among adult patients with haemophilic arthropathy. An observational study. <i>BMC Musculoskeletal Disorders</i> . 2021;22(1):448.	No relevant outcomes
174.	Uminski K, Rydz N, Goodyear MD. Factor First: An Assessment of Emergency Department Care of Patients with Hemophilia. <i>Blood</i> . 2023;142(Supplement 1):3689.	No relevant outcomes
175.	Varughese N, Vaillancourt R, Klaassen MR, et al. Pharmacist integration into the hemophilia treatment centre: A Canadian pilot project to optimize treatment and improve cost-savings using pharmacokinetic assessments of hemophilia patients. <i>Canadian Pharmacists Journal</i> . 2023;156(5):14.	No relevant outcomes
176.	Von Mackensen S, Halimeh S. Monitoring of Patient-Reported Outcomes in Patients with Bleeding Disorders to Assure Quality of Care: Results from a Single Outpatient Haemophilia Treatment Centre in Germany. <i>Blood</i> . 2022;140(Supplement 1):13065.	Irrelevant population
177.	Von Mackensen S, Schmoldt D, Rosch A, et al. Assessment of Health-Related Quality of Life and Chronic Pain in Patients with Haemophilia A and B by Using an	No relevant outcomes

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#	Reference	Reason for exclusion
	Electronic Mobile App - Results of the Emiqol Study. <i>American Journal of Hematology</i> . 2023;98(Supplement 1):E117.	
178.	Von Mackensen S, Siebert M, Rosenthal M, et al. A Comparison of Health-Related Quality of Life, Pain and Functional Parameters between People with Hemophilia and People with Osteoarthritis - Preliminary Results of the Physio-FUN Study. <i>Blood</i> . 2023;142(Supplement 1):7232.	No relevant outcomes
179.	Wang S, Li Q, Zhang Z, et al. Ankle arthrodesis for end-stage haemophilic ankle arthropathy using a Ilizarov method. <i>International Orthopaedics</i> . 2020;44(5):995-1001.	Incorrect publication type
180.	Xiang SC, Shen SN, Wang R, et al. Intra-articular injection of tranexamic acid in patients with haemophilia arthritis: retrospective controlled study in total knee arthroplasty. <i>International Orthopaedics</i> . 2024;48(3):683–692.	No relevant outcomes
181.	Xing S, Batt K, Kuharic M, et al. Evaluation of clinical characteristics, health care resource utilization, and cost outcomes of hemophilia A carriers and noncarriers in the United States: A real-world comparative analysis. <i>Journal of Managed Care & Specialty Pharmacy</i> . 2023;29(6):626–634.	Irrelevant population
182.	Yan S, Tomic R, Panebianco M, et al. Budget impact of increasing rVIII-SingleChain use in patients in Italy with moderate and severe hemophilia A. Research and Practice in Thrombosis and Haemostasis. Conference. 2022;6(Supplement 1):2719.	No relevant outcomes
183.	Yan S, Tomic R, Panebianco M, et al. Budget Impact Of RVIII-Singlechain In Moderate And Severe Haemophilia A Treatment In Italy. <i>Haemophilia</i> . 2022;28(Supplement 1):42–43.	No relevant outcomes
184.	Young G, Callaghan M, Balasa V, et al. Effects of PK assessment on FVIII consumption and estimated costs for patients with moderate to severe hemophilia A. Research and Practice in Thrombosis and Haemostasis. Conference. 2022;6(Supplement 1):2731.	No relevant outcomes
185.	Young G, Callaghan MU, Balasa V, et al. Effects of PK-guided prophylaxis on clinical outcomes and FVIII consumption for patients with moderate to severe Haemophilia A. <i>Haemophilia</i> . 2023;29(5):1234–1242.	No relevant outcomes
186.	Young L, Ban L, Chen Y, et al. Bleeds and resource use in hemophilia B: retrospective observational study. <i>American Journal of Managed Care</i> . 2024;30(5):e157–e164.	Irrelevant population
187.	Young L, Chen Y, Alvir J, et al. The impact of bleeding event frequency on health-related quality of life and work productivity outcomes in a European cohort of adults with haemophilia A: insights from the CHES II study. <i>Orphanet Journal Of Rare Diseases</i> . 2023;18(1):227.	No relevant outcomes
188.	Young L, Markson L, Alvir J, et al. Association Between Annual Bleeding Events And Health-Related Quality Of Life In Adults With Haemophilia A Prescribed Prophylaxis. <i>Haemophilia</i> . 2022;28(Supplement 1):40.	Irrelevant population
189.	Zale C, Leslie D, Ba D, et al. Those with hemophilia or von Willebrand disease do not have increased perioperative complications following anterior cruciate ligament reconstruction: Results of a case-control large-database study. <i>Knee</i> . 2020;27(6):1729–1734.	Irrelevant population
190.	Zemplenyi A, Leonard J, DiStefano MJ, et al. Using Real-World Data to Inform Value-Based Contracts for Cell and Gene Therapies in Medicaid. <i>Pharmacoeconomics</i> . 2024;42(3):319–328.	No relevant outcomes

Table 75. Economic evaluations deprioritised for extraction in the economic SLR (original and update)

#	Reference
1.	Aiello, A., Mancuso, M. E., Colombo, A., et al. Budget impact analysis of extended half-life recombinant factor IX (rFIXFc) in the treatment of haemophilia B. <i>Global & Regional Health Technology Assessment</i> . 2020;7:40-49.
2.	Fujii, T., Kidoguchi, Y., Takahashi, N., et al. Budget impact analysis of Jivi (damoctocog alfa pegol, Bay 94-9027) in severe hemophilia A in Japan. <i>Journal of Medical Economics</i> . 2021;24:218-225.
3.	Wang, T., Chen, E., Regan, C., et al. Impact of gene therapy on the economic burden of adults with severe hemophilia a managed with prophylaxis in the United States. <i>Journal of Managed Care and Specialty Pharmacy</i> . 2022;28(10 A-Supplement):S41-S42.
4.	Wang, T., Chen, E., Regan, C., et al. National Economic Burden of Adults with Severe Hemophilia A Managed with Prophylaxis in the United States. <i>American Journal of Hematology</i> . 2023;98(Supplement 1):E118.
5.	Wang, T., Chen, E., Regan, C., et al. EE706 Impact of Valoctocogene Roxaparvec on the Economic Burden of Adults with Severe Hemophilia A Managed with Prophylaxis in the United States. <i>Value in Health</i> . 2023;26(12 Supplement):S190.
6.	Wilson, M., McDade, C., Thiruvillakkat, K., et al. Assessing health plan payer's budget impact of etranacogene dezaparvec for the treatment of hemophilia B in the United States. <i>Journal of Managed Care & Specialty Pharmacy</i> . 2024;45627.
7.	Yan, S., McDade, C., Thiruvillakkat, K., et al. Analysis of long-term clinical and cost impact of etranacogene dezaparvec for the treatment of hemophilia B population in the United States. <i>Journal of Medical Economics</i> . 2024;41275.
8.	Yu, J. K., Wong, W. W. L., Keepanasseril, A., et al. Cost-utility analysis of emicizumab for the treatment of severe hemophilia A patients in Canada. <i>Haemophilia</i> . 2023;29(2):488-497.
9.	Sun, SX, Wu, et al. Cost-effectiveness model of recombinant FVIII versus emicizumab treatment of patients with severe hemophilia a without inhibitors. <i>Blood</i> . 2019;134.
10.	Polack, B, Trossaert, et al. Cost-effectiveness of emicizumab versus by-passing agents in patients with haemophilia A and FVIII inhibitors in France. <i>HemaSphere</i> . 2019;3118.
11.	Machin N, Ragni MV, Smith KJ. Gene therapy in hemophilia A: a cost-effectiveness analysis. <i>Blood Adv</i> . 2018 Jul 24;2(14):1792-1798. doi: 10.1182/bloodadvances.2018021345. PMID: 30042145; PMCID: PMC6058236.
12.	Farrugia A, Cassar J, et al. Treatment for life for severe haemophilia A: a cost-utility model for prophylaxis vs. on-demand treatment (Structured abstract). Treatment for life for severe haemophilia A: a cost-utility model for prophylaxis vs. on-demand treatment. 2013; 19:e228–e238.
13.	Cortesi, PA, Castaman, et al. Cost-Effectiveness and Budget Impact of Emicizumab Prophylaxis in Haemophilia A Patients with Inhibitors. <i>Thrombosis and Haemostasis</i> . 2020;120216-228.
14.	Mareque, M, Mingot-Castellano, et al. Prophylaxis therapy with bypassing agents in patients with haemophilia A and inhibitors undergoing surgery: A cost analysis in Spain. <i>European Journal of Haematology</i> . 2020;10594-100.
15.	Zhou, ZY, Raimundo, et al. Model of Short- and Long-Term Outcomes of Emicizumab Prophylaxis Treatment for Persons with Hemophilia A. <i>Journal of managed care & specialty pharmacy</i> . 2020;1-12.
16.	Bullement, A, McMordie, et al. Cost-Effectiveness Analysis of Recombinant Factor VIII Fc-Fusion Protein (rFVIII-Fc) for the Treatment of Severe Hemophilia A in Italy Incorporating Real-World Dosing and Joint Health Data. <i>PharmacoEconomics - Open</i> . 2020;4133-142.
17.	Patel, AM, Corman, et al. Economic impact model of delayed inhibitor development in patients with hemophilia a receiving emicizumab for the prevention of bleeding events. <i>Journal of Medical Economics</i> . 2019;221328-1337.
18.	Neufeld, EJ, Sidonio, et al. Cost analysis of plasma-derived factor VIII/von Willebrand factor versus recombinant factor VIII for treatment of previously untreated patients with severe hemophilia A in the United States. <i>Journal of Medical Economics</i> . 2018;21762-769.

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#	Reference
19.	Messori, A, Peyvandi, et al. High-titre inhibitors in previously untreated patients with severe haemophilia A receiving recombinant or plasma-derived factor VIII: A budget-impact analysis. <i>Blood Transfusion</i> . 2018;16215-220.
20.	Lorenzoni, V, Triulzi, et al. Budget impact analysis of the use of extended half-life recombinant factor VIII (efmoroctocog alfa) for the treatment of congenital haemophilia a: the Italian National Health System perspective. <i>BMC health services research</i> . 2018;18596.
21.	Mahajerin, A, Zhou, et al. Model of short and long-term outcomes of emicizumab prophylaxis treatment for persons with hemophilia A. <i>Blood</i> . 2018;132.
22.	Iannazzo, S, Cortesi, et al. Cost-effectiveness analysis of pharmacokinetic-driven prophylaxis vs. standard prophylaxis in patients with severe haemophilia A. <i>Blood Coagulation and Fibrinolysis</i> . 2017;28425-430.
23.	McMullen, S, Buckley, et al. Budget Impact Analysis of Prolonged Half-Life Recombinant FVIII Therapy for Hemophilia in the United States. <i>Value in Health</i> . 2017;2093-99.
24.	Villarrubia, R, Oyaguez, et al. Cost analysis of prophylaxis with activated prothrombin complex concentrate vs. on-demand therapy with activated factor VII in severe haemophilia A patients with inhibitors, in Spain. <i>Haemophilia</i> . 2015;21320-329.
25.	Earnshaw, SR, Graham, et al. Factor VIII alloantibody inhibitors: Cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. <i>Haemophilia</i> . 2015;21310-319.
26.	Abrahamyan, L, Willan, et al. Using value-of-information methods when the disease is rare and the treatment is expensive - The example of hemophilia A. <i>Journal of General Internal Medicine</i> . 2014;29S767-S773.
27.	Jimenez-Yuste, V, Nunez, et al. Cost-effectiveness of recombinant activated factor VII vs. plasma-derived activated prothrombin complex concentrate in the treatment of mild-to-moderate bleeding episodes in patients with severe haemophilia A and inhibitors in Spain. <i>Haemophilia</i> . 2013;19841-846.
28.	Colombo, GL, di Matteo, et al. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. <i>ClinicoEconomics and Outcomes Research</i> . 2011;355-61.
29.	Kim, Hae Kyung, Peral, et al. Cost of patients with hemophilia A treated with standard half-life or extended half-life FVIII in Spain. <i>Expert review of pharmacoeconomics & outcomes research</i> . 2020;1-6.
30.	Hay, JW, Zhou, et al. Economical comparison of APCC vs. rFVIIa for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors. <i>Haemophilia : the official journal of the World Federation of Hemophilia</i> . 2011;17e969-74.
31.	Lippert, Barbara, Berger, et al. Cost effectiveness of haemophilia treatment: a cross-national assessment. <i>Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis</i> . 2005;16477-85.

Table 76. Economic evaluations included in the economic SLR

#	Study name	Reference
SLR Update (May 2024)		
1	Benson 2021	Benson G, Morton T, Thomas H, Lee XY. Long-term outcomes of previously treated adult and adolescent patients with severe hemophilia A receiving Prophylaxis with extended half-life FVIII treatments: an economic analysis from a United Kingdom perspective. <i>ClinicoEconomics and Outcomes Research</i> . 2021 Jan 18:39-51.
2	Bolous 2021	Bolous NS, Chen Y, Wang H, et al. The cost-effectiveness of gene therapy for severe hemophilia B: a microsimulation study from the United States perspective. <i>Blood</i> . 2021;138(18):1677-1690.
3	Bolous 2022	Bolous N, Chen Y, Wang H, et al. EE166 Cost-Effectiveness of Treatment Strategies for Severe Hemophilia A Patients in the United States. <i>Value in Health</i> . 2022;25(7 Supplement):S366.
4	Bullement 2021	Bullement A, Knowles ES, DasMahapatra P, Ali T, Preblich R. Cost-effectiveness analysis of rFVIIIIFc versus contemporary rFVIII treatments for patients with

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#	Study name	Reference
		severe hemophilia A without inhibitors in the United States. <i>PharmacoEconomics-Open</i> . 2021 Dec;5:625-33.
5	Decker-Palmer 2022	Decker-Palmer M, Lin CW, Wilson M, et al. Cost-Effectiveness of Emicizumab for Prophylaxis in People with Severe Hemophilia A without Inhibitors. <i>Blood</i> . 2022;140(Supplement 1):13041-13042.
6	ICER 2020	Institute for Clinical and Economic Review (ICER). Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value. 2020.
7	Ito 2023	Ito S, Potnis KC, Allen C, et al. Equitable Care for Severe Hemophilia A: Distributional Cost-Effectiveness of Prophylactic Weekly Efanesoctocog Alfa Versus Standard-Care Factor VIII in Patients with Severe Hemophilia A in the United States. <i>Blood</i> . 2023;142(Supplement 1):492.
8	NICE 2023	National Institute for Health and Care Excellence (NICE). Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812], 2023.
9	NICE 2024	National Institute for Health and Care Excellence (NICE). Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170], 2024.
10	Pochopien 2022	Pochopien M, Tytula A, Toumi M, et al. EE105 Cost-Effectiveness of Recombinant Factor IX Fc Prophylaxis and Recombinant Factor IX On-Demand Treatment in Patients With Haemophilia B Without Inhibitors. <i>Value in Health</i> . 2022;25(12 Supplement):S73-S74.
11	Tice 2023	Tice JA, Walton SM, Sarker J, et al. The effectiveness and value of gene therapy for hemophilia: A Summary from the Institute for Clinical and Economic Review's California Technology Assessment Forum. <i>Journal of Managed Care and Specialty Pharmacy</i> . 2023;29(5):576-581.
Original SLR (August 2020)		
1	Cook 2020	Cook K, Forbes SP, Adamski K, et al. Assessing the potential cost-effectiveness of a gene therapy for the treatment of hemophilia A. <i>Journal of Medical Economics</i> . 2020;23:501–512.

G.1.4. Summary of published economic evaluations identified in the review

The 12 economic evaluations included in the cost-effectiveness SLR are presented in this section. The methodological details and results of studies included in the SLR are presented in Table 77 and Table 78, respectively.

Critical appraisals of each economic evaluation were conducted using the Drummond checklist,¹⁶ as required by NICE, and are presented in Table 79.

Table 77. Summary of published economic evaluations included in the economic SLR

Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
Benson 2021	To develop a pharmacodynamic–pharmacokinetic decision model to predict comparative bleed outcomes of adolescents and adults with HA receiving treatment with various EHL FVIII therapies, capturing differences in cumulative bleeding episodes, breakthrough bleed resolution and resource costs, as well as QALYs	UK, NHS perspective	Type of study: cost-effectiveness Type of model and rationale: PD–PK decision model (rationale NR) Model health states: severe (<1% FVIII activity), moderate (1% to 5% FVIII activity), mild (>5% to 49% FVIII activity), normal (>50% FVIII activity) and death Interventions and comparators modelled: turoctocog alfa pegol, rurioctocog alfa pegol, efmoctocog alfa and damoctocog alfa pegol Time horizon and cycle lengths, plus rationale: 70-year time horizon, with cycle length of 28 days; this time period was chosen as it was a multiple of the dosing frequencies (every 4 days and twice weekly dosing) for all products studied in the model, enabling comparability Source of inputs used: ABRs were derived from the pathfinder 2 clinical trial; patient-level efficacy data were taken from the main phase and first extension phase of the trial FVIII activity levels were estimated on an hourly basis for each patient using dosing data reported in their patient diaries and an FVIII activity equation Other clinical inputs were derived from the SPINART study and PROTECT-VIII trials	Simulated cohort of previously treated patients with SHA, who start treatment at age 12 years	Data on target joints were not captured in the Pathfinder 2 trial, and thus the long-term consequences of joint bleeds were not captured in the model It was also assumed that the modelled relationship between ABR and FVIII levels based on Pathfinder 2 trial data was consistent for all FVIII comparators Pricing assumptions were required for the cost analysis due to the lack of availability of publicly available	The economic evaluation was conducted from a UK healthcare payer perspective, and is therefore applicable to decision making in England

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
			Costs and utilities were calculated based on the number of bleeds experienced in each cycle, and time spent in each health state throughout the cycle, aggregated over the model time horizon. Cost outcomes included total and disaggregated costs, total FVIII prophylaxis costs, breakthrough bleed resolution costs and resource use costs The cost of FVIII prophylactic treatment per cycle was calculated using the number of units used per cycle. FVIII treatment costs were based on the SmPC range mid-point As UK costs per unit were not available for rurioctocog alfa pegol, efmoroctocog alfa, and damoctocog alfa pegol, these were calculated by assuming parity in annual prophylaxis treatment costs to turoctocog alfa pegol, which has a UK list price of £0.85 per unit Estimates for resource use costs were informed by interviews with three UK clinical experts Discount rate: 3.5% per year Cost year and currency: cost year NR, GBP Details of any sensitivity analyses: formal sensitivity analysis NR; scenario analysis was undertaken to model bleeds, costs and QALYs using low and high dosing regimens stated in the EMA SmPCs for each product		prices for all comparators in the UK. Consequently, treatment costs were calculated for comparators by assuming parity in annual prophylaxis treatment costs to turoctocog alfa pegol, and may not be reflective of realised tender prices Perioperative care resulting from joint surgery due to long-term joint damage was not modelled in the analysis, and therefore the true costs to the healthcare system for treatments may be underestimated	

Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
Bolous 2021	To compare the cost and potential cost-effectiveness of AAV-FIX-Padua gene therapy for severe HB vs those of on-demand and prophylactic factor replacement therapies	US, healthcare payer	Type of study: cost-utility analysis Type of model and rationale: microsimulation Markov model, no explicit rationale provided Model health states: 3 health states: (1) alive, (2) alive with joint damage, (3) dead Interventions and comparators modelled: The intervention was AAV-mediated FIX-Padua gene therapy. The comparators were on-demand FIX replacement and primary FIX prophylaxis, using either SHL or EHL FIX products (BeneFix and Alprolix, respectively) Time horizon and cycle lengths, plus rationale: Lifetime time horizon, with starting age set at 18 years (the youngest age at which patients could receive gene therapy treatment). A 1-week cycle length was used to ensure mutually exclusive health states Treatment sequencing: NA Source of inputs used: - The number of patients was selected based on trial simulation to ensure stable model outputs - Dosages were obtained from product package inserts, Lexicomp and Srivastava et al. 2020 - Clotting factor costs were calculated by multiplying the wholesale acquisition cost (obtained from Redbook Online from Micromedex Solutions) by the body weight	Male patients with severe HB (defined as <1% factor activity)	Select data were borrowed from the haemophilia population as a whole Not enough data to inform the long-term durability of factor levels or safety parameters after gene therapy administration Variability across various gene therapy products and between individual patients cannot be defined at this early point Capital expenditure costs, research and development costs were not considered in one of the 1-way	The patient population is aligned with the decision problem. However, the economic evaluation was conducted from a US healthcare payer's perspective, and therefore has limited applicability to decision making in England

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
			of the average US male in every year of life (obtained from CDC NHANES) • Gene therapy costs were assumed based on proposed pricing announcements and Cook et al. 2020 • Inpatient stay costs were obtained from the WHO-CHOICE tool • Outpatient visits, investigations, and imaging studies costs were obtained from Centers for Medicare & Medicaid Services Online Database • Utilities were input using published data measuring EQ-5D • Annual bleeding rates (minor and major), and joint damage and total joint replacement surgery rates were obtained from published literature • Hospitalisation rate was obtained from product package inserts, Lexicomp, and published literature (Colowick et al. 2000, Knight et al. 2003) • Mortality rate was calculated based on US general population mortality rates (obtained from CDC WONDER) adjusted with relative risk of death due to haemophilia obtained from Hassan et al. 2020 Discount rate: 3% per year for costs and effects Cost year and currency: Cost year NR, USD (\$)		sensitivity analyses Focused only on current ongoing gene therapy intervention eligibility groups such as adult patients without inhibitors or AAV8 antibodies Other treatment strategies, including secondary prophylaxis, low-dose prophylaxis, and on-demand treatment followed by gene therapy, were not analysed	

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
			Details of any sensitivity analyses: One-way sensitivity analyses and probabilistic sensitivity analyses were performed			
Bolous 2022	To examine the cost-effectiveness of n=8 treatment strategies: on-demand and prophylaxis using either SHL-FVIII or EHL-FVIII, with and without gene therapy	US, societal perspective	Type of study: cost-effectiveness Type of model and rationale: microsimulation Markov model Model health states: NR Interventions and comparators modelled: on-demand and prophylaxis treatment using either SHL-FVIII or EHL-FVIII, with and without gene therapy (administered at 18 years of age) Time horizon: lifetime horizon Source of inputs used: model input parameters were derived from the literature. Gene therapy price was assumed at USD (\$) 2,000,000/patient. Waning therapeutic response was extrapolated based on 5 years of clinical trial follow-up and estimated that patients would restart prophylaxis/on-demand after 6 years Discount rate: 3% per annum	Individuals with SHA (including individuals with FVIII inhibitors and/or AAV antibodies)	NR	The economic evaluation was conducted from a US societal perspective, and therefore has limited applicability to decision making in England
Bullement 2021	To determine the cost-effectiveness of contemporary rFVIII-based treatments for SHA adult patients without inhibitors in the US, and to establish the key drivers of CEA results in this patient population.	US, healthcare payer perspective	Type of study: cost-effectiveness Type of model and rationale: semi-Markov model, building on a previously published structure, based on the ability to capture the impact of treatment on joint health and translate this into both costs and outcomes within the model Model health states: no target joints, ≥ 1 target joint, death Intervention and comparators modelled: Three prophylaxis treatments were compared: (i)	Male patients with SHA without inhibitors, initiating prophylaxis from the age of 1 year	The lack of available data regarding joint health is a key limitation. Limited data were available to inform the model transition probabilities (i.e., the development or resolution of TJs)	The economic evaluation was conducted from a US healthcare payer, and is of limited relevance to decision

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
	The CEA adopts a US healthcare payer perspective		rFVIII Fc (EHL), (ii) PEG-rFVIII (EHL), and (iii) SHL rFVIII Time horizon and cycle lengths, plus rationale: lifetime horizon, in line with ICER assessment of emicizumab; 1-year cycles, based on published guidance Source of inputs: ABRs were identified from published literature; resolution of target joints based on A-LONG, Mullins et al. 2017, Panicker et al. 2003; mortality informed by US life tables; health state utilities informed by O'Hara et al. 2018; breakthrough bleeding episode utility decrement informed by Neufeld et al. 2012; only drug acquisition costs included from AnalySource Discount rate: 3% for costs and health outcomes Cost year and currency: 2020 USD (\$) Details of any sensitivity analyses: OWSA was not performed; instead, scenario analyses explored bleed duration, bleed disutilities, proxy country utilities, target joint resolution, costs and dosing assumptions		To inform utility values, patients from Germany were assumed to serve as a proxy for the US Patients with a lower ABR would theoretically have a lower medical resource use cost, and so the cost-effectiveness of treatments that reduce ABR may be underestimated by this analysis The acquisition costs for each product may be subject to a number of confidential pricing agreements	making in England

Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
Cook 2020	To assess the potential cost-effectiveness of treating patients with valoctocogene roxaparvovec rather than prophylactic therapy	US, health care system	Type of study: cost-effectiveness Type of model and rationale: individual-based, state-transition microsimulation model Model health states: no bleed, joint bleed, non-joint bleed and dead Interventions and comparators modelled: valoctocogene roxaparvovec with prophylactic exogenous FVIII protein for the first four weeks following gene therapy administration The comparator arm received three weight-based doses of standard half-life exogenous FVIII protein during each weekly cycle Time horizon and cycle lengths, plus rationale: lifetime horizon, weekly cycle, justification NR Source of inputs used: administration assumption from prior cost-effectiveness analysis of a hypothetical gene therapy for haemophilia A; Clinical inputs (bleed propensity and bleed events) from a phase 2 clinical trial and published real-world evidence; Mortality was based off of published standardised mortality ratios; Weights were based on CDC data; Costs were sourced from the phase 1/2 clinical trial, CMS Physician Fee Schedule or other published sources and were inflated using either the Personal Health Care Expenditure index or the Personal Consumption Expenditure index; Utilities from published sources (Fischer 2016, Neufeld 2012, Mazza 2016) Discount rate: 3% per annum	US male population, 30 years old with SHA, without inhibitors who previously received prophylactic FVIII treatment	Uncertainty surrounding the valoctocogene roxaparvovec response, particularly concerning initial non-response, overall durability, and HRQoL Long-term follow-up results from the phase 3 trial are needed to validate model assumptions, but those data will be unavailable for years The model only compares gene therapy with prophylactic FVIII and not with on-demand or episodic FVIII replacement therapy treatment regimens The model assumes no	The economic evaluation was conducted from the US perspective, and therefore has limited applicability to decision making in England The population considered is also relevant to the decision problem for this submission

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
			Cost year and currency: 2019, USD (\$) Details of any sensitivity analyses: probabilistic sensitivity analyses were not performed; four scenario analyses were compared to the base case: (1) limiting the model horizon to 10 years, to roughly coincide with some estimates of gene therapy's potential; (2) increasing the utility for valoctocogene roxaparvovec across all health states to reflect the additional HRQoL benefits beyond what was captured in the health states; and incorporating (3) emicizumab-kxwh and (4) EHL prophylaxis as comparator treatment arms		correlation between the ABR a patient experiences after treatment with gene therapy and that patient's ABR after transitioning to FVIII prophylaxis. While this provides a more conservative approach by allowing patients to bleed more when receiving valoctocogene roxaparvovec compared with FVIII prophylaxis, it is not likely to be clinically realistic	
Decker-Palmer 2022	To estimate the cost-effectiveness of emicizumab compared to valoctogene roxaparvovec gene therapy, standard half-life factor VIII (FVIII) and	US, payer perspective	Type of study: cost-effectiveness Type of model and rationale: Markov model Model health states: life with no arthropathy, life with arthropathy, life after joint replacement surgery, and death Interventions and comparators modelled: emicizumab, valoctogene roxaparvovec gene therapy, standard half-life FVIII and extended half-life FVIII replacement products	People with SHA without inhibitors	Uncertainties around the effectiveness and durability of gene therapy make assessment of 2- and 5-year cost-effectiveness challenging	The economic evaluation was conducted from a US payer's perspective, and therefore has limited

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
	extended half-life FVIII replacement products		Time horizon: time horizon: 2-year, 5-year and a lifetime horizon Source of inputs used: costs reported from published literature (Ozelo 2022, Mahlangu 2018, Tarantino 2004, Recht 2009, Konkle 2015), utilities derived from patient-reported outcomes in published real world data. Gene therapy price was assumed at USD (\$) 2,500,000/patient. Discount rate: NR Cost year and currency: 2022 USD (\$) Details of any sensitivity analyses: NR			applicability to decision making in England
ICER 2020	To estimate the cost-effectiveness of valoctocogene roxaparvovec compared to prophylaxis with factor VIII preparations in adult patients with SHA without inhibitors to factor VIII	US, healthcare payer perspective	Type of study: cost-effectiveness Type of model and rationale: Markov model (rationale NR) Model health states: no arthropathy, arthropathy (3 states based on Pettersson scores), joint replacement surgery and death Interventions and comparators modelled: the intervention was valoctocogene roxaparvovec the comparator was prophylaxis with factor VIII preparations (Advate and Eloctate) Time horizon and cycle lengths, plus rationale: Lifetime horizon, with cycle length of 6 months, based on the literature related to bleed rates and subsequent long-term development of joint damage from target joint bleeds as tracked by Pettersson scores Source of inputs used: Bleed rates for valoctocogene roxaparvovec from available data and literature estimates (Den Uji et al. 2011). Bleed rates for factor VIII prophylaxis from Malec et al. 2020.	Male patients ≥18 years old with SHA without inhibitors being treated with valoctocogene roxaparvovec, or factor VIII prophylaxis	The relationship between joint bleeds and surgery is imperfect and the model assumes one joint requiring surgery at a time which may undercount surgeries Utility scores for bleeds came from patients with inhibitors and these may be different in patients without inhibitors	The economic evaluation was conducted from a US healthcare sector's perspective, and therefore has limited applicability to decision making in England

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
			Proportion of all bleeds relative to treated bleeds, and the proportion of all bleeds that are joint bleeds were taken from the HAVEN 3 and POTTER trials. Survival was weighted by health state utilities derived from published literature. Non-pharmacological costs were from Shrestha et al. 2017. Costs from lost time at work from Zhou et al 2015 Discount rate: 3% per year Cost year and currency: 2019 USD (\$) Details of any sensitivity analyses: one-way sensitivity analyses and probabilistic sensitivity analyses		Placeholder price for valoctocogene roxaparvovec used Advate and Eloctate used as representative treatments and average doses from ATHN data. There are numerous other factor VIII products on the market and a wide variance of treatment regimens	
Ito 2023	To evaluate the conventional and distributional cost-effectiveness of prophylaxis with efanesoctocog alfa versus with standard-care factor VIII for patients with SHA	US, perspective NR	Type of study: cost-effectiveness Type of model and rationale: Markov model Interventions and comparators modelled: efanesoctocog alfa prophylaxis and standard-care factor VIII Source of inputs used: Transitional probabilities for ABRs and product utilisation from phase 3 study data and FDA package insert information; costs for base-case reported from the Centers for Medicare & Medicaid Services and cost of efanesoctocog alfa supplied from the Veterans Affairs Federal Supply Schedule Service (VA-FSS); utilities informed from extensive literature Currency: USD Details of any sensitivity analyses: Deterministic sensitivity analysis to assess which	Patients with SHA	NR	The economic evaluation was conducted from the US perspective, and therefore has limited applicability to decision making in England

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
			parameter the model was most sensitive to; probabilistic sensitivity analysis to check the cost-effectiveness of efanesoctocog alfa using 10,000 Monte Carlo simulations			
NICE 2023	To evaluate the cost-effectiveness of etranacogene dezaparvovec against Alprolix, BeneFIX, Idelvion, and Refixia® in patients with moderately severe or severe HB	UK, NHS and PSS perspectives	Type of study: cost-utility Type of model and rationale: Markov model Model health states: 4 health states: (1) No bleeds, (2) non-joint bleeds, (3) joint bleeds, (4) death Interventions and comparators modelled: The intervention was etranacogene dezaparvovec. The comparators were Alprolix, BeneFIX, Idelvion and Refixia Time horizon and cycle lengths, plus rationale: Lifetime time horizon (59 years), set based on the HOPE-B trial population, who entered the model at a mean age of 41.5 years and were not expected to live beyond 100 years. Weekly cycle length was chosen to capture the disutility of a bleed event Source of inputs used: Cost data from NHS cost reference 2019/20; clinical data from HOPE-B trial; ITC (including results from HOPE-B and other sources identified from Davis et al. 2019) was used to generate annualised bleeding rate and annualised joint bleeding rate ratios; utilities from HOPE-B trial¹⁷ and US-ICER (2022); patient characteristics from the B-long trial; extrapolation data for the long-term durability of etranacogene dezaparvovec from Shah et al. 2022	Patients with moderately severe or severe HB from HOPE-B trial (100% male, mean baseline age: 41.5 years, average weight: 85.10kg)	The model did not take into account the benefits from avoiding long-term joint damage The model made the assumption that there was no effect of HB on the mortality of patients	The economic evaluation was conducted from the NHS perspective, and is therefore applicable to decision making in England. The population is also aligned with the decision problem

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
			Discount rate: 3.5% for costs and effects Cost year and currency: Cost year NR; GBP Details of any sensitivity analyses: One-way sensitivity analysis, scenario analysis and probabilistic sensitivity analysis were performed			
NICE 2024	The submission focusses on part of the technology's marketing authorisation for efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A	UK, NHS/PSS perspective	Type of study: cost-effectiveness Type of model and rationale: Markov model Model health states: No bleeds, any bleeds and dead Interventions and comparators modelled: intervention, efanesoctocog alfa (IV 50 IU/Kg QW). Comparators, PUPs emicizumab and efmoroctocog alfa, and PTPs emicizumab Time horizon and cycle lengths, plus rationale: lifetime horizon, which was expected to adequately capture long-term clinical and economic consequences of haemophilia A. 6-month cycle length, considered sufficiently long to account for health events Source of inputs used: costs reported from PAS and NHS BSA, national schedule of NHS costs and PSSRU. Utilities reported from XTEND-1 clinical trial data. Clinical efficacy and safety reported from XTEND-1 and XTEND-Kids trials Discount rate: 3.5% for costs and benefits Currency: GBP (£) Details of any sensitivity analyses: deterministic and probabilistic sensitivity analyses were conducted. Scenario analyses varied the discount rate, clinical parameters, disutilities and drug wastage assumptions	SHA in PUPs and PTPs	Limited evidence to differentiate utility values between Pettersson score based health states A key weakness of this analysis is the lack of a comparator arm in XTEND-1, meaning the analysis relies on ITCs and naïve comparisons to inform outcomes for comparators Another weakness is the inability of the model to capture some of the long-term outcomes of SHA	The economic evaluation was conducted from an NHS England Wales healthcare payer's perspective, and therefore is highly relevant to decision making in England The economic evaluation considered people with SHA, previously treated and untreated, and therefore is of some

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
						relevance to the decision problem for this submission
Pochopien 2022	To estimate the cost-effectiveness of prophylaxis with EHL rFIXFc compared to on-demand treatment with SHL rFIX	Italy, NHS perspective	Type of study: cost-utility analysis Type of model and rationale: Markov model Model health states: 3 health states: (1) no bleeds, (2) any bleeds, (3) death Interventions and comparators modelled: rFIXFc prophylaxis (once weekly, individualised interval) and on-demand rFIX Time horizon and cycle lengths, plus rationale: To capture all differences between treatment arms, a life-long time horizon of 67 years was implemented, with 6 month cycle length Source of inputs used: costs reported from Italian National Health Service perspective; patient characteristics sourced from the B-LONG trial; utilities were sourced for the haemophilia A A-LONG and ASPIRE trials (as no utilities were identified for the health states included in the model for patients with haemophilia B) Discount rate: NR Cost year and currency: NR Details of any sensitivity analyses: one-way deterministic sensitivity analyses and probabilistic sensitivity analyses were performed	Adolescent and adult males ≥ 12 years old, with severe HB (defined as ≤ 2 IU/dL) without inhibitors	NR	The economic evaluation was conducted from an Italian healthcare payer's perspective, and therefore has limited applicability to decision making in England

Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
Tice 2023	To evaluate the health and economic outcomes of etranacogene dezaparvovec and valoctocogene roxaparvovec gene therapies for haemophilia B and haemophilia A, respectively	US, healthcare sector perspective	Type of study: cost-effectiveness Type of model and rationale: decision analytic model, type not specified and no explicit rationale provided Model health states: NR Intervention and comparators modelled: etranacogene dezaparvovec and valoctocogene roxaparvovec Time horizon: Lifetime horizon Source of inputs: models were informed by key clinical trials, RWE, previous relevant economic models, other published studies on haemophilia B and haemophilia A, and stakeholder input. A specific outcomes-based warranty design was incorporated as the base case pricing assumption for valoctocogene roxaparvovec Discount rate: 3% Cost year and currency: 2022, USD Details of any sensitivity analyses: specific scenario analyses looking at optimistic and conservative assumptions about the duration of effect and different ways to “share” the value of cost offsets between the manufacturer and the health system	Individuals with haemophilia B and haemophilia A without inhibitors	Both gene therapies were evaluated in small, single-arm trials of limited duration Factor VIII levels fell steadily with time following treatment with valoctocogene roxaparvovec, so the long-term benefits are uncertain The decline in factor IX levels appeared slower following treatment with etranacogene dezaparvovec, but follow-up was limited, so projections may not be accurate A placeholder price for valoctocogene roxaparvovec	The economic evaluation was conducted from a US healthcare payer's perspective, and therefore has limited applicability to decision making in England

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Study	Objective	Country and perspective	Summary of model	Patient population	Model limitations	Applicability to decision making in England
					was used as it had not been approved by the FDA at the time of analysis	

Abbreviations: AAV: adeno-associated virus; ABR: annualised bleeding rate; BSA: Business Services Authority; CDC: Centers for Disease Control and Prevention; CEA: cost-effectiveness analysis; EHL: extended half-life; EHL-FVIII: extended half-life factor VIII; EQ-5D: Euro-QoL 5-Dimension 5-Level; EMA: European Medicines Agency; FDA: Food and Drug Administration; FVIII: factor VIII; FIX: factor IX; HA: haemophilia A; HB: haemophilia B; HRQoL: health-related quality of life; IU: International Units; IV: intravenous; NA: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: not reported; OWSA: one-way sensitivity analysis; PAS: Patient Access Scheme; PD-PK: pharmacokinetic/pharmacodynamic; PEG-rFVIII: pegylated recombinant factor VIII; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; PTPs: previously treated patients; PUPs: previously untreated patients; QALY: quality adjusted life year; QW: once weekly; rFVIII: recombinant factor VIII; rFVIII-Fc: recombinant factor VIII Fc fusion protein; RWE: real-world evidence; SHA: severe haemophilia A; SHL: standard half-life; SHL-FVIII: standard half-life factor VIII; SLR: systematic literature review; SmPC: Summary of Product Characteristics; TJ: target joint; UK: United Kingdom; US: United States; USD: United States Dollar; VA-FSS: Veterans Affairs Federal Supply Schedule Service; WHO: World Health Organisation.

Table 78. Summary of the results of published economic evaluations included in the economic SLR

Study	Results (QALYs, costs, ICER [per QALY gained])						Model Drivers	Model conclusion (as reported by the study)
Benson 2021	Modelled costs and QALYs per patient over a 70-year time horizon, by category (discounted):						Dose and dose frequency are major drivers of bleeding frequency, costs and QALYs	In the base-case scenario, prophylactic use of turoctocog alfa pegol in adult and adolescent patients with SHA was found to be both more efficacious and
	Comparator	FVIII Prophylaxis	Breakthrough Bleed Resolution (FVIII Costs Only)	Resource Use	Total Costs^a	Total QALYs		
	Turoctocog alfa pegol	£7,795,958	£151,216	£54,342	£8,001,516	20.97		

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Study	Results (QALYs, costs, ICER [per QALY gained])						Model Drivers	Model conclusion (as reported by the study)	
	Rurioctocog alfa pegol	£7,795,958	£177,637	£54,448	£8,028,043	19.92		cost-saving versus other EHL FVIII treatments	
	Efmoroctocog alfa	£7,795,958	£171,991	£54,434	£8,022,383	20.07			
	Damoctocog alfa pegol	£7,795,958	£221,277	£54,379	£8,071,614	20.62			
	^a Totals may not sum exactly due to rounding.								
	In all cases, the cost of FVIII prophylaxis accounted for the largest share (97%) of total costs, and resource use the smallest share (0.67–0.68%). Breakthrough bleed resolution costs accounted for 1.9–2.7% of total costs. Costs due to FVIII prophylaxis were the same for each treatment, as the cost/unit values for rurioctocog alfa pegol, efmoroctocog alfa and damoctocog alfa pegol were calculated by assumed price matching to turoctocog alfa pegol on an annual prophylaxis cost basis. Prophylaxis with turoctocog alfa pegol resulted in the lowest breakthrough bleed resolution costs and lowest resource use costs of all the EHL FVIII treatments modelled. Combined breakthrough bleed resolution and resource use costs were 9–25% lower for turoctocog alfa pegol versus comparators								
	In the base case scenario, prophylaxis with turoctocog alfa pegol was associated with the most QALYs of the comparators studied, representing a discounted QALY gain of 0.35–1.05 compared with the other treatments. Rurioctocog alfa pegol prophylaxis resulted in the least QALYs								
Bolous 2021	Base case cost-effectiveness results:						Time horizon	Gene therapy seemed more cost-effective than either prophylaxis or on-demand treatment of severe HB when analysed from a US healthcare payer perspective	
		On-demand		Prophylaxis		Gene therapy			
		SHL FIX	EHL FIX	SHL FIX	EHL FIX	SHL FIX	EHL FIX		
	Costs, \$	11,596,617	7,917,721	15,109,058	20,324,299	6,293,502	7,315,914		
	QALYs	11.81	12.20	20.95	21.57	23.00	23.04		
	Cost/QALY, \$	981,932	648,994	721,196	942,248	273,631	317,531		
	Gene ICER, \$	Dominant	Dominant	Dominant	Dominant	Reference	25,560,300		
								Durability of gene therapy	
								Price of gene therapy	
								Unit cost of factor concentrate	

Study	Results (QALYs, costs, ICER [per QALY gained])	Model Drivers	Model conclusion (as reported by the study)																														
Bolous 2022	Cost-effectiveness results: <table> <tr> <th></th><th></th><th>Costs, USD</th><th>Total QALYs</th></tr> <tr> <td rowspan="4">Prophylaxis</td><td>SHL–FVIII alone</td><td>20,144,062</td><td>23.18</td></tr> <tr> <td>EHL–FVIII alone</td><td>24,147,829</td><td>23.73</td></tr> <tr> <td>SHL–FVIII + gene therapy</td><td>19,703,755</td><td>24.12</td></tr> <tr> <td>EHL–FVIII + gene therapy</td><td>23,383,234</td><td>24.57</td></tr> <tr> <td rowspan="4">On-Demand</td><td>SHL–FVIII alone</td><td>8,234,037</td><td>14.23</td></tr> <tr> <td>EHL–FVIII alone</td><td>8,764,330</td><td>14.67</td></tr> <tr> <td>SHL–FVIII + gene therapy</td><td>8,896,892</td><td>15.36</td></tr> <tr> <td>EHL–FVIII + gene therapy</td><td>9,378,153</td><td>15.66</td></tr> </table>			Costs, USD	Total QALYs	Prophylaxis	SHL–FVIII alone	20,144,062	23.18	EHL–FVIII alone	24,147,829	23.73	SHL–FVIII + gene therapy	19,703,755	24.12	EHL–FVIII + gene therapy	23,383,234	24.57	On-Demand	SHL–FVIII alone	8,234,037	14.23	EHL–FVIII alone	8,764,330	14.67	SHL–FVIII + gene therapy	8,896,892	15.36	EHL–FVIII + gene therapy	9,378,153	15.66	NR	Considering a \$150,000/QALY threshold, gene therapy was dominant compared to prophylaxis but not cost-effective compared to on-demand strategy. At a gene therapy price of \$625,000 and \$1,925,000, SHL–FVIII + gene therapy would be cost-effective compared to on-demand SHL–FVIII and on-demand EHL–FVIII, respectively Results suggest if current gene therapy products are only effective for 6 years, the commercially proposed
		Costs, USD	Total QALYs																														
Prophylaxis	SHL–FVIII alone	20,144,062	23.18																														
	EHL–FVIII alone	24,147,829	23.73																														
	SHL–FVIII + gene therapy	19,703,755	24.12																														
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Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Results (QALYs, costs, ICER [per QALY gained])				Model Drivers	Model conclusion (as reported by the study)
						\$2,000,000 price point will not be cost-effective for all patient subgroups
Bullement 2021	Arm	Costs	QALYs	ICER	Costs were found to be most sensitive to acquisition costs, weight, and dosing assumptions, with QALYs most sensitive to the application of improved joint health via the mHJHS	rFVIIIFc may offer a clinically and cost-effective option for patients with SHA, especially compared with PEG-rFVIII, with cost savings in the region of \$2 million over a lifetime horizon
	rFVIIIFc	\$18.235m	27.922	-		
	SHL rFVIII	\$18.825m	27.071	rFVIIIFc dominates		
	PEG-rFVIII	\$20.198m	27.454	rFVIIIFc dominates		
Cook 2020	Base case results	Valoctocogene roxaparvovec	Prophylaxis	Valoctocogene roxaparvovec vs. Prophylaxis	The durability of the response to valoctocogene roxaparvovec is a key driver of cost-effectiveness in the model, and under current durability assumptions the majority of	Valoctocogene roxaparvovec is projected to be a dominant treatment choice, being both cost-saving and producing superior patient HRQoL compared with prophylactic FVIII over a
	Discounted LYs, mean (SE)	23.565 (0.051)	23.565 (0.051)	0 (0)		
	Discounted QALYs, mean (SE, range)	18.068 (0.039, 0.06–23.38)	17.318 (0.038, 0.05–22.54)	0.750 (0.005, –0.75–4.13)		
	Summary of scenario analyses results	Valoctocogene roxaparvovec	Prophylaxis	Valoctocogene roxaparvovec vs. Prophylaxis		
	10-year model horizon					

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Results (QALYs, costs, ICER [per QALY gained])				Model Drivers	Model conclusion (as reported by the study)	
	Discounted QALYs, mean (SE)	6.875 (0.007)	6.370 (0.006)	0.504 (0.002)	clinical and health benefits occur in the first 10 years following administration	patient's lifetime, in men who are 30 years of age, with SHA and no history of FVIII inhibitors	
	Increased utility for gene therapy						
	Discounted QALYs, mean (SE)	18.340 (0.039)	17.318 (0.038)	1.022 (0.005)			
	Emicizumab comparator arm						
	Discounted QALYs, mean (SE)	18.793 (0.041)	18.497 (0.040)	0.296 (0.004)			
	EHL prophylaxis						
	Discounted QALYs, mean (SE)	18.358 (0.039)	17.790 (0.039)	0.569 (0.005)			
Decker-Palmer 2022	Cost effectiveness of emicizumab compared with gene therapy:				NR	In comparison with gene therapy, emicizumab was estimated to be less costly with similar effectiveness over a 2-year horizon, less costly and more effective over a 5-year horizon and more costly but cost-effective over a lifetime horizon. In comparison with standard half-life FVIII prophylaxis and extended half-life FVIII	
	Time horizon		Cost difference, USD (\$)	QALY difference			ICER, USD (\$)/QALY
	2-year	Gene therapy	-	-			-
		Emicizumab	-1,395,000	0.00			NR
	5-year	Gene therapy	-	-			-
		Emicizumab	-125,215	0.02			NR
	Lifetime	Gene therapy	-	-			-
		Emicizumab	8,945	0.95			9,406
	Cost effectiveness of emicizumab compared with standard half-life FVIII prophylaxis and extended half-life FVIII prophylaxis:						
							ICER, USD (\$)/QALY
	2-year	Standard half-life FVIII prophylaxis and extended half-life FVIII prophylaxis					-
		Emicizumab					Dominant
	5-year	Standard half-life FVIII prophylaxis and extended half-life FVIII prophylaxis					-

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Results (QALYs, costs, ICER [per QALY gained])				Model Drivers	Model conclusion (as reported by the study)																											
		Emicizumab	Dominant			prophylaxis, emicizumab was dominant (less costly and more effective) over each model time horizon																											
	Lifetime	Standard half-life FVIII prophylaxis and extended half-life FVIII prophylaxis	-																														
		Emicizumab	Dominant																														
ICER 2020	Results for the base-case: <table><tr><th>Treatment</th><th>Drug costs</th><th>Total Costs</th><th>LYs</th><th>QALYs</th></tr><tr><td>Factor VIII</td><td>\$18,269,000</td><td>\$18,722,000</td><td>26.53</td><td>19.087</td></tr><tr><td>Valoctocogene roxaparvovec</td><td>\$13,293,000</td><td>\$13,693,000</td><td>26.53</td><td>19.091</td></tr></table> Incremental analysis: <table><tr><th>Treatment</th><th>Incremental cost</th><th>Incremental QALYs</th><th>ICER</th></tr><tr><td>Factor VIII</td><td>Reference</td><td>Reference</td><td>Reference</td></tr><tr><td>Valoctocogene Roxaparvovec</td><td>-\$4,988,000</td><td>0.004</td><td>Dominant</td></tr></table> Though dominant in the base case, there are nearly 6% of simulations where factor VIII becomes cost effective at various thresholds In each of the scenarios applied (higher bleed duration, higher bleed rate, societal perspective, older age and Pettersson score start, Pettersson score return to 13), valoctocogene roxaparvovec, at its placeholder price, was found to be a dominant treatment				Treatment	Drug costs	Total Costs	LYs	QALYs	Factor VIII	\$18,269,000	\$18,722,000	26.53	19.087	Valoctocogene roxaparvovec	\$13,293,000	\$13,693,000	26.53	19.091	Treatment	Incremental cost	Incremental QALYs	ICER	Factor VIII	Reference	Reference	Reference	Valoctocogene Roxaparvovec	-\$4,988,000	0.004	Dominant	The drug costs and prophylactic drug dosing for the factor VIII products have a substantial influence on the projected incremental costs	Valoctocogene roxaparvovec was found to be a dominant treatment for adult patients with haemophilia A without inhibitors when using doses of factor VIII typical of US patients at haemophilia treatment centers. This finding varied in the sensitivity analyses and valoctocogene roxaparvovec was not at all
Treatment	Drug costs	Total Costs	LYs	QALYs																													
Factor VIII	\$18,269,000	\$18,722,000	26.53	19.087																													
Valoctocogene roxaparvovec	\$13,293,000	\$13,693,000	26.53	19.091																													
Treatment	Incremental cost	Incremental QALYs	ICER																														
Factor VIII	Reference	Reference	Reference																														
Valoctocogene Roxaparvovec	-\$4,988,000	0.004	Dominant																														
				The net drug cost of emicizumab and its dose were also key drivers																													

Study	Results (QALYs, costs, ICER [per QALY gained])						Model Drivers	Model conclusion (as reported by the study)
								cost effective when the model incorporated doses of factor VIII and efficacy results from the trial used in the network meta-analysis
Ito 2023	Cost-effectiveness base case results:						Costs of efanesoctocog alfa and factor VIII	As compared to standard-care factor VIII and at VA-FSS pricing, efanesoctocog alfa prophylaxis is conventionally cost ineffective for patients with SHA. Prophylaxis with efanesoctocog alfa does not meet commonly used distributive equity standards in the
		Total QALYs	Incremental QALYs	Mean costs	Incremental Cost	Threshold inequality aversion parameter		
	Efanesoctocog alfa	19.4	4.03	\$17.3 million	\$7.62 million	7.4		
	Standard care factor VIII	15.4	-	\$9.7 million	-			
	ICER (95% CrI): \$1,890,000/QALY (1,190,000–3,330,00)							
	Threshold analysis showed that prophylaxis with efanesoctocog alfa became cost-effective when the price decreased by at least 59%							
In probabilistic sensitivity analysis, standard-care factor VIII was favoured over efanesoctocog alfa in 100% of 10,000 Monte Carlo simulations								

Study	Results (QALYs, costs, ICER [per QALY gained])					Model Drivers	Model conclusion (as reported by the study)
							United States at this time
NICE 2023	Pairwise base-case incremental cost effectiveness results ^a :					The qualitative conclusions of the cost-effectiveness model are sensitive to only one variable in the model, which is the durability of the effect of etranacogene dezaparvovec. Otherwise, none of the individual variables affect the net monetary benefit substantially to change the cost-effectiveness conclusions	Etranacogene dezaparvovec was found to be cost-effective compared to all the comparators considered in the decision problem
							Etranacogene dezaparvovec from the perspective of a cost-effectiveness analysis, is cost saving to the NHS and PSS. By replacing years of FIX treatments with a single infusion, etranacogene
		Total LYGs	Incremental LYGs	Incremental QALYs	ICER versus baseline (cost per QALY, GBP)		ICER incremental (cost per QALY, GBP)
BeneFix							
Etranacogene dezaparvovec	21.356	-	-	-	-		
BeneFIX	21.356	0	1.506	Dominating	Dominating		
Alprolix							
Etranacogene dezaparvovec	21.356	-	-	-	-		
Alprolix	21.356	0	1.477	Dominating	Dominating		
Idelvion							
Etranacogene dezaparvovec	21.356	-	-	-	-		
Idelvion	21.356	0	1.502	Dominating	Dominating		
Refixia							
Etranacogene dezaparvovec	21.356	-	-	-	-		
Refixia	21.356	0	1.443	Dominating	Dominating		

Study	Results (QALYs, costs, ICER [per QALY gained])	Model Drivers	Model conclusion (as reported by the study)																												
	^aResults for etranacogene dezaparvovec and other costs of comparators were redacted PSA shows consistent results to pairwise base case, etranacogene dezaparvovec dominates all comparators considerably		dezaparvovec not only brings benefits to patients, but also reduces the long-term cost to the NHS and PSS Etranacogene dezaparvovec dominates all comparators for all positive willingness-to-pay values, as it offers more total QALYs at a lower total cost.																												
NICE 2024	Base-case results, PUPs: <table><tr><th>Technologies</th><th>Total LYG</th><th>Incremental LYG</th><th>ICER vs. baseline (£/QALY)</th><th>ICER incremental (£/QALY)</th></tr><tr><td>Efmoroctocog alfa</td><td>27.054</td><td>–</td><td>–</td><td>–</td></tr><tr><td>Efanesoctocog alfa</td><td>27.054</td><td>0.000</td><td>£18,211</td><td>£18,211</td></tr><tr><td>Emicizumab</td><td>27.054</td><td>0.000</td><td>Dominated</td><td>Dominated</td></tr></table> Net health benefit, PUPs: <table><tr><th>Technologies</th><th>Total QALYs</th><th>NHB at £20,000/QALY</th><th>NHB at £30,000/QALY</th></tr><tr><td>Efmoroctocog alfa</td><td>22.940</td><td>–</td><td>–</td></tr></table>	Technologies	Total LYG	Incremental LYG	ICER vs. baseline (£/QALY)	ICER incremental (£/QALY)	Efmoroctocog alfa	27.054	–	–	–	Efanesoctocog alfa	27.054	0.000	£18,211	£18,211	Emicizumab	27.054	0.000	Dominated	Dominated	Technologies	Total QALYs	NHB at £20,000/QALY	NHB at £30,000/QALY	Efmoroctocog alfa	22.940	–	–	The main model drivers were disutilities associated with lower FVIII levels, the proportion of patients experiencing a bleed and the	Base-case results showed that efanesoctocog alfa is associated with more QALYs compared with emicizumab or efmoroctocog alfa. When using the PAS
Technologies	Total LYG	Incremental LYG	ICER vs. baseline (£/QALY)	ICER incremental (£/QALY)																											
Efmoroctocog alfa	27.054	–	–	–																											
Efanesoctocog alfa	27.054	0.000	£18,211	£18,211																											
Emicizumab	27.054	0.000	Dominated	Dominated																											
Technologies	Total QALYs	NHB at £20,000/QALY	NHB at £30,000/QALY																												
Efmoroctocog alfa	22.940	–	–																												

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Results (QALYs, costs, ICER [per QALY gained])				Model Drivers	Model conclusion (as reported by the study)	
	Efanesoctocog alfa	23.500	0.05	0.22	annual bleeding rate for emicizumab	prices for efanesoctocog alfa and efmoroctocog alfa, efanesoctocog alfa was associated with an ICER of £18,211 versus efmoroctocog alfa and dominated emicizumab	
	Emicizumab	22.806	-411.01	-274.05			
	Base-case results, PTPs:						
	Technologies	Total LYG	Incremental LYG	ICER vs. baseline (£/QALY)			ICER incremental (£/QALY)
	Efanesoctocog alfa	22.369	-	-			-
	Emicizumab	22.369	0.000	Dominated			Dominated
	Net health benefit, PTPs:						
	Technologies	NHB at £20,000/QALY		NHB at £30,000/QALY			
	Efanesoctocog alfa	-		-			
	Emicizumab	-475.60		-317.26			
	Probabilistic results, PUPs:						
	Technologies	ICER vs. baseline (£/QALY)		ICER incremental (£/QALY)			
	Efmoroctocog alfa	-		-			
	Efanesoctocog alfa	£19,633		£19,633			
	Emicizumab	Dominated		Dominated			
	Probabilistic results, PTPs:						
	Technologies	ICER vs. baseline (£/QALY)		ICER incremental (£/QALY)			
Efanesoctocog alfa	-		-				
Emicizumab	Dominated		Dominated				
Scenario analysis, PUPs:							
Scenario	vs. efmoroctocog alfa ICER (£/QALY)		vs. emicizumab ICER (£/QALY)				
Base case	£18,211		Dominant				

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Results (QALYs, costs, ICER [per QALY gained])			Model Drivers	Model conclusion (as reported by the study)
	Discount rate of 6%	Dominant	Dominant		
	No discounting	£54,211	Dominant		
	Treated bleeds only	£19,345	Dominant		
	Baseline ABR from HAVEN 3 Arm B	£36,995	Dominant		
	Baseline ABR from XTEND-1 Arm B	£20,593	Dominant		
	Baseline ABR from HAVEN 3 Arm D	£11,432	Dominant		
	% of patients with bleeds on efanesoctocog alfa from XTEND-1 12-month data	£18,028	Dominant		
	% of patients with bleeds on emicizumab from HAVEN 3 Arm A	£18,211	Dominant		
	% of patients with bleeds on emicizumab from HAVEN 3 Arm B	£18,211	Dominant		
	Chromogenic assay for assessing FVIII levels	£13,821	Dominant		
	No disutility associated with lower FVIII levels	£36,345	Dominant		
	Disutility for FVIII <5%	£10,648	Dominant		
	Drug wastage for emicizumab	£18,211	Dominant		
	Scenario analysis, PTPs:				
	Scenario		ICER (£/QALY)		
	Base case		Dominant		
	Discount rate of 6%		Dominant		
	No discounting		Dominant		
	Treated bleeds only		Dominant		
	Baseline ABR from HAVEN 3 Arm B		Dominant		
	Baseline ABR from XTEND-1 Arm B		Dominant		
	Baseline ABR from HAVEN 3 Arm D		Dominant		
	% of patients with bleeds on efanesoctocog alfa from XTEND-1 pooled arms		Dominant		
	% of patients with bleeds on emicizumab from HAVEN 3 Arm A		Dominant		
	% of patients with bleeds on emicizumab from HAVEN 3 Arm B		Dominant		
	Chromogenic assay for assessing FVIII levels		Dominant		

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Study	Results (QALYs, costs, ICER [per QALY gained])			Model Drivers	Model conclusion (as reported by the study)																																												
	<table><tr><td>No disutility associated with lower FVIII levels</td><td>Dominant</td></tr><tr><td>Disutility for FVIII <5%</td><td>Dominant</td></tr><tr><td>Drug wastage for emicizumab</td><td>Dominant</td></tr></table>			No disutility associated with lower FVIII levels	Dominant	Disutility for FVIII <5%	Dominant	Drug wastage for emicizumab	Dominant																																								
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Pochopien 2022	- Prophylaxis with rFIXFc was associated with lower costs (prophylactic treatment, bleeding management [drugs and procedures] and surgery) and a greater number of QALYs than on-demand treatment with rFIX - rFIXFc was the dominant strategy over rFIX across most uncertain parameters - In the probabilistic sensitivity analysis (1,000 simulations), rFIXFc once weekly and individualised interval prophylaxis were the dominant strategies in 61% and 53% of the runs, respectively Base-case results for rFIXFc once weekly prophylaxis vs on-demand treatment with rFIX: <table><tr><th></th><th>rFIXFc prophylaxis</th><th>rFIX on demand</th><th>Incremental</th></tr><tr><td>Total costs, EUR</td><td>5,308,625</td><td>6,564,510</td><td>-1,255,885</td></tr><tr><td>Prophylaxis treatment – drug costs</td><td>4,715,315</td><td>0</td><td>4,715,315</td></tr><tr><td>Bleeding management – drug costs</td><td>323.730</td><td>3,820,085</td><td>-3,496,355</td></tr><tr><td>Surgery costs</td><td>229,888</td><td>2,418,138</td><td>-2,188,250</td></tr><tr><td>Indirect costs</td><td>28,526</td><td>300,446</td><td>-271,920</td></tr><tr><td>Total QALYs</td><td>15.936</td><td>11.943</td><td>3.993</td></tr><tr><td>QALYs in no bleeds state</td><td>3.7883</td><td>0.0000</td><td>3.7883</td></tr><tr><td>QALYs in any bleed state</td><td>12.2066</td><td>12.5203</td><td>-0.3137</td></tr><tr><td>QALY loss due to bleed</td><td>0.058</td><td>0.572</td><td>-0.514</td></tr><tr><td>QALY loss due to surgery</td><td>0.001</td><td>0.005</td><td>-0.004</td></tr></table>				rFIXFc prophylaxis	rFIX on demand	Incremental	Total costs, EUR	5,308,625	6,564,510	-1,255,885	Prophylaxis treatment – drug costs	4,715,315	0	4,715,315	Bleeding management – drug costs	323.730	3,820,085	-3,496,355	Surgery costs	229,888	2,418,138	-2,188,250	Indirect costs	28,526	300,446	-271,920	Total QALYs	15.936	11.943	3.993	QALYs in no bleeds state	3.7883	0.0000	3.7883	QALYs in any bleed state	12.2066	12.5203	-0.3137	QALY loss due to bleed	0.058	0.572	-0.514	QALY loss due to surgery	0.001	0.005	-0.004	Bleeding management	In comparison with on-demand rFIX, prophylaxis with rFIXFc was the dominant treatment strategy Prophylactic rFIXFc is likely to be cost-saving compared with on-demand rFIX
	rFIXFc prophylaxis	rFIX on demand	Incremental																																														
Total costs, EUR	5,308,625	6,564,510	-1,255,885																																														
Prophylaxis treatment – drug costs	4,715,315	0	4,715,315																																														
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Study	Results (QALYs, costs, ICER [per QALY gained])				Model Drivers	Model conclusion (as reported by the study)																									
	Total LYs	22.91	22.91	0.00																											
	ICER (cost/QALYG)	71.48	753.77	-682.29																											
	ICER (cost/bleed avoided)	0.14	0.53	-0.39																											
Tice 2023	Both etranacogene dezaparvovec at \$3,500,000 and valoctocogene roxaparvovec at a placeholder price of \$2,500,000 were dominant treatments with substantial cost savings compared with prophylactic factor therapy or eculizumab (haemophilia A only). These findings were robust to numerous sensitivity analyses and scenario analyses The calculated HBPB ranges for the therapies, using a \$150,000 annual cap on offsets are below: <table><tr><th></th><th>Unit price (USD) to achieve \$50,000 per QALY gained</th><th>Unit price (USD) to achieve \$100,000 per QALY gained</th><th>Unit price (USD) to achieve \$150,000 per QALY gained</th><th>Unit price (USD) to achieve \$200,000 per QALY gained</th></tr><tr><td colspan="5">Haemophilia B</td></tr><tr><td>Etranacogene dezaparvovec</td><td>2,894,000</td><td>2,926,000</td><td>2,958,000</td><td>2,990,000</td></tr><tr><td colspan="5">Haemophilia A</td></tr><tr><td>Valoctocogene roxaparvovec</td><td>1,951,000</td><td>1,956,000</td><td>1,961,000</td><td>1,966,000</td></tr></table>					Unit price (USD) to achieve \$50,000 per QALY gained	Unit price (USD) to achieve \$100,000 per QALY gained	Unit price (USD) to achieve \$150,000 per QALY gained	Unit price (USD) to achieve \$200,000 per QALY gained	Haemophilia B					Etranacogene dezaparvovec	2,894,000	2,926,000	2,958,000	2,990,000	Haemophilia A					Valoctocogene roxaparvovec	1,951,000	1,956,000	1,961,000	1,966,000	Analyses showed that more than 99% of the HBPB for both valoctocogene roxaparvovec and etranacogene dezaparvovec calculated from traditional cost-effectiveness analysis comes from cost offsets of eliminating the need for future factor prophylaxis	Using the alternative method of calculating HBPB with an annual price cap on offsets, for valoctocogene roxaparvovec, the HBPB was approximately \$2,000,000, and for etranacogene dezaparvovec, the HBPB was approximately \$3,000,000
	Unit price (USD) to achieve \$50,000 per QALY gained	Unit price (USD) to achieve \$100,000 per QALY gained	Unit price (USD) to achieve \$150,000 per QALY gained	Unit price (USD) to achieve \$200,000 per QALY gained																											
Haemophilia B																															
Etranacogene dezaparvovec	2,894,000	2,926,000	2,958,000	2,990,000																											
Haemophilia A																															
Valoctocogene roxaparvovec	1,951,000	1,956,000	1,961,000	1,966,000																											

Abbreviations: ABR: annual bleeding rate; CrI: credible interval; EHL: extended half-life; EHL-FVIII: extended half-life factor VIII; EUR: euro; FVIII: factor VIII; FIX: factor IX; HB: haemophilia B; HBPB: Health Benefit Price Benchmark; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; LY: life year; LYG: life year gained; mHJHS: modified Haemophilia Joint Health Score; NHB: net health benefit; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: not reported; PAS: Patient Access Scheme; PEG-rFVIII: pegylated recombinant factor viii; PSS: Personal Social Services; PTPs: previously treated patients; PUPs: previously untreated patients; QALY: quality-adjusted life year; QALYG: quality-adjusted life-years gained; rFIX: recombinant factor IX; rFIXFc: recombinant factor IX covalently fused to the Fc domain of human immunoglobulin G1; rFVIII: recombinant factor viii; rFVIII-Fc: recombinant factor VIII Fc fusion protein; rIX-FP: recombinant FIX albumin fusion protein; SE: standard error; SHA: severe haemophilia A; SHL: standard half-life; SHL-FVIII: standard half-life factor VIII; SLR: systematic literature review; US: United States; USD: United States Dollars; VA-FSS: Veterans Affairs Federal Supply Schedule Service.

Table 79. Quality assessments of economic evaluations included in the economic systematic literature review using the Drummond checklist (1/2)¹⁶

Drummond Checklist Questions	Benson 2021	Bolous 2021	Bolous 2022	Bullement 2021	Cook 2020	ICER 2020
Was the research question stated?	Y – the objective was well defined	Y – the objective was well defined	Y – the objective was well defined	Y – the objective was well defined	Y – the objective was well defined	Y – the objective was well defined
Was the economic importance of the research question stated?	Y – the economic importance was clear	Y – the economic importance of the research question was stated	Y – importance related to introduction of gene therapy stated	Y – the economic importance is implied	Y – the economic importance was clearly stated	Partly – economic importance not clearly stated, some reference to productivity loss for patients
Was/were the viewpoint(s) of the analysis clearly stated and justified?	Y – viewpoint was clearly stated, and justification was evident	Y – viewpoint was clearly stated and justified	Partly – viewpoint was clearly stated, but justification not provided	Partly – viewpoint was clearly stated, but justification not provided	Y – viewpoint was provided and justification was clear	Y– viewpoint clearly stated and justified
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y – rationale for choosing interventions was clear	Partly - comparators were described, but no explicit explanation was given for why they were chosen	Partly – rationale for the list of treatments is partly given in the introduction	Y – contemporary rFVIII products stated and justified	Y – rational for comparator was clear	Y– rationale for choosing alternative therapies clearly stated
Were the alternatives being compared clearly described?	Y– the comparators were clearly described	Y – comparators were clearly described	Partly – limited details of the comparators were given	Y – the comparators and dosing regimens were clearly described	Y – the comparator was clearly described	Y– comparators and treatment regimens clearly described
Was the form of economic evaluation stated?	Y – PD-PK decision model was described	Y – cost-utility analysis clearly stated	Y – cost-effectiveness analysis clearly stated	Y – cost-effectiveness analysis clearly stated	Y – cost-effectiveness analysis clearly stated	Y – cost-effectiveness analysis clearly stated
Was the choice of form of economic evaluation justified in relation to the questions addressed?	Y – choice of analysis was explained	Y – choice of analysis type was justified	N – choice of analysis not justified	Y – cost-effectiveness analysis justified	Y – the benefits of using a microstimulation model were stated	Partly – choice of analysis type not explained; however, details explaining how the model works were provided

Drummond Checklist Questions	Benson 2021	Bolous 2021	Bolous 2022	Bullement 2021	Cook 2020	ICER 2020
Was/were the source(s) of effectiveness estimates used stated?	Y – sources clearly stated	Y – sources clearly stated	N – original sources not provided	Y – sources clearly stated	Y – sources clearly stated	Y – sources clearly stated
Were details of the design and results of the effectiveness study given (if based on a single study)?	Partly – details on the study design were given but results are not reported in this publication	NA	N – information not provided	NA – based on multiple studies	NA	NA
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	N - no description for synthesis or meta-analysis was given	NA	N – no synthesis mentioned	NA – no synthesis mentioned	Y – breakdown of sources and synthesis of data provided
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – primary outcome measure clearly stated	Y – primary outcomes clearly stated	N – primary outcome measure not stated in the methods	Y – QALYs stated as outcome measure	Partly – evaluation outcomes were clearly stated, however, the primary outcome is unclear	Y – QALYs stated as outcome measure
Were the methods used to value health states and other benefits stated?	Y – information included in the methods	Y – methods clearly stated	N – information not provided	N – source provided, but methodological information not provided	Y – valuation methods were described	Y – clearly states model used EQ-5D
Were the details of the subjects from whom valuations were obtained given?	Y – source of population utilities reported in the methods	N – information not provided	N – information not provided	N – information not provided	N – not reported in this article	Y – utility values clearly described
Were productivity changes (if included) reported separately?	N – productivity changes not described	NA	N – productivity changes not described	N – productivity changes not described	N – productivity changes not described	Partly – costs from work days lost were reported but not overall productivity changes

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Drummond Checklist Questions	Benson 2021	Bolous 2021	Bolous 2022	Bullement 2021	Cook 2020	ICER 2020
Was the relevance of productivity changes to the study question discussed?	NA	NA	NA	N – relevance of productivity changes not described	NA	N – relevance of productivity changes not described
Were quantities of resources reported separately from their unit cost?	Y – quantity of resource reported separately from unit cost	Y – quantity of resource reported separately from unit cost	N – quantities of resource and unit costs not reported	Y – quantity of resource reported separately from unit cost	Y – quantity of resource reported separately from unit cost	Y – quantity of resource reported separately from unit cost
Were the methods for the estimation of quantities and unit costs described?	Y – estimation methods were reported	Y – references for dosage and costs were clearly provided	N – as above	Y – sources, methods and calculations described	Y – notes were provided as to how the quantities and unit costs were estimated	Y – estimations of quantities and unit costs clearly described
Were currency and price data recorded?	Y – currency and price data were recorded	Y – USD	Partly – currency is reported but price data were not	Y – currency and cost year reported	Y – currency and price data were recorded	Y – currency and price data recorded
Were details of price adjustments for inflation or currency conversion given?	N – details of price adjustments and currency conversion were not reported	N – information not provided	N – price adjustments not reported	NA	Y – sources used to adjust inflation were recorded	Y – details of price adjustments given
Were details of any model used given?	Y – model was well described	Y – model was well described	Partly – some key details of the model were described	Y – model was well described	Y – model details were well described	Y – model was well described
Was there a justification for the choice of model used and the key parameters on which it was based?	Y – explanation for the type of model and parameters were given	N – no justification provided	N – no justification is given for the type of model and the key parameters	Partly – based on precedence	Partly – benefits of model were discussed throughout the publication	Y – justification for model and key parameters given
Was the time horizon of cost and benefits stated?	Y – the time horizon was stated	Y – time horizon clearly stated	Y – time horizon was stated	Y – lifetime horizon stated	Y – time horizon stated	Y – time horizon clearly stated
Was the discount rate stated?	Y – the discount rate was stated	Y – discount rate clearly stated	Y – discount rate was stated	Y – discount rate provided	Y – discount rate stated	Y – discount rate clearly stated

Drummond Checklist Questions	Benson 2021	Bolous 2021	Bolous 2022	Bullement 2021	Cook 2020	ICER 2020
Was the choice of rate justified?	Y – the choice of rate was justified	Y – choice of discount rate was justified	N – choice of discount rate was not justified	Y – justification provided	Y – discount rate was justified	Y – discount rate clearly justified
Was an explanation given if cost or benefits were not discounted?	NA	NA	N – no details reported	NA	NA	NA
Were the details of statistical test(s) and confidence intervals given for stochastic data?	NA	Y – details were given	N – no details on statistical tests were reported	N – no statistical tests carried out	N – no details on statistical tests were reported	N – information not provided
Was the approach to sensitivity analysis described?	Partly – formal sensitivity analysis not performed but details of scenario analyses were given	Y – approach to sensitivity analyses clearly described	N – sensitivity analyses were not described	Y – sensitivity analyses well described	Y – the approach to sensitivity analyses was described	Y – sensitivity analysis clearly described
Was the choice of variables for sensitivity analysis justified?	NA	N – no justification given	N – as above	Y – justifications provided for scenario analyses conducted	NA – formal sensitivity analyses were not performed	Y – variables clearly justified
Were the ranges over which the parameters were varied stated?	NA	Y – ranges were clearly stated	N – ranges were not specified	Y – scenario analysis inputs provided	NA – as above	Y – ranges clearly stated
Were relevant alternatives compared in the incremental analysis?	NA – incremental analysis not performed	Y – relevant alternatives were compared	N – incremental analysis was not performed	Y – all relevant alternatives included in incremental analysis	Y – relevant alternatives were compared	Y – relevant alternatives compared
Was an incremental analysis reported?	N – incremental analysis not performed	Y – incremental analysis was reported	N – as above	Y – incremental analysis reported	Y – incremental analysis was reported	Y – incremental analysis provided
Were major outcomes presented in a disaggregated as well as aggregated form?	Y – outcomes were presented in aggregated and disaggregated form	Y – major outcomes were presented in a disaggregated and aggregated form	N – outcomes are presented in an aggregated form	N – aggregated results only	N – only aggregated outcomes presented	Y – LY, LYG and total costs provided

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Drummond Checklist Questions	Benson 2021	Bolous 2021	Bolous 2022	Bullement 2021	Cook 2020	ICER 2020
Was the answer to the study question given?	Y – the study question was answered by the results presented	Y – the study question was answered by the results presented	Y – the study question was answered by the results presented	Y – the study question was answered by the results presented	Y – the study question was answered by the results presented	Y – the study question was answered by the results presented
Did conclusions follow from the data reported?	Y – conclusions were in line with presented data	Y – conclusions were in line with the presented data	Y – conclusions were in line with presented data	Y – conclusions were in line with presented data	Y – conclusions were in line with presented data	Y – conclusions were in line with presented data
Were conclusions accompanied by the appropriate caveats?	Y – model limitations were noted	Y - limitations were described	N – no caveats were noted	Y – discussion of limitations provided	Y – limitations were noted	Y – limitations clearly reported

Table 54 (continued). Quality assessments of economic evaluations included in the economic systematic literature review using the Drummond checklist (2/2)

Drummond Checklist Questions	NICE 2023	Pochopien 2022	NICE 2024	Decker-Palmer 2022	Ito 2023	Tice 2023
Was the research question stated?	Y – the objective was well defined	Y – the objective was well defined	Partly – general research question asked	Partly – the objective was not clearly stated in the background but referenced in the methods	Y – the objective was well defined	Y – the objective was well defined
Was the economic importance of the research question stated?	Y – the economic importance was stated	Partly – economic background to the research question was provided, but the importance was not stated	Y – the economic importance is implied	Y – importance related to introduction of gene therapy stated	Y – economic importance implied	Y – the economic importance is clearly implied
Was/were the viewpoint(s) of the analysis clearly stated and justified?	Y – viewpoint was clearly stated and justified	Partly – viewpoint was clearly stated, but justification not provided	Y – the perspective was justified	Partly – viewpoint was clearly stated, but justification not provided	N – viewpoint and justification were not clearly provided	Y – viewpoint was clearly stated and justification was clear

Drummond Checklist Questions	NICE 2023	Pochopien 2022	NICE 2024	Decker-Palmer 2022	Ito 2023	Tice 2023
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y – rationale for choosing Alprolix, BeneFIX, Idelvion and Refixia was stated	Y – rationale for choosing rFIX was stated	Y – rationale for choosing emicizumab and efmoctocog alfa has been provided	Partly – rationale for alternative interventions was partly stated	N – rationale is not clearly stated	Y – rationale for choosing interventions is clearly stated
Were the alternatives being compared clearly described?	Partly – the comparators were described, but no dose or schedule was given	Partly – the comparator was described, but no dosing regimen was provided	Y – the comparators were described alongside their dosing regimen	Partly – the comparator was described, however, no dosing regimen was provided	Partly – the comparator was described, however, no dosing regimen was provided	Y – the comparators were described fully
Was the form of economic evaluation stated?	Y – cost-utility analysis clearly stated	Y – cost-effectiveness analysis clearly stated	Y – cost-effectiveness analysis clearly stated	Y – cost-effectiveness analysis clearly stated	Y – cost-effectiveness analysis clearly stated	Y – cost-effectiveness analysis clearly stated
Was the choice of form of economic evaluation justified in relation to the questions addressed?	Y – form of evaluation was justified	Y – form of evaluation was justified	Partly – choice of analysis type not explained; however, details explaining how the model works were provided	N – justification of choice of economic evaluation not provided	N – choice of analysis type not explained	Partly – choice of analysis type not explained; however, some model details were given
Was/were the source(s) of effectiveness estimates used stated?	Y – sources clearly stated	Y – sources clearly stated	Y – sources clearly stated	Y – sources of clinical parameters provided	Partly – specific sources not stated, beyond study type	Y – sources clearly stated
Were details of the design and results of the effectiveness study given (if based on a single study)?	Y – details of the design and results of the effectiveness study were given	N – details of the design and result of the effectiveness study were not given	Y – details and design clearly stated	Partly – study types reported, but no detailed information	NA	Y – details clearly described

Drummond Checklist Questions	NICE 2023	Pochopien 2022	NICE 2024	Decker-Palmer 2022	Ito 2023	Tice 2023
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	NA	Y – details of indirect treatment comparison provided	NA	N – details were not provided	NA
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – primary outcomes clearly stated	Y – primary outcomes clearly stated	Y – ICER stated as outcome	Y – QALYs stated as outcome measure	Y – the primary outcomes were clearly states as the ICER in USD/QALY	N – primary outcome of analysis not stated
Were the methods used to value health states and other benefits stated?	Y – methods clearly stated	N – information not provided	Y – methods to produce health state utility values are described	Partly – utility methods partially described	N – information not provided	N – information not provided
Were the details of the subjects from whom valuations were obtained given?	Y – details of the subjects were provided	N – information not provided	Y – valuation methods described	N – information not provided	N – information not provided	N – information not provided
Were productivity changes (if included) reported separately?	Y – productivity changes were described in a scenario analysis	N – productivity changes not reported	N – productivity changes not described	N – productivity changes not described	N – productivity changes not described	N – productivity changes not described
Was the relevance of productivity changes to the study question discussed?	N – relevance of productivity changes not described	N – relevance of productivity changes not described	NA – relevance of productivity changes not described	N – relevance of productivity changes not described	NA	NA
Were quantities of resources reported separately from their unit cost?	N – quantities of resources not reported	N – quantities of resources not reported	Y – quantity of resource reported separately from unit cost	N – unit costs not provided	Partly – quantity of resource reported separately, however, specific values have not been reported	N – quantity of resources and unit costs not reported

Drummond Checklist Questions	NICE 2023	Pochopien 2022	NICE 2024	Decker-Palmer 2022	Ito 2023	Tice 2023
Were the methods for the estimation of quantities and unit costs described?	N – methods not described	N – methods not described	Partly – sources were described but methods were not	N – information not provided	Partly – the cost sources are reported, however, the negotiated lower cost is not specified	N – as above
Were currency and price data recorded?	Partly – currency reported as GBP, but no price data recorded	N – currency and price data not recorded	Y – currency was recorded	Y – currency provided	Partly – currency is USD, however price data is not recorded	Y – currency and price data were reported
Were details of price adjustments for inflation or currency conversion given?	N – information not provided	N – information not provided	N – inflation was not considered	N – information not provided	N – specific adjustments and conversions were not included	N – price adjustments were not reported
Were details of any model used given?	Y – model was well described	Y – model was well described	Y – model was well described	Y – model was well described	Y – model was well described	Partly – some model details were reported in the article (full details given in linked ICER report)
Was there a justification for the choice of model used and the key parameters on which it was based?	N – no justification provided	N – no justification provided	Partly – model chosen not justified but the key parameters were	Partly – no justification for model provided, but health states described	N – no justification was provided	N – justifications not provided in article
Was the time horizon of cost and benefits stated?	Y – time horizon clearly stated	N – time horizon not stated	Y – time horizon was stated	Y – time horizons provided	N – no time horizon stated	Y – time horizon was stated
Was the discount rate stated?	Y – discount rate clearly stated	N – discount not stated	Y – discount rate was stated	N – information not provided	N – no discount rate stated	N – discount rate was not stated in the article (full details given in linked ICER report)
Was the choice of rate justified?	Y – choice of discount rate was justified	NA	Y – they were justified	N – no justification provided	N – rate was not justified	N – as above

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Drummond Checklist Questions	NICE 2023	Pochopien 2022	NICE 2024	Decker-Palmer 2022	Ito 2023	Tice 2023
Was an explanation given if cost or benefits were not discounted?	NA	N – no explanation provided	NA	N – information not provided	NA – costs were discounted	N – no details reported
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N – details were not given	N – details were not given	N – CI not reported	N – information not provided	NA	N – no details on statistical tests were reported
Was the approach to sensitivity analysis described?	Y – the approach to sensitivity analysis was described	Y – approach to sensitivity analyses clearly described	Y – the approach was described	N – no sensitivity analysis undertaken	N – the approach was not described for deterministic and probabilistic sensitivity analysis	Partly – some topics explored in sensitivity analyses were described
Was the choice of variables for sensitivity analysis justified?	Y – the choice of variables were justified	N – no justification given	N – the choice of variables were not justified	N – no sensitivity analysis undertaken	N – All variables and the reason they were chosen were not stated or verified	N – justification for variables not given in the article (full details given in linked ICER report)
Were the ranges over which the parameters were varied stated?	Y – ranges were clearly stated	N – ranges not stated	N – ranges of parameters were not fully clear	N – no sensitivity analysis undertaken	N – ranges were not stated	N – ranges were not specified
Were relevant alternatives compared in the incremental analysis?	Y – relevant alternatives were compared	NA	Y – relevant alternatives were compared	Y – alternative therapy included in the incremental analysis	Y – incremental analysis compared the two treatments	N – incremental analysis was not performed
Was an incremental analysis reported?	Partly – incremental LYG and ICER were reported, but incremental costs and QALYs were redacted	N – incremental analysis was not reported	Y – incremental analysis was reported	Y – ICERs (or dominance) reported	Y – incremental analysis compared the two treatments	N – as above
Were major outcomes presented in a disaggregated as well as aggregated form?	Partly – disaggregated data were reported, but redacted	N – outcomes only presented in aggregated form	N – only aggregated results presented	N – no disaggregated outcomes provided	N – only aggregated outcomes presented	N – outcomes are presented in an aggregated form

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Drummond Checklist Questions	NICE 2023	Pochopien 2022	NICE 2024	Decker-Palmer 2022	Ito 2023	Tice 2023
Was the answer to the study question given?	Y – the study question was answered by the results presented	Y – study question was answered by the results presented	Y – the study question was answered by the results presented	Y – the study question was answered by the results presented	Y – the study question was answered by the results presented	Y – the study question was answered by the results presented
Did conclusions follow from the data reported?	Y – conclusions were in line with the presented data	Y – conclusions were in line with the presented data	Y – conclusions were in line with presented data	Y – conclusions were in line with presented data	Y – conclusions were in line with presented data	Y – conclusions were in line with presented data
Were conclusions accompanied by the appropriate caveats?	Y – limitations were described	N – no caveats were noted	Y – weaknesses stated in the conclusion	Y – uncertainties with 2- and 5-year gene therapy data reported in conclusion	N – no caveats were noted	Y – limitations of the model were described

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; LYG: life year gained; N: no; NA: not applicable; NICE: National Institute for Health and Care Excellence; PD-PK: pharmacokinetic/pharmacodynamic; QALY: quality-adjusted life year; rFIX: recombinant factor IX; USD: United States dollars; Y: ye

Appendix H Health-related quality of life studies

H.1 Identification of studies

The databases and hand searches were conducted simultaneously for the utility/HRQoL stream alongside the cost-effectiveness stream (Appendix G), and HCRU stream (Appendix I). Each record identified in these searches was assessed for eligibility across all three data streams (cost-effectiveness, utility/HRQoL, and HCRU). Each study identified could therefore be included in one or more of the evidence streams.

H.1.1. Search strategy

The information for evidence sources searched for the utilities stream are presented in Appendix G.

Electronic databases

A list of the search terms used in the electronic databases are provided in Appendix G.1.1 for the original SLR and SLR update.

Grey literature sources

Conference proceedings

An overview of the conference website searches undertaken in the SLR update is provided in Table 69 (Appendix G.1.1).

HTA websites and additional sources

Search terms used in the HTA and economic website searches, are provided in Table 70 and Table 71, respectively, for the SLR update (Appendix G.1.1).

H.1.2. Study selection

The methods used for study selection are detailed in Appendix G.1.2. The review of abstracts and full texts was performed using predefined eligibility criteria (Table 80), based on the decision problem for this submission and developed using the PICOS framework.

Evidence prioritisation for data extraction

Due to a large volume of evidence identified as relevant after the full-text review stage, a number of steps were taken to ensure that the most recent and relevant studies to the decision problem for this submission were prioritised for extraction. For the utility/HRQoL stream, studies were prioritised if they:

- Fulfilled the following criteria:
 - Reported utilities derived using UK preference weights, in line with NICE preferences
 - And, were identified during the SLR update
- Or, were key studies chosen to inform utilities in the economic model for this submission, based on prior NICE evaluations in haemophilia

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Eligibility criteria

The eligibility of each study captured in the database and grey literature searching was reviewed for inclusion across all three evidence streams (cost effectiveness studies, utility/HRQoL, and HCRU). The eligibility presented here is specific to that assessed for inclusion into the utility/HRQoL evidence stream (see Table 80), eligibility for the other streams are reported in other appendices (cost-effectiveness studies; Appendix G.1.2 and HCRU; Appendix H.1.2).

Table 80. Eligibility criteria for the utility studies

Category	Inclusion Criteria	Exclusion Criteria
Population	- Paediatric or adult patients with inherited moderately severe-to-severe haemophilia A or haemophilia B - Subgroups of above target population in studies among mixed haemophilia A/haemophilia B, mixed severity, mixed treatment history or mixed age patient population, if data are separately reported for the target subgroup	- Studies on other diseases - Studies on patients with acquired haemophilia A or haemophilia B - Studies with only subpopulations (e.g. with specific comorbidities)
Intervention	Any or none	N/A
Comparators	Any or none	N/A
Outcomes^a	- EQ-5D - EQ-5D-5L - HAL (all versions) - Haem-A-QoL - SF-36 - SF-12 - SF-6D - HUI - Utilities/disutilities - Time trade-off assessments (planned and unplanned) - Standard gamble scores - FISH - HEMO-QoL - PROBE	Publications that only reported data on following types of outcomes including: - Laboratory based studies that report on cellular work or biomarker analyses that are not correlated with outcomes of interest - Validation/accuracy of diagnostic techniques/tests - Validation of HRQoL or PRO questionnaires - Pharmacokinetics/pharmacodynamics

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Category	Inclusion Criteria	Exclusion Criteria
	• QUAL-HEMO • Caregiver utilities and QoL burden	
Study design	• Clinical trials (phase II/III RCTs, single-arm, non-RCTs) • Observational studies, including prospective and retrospective cohort studies and cross-sectional analyses • SLRs/(N)MAs (N.B. included for hand-searching at title/abstract stage, but excluded at full-text stage)^b	• Animal studies • In vitro/ex vivo studies • Gene expression/protein expression studies • Narrative publications • Non-systematic reviews • Phase I studies • Case studies • Case series • Case reports • Editorials
Other considerations	• Studies were limited to those conducted within the following regions/countries: ○ North America (United States and Canada) ○ EU4 + United Kingdom ○ Japan ○ Australia ○ South Korea ○ International studies • Only English language articles were included • Publications from 2020 onwards^a • For SLR/(N)MAs, HTAs and economic evaluations reference lists: publications from 2020 onwards • Abstracts and other materials from conferences: published from 2022 onwards	• Countries not of interest • Journal articles not available in English • Articles and abstracts published before the search cut-offs

Footnotes: Items in **bold** were added for the SLR update in May 2024. ^aDue to the large volume of evidence identified after the full text review stage, utilities (from any instrument) derived using UK preference weights, and publications from 2020 onwards were prioritised for extraction. ^bThe reference lists of SLRs/(N)MAs, HTAs and economic evaluations were screened to identify articles of importance that may not have been identified during search or screening.

Abbreviations: EU4: France, Germany, Italy and Spain; FISH: Functional Independence Score in Hemophilia; Haem-A-QoL: Haemophilia Quality of Life Questionnaire for Adults; HAL: Hemophilia Activities List; HEMO-QoL: Hemophilia-Specific Quality of Life; HTA: health technology assessment; HRQoL: health-related quality of life; HUI: Health

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Utilities Index; NA: not applicable; (N)MA: (network) meta-analysis; PRO: patient-reported outcome; PROBE: Patient Reported Outcomes, Burdens and Experiences; QUAL HEMO: Haemophilia age group-specific Quality of life questionnaire; RCT: randomised controlled trial; SF-6D: Six Dimensions Short Form Health Survey; SF-12: 12-item Short Form health Survey; SF-36: 36-item Short Form Health Survey; SLR: systematic literature review.

H.1.3. Description of identified studies

The PRISMA flow diagram for all three evidence streams is presented in Figure 4.

Original and update searches

The results of the original and update SLR searches are as described in Appendix G.1.3. Briefly, following evidence prioritisation, 4 records from the original SLR and 26 records from the updated SLR were prioritised for extraction across all three evidence streams.

Lists of the studies deprioritised for data extraction in each evidence stream are presented in Table 75 (economic evaluations), Table 81 (utility/HRQoL) and Table 86 (HCRU).

Total utility/HRQoL evidence

Of the 30 prioritised records, 10 records reporting on 8 unique studies were prioritised in the utility/HRQoL evidence stream of the SLR. A full list of these studies is presented in

Table 82. Full details of the prioritised utility/HRQoL studies are provided in Table 83 and Table 84.

Table 81. Utility/HRQoL studies deprioritised for extraction in the economic SLR (original and update)

#	Reference
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151.	Wu, J, Lou, et al. Impact of pain on health-related quality of life in persons with hemophilia from the hemophilia utilization group studies part VI (HUGS VI): USA experience. <i>Haemophilia</i> . 2018;24176.
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Table 82: Utility/HRQoL studies included in the economic SLR

#	Study name	Reference
SLR Update (May 2024)		
1	Chowdary 2024	Chowdary P, Ofori-Asenso R, Nissen F, et al. Disease Burden, Clinical Outcomes, and Quality of Life in People with Hemophilia A without Inhibitors in Europe: Analyses from CHES II/CHES PAEDs. <i>TH Open</i> . 2024;8(2):E181-E193.
	Chowdary 2023	Chowdary P, Nissen F, Burke T, et al. The humanistic and economic burden of problem joints for children and adults with moderate or severe haemophilia A: Analysis of the CHES population studies. <i>Haemophilia</i> . 2023;29(3):753-760.
2	Madan 2024	Madan B, Ozelo MC, Raheja P, et al. Three-year outcomes of valoctocogene roxaparvovec gene therapy for hemophilia A. <i>Journal of Thrombosis & Haemostasis</i> . 2024;12:12.
3	O'Hara 2021	O'Hara S, Castro FA, Black J, Chaplin S, Ruiz L, Hampton RJ, Sima CS, O'Hara J. Disease burden and remaining unmet need in patients with haemophilia A treated with primary prophylaxis. <i>Haemophilia</i> . 2021 Jan;27(1):113-9.
	O'Hara 2017 (original SLR)	O'Hara J, Hughes D, Camp C, Burke T, Carroll L, Diego DA. The cost of severe haemophilia in Europe: the CHES study. <i>Orphanet journal of rare diseases</i> . 2017 Dec;12:1-8.
4	Oldenburg 2021	Oldenburg J, Tran H, Peyvandi F, Núñez R, Trask P, Chebon S, Mahlangu JN, Lehle M, Jiménez-Yuste V, von Mackensen S. Health-related quality of life and health status in adolescent and adult people with haemophilia A without factor VIII inhibitors—a non-interventional study. <i>Haemophilia</i> . 2021 May;27(3):398-407.
5	O'Mahoney 2024	O'Mahoney B, Mancuso ME, Brighton S, et al. Health-related quality of life and chronic pain burden on a cohort of people with haemophilia in 5 European countries: an updated snapshot from the cost of haemophilia in Europe: A longitudinal socio-economic survey (chess). 2024; MP-051 (1692242).

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#	Study name	Reference
6	Skinner 2021	Skinner MW, Négrier C, Paz-Priel I, Chebon S, Jiménez-Yuste V, Callaghan MU, Lehle M, Niggli M, Mahlangu J, Shapiro A, Shima M. The effect of emicizumab prophylaxis on long-term, self-reported physical health in persons with haemophilia A without factor VIII inhibitors in the HAVEN 3 and HAVEN 4 studies. <i>Haemophilia</i> . 2021 Sep;27(5):854-65.
7	Steen Carlsson 2022	Steen Carlsson K, Winding B, Astermark J, et al. Pain, depression and anxiety in people with haemophilia from three Nordic countries: Cross-sectional survey data from the MIND study. <i>Haemophilia</i> . 2022;28(4):557-567.
Original SLR (August 2020)		
1	Neufeld 2012	Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. <i>Value Health</i> . 2012;15(6):916-925.

H.1.4. Summary of published utility/HRQoL studies identified in the review

The 8 studies included in the utility studies SLR are presented in this section. The methodological details and results of studies are presented in Table 83 and Table 84, respectively.

Table 83. Summary of utility studies included in the economic SLR

Source (study/publication, publication year)	Objective	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation				
Chowdary 2024 (CHESS II and CHESS PAEDS) Supplementary sources: Chowdary 2023	To provide a comprehensive overview of unmet needs in people with HA using data generated from the CHESS II and CHESS PAEDs studies	Retrospective analyses of the interim CHESS-II and final CHESS-PAEDs study populations CHESS-II and CHESS-PAEDS population studies reporting costs by number of PJs (0, 1 or ≥2) and treatment regimen (prophylaxis or other) Data were analysed from the CHESS-II study; a retrospective cross-sectional burden of illness study of European male adults (≥18 years) with mild, moderate or severe haemophilia A or B CHESS-PAEDs used a similar design with male children and adolescents (≤17 years old) with moderate (clotting factor 1–5%) or severe (clotting factor <1%) haemophilia A or haemophilia B, with or without inhibitors For this analysis, data from all CHESS participants with inhibitors to FVIII, mild HA, or HB of any severity were excluded Baseline characteristics: <table><tr><th>Characteristic</th><th>Patients with HA N=468</th></tr><tr><td></td><td></td></tr></table>	Characteristic	Patients with HA N=468			Multinational (CHESS-II: Denmark, France, Germany, Italy, the Netherlands, Romania, Spain and the UK; CHESS-PAEDs: France, Germany, Italy, Spain and the UK)	CHESS-II: n=278 participants with SHA CHESS-PAEDS: n=409 participants with SHA For the PJ subgroup analysis (Chowdary 2023), evaluable EQ-5D data was available for n=205 and n=151 in CHESS-II and CHESS-	Utilities are presented for all patients with SHA and by number of PJs Utilities are not reported for specific health states or AEs	HRQoL was assessed using the EQ-5D-5L questionnaire in CHESS-II and the paediatric version of the EQ-5Q-3L (EQ-5D-Y) in CHESS PAEDs CHESS PAEDs participants aged 8–17 completed the EQ-5D-Y themselves	The study was conducted included participants from the UK as well as other European settings, therefore the study results are likely to be relevant to NICE decision-making Utilities were derived using the EQ-5D in a population relevant to the decision problem and with and a UK value set (for adult participants), in line with NICE preferences
Characteristic	Patients with HA N=468										

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Source (study/ publication, publication year)	Objective	Description of population and recruitment method		Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation
		Male, n (%)	468 (100)		PAEDs, respectively		CHESS II EQ-5D-5L index scores were derived via the UK value set for the EQ-5D-3L and cross-walk function EQ-5D-Y index scores were valued using the Spanish EQ-5D-Y value set	
		Mean age (SD), years	38.71 (13.95)					
		Median age (IQR), years	37.50 (22)					
		Severe HA, n (%)	278 (59.4)					
Madan 2024	To present 3-year efficacy and safety in the multicentre, open-label, single arm, phase 3 GENER8-1 trial	The 3-year HRQoL data of 134 enrolled adult males (>18 years) with SHA who were receiving FVIII prophylaxis and had no history of FVIII inhibitors Baseline characteristics: NR		NR (GENER8-1 was conducted internationally, including UK study sites)	At 156 weeks, 131 of 134 participants who received valoctocogene roxaparvovec remained in the study	Utility was presented for patients with a general SHA state. Utilities are not reported	HRQoL was assessed using the EQ-5D-5L questionnaire. Participants completed HRQoL	The study included UK sites, therefore may be relevant to NICE decision-making. Utilities were derived using the EQ-5D-5L and using a UK value set in line

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Source (study/publication, publication year)	Objective	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation
				Two participants were lost to follow-up (1 each at weeks 66 and 104), and 1 participant died at week 96 in an event considered unrelated to treatment EQ-5D-5L was completed by 121 patients	for specific AEs	instruments at baseline and at weeks 4, 12, 26, 52, 76, 104, 128, and 156; change from baseline to years 1, 2, and 3 in mean scores was assessed for the mITT population Index scores (valuation) were calculated using van Hout, 2012	with NICE preferences The population of this study is relevant to the decision problem for this submission
Neufeld 2012	To evaluate the impact of bleeding episodes on patients/caregivers	Male patients with congenital haemophilia with inhibitors, who experienced spontaneous bleeding were eligible for this observational study if they required treatment with bypassing agents for ≥ 4	US	N=52 patients enrolled in the study,	Utilities were presented for	HRQoL was assessed through	The study was conducted in the US, therefore the study may

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Source (study/ publication, publication year)	Objective	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation																								
	/ families and the association between monthly HRQoL scores and patients' average diary experiences	bleeding episodes of any type in the prior 3 months and were prescribed recombinant activated factor VII as first-line therapy for bleeding episodes DOSE was a phase 4 diary study conducted between January 2008–July 2009, in patients attending designated haemophilia treatment centres Baseline characteristics <table><tr><th></th><th>Enrolled population (N=52)</th><th>HRQoL population (n=37)</th></tr><tr><td>Male</td><td>100%</td><td>100%</td></tr><tr><td>Mean age (SD), years</td><td>23.3 ± 17.8</td><td>25.6 ± 19.4</td></tr><tr><td>Median age (range), years</td><td>18.3 ± 1.5–60.9</td><td>17.2 ± 2.1–60.9</td></tr><tr><td colspan="3">Treatment type, n (%)</td></tr><tr><td>On-demand</td><td>37 (71.2)</td><td>22 (59.5)</td></tr><tr><td>Prophylaxis</td><td>12 (23.1)</td><td>12 (32.4)</td></tr><tr><td>Immune tolerance induction</td><td>5 (9.6)</td><td>5 (13.5)</td></tr></table>		Enrolled population (N=52)	HRQoL population (n=37)	Male	100%	100%	Mean age (SD), years	23.3 ± 17.8	25.6 ± 19.4	Median age (range), years	18.3 ± 1.5–60.9	17.2 ± 2.1–60.9	Treatment type, n (%)			On-demand	37 (71.2)	22 (59.5)	Prophylaxis	12 (23.1)	12 (32.4)	Immune tolerance induction	5 (9.6)	5 (13.5)		n=37 completed daily HRQoL assessments (n=19 adults, n=18 caregivers on behalf of patients)	patients on bleeding days and non-bleeding days	EQ-5D-3L and EQ-5D-VAS (0–100) through patient or caregiver daily diary records US preference-weighted EQ-5D index scores were calculated on the basis of the method developed by Shaw et al Adult patients (>18 years of age) completed their own assessments; caregivers	have limited relevance to NICE decision-making. However, utilities were derived using the EQ-5D-3L, in line with NICE preferences. Additionally, this study has previously been accepted by NICE (ID3812)
	Enrolled population (N=52)	HRQoL population (n=37)																													
Male	100%	100%																													
Mean age (SD), years	23.3 ± 17.8	25.6 ± 19.4																													
Median age (range), years	18.3 ± 1.5–60.9	17.2 ± 2.1–60.9																													
Treatment type, n (%)																															
On-demand	37 (71.2)	22 (59.5)																													
Prophylaxis	12 (23.1)	12 (32.4)																													
Immune tolerance induction	5 (9.6)	5 (13.5)																													

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Source (study/ publication, publication year)	Objective	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation															
						proxy-completed assessments of behalf of individuals adolescents <18 years of age																
O'Hara 2021 (CHESS) Supplementary source: O'Hara 2017	To evaluate quality of life among people with severe haemophilia managed with primary prophylaxis using the CHESS database	CHESS overall population: Adult patients (≥18 years) with severe inherited haemophilia A or B, regardless of prior treatment status or history of inhibitors O'Hara 2021: Subgroup with haemophilia A aged 18–35 years at enrolment, who had been treated with prophylaxis with SHL clotting factors since diagnosis (primary prophylaxis), and who did not have a history of inhibitors or inhibitor therapy O'Hara 2017: Subgroup of patients in the UK Baseline characteristics: <table><tr><th></th><th>O'Hara 2021 (n=166)</th><th>O'Hara 2017 (n=321)</th></tr><tr><td colspan="3">Haemophilia subtype, n (%)</td></tr><tr><td>A</td><td>166 (100)</td><td>246 (77)</td></tr><tr><td>B</td><td>-</td><td>75 (23)</td></tr><tr><td>Age, years</td><td>Median (IQR): 24 (21, 26)</td><td>Mean (SD): 36.0 (15.9)</td></tr></table>		O'Hara 2021 (n=166)	O'Hara 2017 (n=321)	Haemophilia subtype, n (%)			A	166 (100)	246 (77)	B	-	75 (23)	Age, years	Median (IQR): 24 (21, 26)	Mean (SD): 36.0 (15.9)	France, Germany, Italy, Spain and UK	O'Hara 2021: n=166 in total; n=55 (33%) had EQ-5D-3L data available O'Hara 2017: n=321 in total; patient self-complete forms available for n=37 (37%)	Utility was presented for patients with a general severe haemophilia state Utilities are not reported for specific AEs	Data were collected by means of a paper patient self-completion form EQ-5D-3L was self-administered by patients Index scores were reported by applying the UK preference weights	The study was conducted across European countries and a UK value set was used; therefore, the study is likely to be relevant to NICE decision-making Utilities were derived using the EQ-5D-3L, in line with NICE preferences
	O'Hara 2021 (n=166)	O'Hara 2017 (n=321)																				
Haemophilia subtype, n (%)																						
A	166 (100)	246 (77)																				
B	-	75 (23)																				
Age, years	Median (IQR): 24 (21, 26)	Mean (SD): 36.0 (15.9)																				

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Source (study/ publication, publication year)	Objective	Description of population and recruitment method			Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation																				
		Treatment strategy: Prophylaxis, n (%)	166 (100)	175 (55)																									
		Inhibitor history, n (%)																											
		Never	166 (100)	289 (90)																									
		Previously	-	17 (5)																									
		Currently	-	15 (5)																									
		Median (range) number of bleed events in the last 12 months	1 (0, 3)	NR																									
		% of patients with at least 1 bleed, n (%)	122 (73)	NR																									
		Patients with coinfection, n (%)																											
		HIV	0 (0)	19 (6)																									
		HCV	1 (1)	21 (7)																									
Oldenburg 2021	To report on HRQoL data from the non-FVIII inhibitor population of PwHA from the global, multicentre, non-interventional study (NIS; NCT02476942)	Persons aged ≥12 years with SHA (FVIII activity <1%) without FVIII inhibitors, with recorded use of episodic or prophylactic FVIII for ≥150 days prior to study entry Baseline characteristics: <table><tr><th>Characteristic</th><th>Episodic (n=45)</th><th>Prophylaxis (n=49)</th><th>All (N=94)</th></tr><tr><td colspan="4">Age</td></tr><tr><td>(Median, min-max years)</td><td>33.0 (12-76)</td><td>35.0 (13-68)</td><td>34.0 (12-76)</td></tr><tr><td>≥12 and <18 years, n (%)</td><td>8 (17.8)</td><td>6 (12.2)</td><td>14 (14.9)</td></tr><tr><td>≥18 years, n (%)</td><td>37 (82.2)</td><td>43 (87.8)</td><td>80 (85.1)</td></tr></table>			Characteristic	Episodic (n=45)	Prophylaxis (n=49)	All (N=94)	Age				(Median, min-max years)	33.0 (12-76)	35.0 (13-68)	34.0 (12-76)	≥12 and <18 years, n (%)	8 (17.8)	6 (12.2)	14 (14.9)	≥18 years, n (%)	37 (82.2)	43 (87.8)	80 (85.1)	Global (10 countries NR)	94 enrolled EQ-5D completion rate >91% at baseline and >68% until study end	Utility was presented for patients with a general SHA state Utilities are not reported for specific AEs	Participants completed EQ-5D-5L Responses were combined into an IUS using the UK 'crosswalk' value set	The study was conducted across 10 countries, but used a UK value set, so is likely to be relevant to NICE decision-making Utilities were derived using the EQ-5D-5L in line with NICE preferences
Characteristic	Episodic (n=45)	Prophylaxis (n=49)	All (N=94)																										
Age																													
(Median, min-max years)	33.0 (12-76)	35.0 (13-68)	34.0 (12-76)																										
≥12 and <18 years, n (%)	8 (17.8)	6 (12.2)	14 (14.9)																										
≥18 years, n (%)	37 (82.2)	43 (87.8)	80 (85.1)																										

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Source (study/publication, publication year)	Objective	Description of population and recruitment method				Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation																																																
		<table><tr><td colspan="4">Race, n (%)</td></tr><tr><td>White</td><td>16 (35.6)</td><td>37 (75.5)</td><td colspan="2">53 (56.4)</td></tr><tr><td>Asian</td><td>13 (28.9)</td><td>9 (18.4)</td><td colspan="2">22 (23.4)</td></tr><tr><td>Black/African American</td><td>6 (13.3)</td><td>1 (2.0)</td><td colspan="2">7 (7.4)</td></tr><tr><td>Multiple race</td><td>1 (2.2)</td><td>1 (2.0)</td><td colspan="2">2 (2.1)</td></tr><tr><td>Unknown</td><td>9 (20.0)</td><td>1 (2.0)</td><td colspan="2">10 (10.6)</td></tr><tr><td colspan="4">Bleeds in previous 6 months</td></tr><tr><td>Participants, n</td><td>43</td><td>32</td><td colspan="2">75</td></tr><tr><td>Mean (SD)</td><td>10.6 (7.5)</td><td>2.6 (3.7)</td><td colspan="2">7.2 (7.3)</td></tr><tr><td>Median (min-max)</td><td>8.0 (5-32)</td><td>1.0 (0-13)</td><td colspan="2">5.0 (0-32)</td></tr></table>				Race, n (%)				White	16 (35.6)	37 (75.5)	53 (56.4)		Asian	13 (28.9)	9 (18.4)	22 (23.4)		Black/African American	6 (13.3)	1 (2.0)	7 (7.4)		Multiple race	1 (2.2)	1 (2.0)	2 (2.1)		Unknown	9 (20.0)	1 (2.0)	10 (10.6)		Bleeds in previous 6 months				Participants, n	43	32	75		Mean (SD)	10.6 (7.5)	2.6 (3.7)	7.2 (7.3)		Median (min-max)	8.0 (5-32)	1.0 (0-13)	5.0 (0-32)						
Race, n (%)																																																										
White	16 (35.6)	37 (75.5)	53 (56.4)																																																							
Asian	13 (28.9)	9 (18.4)	22 (23.4)																																																							
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Multiple race	1 (2.2)	1 (2.0)	2 (2.1)																																																							
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Mean (SD)	10.6 (7.5)	2.6 (3.7)	7.2 (7.3)																																																							
Median (min-max)	8.0 (5-32)	1.0 (0-13)	5.0 (0-32)																																																							
O'Mahony 2024 (CHESS)	To provide up-to-date economic, clinical and humanistic information on a cohort of people with haemophilia	The HRQoL data of patients with haemophilia were collected as part of the CHESS study; a 12-month retrospective burden-of-illness study collecting physician-reported clinical and health-resource use information. People with haemophilia were recruited via their physicians according to consultation order (or followed-on from previous data collection). Data on chronic pain and HRQoL captured by CHESS in 2022 was analysed Baseline characteristics (haemophilia severity and chronic pain): <table><tr><td></td><td colspan="3">Haemophilia severity</td></tr><tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr><tr><td>Participants, %</td><td>19</td><td>31</td><td>50</td></tr></table>					Haemophilia severity				Mild	Moderate	Severe	Participants, %	19	31	50	Conducted in Europe; individual countries NR	A total of 754 physician-forms and 166 corresponding patient-forms were captured in the study	Utilities were presented for patients with mild, moderate and severe haemophilia. Utilities are not reported for specific AEs	EQ-5D-5L was captured via the patient-questionnaire and evaluated using UK tariffs	The study was conducted in 5 European countries (individual countries NR); however, utilities were evaluated using UK tariffs and therefore the study is likely relevant to NICE decision-making																																				
	Haemophilia severity																																																									
	Mild	Moderate	Severe																																																							
Participants, %	19	31	50																																																							

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Source (study/ publication, publication year)	Objective	Description of population and recruitment method				Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation																
		Chronic pain level <table><tr><td>None, n (%)</td><td>76 (53)</td><td>102 (44)</td><td>102 (27)</td></tr><tr><td>Mild, n (%)</td><td>60 (42)</td><td>106 (46)</td><td>178 (47)</td></tr><tr><td>Moderate, n (%)</td><td>7 (5)</td><td>23 (10)</td><td>95 (25)</td></tr><tr><td>Severe, n (%)</td><td>–</td><td>–</td><td>5 (1)</td></tr></table> Note: Chronic pain levels are defined as: 'None' (no functional deficit; no analgesic use (except with acute haemarthrosis); 'Mild' (does not interfere with occupation nor with activities of daily living; may require occasional non-narcotic analgesic); 'Moderate' (partial or occasional interference with occupation or activities of daily living; use of non-narcotic analgesic; 'Severe' (interferes with occupation or activities of daily living; requires frequent use of non-narcotic and narcotic analgesics).				None, n (%)	76 (53)	102 (44)	102 (27)	Mild, n (%)	60 (42)	106 (46)	178 (47)	Moderate, n (%)	7 (5)	23 (10)	95 (25)	Severe, n (%)	–	–	5 (1)					
None, n (%)	76 (53)	102 (44)	102 (27)																							
Mild, n (%)	60 (42)	106 (46)	178 (47)																							
Moderate, n (%)	7 (5)	23 (10)	95 (25)																							
Severe, n (%)	–	–	5 (1)																							
Skinner 2021	To report secondary/exploratory objectives of the HAVEN 3 and 4 studies assessing the impact of up to 73 weeks of prophylactic emicizumab on HRQoL	HAVEN 3: Adults/adolescents (≥ 12 years) severe congenital HA without FVIII inhibitors who were receiving episodic or prophylactic FVIII HAVEN 4: adults/adolescents (≥ 12 years) with severe congenital HA, with or without FVIII inhibitors, who were receiving either FVIII or BPAs at enrolment This is a pooled analysis only including those without FVIII inhibitors				NR	HAVEN 3: N=143 HAVEN 4 (excluding those with inhibitors): n=34 Total: n=176	Utility was presented for patients with a general HA state Utilities are not reported	EQ-5D-5L was administered to patients using an electronic tablet; the five dimensions were combined into a	The study locations are not reported, but a UK value set was used; therefore, the study may be relevant to NICE decision-making Utilities were derived using																

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Source (study/ publication, publication year)	Objective	Description of population and recruitment method				Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriatene ss of study for cost- effectiveness evaluation
		Baseline characteristics:					The questionnair e completion rates across all scheduled timepoints were 94.3% in HAVEN 3 and 99.0% in HAVEN 4	for specific AEs	single score using the UK crosswalk value set	the EQ-5D in line with NICE preferences
		Characterist ic	HAVE N 3 (N=14 3)	HAVE N 4 (n=33)	Total (n=17 6)					
		Median age, years (range)	39.0 (19– 77)	41.0 (22– 66)	39.0 (19– 77)					
		Bleeds in the past 24 weeks, mean (SD)	13.5 (16.5)	9.6 (16.7)	12.8 (16.5)					
		≥9, n (%)	79 (55)	10 (30)	89 (51)					
		<9, n (%)	64 (45)	23 (70)	87 (49)					
		One or more target joints prior to study, n (%)	100 (70)	24 (73)	124 (70)					
		Prior treatment, n (%)								
		Episodic	87 (61)	9 (27)	96 (55)					
		Prophylactic	56 (39)	24 (73)	80 (45)					
Steen Carlsson 2022 (NCT03276130)	To explore the perspectives of people with haemophilia from Sweden, Finland and Denmark on	HRQoL data of people with haemophilia A or B with or without inhibitors were collected. A survey was developed by the MIND (NCT03276130) study team, including EQ-5D-5L				Sweden, Finland and Denmark	N=343 people with haemophilia (n=180 with severe	Utility was presented generally for people with haemophili	HRQoL was assessed using the EQ-5D-5L	The study was conducted in three Nordic countries, however, a UK value set was

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Source (study/ publication, publication year)	Objective	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation																												
	the management of haemophilia-related pain, depression and anxiety using cross-sectional survey data from the MIND study	The study was performed in adherence to each country's practice for surveys in the healthcare sector, including age cut-offs. Invitations were distributed between October 2018–July 2019 The surveys were sent to people with haemophilia aged ≥16 (Sweden) or ≥18 (Finland and Denmark) years Baseline characteristics: <table><tr><th>Characteristic, n (%)</th><th>Patients with severe haemophilia n=180</th></tr><tr><td colspan="2">Age category</td></tr><tr><td>16–19</td><td>17 (9)</td></tr><tr><td>20–29</td><td>24 (13)</td></tr><tr><td>30–39</td><td>44 (24)</td></tr><tr><td>40–49</td><td>28 (16)</td></tr><tr><td>50–59</td><td>36 (20)</td></tr><tr><td>60–69</td><td>16 (9)</td></tr><tr><td>70+</td><td>15 (8)</td></tr><tr><td>Haemophilia A</td><td>149 (83)</td></tr><tr><td>Haemophilia B</td><td>31 (17)</td></tr><tr><td>Currently has inhibitors</td><td>10 (6)</td></tr><tr><td>Previously had inhibitors</td><td>27 (15)</td></tr><tr><td>Never had inhibitors</td><td>130 (72)</td></tr></table>	Characteristic, n (%)	Patients with severe haemophilia n=180	Age category		16–19	17 (9)	20–29	24 (13)	30–39	44 (24)	40–49	28 (16)	50–59	36 (20)	60–69	16 (9)	70+	15 (8)	Haemophilia A	149 (83)	Haemophilia B	31 (17)	Currently has inhibitors	10 (6)	Previously had inhibitors	27 (15)	Never had inhibitors	130 (72)		haemophilia)	a, by severity level Utilities are not reported for specific AEs	questionnaire Utilities were derived using the UK value set by Devlin et al. 2018	used, therefore the study may be partially relevant to NICE decision-making Utilities were derived using the EQ-5D-5L; NICE's preference for utility elicitation is the EQ-5D-3L
Characteristic, n (%)	Patients with severe haemophilia n=180																																		
Age category																																			
16–19	17 (9)																																		
20–29	24 (13)																																		
30–39	44 (24)																																		
40–49	28 (16)																																		
50–59	36 (20)																																		
60–69	16 (9)																																		
70+	15 (8)																																		
Haemophilia A	149 (83)																																		
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Never had inhibitors	130 (72)																																		

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Source (study/publication, publication year)	Objective	Description of population and recruitment method		Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation
		No answer	13 (7)					

Abbreviations: AB: annual bleeds; ABR: annual bleeding rate; AE: adverse event; BE: bleeding episode; CHES: Cost of Haemophilia in Europe: a Socioeconomic Survey; EHL: extended half-life; EQ-5D-5L: EuroQol-5 Dimension-5 levels; FIX: factor IX; FVIII: factor VIII; HA: haemophilia A; HB: haemophilia B; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HRQoL: health-related quality of life; IQR: interquartile range; IU: international unit; IUS: index utility score; n: number; mITT: modified intent-to-treat; NICE: National Institute for Health and Care Excellence; NIS: non-interventional study; NR: not reported; PJ: problem joints; PRO: patient-reported outcome; PwH: people with haemophilia; QoL: quality of life; SD: standard deviation; SF-6D: Short-Form 6 dimensions; SHA: severe haemophilia A; SHL: standard half-life; SLR: systematic literature review; UK: United Kingdom; US: United States; VAS: visual analogue scale.

Table 84. Summary of the results of utility studies included in the economic SLR

Source (study/publication, publication year)	Utility values and uncertainty around values	Study conclusions																												
Chowdary 2024 (CHES II and CHES PAEDS) Supplementary sources: Chowdary 2023	EQ-5D-5L IUS (CHES-II): <table> <tr> <th rowspan="2">EQ-5D</th><th colspan="2">SHA (n=278)</th></tr> <tr> <th>Prophylaxis (n=157)</th><th>Other (n=121)</th></tr> <tr> <td>n</td><td>81</td><td>54</td></tr> <tr> <td>Mean (SD)</td><td>0.68 (0.28)</td><td>0.69 (0.22)</td></tr> <tr> <td>Median (IQR)</td><td>0.71 (0.32)</td><td>0.71 (0.30)</td></tr> </table> EQ-5D-Y IUS (CHES-PAEDS): <table> <tr> <th rowspan="2">EQ-5D</th><th colspan="2">SHA (n=409)</th></tr> <tr> <th>Prophylaxis (n=332)</th><th>Other (n=77)</th></tr> <tr> <td>n</td><td>76</td><td>18</td></tr> <tr> <td>Mean (SD)</td><td>0.65 (0.25)</td><td>0.69 (0.17)</td></tr> <tr> <td>Median (IQR)</td><td>0.65 (0.29)</td><td>0.70 (0.22)</td></tr> </table>	EQ-5D	SHA (n=278)		Prophylaxis (n=157)	Other (n=121)	n	81	54	Mean (SD)	0.68 (0.28)	0.69 (0.22)	Median (IQR)	0.71 (0.32)	0.71 (0.30)	EQ-5D	SHA (n=409)		Prophylaxis (n=332)	Other (n=77)	n	76	18	Mean (SD)	0.65 (0.25)	0.69 (0.17)	Median (IQR)	0.65 (0.29)	0.70 (0.22)	EQ-5D scores reported in CHES-II were low compared with the norms for the general population published previously Similar scores were reported in CHES-PAEDs, indicating a Similar deficiency in HRQoL, although general population norms are unavailable for comparison Those receiving prophylaxis reported greater impact on their QoL compared with those receiving other treatment. However, the majority of those receiving prophylaxis are likely to have SHA, per the treatment guidelines, and results may therefore be impacted primarily by disease severity, rather than treatment received For the PJ subgroup analysis, the results show the negative impact of increasing joint morbidity on HRQoL for children, adolescents and adults with SHA. Taken together, the holistic importance of early and effective joint health management may be substantial. Specifically,
EQ-5D	SHA (n=278)																													
	Prophylaxis (n=157)	Other (n=121)																												
n	81	54																												
Mean (SD)	0.68 (0.28)	0.69 (0.22)																												
Median (IQR)	0.71 (0.32)	0.71 (0.30)																												
EQ-5D	SHA (n=409)																													
	Prophylaxis (n=332)	Other (n=77)																												
n	76	18																												
Mean (SD)	0.65 (0.25)	0.69 (0.17)																												
Median (IQR)	0.65 (0.29)	0.70 (0.22)																												

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Source (study/ publication, publication year)	Utility values and uncertainty around values	Study conclusions																														
	EQ-5D-5L IUS by PJs (CHESS-II): <table><tr><th rowspan="2">EQ-5D</th><th colspan="3">SHA (n=136)</th></tr><tr><th>0 PJs</th><th>1 PJ</th><th>≥2 PJs</th></tr><tr><td>n</td><td>73</td><td>35</td><td>28</td></tr><tr><td>Mean (SD)</td><td>0.79 (NR)</td><td>0.62 (NR)</td><td>0.51 (NR)</td></tr></table> EQ-5D-Y IUS by PJs (CHESS-PAEDS): <table><tr><th rowspan="2">EQ-5D</th><th colspan="3">SHA (n=103)*</th></tr><tr><th>0 PJs</th><th>1 PJ</th><th>≥2 PJs</th></tr><tr><td>n</td><td>88</td><td>22</td><td>3</td></tr><tr><td>Mean (SD)</td><td>0.70 (NR)</td><td>0.53 (NR)</td><td>0.33 (NR)</td></tr></table> *n numbers as reported in original article (N.B. numbers for each PJ group do not add to n=103)	EQ-5D	SHA (n=136)			0 PJs	1 PJ	≥2 PJs	n	73	35	28	Mean (SD)	0.79 (NR)	0.62 (NR)	0.51 (NR)	EQ-5D	SHA (n=103)*			0 PJs	1 PJ	≥2 PJs	n	88	22	3	Mean (SD)	0.70 (NR)	0.53 (NR)	0.33 (NR)	HRQoL scores for patients with ≥1 PJ, regardless of age, were markedly worse than for those with none
EQ-5D	SHA (n=136)																															
	0 PJs	1 PJ	≥2 PJs																													
n	73	35	28																													
Mean (SD)	0.79 (NR)	0.62 (NR)	0.51 (NR)																													
EQ-5D	SHA (n=103)*																															
	0 PJs	1 PJ	≥2 PJs																													
n	88	22	3																													
Mean (SD)	0.70 (NR)	0.53 (NR)	0.33 (NR)																													
Madan 2024	EQ-5D-5L IUS: <table><tr><th rowspan="2">Variable</th><th rowspan="2">CID</th><th colspan="3">Utility value</th></tr><tr><th>Year 1 (n=130)</th><th>Year 2 (n=126)</th><th>Year 3 (n=121)</th></tr><tr><td>Mean change from Baseline (95% CI)</td><td>0.03</td><td>0.04 (0.02, 0.07)</td><td>0.02 (0.00, 0.05)</td><td>0.02 (-0.01,0.05)</td></tr></table>	Variable	CID	Utility value			Year 1 (n=130)	Year 2 (n=126)	Year 3 (n=121)	Mean change from Baseline (95% CI)	0.03	0.04 (0.02, 0.07)	0.02 (0.00, 0.05)	0.02 (-0.01,0.05)	Participants reported improvements in HRQoL at year 3 compared with baseline, suggesting real-world benefits related to the ability to perform daily activities, role functioning, worry about bleeds, and more. However, the impact of lifelong coping (ie, disability paradox) may have contributed to higher-than-anticipated ratings on HRQoL assessments (ie, EQ-5D-5L), limiting opportunities to observe improvements over time																	
Variable	CID			Utility value																												
		Year 1 (n=130)	Year 2 (n=126)	Year 3 (n=121)																												
Mean change from Baseline (95% CI)	0.03	0.04 (0.02, 0.07)	0.02 (0.00, 0.05)	0.02 (-0.01,0.05)																												
Neufeld 2012	HRQoL cohort n=37 Across all diary days: <table><tr><th></th><th>Utility value, median (range)</th></tr><tr><td>EQ-5D-3L index</td><td>0.81 (−0.11–1.0)</td></tr></table>		Utility value, median (range)	EQ-5D-3L index	0.81 (−0.11–1.0)	The study shows that EQ-5D utilities were lower (poorer) on bleed days																										
	Utility value, median (range)																															
EQ-5D-3L index	0.81 (−0.11–1.0)																															

Source (study/ publication, publication year)	Utility values and uncertainty around values					Study conclusions
	Parameters	OD	ITT	PPX	All	
	Patient mean score by treatment group					
	EQ-5D-3L index, mean ± SD					
	n	21	5	12	36	
	Bleed days	0.60 ± 0.26	0.73 ± 0.16	0.71 ± 0.20	0.64 ± 0.23	
	Non-bleed days	0.79 ± 0.19	0.90 ± 0.08	0.91 ± 0.09	0.84 ± 0.16	
	Across all diary days					
	EQ-5D-3L index, mean ± SD					
	Diary days, n (bleed/non-bleed)	2397 (210/2187)	450 (135/315)	1102 (171/931)	3771 (472/3299)	
	Bleed days	0.64 ± 0.27	0.70 ± 0.22	0.67 ± 0.29	0.66 ± 0.26	
	Non-bleed days	0.78 ± 0.21	0.91 ± 0.10	0.91 ± 0.11	0.82 ± 0.19	
	Parameters	Age ≤18 y		Age >18 y		
	Patient mean score by age group					
	EQ-5D-3L index, mean ± SD					
	n	19		18		
	Bleed days	0.76 ± 0.111		0.52 ± 0.264		
	Non-bleed days	0.92 ± 0.086		0.75 ± 0.180		
	All days	0.89 ± 0.096		0.72 ± 0.176		
	Across all diary days					
	EQ-5D-3L index, mean ± SD					
	Diary days, n (bleed/non-bleed)	1722 (219/1451)		2049 (201/1848)		
	Bleed days	0.75 ± 0.190		0.54 ± 0.293		
	Non-bleed days	0.93 ± 0.104		0.74 ± 0.206		

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Source (study/ publication, publication year)	Utility values and uncertainty around values				Study conclusions				
	All days	0.90 ± 0.138	0.72 ± 0.225						
O'Hara 2021 (CHESS)	EQ-5D-3L index score:				Clinical outcomes and quality of life remain impaired compared with the general population				
Supplementary source: O'Hara 2017		O'Hara 2021	O'Hara 2017						
	Mean EQ-5D-3L index score	0.87	0.59 (SD: 0.36)						
Oldenburg 2021	Baseline EQ-5D-5L index scores:				Adult and adolescent PwHA without FVIII inhibitors experience impairments in HRQoL regardless of whether they are treated episodically or prophylactically with FVIII. This highlights an unmet need for a treatment that reduces the burden of PwHA without FVIII inhibitors				
	Treatment Type		Mean EQ-5D-5L IUS (SD)						
	Episodic Treatment (n=41)		0.8 (0.1)						
	Prophylaxis (n=47)		0.9 (0.1)						
	Figure 5 in Oldenburg 2021 depicts the effect of bleeding on EQ-5D-5L IUS, but numerical data are not available								
O'Mahony 2024 (CHESS)	EQ-5D-5L IUS scores by clinical severity:				Haemophilia was shown to have an impact HRQoL across clinically diagnosed severity, with a decrement in HRQoL observed as severity increased				
	EQ-5D	Mild	Moderate	Severe					
	Index score, mean (SD)	0.88 (0.10)	0.79 (0.19)		0.69 (0.21)				
Skinner 2021	Mean EQ-5D-5L IUS:				The health status measured by EQ-5D-5L IUS indicated no notable improvement over time in HAVEN 3 and 4				
		No target joints		≥1 target joint			Pooled		
		n	Mean	n			Mean	n	Mean (SD)
	Baseline	49	0.8	121			0.71	170	0.74 (0.20)
	Week 13	51	0.82	114			0.76	NR	NR
	Week 25	49	0.83	114			0.73	NR	NR
	Week 49	47	0.83	113			0.77	NR	NR
	Week 73	34	0.83	84	0.77	118	0.79 (0.17)		

Source (study/ publication, publication year)	Utility values and uncertainty around values	Study conclusions
Steen Carlsson 2022 (NCT03276130)	EQ-5D-5L IUS* Among PwH, EQ-5D utility values decreased with increasing disease severity, with a statistically significant difference between disease severities (p<0.001) *EQ-5D-5L utility values by severity are presented graphically in Figure 5 of Steen Carlsson et al. 2022	Pain, as measured by EQ-5D, was more frequent in severe haemophilia. Therefore, despite the wide availability of clotting factor replacements, PwH - especially those with severe disease -were less likely to enjoy a quality of life comparable to people without haemophilia

Abbreviations: CHES: Cost of Haemophilia in Europe: a Socioeconomic Survey; CI: confidence interval; CID: clinically important difference; FVIII: factor VIII; HA: haemophilia A; HRQoL: health-related quality of life; IQR: interquartile range; ITT: immune tolerance therapy; IUS: index utility score; NR: not reported; OD: on-demand; PJ: problem joints; PPX: secondary prophylaxis with bypassing agent; PwH: people with haemophilia; PwHA: people with haemophilia A; SD: standard deviation; SF-6D: Short-Form 6 dimensions; SHA: severe haemophilia A; SLR: systematic literature review; UK: United Kingdom; VAS: visual analogue scale; y: year

Appendix I Costs and healthcare resource identification, measurement and validation

I.1 Identification of studies

The databases and hand searches were conducted simultaneously for the HCRU stream alongside the cost-effectiveness stream (Appendix G), and utility/HRQoL stream (Appendix I). Each record identified in these searches was assessed for eligibility across all three data streams (cost-effectiveness, utility/HRQoL, and HCRU). Each study identified could therefore be included in one or more of the evidence streams.

I.1.1. Search Strategy

The information for evidence sources searched for the HCRU SLR are presented in Appendix G.

Electronic databases

A list of the search terms used in the electronic databases are provided in Appendix G.1.1 for the original SLR and SLR update.

Grey literature sources

Conference proceedings

An overview of the conference website searches undertaken in the SLR update is provided in Table 69 (Appendix G.1.1).

HTA websites and additional sources

Search terms used in the HTA and economic website searches, are provided in Table 70 and Table 71, respectively, for the SLR update (Appendix G.1.1).

I.1.2. Study selection

The methods used for study selection are detailed in Appendix G.1.2. The review of abstracts and full texts was performed using predefined eligibility criteria, based on the decision problem for this submission and developed using the PICOS framework.

Evidence prioritisation for data extraction

Due to a large volume of evidence identified as relevant after the full-text review stage, a number of steps were taken to ensure that the most recent and relevant studies to the decision problem for this submission were prioritised for extraction. For the HCRU evidence stream, studies were prioritised if they:

- Fulfilled the following criteria:
 - Included patients in the UK
 - And, were identified during the SLR update

- And, did not report solely indirect costs and/or incidental HCRU (defined for this SLR as HCRU data that were not pre-specified as a study outcome, treatment doses, factor consumption and treatment usage)
- Or, were key studies chosen to inform HCRU in the economic model for this submission based on prior NICE evaluations in haemophilia

Eligibility criteria

The eligibility of each study captured in the database and grey literature searching was reviewed for inclusion across all three streams (cost effectiveness studies, HRQoL/utilities, and HCRU). The eligibility presented here is specific to that assessed for inclusion into the HCRU evidence stream (see Table 85), eligibility for the other streams are reported in other appendices (cost-effectiveness studies; Appendix G.1.2 and HRQoL/utility studies; Appendix H.1.2).

Table 85. Eligibility criteria for the HCRU studies

Category	Inclusion Criteria	Exclusion Criteria
Population	- Paediatric or adult patients with inherited moderately severe-to-severe haemophilia A or haemophilia B - Subgroups of above target population in studies among mixed haemophilia A/haemophilia B, mixed severity, mixed treatment history or mixed age patient population, if data are separately reported for the target subgroup	- Studies on other diseases - Studies on patients with acquired haemophilia A or haemophilia B - Studies with only subpopulations (e.g. with specific comorbidities)
Intervention	Any or none	N/A
Comparators	Any or none	N/A
Outcomes	Costs^a - Total direct costs (medical, non-medical) - Medication costs - Costs due to resource use (inpatient, outpatient costs, etc.) - Indirect costs - Caregiver costs - Cost drivers HCRU^a (including those associated with joint procedures and pain due to hemophilia) - Hospitalisations - ICU stays - Length of stays - ER visits	Publications that only reported data on following types of outcomes including: - Laboratory based studies that report on cellular work or biomarker analyses that are not correlated with outcomes of interest - Validation/accuracy of diagnostic techniques/tests - Validation of HRQoL or PRO questionnaires - Pharmacokinetics/pharmacodynamics

Category	Inclusion Criteria	Exclusion Criteria
Study design	- Clinical trials (phase II/III RCTs, single-arm, non-RCTs) - Observational studies, including prospective and retrospective cohort studies and cross-sectional analyses - SLRs/(N)MAs (N.B. included for hand-searching at title/abstract stage, but excluded at full-text stage)^b	- Animal studies - In vitro/ex vivo studies - Gene expression/protein expression studies - Narrative publications - Non-systematic reviews - Phase I studies - Case studies - Case series - Case reports - Editorials
Other considerations	- Studies were limited to those conducted within the following regions/countries:^a - North America (United States and Canada) - EU4 + United Kingdom - Japan - Australia - South Korea - International studies - Only English language articles were included Publications from 2020 onwards For SLR/(N)MAs, HTAs and economic evaluations reference lists: publications from 2020 onwards Abstracts and other materials from conferences: published from 2022 onwards	- Countries not of interest - Journal articles not available in English - Articles and abstracts published before the search cut-offs

Footnotes: Items in **bold** were added for the SLR update in May 2024. ^aDue to the large volume of evidence identified after the full text review stage, studies including patients in the UK were prioritised for extraction and studies only reporting on incidental CRU and indirect costs were deprioritised for extraction. ^bThe reference lists of SLRs/(N)MAs, HTAs and economic evaluations were screened to identify articles of importance that may not have been identified during search or screening.

Abbreviations: ER: emergency room; EU4: France, Germany, Italy and Spain; HTA: health technology assessment; HRQoL: health-related quality of life; ICU: intensive care unit; NA: not applicable; (N)MA: (network) meta-analysis; PRO: patient-reported outcome; RCT: randomised controlled trial; SLR: systematic literature review.

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I.1.3. Description of identified studies

The PRISMA flow diagram for all three evidence streams is presented in Figure 4.

Original and update searches

The results of the original and update SLR searches are as described in Appendix G.1.3. Briefly, following evidence prioritisation, 4 records from the original SLR and 26 records from the update SLR were prioritised for extraction across all three evidence streams.

Lists of the studies deprioritised for data extraction in each evidence stream are presented in Table 75 (economic evaluations), Table 81 (utility/HRQoL) and Table 86 (HCRU).

Total HCRU evidence

Of these, 12 records reporting on 10 unique studies were prioritised for the HCRU evidence stream. A full list of these studies is presented in Table 87. Full details of the prioritised HCRU studies are provided in Table 88 and Table 89.

Table 86. HRQoL/utility studies deprioritised for extraction in the economic SLR (original and update SLR)

#	Reference
1.	Abbonizio, F, Giampaolo, et al. Therapeutic management and costs of severe haemophilia A patients with inhibitors in Italy. <i>Haemophilia</i> . 2014;20:e243-e250.
2.	Alam A, Goodyear M, Wu C, and Sun H. Increased acute care utilisation, comorbidities and mortality in adults with haemophilia: A population-based cohort study from 2012 to 2019. <i>Haemophilia</i> . 2023;29(1):219-229.
3.	Álvarez Román MT, Oldenburg J, Ettingshausen CE, et al. Real-world effectiveness and safety of a recombinant factor VIII Fc in patients with haemophilia A by disease severity: Pooled analysis (A-SURE/PREVENT). <i>Haemophilia</i> . 2024;30(Supplement 1):34-188 (PO056).
4.	Arvanitakis A, Holme PA, Berntorp E, and Astermark J. Impact of timing of prophylaxis commencement, F8 genotype and age on factor consumption and health-related quality of life in patients with severe haemophilia A. <i>Haemophilia</i> . 2023;29(4):1032-1038.
5.	Astermark J, Ay C, Carvalho M, et al. New Inhibitors in the Ageing Population: A Retrospective, Observational, Cohort Study of New Inhibitors in Older People with Hemophilia. <i>Thrombosis and Haemostasis</i> . 2022;122(6):905-912.
6.	Astermark J, Hermans C, Ezzalfani M, et al. Recombinant factor IX Fc prophylaxis reduces pain and increases levels of physical activity, with sustained, long-term improvements in patients with hemophilia B: post hoc analysis of phase III trials using patient-reported outcomes. <i>Therapeutic Advances in Hematology</i> . 2023;14:2.04062E+16.
7.	Aznar, JA, Magallon, et al. The orthopaedic status of severe haemophiliacs in Spain. <i>Haemophilia : the official journal of the World Federation of Hemophilia</i> . 2000;6:170-6.
8.	Bae JK, Kim KI, Lee SH, and Yoo MC. Mid-to long-term survival of total knee arthroplasty in hemophilic arthroplasty. <i>Journal of Clinical Medicine</i> . 2020;9(10):41275.
9.	Batt K, Cockerham A, Sacks N, Jin H, and Nguyen ATH. THE CLINICAL and ECONOMIC IMPACT of RECOMBINANT FACTOR VIII FC FUSION PROTEIN (RFVIII FC) on LONG-TERM JOINT HEALTH in PEOPLE with HEMOPHILIA A (PWHA). <i>Haemophilia</i> . 2022;28(SUPPL 1):93-94.
10.	Batt K, Xing S, Kuharic M, et al. Correction to Batt K, Xing S, Kuharic M, et al. Real-world analysis of patients with haemophilia A and haemophilia A carriers in the United States: Demographics, clinical characteristics and costs. <i>Haemophilia</i> . 2024;30(3):872.
11.	Benitez-Hidalgo O, Bosch Schips M, Juarez Gimenez JC, and Gironella M. Benefits of rIX-FP prophylaxis in patients with Haemophilia B: real-world evidence from a Spanish reference centre. <i>Hematology (United Kingdom)</i> . 2023;28(1) (no pagination).
12.	Bidlingmaier, C, Deml, et al. Continuous infusion of factor concentrates in children with haemophilia A in comparison with bolus injections. <i>Haemophilia : the official journal of the World Federation of Hemophilia</i> . 2006;12:212-7.
13.	Blenkiron T, Hinds D, Santos S, et al. RWD63 Clinical Outcomes in Non-Inhibitor Severe Haemophilia A Patients Receiving Prophylaxis Across Currently Available Haemophilia A

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#	Reference
	Treatments: Insights From the 'Cost of Haemophilia: A Socioeconomic Survey III' (CHESS III) Study. <i>Value in Health</i> . 2023;26(12 Supplement):S516.
14.	Bolous N, Poudyal B, Loayza N, et al. Cost of clinical care for patients with severe haemophilia in six low- and middle-income countries. <i>Haemophilia</i> . 2022;28(Supplement 3):5–97:LR-06.01 (1160290).
15.	Brown LJ, La HA, Li J, et al. The societal burden of haemophilia A. II - The cost of moderate and severe haemophilia A in Australia. <i>Haemophilia</i> . 2020;26(Suppl 5):44136.
16.	Buckley, B, Dreyfus, et al. Burden of illness and costs among paediatric haemophilia patients with and without central venous access devices treated in US hospitals. <i>Haemophilia : the official journal of the World Federation of Hemophilia</i> . 2018;24e93-e102.
17.	Buckner TW, Bocharova I, Hagan K, et al. Health care resource utilization and cost burden of hemophilia B in the United States. <i>Blood Advances</i> . 2021;5(7):1954-1962.
18.	Burke T, Asghar S, O'Hara J, et al. Clinical, humanistic, and economic burden of severe hemophilia B in the United States: Results from the CHESS US and CHESS US+ population surveys. <i>Orphanet Journal Of Rare Diseases</i> . 2021;16(1):143.
19.	Burke T, Rodriguez-Santana I, Chowdary P, et al. Humanistic burden of problem joints for children and adults with haemophilia. <i>Haemophilia</i> . 2023;29(2):608-618.
20.	Cano AH, Candel FG, Villalobos MS, et al. Real experience of prophylaxis with emicizumab in patients with congenital haemophilia A with and without FVIII inhibitors in the HCUVA. <i>Haemophilia</i> . 2024;30(Supplement 2):3–223:PP-022(1693419).
21.	Carcao M, Staber J, Nolan B, et al. Quality of life in children with haemophilia A: Phase 3 XTEND-kids study of efanesoctocog alfa. <i>Haemophilia</i> . 2024;30(Supplement 1):34-188 (PO134).
22.	Carcao M, Zak M, Abdul Karim F, et al. Nonacog beta pegol in previously treated children with hemophilia B: results from an international open-label phase 3 trial. <i>J Thromb Haemost</i> . 2016;14(8):1521-1529.
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24.	Cavazza, M, Kodra, et al. Social/economic costs and quality of life in patients with haemophilia in Europe. <i>European Journal of Health Economics</i> . 2016;1753-65.
25.	Chen, CX, Baker, et al. Economic Burden of Illness among Persons with Hemophilia B from HUGS Vb: Examining the Association of Severity and Treatment Regimens with Costs and Annual Bleed Rates. <i>Value in Health</i> . 2017;201074-1082.
26.	Chhabra, A, Fogarty, et al. Real-World Analysis of Dispensed International Units of Coagulation Factor VIII and Resultant Expenditures for Hemophilia A Patients: A Comparison Between Standard Half-Life and Extended Half-Life Products. <i>Managed care (Langhorne, Pa.)</i> . 2018;2739-50.
27.	Chowdary P, Khoo L, Wang M, et al. Prospective, Observational Study of the Clinical Characteristics of Adults and Adolescents with Severe Hemophilia A. <i>Research and Practice in Thrombosis and Haemostasis</i> . Conference: ISTH 2023 Congress. Montreal Canada. 2023;7(Supplement 2) (no pagination).
28.	Chowdary P, Mullins ES, Konkle BA, et al. 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. <i>Haemophilia</i> . 2020;26(4):e168-e178.
29.	Chowdary P, Polito L, Chafaie R, et al. Exploring baseline characteristics, treatment decisions and patient-centred outcomes of people with severe haemophilia A receiving prophylaxis: Early findings from the multi-country 'Cost of Haemophilia: A Socioeconomic Survey III' (CHESS III) study. <i>Haemophilia</i> . 2024;30(Supplement 2):3–223:FP-028(1691365).
30.	Cutter, S, Molter, et al. Impact of mild to severe hemophilia on education and work by US men, women, and caregivers of children with hemophilia B: The Bridging Hemophilia B Experiences, Results and Opportunities into Solutions (B-HERO-S) study. <i>European Journal of Haematology</i> . 2017;9818-24.
31.	De, D, Datta, et al. Very low dose prophylaxis in children with haemophilia A: A rural Indian experience. <i>HemaSphere</i> . 2018;2394-395.
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33.	Duncan, N, Roberson, et al. A haemophilia disease management programme targeting cost and utilization of specialty pharmaceuticals. <i>Haemophilia</i> . 2014;20519-526.
34.	Eichler H, Nagao A, Waller J, and Stuber A. Real-World Experience of People with Hemophilia A Receiving Turoctocog Alfa Pegol (N8-GP): Results from a Patient Experience Survey. <i>Patient preference & adherence</i> . 2023;17:3001-3014.

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35.	Ettingshausen CE, Hermans C, Holme PA, et al. Real-world data in patients with congenital hemophilia and inhibitors: final data from the FEIBA Global Outcome (FEIBA GO) study. <i>Therapeutic Advances in Hematology</i> . 2023;14:2.04062E+16.
36.	Evans J, Burke T, Skerit M, et al. RWD44 The Cost of Haemophilia in Adults, a Socioeconomic Survey of People With Severe Haemophilia in Latin America: The 'Chess Latam' Study. <i>Value in Health</i> . 2022;25(12 Supplement):S456.
37.	Ferri Grazzi E, Blenkiron T, Aragon MJ, et al. PCR192 Treatment Burden and Its Relationship With Health-Related Quality of Life, Work Productivity and Activity Impairment in Adults With Severe Non-Inhibitor Hemophilia A in the United States: Data Analysis From the CHES US+ Study. <i>Value in Health</i> . 2022;25(12 Supplement):S427.
38.	Ferri Grazzi E, Blenkiron T, O'Hara J, et al. The Economic Burden of Severe Haemophilia a without Inhibitors Among Adults with Health Insurance Coverage in the United States: Insights from the "Cost of Haemophilia across the US: A Socioeconomic Survey" CHES US and CHES US+ Studies. <i>Value in Health</i> . 2022;25(7 Supplement):S339.
39.	Gringeri, A, Leissinger, et al. Health-related quality of life in patients with haemophilia and inhibitors on prophylaxis with anti-inhibitor complex concentrate: results from the Pro-FEIBA study. <i>Haemophilia : the official journal of the World Federation of Hemophilia</i> . 2013;19:36-43.
40.	Gringeri, A, Mantovani, et al. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: The COCIS study group. <i>Blood</i> . 2003;102:2358-2363.
41.	Guh, S, Grosse, et al. Health care expenditures for Medicaid-covered males with haemophilia in the United States, 2008. <i>Haemophilia : the official journal of the World Federation of Hemophilia</i> . 2012;18:276-283.
42.	Gupta, A, Hannan, et al. Associated co-morbidities, healthcare utilization, and mortality in hospitalized children and adults with hemophilia in the united states: Updated nationally representative estimates and a comparative analysis. <i>Blood</i> . 2019;134.
43.	Hay CRM, Makris M, Shima M, et al. Association of patient, treatment and disease characteristics with patient-reported outcomes: Results of the ECHO Registry. <i>Haemophilia</i> . 2024;30(1):106-115.
44.	Hirniak S, Edginton AN, Iorio A, et al. Health utilities in adults with hemophilia A: A retrospective cohort study. <i>Haemophilia</i> . 2024;30(3):733-742.
45.	Huguenin Y, Harroche A, Dargaud Y, et al. French real-word data on rIX-Fp prophylaxis use in adolescent-adult patients with haemophilia B. <i>Haemophilia</i> . 2024;30(Supplement 1):34-188 (PO113).
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48.	Kempton CL, and Fedewa SA. Defining the impact of immune tolerance induction on clinically relevant outcomes in a US cohort of severe hemophilia A. <i>Blood Advances</i> . 2024;8(5):1190-1199.
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67.	Mahajerin, A, Yang, et al. Characteristics of hemophilia a patients treated with emicizumab: An early view using claims database analysis. <i>Blood</i> . 2019;134.
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94.	Pipe S, Arbor A, Leebeek F, et al. Phase 3 HOPE-B trial of etranacogene dezaparvovec in severe/moderately severe hemophilia B: A post hoc responder analysis of participants who received full dose and responded to treatment. <i>ISTH Academy</i> . 2023;392367:OC 52.5.
95.	Pipe S, van der Valk P, Kampmann P, et al. Long-Term Bleeding Protection, Sustained FIX Activity, Reduction of FIX Consumption and Safety of Hemophilia B Gene Therapy: Results from the HOPE-B Trial 3 Years after Administration of a Single Dose of Etranacogene Dezaparvovec in Adult Patients with Se. <i>Blood</i> . 2023;142(Supplement 1):1055.
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98.	Polack, B, Trossaert, et al. Cost-effectiveness of emicizumab versus by-passing agents in patients with haemophilia A and FVIII inhibitors in France. <i>HemaSphere</i> . 2019;3118.
99.	Poon MC, Lee A, Germini F, et al. Real-World Outcomes of Emicizumab in Hemophilia A with or without FVIII Inhibitors from the Canadian Hemophilia Bleeding Disorder Registry. <i>Blood</i> . 2022;140(Supplement 1):8465-8467.
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101.	Rosas, S, Buller, et al. Total Knee Arthroplasty among Medicare Beneficiaries with Hemophilia A and B Is Associated with Increased Complications and Higher Costs. <i>The journal of knee surgery</i> . 2019;.
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#	Reference
103.	Santos S, Santos J, Hinds D, et al. Understanding the real-world health care resource utilization and costs of severe hemophilia A without inhibitors among adults treated with long-term prophylaxis in the United States by payer type. <i>Journal of Managed Care and Specialty Pharmacy</i> . 2024;30(4-a Supplement):S34-S35.
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105.	Shaikh A, Pedra G, Cawson M, and Wiseman C. Examining the impact of haemophilia treatment on health-related quality of life. <i>Haemophilia</i> . 2022;28(5):796-805.
106.	Shapiro AD, Ragni MV, Borhany M, et al. Natural history study of factor IX deficiency with focus on treatment and complications (B-Natural). <i>Haemophilia</i> . 2021;27(1):49-59.
107.	Shrestha, A, Eldar-Lissai, et al. Real-world resource use and costs of haemophilia A-related bleeding. <i>Haemophilia</i> . 2017;23e267-e275.
108.	Simpson ML, Desai V, Maro GS, and Yan S. Comparing Factor Use and Bleed Rates in U.S. Hemophilia A Patients Receiving Prophylaxis with 3 Different Long-Acting Recombinant Factor VIII Products. <i>Journal of Managed Care & Specialty Pharmacy</i> . 2020;26(4):504-512.
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110.	Skinner, M, Negrier, et al. Emicizumab prophylaxis improves long-term physical health scores in persons with haemophilia A (PWA) with and without inhibitors: Update from the haven 3 and haven 4 studies. <i>Research and Practice in Thrombosis and Haemostasis</i> . 2019;3328-329.
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113.	Stieltjes, N, Torchet, et al. Epidemiological survey of haemophiliacs with inhibitors in France: Orthopaedic status, quality of life and cost - The 'Statut Orthopedique des Patients Hemophiles' avec Inhibiteur study. <i>Blood Coagulation and Fibrinolysis</i> . 2009;204-11.
114.	Sun H, Yang M, Poon MC, et al. Factor product utilization and health outcomes in patients with haemophilia A and B on extended half-life concentrates: A Canadian observational study of real-world outcomes. <i>Haemophilia</i> . 2021;27(5):751-759.
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116.	Susen S, Oldenburg J, Konigs C, et al. Efanesoctocog alfa prophylaxis outcomes in European patients from the XTEND-1 trial. <i>Haemophilia</i> . 2024;30(Supplement 1):34-188 (PO121).
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120.	Taylor S, Room J, and Barker K. Physical activity levels in men with Haemophilia-A single centre UK survey. <i>Haemophilia</i> . 2020;26(4):718-725.
121.	Tortella, Bartholomew J, Alvir, et al. Real-World Analysis of Dispensed IUs of Coagulation Factor IX and Resultant Expenditures in Hemophilia B Patients Receiving Standard Half-Life Versus Extended Half-Life Products and Those Switching from Standard Half-Life to Extended Half-Life Products. <i>Journal of managed care & specialty pharmacy</i> . 2018;24643-653.
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123.	Tortella, BJ, Chhabra, et al. Long term realworld health care comparison of expenditures and international units dispensed of extended and standard half-life recombinant factor IX products in hemophilia B patients. <i>Haemophilia</i> . 2019;2555-56.
124.	Tran, H, Peyvandi, et al. Health-related quality of life and health status in persons with hemophilia A (PwHA) without inhibitors: Prospective, non-interventional study (NIS) from a real-world setting. <i>Haemophilia</i> . 2018;24177-178.
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#	Reference
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127.	Verma, SP, Dutta, et al. A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia - A success story from a resource limited country. <i>Haemophilia : the official journal of the World Federation of Hemophilia.</i> 2016;22342-8.
128.	Yang, K, Buckley, et al. Characterization of medical healthcare utilization among prophylaxis hemophilia A patients using a commercially-insured and medicare advantage population claims database. <i>Haemophilia.</i> 2018;2496-97.
129.	Young G, Balasa VV, Roberts JC, et al. Identifying Ideal Individuals for PK-Guided Dosing; Recreational Risks and Elevated Breakthrough Bleeding. <i>Blood.</i> 2023;142(Supplement 1):3742.
130.	Young, L, Vendetti, et al. Target joint surgeries and haemophiliarelated hospitalisations of persons with haemophilia with inhibitors-observations from chess II, a european real-world data study. <i>HemaSphere.</i> 2020;4775.
131.	Zakieh, A, Siddiqui, et al. Emergency department utilization by haemophilia patients in United States. <i>Haemophilia.</i> 2017;23e188-e193.
132.	Zhou, ZY, Koerper, et al. Burden of illness: Direct and indirect costs among persons with hemophilia A in the United States. <i>Journal of Medical Economics.</i> 2015;18457-465.

Table 87. HCRU studies included in the economic SLR

#	Study name	Reference
SLR Update (May 2024)		
1	Batt 2022	Batt K, Cockerham A, Sacks N, et al. The clinical and economic impact of recombinant factor viii fc fusion protein (RFVIII-FC) on long-term joint health in people with hemophilia a (PwHA). <i>Haemophilia.</i> 2022; PO132.
2	Burke 2021	Burke T, Asghar S, O'Hara J, et al. Clinical, humanistic, and economic burden of severe haemophilia B in adults receiving factor IX prophylaxis: findings from the CHES II real-world burden of illness study in Europe. <i>Orphanet Journal Of Rare Diseases.</i> 2021;16(1):521.
3	Chowdary 2024	Chowdary P, Ofori-Asenso R, Nissen F, et al. Disease Burden, Clinical Outcomes, and Quality of Life in People with Hemophilia A without Inhibitors in Europe: Analyses from CHES II/CHES PAEDs. <i>TH Open.</i> 2024;8(2):E181-E193.
	Chowdary 2023	Chowdary P, Nissen F, Burke T, et al. The humanistic and economic burden of problem joints for children and adults with moderate or severe haemophilia A: Analysis of the CHES population studies. <i>Haemophilia.</i> 2023;29(3):753-760.
4	Ferri Grazzi 2022	Ferri Grazzi E, Sun SX, Burke T, et al. The Impact of Pharmacokinetic-Guided Prophylaxis on Clinical Outcomes and Healthcare Resource Utilization in Hemophilia A Patients: Real-World Evidence from the CHES II Study. <i>Journal of Blood Medicine.</i> 2022;13:505-516.
5	Mancuso 2024	Mancuso ME, O'Mahony B, Brighton S, et al. The Burden of Haemophilia in 5 European Countries: Methods and Results from the Cost of Haemophilia in Europe: A Socioeconomic Survey (CHES) 2022. <i>Value in Health.</i> 2024;27(6 Supplement):S370-S371
6	NICE 2023	National Institute for Health and Care Excellence (NICE). Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812], 2023.
7	Rodriguez-Santana 2022a	Rodriguez-Santana I, DasMahapatra P, Burke T, et al. Health-related quality of life, direct medical and societal costs among children with moderate or severe haemophilia in Europe: multivariable models of the CHES-PAEDs study. <i>Orphanet Journal Of Rare Diseases.</i> 2022;17(1):150.
8	Rodriguez-Santana 2022b	Rodriguez-Santana I, DasMahapatra P, Burke T, et al. Differential humanistic and economic burden of mild, moderate and severe haemophilia in European adults: a regression analysis of the CHES II study. <i>Orphanet Journal Of Rare Diseases.</i> 2022;17(1):148.
9	Thakkar 2023	Thakkar S, Wilcox L, Merla V, et al. RWD21 Impact of Haemophilia Severity on Healthcare Resource Usage: Results from a Multinational Real-World Survey. <i>Value in Health.</i> 2023;26(Supplement 12):S507.
Original SLR (August 2020)		

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#	Study name	Reference
10	O'Hara 2018	O'Hara J, Walsh S, Camp C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. <i>Health and Quality of Life Outcomes</i> . 2018;16(1):84.
	O'Hara 2017	O'Hara J, Hughes D, Camp C, Burke T, Carroll L, Diego DG. The cost of severe haemophilia in Europe: the CHES study. <i>Orphanet Journal for Rare Diseases</i> . 2017;12(1):106.

I.1.4. Summary of published cost and healthcare resource use studies identified in the review

The 10 studies included in the HCRU SLR are presented in this section. The methodological details and results of studies are presented in Table 88 and Table 89, respectively.

Table 88. Summary of the methodology of HCRU studies included in the economic SLR

Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis								
Batt 2022	- To assess HCRU over time associated with changes in joint health in people with haemophilia A while undergoing rFVIII Fc treatment - Patient data from A-LONG (NCT01181128) and its extension ASPIRE (NCT01454739) - Included 106 male patients ≥18 years old (mean age [SD]: 34.8 [12.3] years) with SHA (FVIII<1%), a baseline mHJHS score, and no history of detectable inhibitors	- US*, perspective NR - Currency NR, Cost year NR *Assumed by author affiliations	- HCRU data was self-reported by patients in A-LONG and ASPIRE trials - Self-reported HCRU was calculated as: sum of physician appointments, ER visits, and hospitalisations since last study visit	The model used in the study was conducted from a US perspective, and therefore has limited applicability to clinical practice in England								
Burke 2021 (CHESS II)	- To provide updated real-world findings on management practices, disease burden and unmet needs of adults with SHB receiving FIX prophylaxis in Europe - Male adults (≥18 years) with SHB (without inhibitors) receiving continuous EHL or SHL FIX prophylaxis Baseline characteristics: <table><tr><th>Characteristic</th><th>All patients (n=75)</th><th>SHL (n=42)</th><th>EHL (n=33)</th></tr><tr><td>Age, years, mean (SD)</td><td>36.2 (15.97)</td><td>33.7 (14.26)</td><td>39.3 (17.66)</td></tr></table>	Characteristic	All patients (n=75)	SHL (n=42)	EHL (n=33)	Age, years, mean (SD)	36.2 (15.97)	33.7 (14.26)	39.3 (17.66)	- Germany, France, Italy, Spain and the UK, perspective NR - EUR, 2019	- Data were analysed from the CHESS II study, a retrospective cross-sectional burden of illness study - Data in the CHESS II study were collected between 2019 and 2020 across eight European countries	The analysis was conducted on data from patients across multiple European countries, including the UK, and therefore is partly applicable to clinical practice in England
Characteristic	All patients (n=75)	SHL (n=42)	EHL (n=33)									
Age, years, mean (SD)	36.2 (15.97)	33.7 (14.26)	39.3 (17.66)									

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Study	Objective and patient population				Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis
	Weight, kg, mean (SD)	77.3 (11.07)	74.0 (11.58)	79.9 (10.06)		(Denmark, France, Germany, Italy, the Netherlands, Romania, Spain and the UK) Clinical and economic outcomes were reported by the physicians based on review of the medical chart. Patients and their haemophilia-treating physicians each completed questionnaires collecting information on self-reported health status, non-medical costs and work impairment (from patients) and on the patient's medical history (from the physicians) over	People with SHB receiving prophylaxis, without inhibitors, were included, which is in line with the decision problem
	Country, n (%)						
	UK	22 (29)	15 (36)	7 (21)			
	Italy	17 (23)	11 (26)	6 (18)			
	Spain	15 (20)	9 (21)	6 (18)			
	France	11 (15)	4 (10)	7 (21)			
	Germany	10 (13)	3 (7)	7 (21)			
	Medical history, n (%)						
	Anxiety	9 (12)	5 (12)	4 (12)			
	Depression	5 (7)	4 (10)	1 (3)			
	HIV	1 (1)	0	1 (3)			
	Hepatitis B	4 (5)	3 (7)	1 (3)			
	Hepatitis C	9 (12)	4 (10)	5 (15)			
	FIX prophylaxis treatment, n (%)						
	EHL	33 (44)	–	33 (100)			
	SHL	42 (56)	42 (100)	–			

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Study	Objective and patient population				Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis
	Primary FIX prophylaxis, n (%)	57 (76)	29 (69)	28 (85)		the previous 12 months • Direct medical costs were calculated for each country, applying country-specific unit costs for each type of qualifying medical encounter extracted from the patient's medical chart • Indirect costs included loss of wages and productivity due to absenteeism or impairment while at work both for patients and their informal caregivers, using the country-specific average salaries as a proxy for the opportunity costs	
	Secondary FIX prophylaxis, n (%)	18 (24)	13 (31)	5 (15)			

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Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis										
Chowdary 2024 (CHESS II and CHESS PAEDS) Supplementary sources: Chowdary 2023	- To provide a comprehensive overview of unmet needs in people with HA using data generated from the CHESS II and CHESS PAEDs studies - Retrospective analysis of the cross-sectional CHESS-II and CHESS-PAEDS population studies reporting costs by number of PJs (0, 1 or ≥2) and treatment regimen (prophylaxis or other) - Data were analysed from the CHESS-II study; a retrospective cross-sectional burden of illness study of European male adults (≥18 years) with mild, moderate or severe haemophilia A or B - CHESS-PAEDs used a similar design with male children and adolescents (≤17 years old) with moderate (clotting factor 1–5%) or severe (clotting factor <1%) haemophilia A or haemophilia B, with or without inhibitors - Analysis excluded data from CHESS participants with inhibitors to factor VIII replacement therapy Baseline characteristics: <table><tr><th>Characteristic</th><th>Patients with HA N=468</th></tr><tr><td>Male, n (%)</td><td>468 (100)</td></tr><tr><td>Mean age (SD), years</td><td>38.71 (13.95)</td></tr><tr><td>Median age (IQR), years</td><td>37.50 (22)</td></tr><tr><td>Severe HA, n (%)</td><td>278 (59.4)</td></tr></table>	Characteristic	Patients with HA N=468	Male, n (%)	468 (100)	Mean age (SD), years	38.71 (13.95)	Median age (IQR), years	37.50 (22)	Severe HA, n (%)	278 (59.4)	- Multinational (CHESS-II: Denmark, France, Germany, Italy, the Netherlands, Romania, Spain and the UK; CHESS-PAEDS: France, Germany, Italy, Spain and the UK), healthcare system and non-healthcare system perspectives - EUR, cost year NR	- CHESS-II: Patients completed a paper-based questionnaire on self-reported health status (HRQoL) and direct and indirect costs (including work impairment). Providers Completed web-based forms with clinical information derived from the patients' medical records - CHESS-PAEDs: Information on haemophilia-related costs and HRQoL was provided by either the participant or the caregiver (dependent on age and questionnaire)	The study analysed data from the UK, alongside several other European countries, and therefore has some applicability to clinical practice in England People with SHA without inhibitors but with or without prior prophylaxis were included, which is partially in line with the decision problem
Characteristic	Patients with HA N=468													
Male, n (%)	468 (100)													
Mean age (SD), years	38.71 (13.95)													
Median age (IQR), years	37.50 (22)													
Severe HA, n (%)	278 (59.4)													

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Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis																		
			Direct (associated with the health care system), indirect (not associated with the health care system), and total costs were estimated at the patient level for a 12-month retrospective period in accordance with the respective country-level unit cost databases																			
Ferri Grazzi 2022 (CHESS II)	- To describe and compare clinical outcomes and HCRU between patients with haemophilia A treated with or without PK-guided dosing using data from CHESS II database - Male patients ≥18 years old with SHA (FVIII <1%) without inhibitors receiving prophylaxis Baseline characteristics and patient demographics: <table><tr><th>Parameter</th><th>Secondary Prophylaxis</th><th>Primary Prophylaxis</th><th>PK-Guided</th><th>Non-PK-Guided</th><th>Full Sample</th></tr><tr><td>Total patients, N</td><td>128</td><td>153</td><td>47</td><td>73</td><td>281</td></tr><tr><td>Age, years</td><td></td><td></td><td></td><td></td><td></td></tr></table>	Parameter	Secondary Prophylaxis	Primary Prophylaxis	PK-Guided	Non-PK-Guided	Full Sample	Total patients, N	128	153	47	73	281	Age, years						- France, Germany, Italy, Spain, UK, Denmark, the Netherlands and Romania; perspective NR - Currency NR, Cost	- Data were analysed from the CHESS II study: a retrospective cross-sectional burden of illness study of European male adults with non-acquired haemophilia A or B of any severity - Patient data	The analysis was conducted on data from patients across multiple European countries including the UK, and therefore is partly applicable to clinical practice in England
Parameter	Secondary Prophylaxis	Primary Prophylaxis	PK-Guided	Non-PK-Guided	Full Sample																	
Total patients, N	128	153	47	73	281																	
Age, years																						

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Study	Objective and patient population						Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis	
		Mean (SD)	38.3 (14.4)	33.5 (12.9)	38.4 (15.9)	35.3 (14.0)	35.7 (13.8)	year NR	were collected from two questionnaires: a physician-completed, web-based clinical record form and a corresponding paper-based patient self-completion questionnaire	People with SHA without inhibitors receiving prophylaxis were included, which is in line with the decision problem
		Median (range)	38 (19–79)	29 (18–77)	32 (18–79)	29 (19–75)	32 (18–79)			
		Body mass index, kg/m ² , mean (SD)	24.9 (2.7)	24.5 (2.9)	24.8 (2.3)	24.1 (2.6)	24.7 (2.8)			
		Weight, kg, mean (SD)	74.2 (9.3)	75.9 (10.1)	75.6 (9.2)	73.3 (9.7)	75.1 (9.8)			
		Physician targeting a specific FVIII trough level for the patient, n (%)								
	Yes	61 (47.7)	59 (38.6)	47 (100)	0	120 (42.7)				
	No	67 (52.3)	94 (61.4)	0	73 (100)	161 (57.3)				
		Dosage guided by PK profiling, n (%)								
	Yes	17 (27.9)	30 (50.8)	47 (100)	0	47 (39.2)				
	No	44 (72.1)	29 (49.1)	0	73 (100)	73 (60.8)				
		Treatment type, n (%)								
	EHL	21 (16.4)	36 (23.5)	13 (27.7)	13 (17.8)	57 (20.3)				
	SHL	107 (83.6)	117 (76.5)	34 (72.3)	60 (82.2)	224 (79.7)				
Mancuso 2024 (CHESS)	- To quantify haemophilia-related costs, by disease severity, encompassing direct medical costs (e.g. treatment costs, hospital visits) and direct non-medical costs (e.g. health aids/devices, travel costs) - CHESS was a 12-month retrospective, cross-sectional study with questions						Multinational perspective (including UK)	Data were analysed from CHESS, a retrospective cross-sectional burden of illness study of	The study analysed data from the UK, alongside several other	

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Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis												
	covering physician-reported healthcare resource use burden Baseline characteristics: <table><tr><th>Characteristic</th><th>Severe (N=380)</th></tr><tr><td>Mean age, years (SD)</td><td>37.6 (14.7)</td></tr><tr><td>BMI, mean (SD)</td><td>24.7 (3.1)</td></tr><tr><td colspan="2">Subtype, N (%)</td></tr><tr><td>Haemophilia A</td><td>315 (82.9)</td></tr><tr><td>Haemophilia B</td><td>65 (17.1)</td></tr></table>	Characteristic	Severe (N=380)	Mean age, years (SD)	37.6 (14.7)	BMI, mean (SD)	24.7 (3.1)	Subtype, N (%)		Haemophilia A	315 (82.9)	Haemophilia B	65 (17.1)	EUR, cost year 2022	European male adults (≥18 years) with mild, moderate or severe haemophilia A or B. Data were collected Italy, France, Germany, Spain and the UK Cost components were estimated based on reported quantities and unit costs sourced from literature: - Per-patient direct medical cost, based on physician-reported quantities - Direct non-medical costs - Indirect costs associated with the impact of disease and current treatments on work and	European countries, and therefore has some applicability to clinical practice in England People with SHA were included, which is in line with the decision problem
Characteristic	Severe (N=380)															
Mean age, years (SD)	37.6 (14.7)															
BMI, mean (SD)	24.7 (3.1)															
Subtype, N (%)																
Haemophilia A	315 (82.9)															
Haemophilia B	65 (17.1)															

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Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis
			activities • Total costs (per patient) were quantified by summing the costs across components • Population cost was extrapolated by multiplying the mean treatment cost & other direct medical costs by prevalence estimates from the 2021 World Federation of Hemophilia Annual Global Survey	
NICE 2023	• For the economic evaluation of etranacogene dezaparvovec for patients with moderately severe and severe haemophilia B • Patient data came from the phase 3 HOPE-B trial, which included adult males ≥18 years old, with severe or moderately-severe haemophilia B on continuous routine Factor IX prophylaxis and no history of Factor IX inhibitors	• UK, NHS/PSS perspective • GBP, Cost year NR	• The study methodology involved a Markov transition state model	The model used in the study was conducted from a UK and NHS perspective, and is therefore applicable to

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Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis																																			
			Health-state cost and resource use data were obtained from published sources NHS cost reference 2019/20, previous NICE submissions and expert opinion	clinical practice in England																																			
O'Hara 2017 (CHESS) Supplementary sources: O'Hara 2018	- To capture the annualised economic and psychosocial burden of severe haemophilia in the five largest European economies - Adult patients (18 years and over) with severe inherited haemophilia A or B, regardless of prior treatment status or history of inhibitors Demographic data: <table><tr><th></th><th>France N=272</th><th>Germany N=194</th><th>Italy N=280</th><th>Spain N=218</th><th>UK N=321</th><th>CHESS N=1,285</th></tr><tr><td>PSCs received, n (%)</td><td>199 (73)</td><td>97 (50)</td><td>123 (44)</td><td>96 (44)</td><td>37 (12)</td><td>552 (43)</td></tr><tr><td colspan="7">Haemophilia subtype, n (%)</td></tr><tr><td>A</td><td>202 (74)</td><td>153 (79)</td><td>219 (78)</td><td>176 (81)</td><td>246 (77)</td><td>996 (78)</td></tr><tr><td>B</td><td>70 (26)</td><td>41 (21)</td><td>61 (22)</td><td>42 (19)</td><td>75 (23)</td><td>289 (22)</td></tr></table>		France N=272	Germany N=194	Italy N=280	Spain N=218	UK N=321	CHESS N=1,285	PSCs received, n (%)	199 (73)	97 (50)	123 (44)	96 (44)	37 (12)	552 (43)	Haemophilia subtype, n (%)							A	202 (74)	153 (79)	219 (78)	176 (81)	246 (77)	996 (78)	B	70 (26)	41 (21)	61 (22)	42 (19)	75 (23)	289 (22)	- France, Germany, Italy, Spain and the UK; perspective NR - EUR, 2014	- Data were from the CHESS study in which data were collected via two questionnaires for specialists and patients across France, Germany, Italy, Spain and the UK - Data were collected between December 2014	The analysis was conducted on data from patients across multiple European countries including the UK, and therefore is partly applicable to clinical practice in England The population considered is also applicable
	France N=272	Germany N=194	Italy N=280	Spain N=218	UK N=321	CHESS N=1,285																																	
PSCs received, n (%)	199 (73)	97 (50)	123 (44)	96 (44)	37 (12)	552 (43)																																	
Haemophilia subtype, n (%)																																							
A	202 (74)	153 (79)	219 (78)	176 (81)	246 (77)	996 (78)																																	
B	70 (26)	41 (21)	61 (22)	42 (19)	75 (23)	289 (22)																																	

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Objective and patient population							Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis
	Age, years, mean (SD)	36.3 (13.7)	31.1 (12.0)	38.9 (15.5)	36.0 (14.1)	36.0 (15.9)	35.9 (14.7)		and April 2015 and included clinical economic and demographic information, as well as indirect and direct non-medical resource use	to the decision problem for this submission
	Treatment strategy: Prophylaxis, n (%)	159 (58)	117 (60)	143 (51)	143 (66)	175 (55)	737 (57)			
	Inhibitor history, n (%)									
	Never	225 (83)	165 (85)	233 (83)	179 (82)	289 (90)	1,091 (85)			
	Previously	29 (11)	25 (13)	38 (14)	27 (12)	17 (5)	136 (11)			
	Currently	18 (7)	4 (2)	9 (3)	12 (6)	15 (5)	58 (5)			
	Patients with coinfection, n (%)									
	HIV	2 (1)	4 (2)	4 (1)	9 (4)	19 (6)	38 (3)			
	HCV	7 (3)	5 (3)	22 (8)	15 (7)	21 (7)	70 (5)		- Data were collected by means of two questionnaires: the web-based case record forms and the paper patient self-completion form - Costs associated with temporary and long-term work absence (including early retirement) were valued using the	

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis
			traditional human capital approach - Patients who reported early retirement due to haemophilia, or who reported that they were unable to work due to haemophilia in the 3 months prior to responding, were costed at the average annual salary - Per-patient costs were calculated by multiplying the quantities of the resource used with the national unit price of each resource. To extrapolate the sample costs to	

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis
			country population level, the per-patient costs were multiplied by national prevalence weights	
Rodriguez-Santana 2022 (CHESS-PAEDS)	- To quantify the differential direct medical and societal costs, of moderate in relation to severe disease paediatric patients with haemophilia A or B without inhibitors - Patient data came from the 'Cost of Haemophilia across Europe: a Socioeconomic Survey in a Paediatric Population' (CHESS-PAEDs) study	- Germany, Spain, France, Italy and the UK - EUR, Cost year 2018	- Data were obtained from the CHESS PAEDs study - The physicians completed a web-based form that was based on the participant's medical history and consultations from their medical records. Caregivers completed questionnaires related to non-medical haemophilia-related direct costs and	The model was conducted across EU4 countries and the UK, so partially relevant data to clinical practice in England The population included was relevant to the decision problem for this submission

Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis
			indirect costs - Societal costs were defined as the sum of all direct medical, non-medical, and work productivity costs - All costs were captured at the patient level and covered a 12-month period	
Rodriguez-Santana 2022 (CHESS II)	- To quantify the differential direct and societal costs and patient-reported HRQoL of mild in relation to moderate or severe disease - Patient data for adults with haemophilia A or B without inhibitors came from the 'Cost of Haemophilia in Europe: a socioeconomic Survey' (CHESS II) data set	- Germany, Spain, France, Italy, the UK and Romania - EUR, Cost year 2020	- Data were obtained from the CHESS II study - The study consisted of two questionnaires collecting information from patients and their haemophilia healthcare providers. The treating physician completed a	The model was conducted across EU4 countries, the UK and Romania so partially relevant data to clinical practice in England The population of this study is relevant to the decision problem for this submission

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Objective and patient population	Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis						
			web-based patient record form. Patients completed a paper-based questionnaire - Societal costs were defined as the sum of all of direct medical, non-direct medical and indirect costs - Costs were calculated for each country, applying country-specific unit costs for each type of haemophilia-related resource use							
Thakkar 2023	- To describe hospitalisations, surgeries and consultations for patients with haemophilia A and B to better understand HCRU based on disease severity - Male, haemophilia A and B patients Baseline characteristics: <table><tr><th>Characteristic</th><th>Haemophilia A N=1116</th><th>Haemophilia B N=276</th></tr><tr><td></td><td></td><td></td></tr></table>	Characteristic	Haemophilia A N=1116	Haemophilia B N=276				- France, Germany, Italy, Spain, the UK and US, perspective NR - Currency	Data from Adelphi Haemophilia Disease Specific Programme™, a real-world, cross-sectional survey of	The survey was completed by patients across multiple countries, including the UK, and therefore is
Characteristic	Haemophilia A N=1116	Haemophilia B N=276								

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Objective and patient population				Country, cost year and perspective	Valuation methods	Applicability to clinical practice in England and for cost-effectiveness analysis
	Severe haemophilia, n	454	90		NR, Cost year NR	haematologists and their male haemophilia patients conducted February 2020–May 2021	applicable to clinical practice in England The study included people with SHA or haemophilia B, who had received haemophilia treatment
	Mean age, years	28.9	30.1				
	Mean BMI	24.0	23.7				

Abbreviations: BMI: body mass index; CHES: Cost of Haemophilia in Europe: A Socioeconomic Survey; CHES-PAEDs: Cost of Haemophilia across Europe: a Socioeconomic Survey in a Paediatric Population; CRU: cost and resource use; EHL: extended half-life; ER: emergency room; EUR: Euro; EU4: European 4; FIX: Factor IX; FVIII: factor VIII; GBP: Great British Pounds; HA: haemophilia A; HB: haemophilia B; HCV: hepatitis C virus; HCRU: healthcare resource utilisation; HIV: human immunodeficiency virus; HRQoL: health-related quality of life; mHJHS: modified Haemophilia Joint Health Score; N: number; NHS: National Health Service; NR: not reported; PSC: patient self-completion form; PSS: Personal Social Services; PJ: problem joints; PK: pharmacokinetic; QoL: quality of life; rFVIII-Fc: recombinant factor VIII Fc fusion protein; SD: standard deviation; SHA: severe haemophilia A; SHL: short half-life; SLR: systematic literature review; UK: United Kingdom; US: United States.

Table 89. Summary of the results of HCRU studies included in the economic SLR

Study	Cost and resource use data presented	Study conclusion																
Batt 2022	Patients with available HCRU at A-LONG baseline (n=101) with: • ≥1 healthcare service: 79.2% (n=80) • ≥1 physician appointment: 76.2% • ≥1 ER visit: 11.8% • ≥1 hospitalisation: 9.9% Model-estimated healthcare visits per year (n=106; mean [95% CI]): • At A-LONG baseline: 7.7 (5.0–11.7) • At 72 months: 1.7 (0.8–3.4) Healthcare visits reduced due to significant reductions from baseline in physician (p=0.002) and ER visits (p<0.001) at 72 months People with haemophilia A who began treatment with individualised prophylaxis had fewer HCRU events than those with weekly dosing or on-demand treatment, but this was non-significant (p=0.674). People with haemophilia A with target joints at baseline had more HCRU than those without (p=0.029)	In people with haemophilia A on rFVIII Fc therapy, improvements in joint health over time, as evidenced by mHJHS scores, is associated with reductions in HCRU events																
Burke 2021 (CHESS II)	Mean annual FIX treatment consumption and direct medical costs: <table><tr><th></th><th>SHL patients (n=42)</th><th>EHL patients (n=33)</th><th>All patients (n=75)</th></tr><tr><td>Mean annual factor IX consumption (IU) (SD)</td><td>286,969 (153,211)</td><td>191,983 (115,180)</td><td>245,175 (144,903)</td></tr><tr><td>Mean annual factor IX cost per patient (EUR) (SD)</td><td>186,528 (116,403)</td><td>290,620 (176,665)</td><td>232,328 (153,979)</td></tr><tr><td>Mean annual total direct medical cost per patient (EUR) (SD)</td><td>190,247</td><td>293,601</td><td>235,273 (154,953)</td></tr></table> FIX treatment utilisation by country:		SHL patients (n=42)	EHL patients (n=33)	All patients (n=75)	Mean annual factor IX consumption (IU) (SD)	286,969 (153,211)	191,983 (115,180)	245,175 (144,903)	Mean annual factor IX cost per patient (EUR) (SD)	186,528 (116,403)	290,620 (176,665)	232,328 (153,979)	Mean annual total direct medical cost per patient (EUR) (SD)	190,247	293,601	235,273 (154,953)	Indirect costs from early retirement/work stoppage and reduced work productivity for both patients and their caregivers were substantial. The direct costs associated with SHB were substantial, driven almost entirely by FIX treatment. Overall, the study demonstrated a substantial clinical, humanistic economic burden of SHB
	SHL patients (n=42)	EHL patients (n=33)	All patients (n=75)															
Mean annual factor IX consumption (IU) (SD)	286,969 (153,211)	191,983 (115,180)	245,175 (144,903)															
Mean annual factor IX cost per patient (EUR) (SD)	186,528 (116,403)	290,620 (176,665)	232,328 (153,979)															
Mean annual total direct medical cost per patient (EUR) (SD)	190,247	293,601	235,273 (154,953)															

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Study	Cost and resource use data presented			Study conclusion	
	Country	SHL (%)	EHL (%)		
	Germany (n=10)	30	70		
	France (n=11)	36	64		
	Spain (n=15)	60	40		
	Italy (n=17)	65	35		
	UK (n=22)	68	32		
	All patients (n=75)	56	44		
	Mean annual FIX treatment cost by country:				
	Country	Cost (EUR)			
	Germany	393,263			
	France	198,352			
	Spain	186,307			
	Italy	265,100			
	UK	182,219			
	All patients	232,328			
	Mean annual indirect costs:				
		SHL patients (n=25)	EHL patients (n=15)		All patients (n=40)
	Total indirect costs (SD)	€11,907	€4,083		€8,973 (15,398)
	Germany	—	—		€2,447
	Spain	—	—		€16,001
	France	—	—		€36,809

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Study	Cost and resource use data presented				Study conclusion
	Italy	–	–	€4,340	
	UK	–	–	€3,552	
	Early retirement/work stoppage	€7,515	€1,846	€5,389	
	Germany	–	–	€2,447	
	Spain	–	–	€16,001	
	France	–	–	€36,809	
	Italy	–	–	€4,340	
	UK	–	–	€3,552	
	Patient lost productivity	€1,619	€1,158	€1,446	
	Germany	–	–	€2,447	
	Spain	–	–	€426	
	France	–	–	€0	
	Italy	–	–	€654	
	UK	–	–	€3,552	
	Caregiver lost productivity	€2,773	€1,079	€2,138	
	Germany	–	–	€0	
	Spain	–	–	€6,345	
	France	–	–	€0	
	Italy	–	–	€851	
	UK	–	–	€0	
Chowdary 2024 (CHESS II and CHESS PAEDS)	Resource use by PJs, n (%):				- Increasing medical costs with number of PJs underscore the need for effective joint health management through childhood, adolescence and adulthood - The analyses highlight the unmet physical, mental, social, and economic needs faced by
		Severe HA			
	Treatment type	0 PJ	1 PJ	≥2 PJs	
	CHESS-II				

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Study	Cost and resource use data presented						Study conclusion
Supplementary sources: Chowdary 2023	Prophylactic treatment, n (%)	79 (53.7)	41 (56.2)	37 (63.8)			people with HA in Europe. Problem joints were prevalent; this may highlight the suboptimal administration of prophylactic treatment. These observations may reflect the need for improved prophylactic treatment options and optimal administration of such treatments
	CHESS-PAEDS						
	Prophylactic treatment, n (%)	279 (79.7)	44 (84.6)	12 (85.7)			
	Resource use by Treatment Modality, n (%):						
	Treatment type	Severe HA					
	CHESS-II	Prophylaxis (n=157)		Other (n=121)			
	EHL FVIII	24 (15.3)		18 (14.9)			
	SHL or plasma-derived FVIII	129 (82.2)		102 (84.3)			
	No FVIII administered in prior 12 months	0 (0)		0 (0)			
	Unknown	4 (2.5)		1 (0.8)			
N.B. CHESS-PAEDS treatment types in Chowdary 2023 were grouped for moderate and SHA, so have not been extracted here.							
Costs by PJs:							
	Mean Annual Cost per Patient (€)						
Study population	Direct Medical Costs Excluding Treatment			Direct Non-Medical Costs			
	0 PJs	1 PJ	≥2 PJs	0 PJ	1 PJ	≥2 PJs	

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Study	Cost and resource use data presented							Study conclusion
	CHESS-II (N=136 with SHA)	3,749	8,735	9,467	1,152	1,702	4,925	
	CHESS-PAEDS (N=128 with SHA)	3,380	8,326	12,201	304	2,851	1,838	
	Costs by Treatment Modality:							
			Mean Annual Cost per Patient (€)					
	Study population		Direct Costs		Total Cost			
			Prophylaxis (n=157)	Other (n=121)	Prophylaxis (n=82)	Other (n=54)		
	CHESS-II (N=278 with SHA)	Mean (SD)	266,568 (204,870)	89,893 (143,376)	295,630 (216,231)	117,147 (188,619)		
		Median (IQR)	226,910 (313,460)	36,408 (68,481)	254,866 (311,266)	54,455 (62,799)		
			Prophylaxis (n=335)	Other (n=81)	Prophylaxis (n=100)	Other (n=28)		
	CHESS- PAEDS (N=416 with SHA)	Mean (SD)	113,373 (112,214)	15,847 (34,233)	99,634 (97,826)	32,206 (56,255)		
		Median (IQR)	77,780 (123,471)	10,114 (11,010)	70,551 (120,394)	17,228 (17,148)		
Ferri Grazzi 2022 (CHESS II)	Resource Use:							Primary prophylaxis and PK-guided prophylaxis seem to be associated with a reduced need for specialist consultations
		Treatment Strategy (N=281)		Targeting FVIII Trough Level (N=120)				
		Secondary Prophylaxis ^a (n=128)	Primary Prophylaxis ^b (n=153)	PK-Guided (n=47)	Non-PK- Guided (n=73)			

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Study	Cost and resource use data presented					Study conclusion							
	Number of haematologist consultations, mean (SD)	8.0 (5.3)	7.8 (5.6)	7.1 (5.3)	10.7 (5.7)								
	Number of scheduled haematologist consultations, mean (SD)	6.2 (4.0)	6.1 (3.9)	5.2 (3.0)	8.4 (4.2)								
	Number of unscheduled haematologist consultations, mean (SD)	1.8 (2.1)	1.8 (3.2)	1.9 (4.4)	2.3 (2.5)								
	Number of nurse consultations, mean (SD)	7.9 (9.5)	6.5 (6.1)	5.2 (4.2)	10.3 (11.7)								
	Number of scheduled nurse consultations, mean (SD)	5.9 (7.6)	5.1 (5.0)	4.0 (3.3)	8.0 (9.4)								
	Number of unscheduled nurse consultations, mean (SD)	2.0 (2.8)	1.5 (2.3)	1.2 (1.7)	2.3 (3.2)								
	^aSecondary prophylaxis was defined as treatment that was previously on demand but is currently prophylactic. ^bPrimary prophylaxis was defined as treatment that has always been prophylactic Bleed-related hospitalisations: <table><tr><td rowspan="2"></td><td colspan="2">Treatment Strategy (N=281)</td><td colspan="2">Targeting FVIII Trough Level (N=120)</td></tr><tr><td>Secondary Prophylaxis^b (n=128)</td><td>Primary Prophylaxis^c (n=153)</td><td>PK-Guided (n=47)</td><td>Non-PK-Guided (n=73)</td></tr></table>							Treatment Strategy (N=281)		Targeting FVIII Trough Level (N=120)		Secondary Prophylaxis ^b (n=128)	Primary Prophylaxis ^c (n=153)
	Treatment Strategy (N=281)		Targeting FVIII Trough Level (N=120)										
	Secondary Prophylaxis ^b (n=128)	Primary Prophylaxis ^c (n=153)	PK-Guided (n=47)	Non-PK-Guided (n=73)									

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Study	Cost and resource use data presented						Study conclusion						
	Patients requiring hospitalisation during their lifetime, n (%)	107 (83.6)	132 (86.3)	38 (80.9)	66 (90.4)								
	Patients requiring hospitalisation in the 12 months prior to data collection, n (%)	67 (62.6)	114 (86.4)	33 (86.8)	44 (66.7)								
	Hospitalisations occurring in the 12 months prior to data collection, mean (SD)												
	Number of ward hospitalisations	0.5 (0.9)	0.5 (0.9)	0.4 (0.8)	0.6 (1.0)								
	Number of days on ward	5.7 (4.2) (n=51)	6.9 (5.1) (n=44)	8.4 (6.9) (n=14)	5.7 (4.1) (n=27)								
	Number of day cases ^a	0.1 (0.3)	0.1 (0.6)	0.1 (0.4)	0.1 (0.3)								
	Number of day-case days	1.0 (0.0) (n=9)	2.3 (1.5) (n=8)	1.5 (0.6) (n=4)	1.3 (0.6) (n=3)								
	Number of ICU hospitalisations	0.1 (0.3)	0.1 (0.3)	0.1 (0.2)	0.6 (1.0)								
	Number of days in ICU	2.7 (1.3) (n=12)	2.3 (1.1) (n=7)	1.7 (1.2) (n=3)	1.5 (0.6) (n=4)								
	^a A day case was defined as a patient who visited hospital but did not stay overnight. ^b Secondary prophylaxis was defined as treatment that was previously on demand but is currently prophylactic. ^c Primary prophylaxis was defined as treatment that has always been prophylactic												
Mancuso 2024 (CHESS)	Costs for Patients with Severe Haemophilia: <table><tr><th>Cost Component</th><th>Mean (SD) Cost per Patient (€)</th></tr><tr><td>Treatment cost (N=380)</td><td>379,826 (298,632)</td></tr><tr><td>Non-treatment costs (N=106)</td><td></td></tr></table>						Cost Component	Mean (SD) Cost per Patient (€)	Treatment cost (N=380)	379,826 (298,632)	Non-treatment costs (N=106)		The findings demonstrate the significant clinical and financial burden of haemophilia in Europe
Cost Component	Mean (SD) Cost per Patient (€)												
Treatment cost (N=380)	379,826 (298,632)												
Non-treatment costs (N=106)													

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Study	Cost and resource use data presented				Study conclusion
	Direct medical costs		3,219 (4,433)		
	Direct non-medical costs		1,561 (2,554)		
	Total Cost		11,603 (17,284)		
	Non-Treatment Population Costs:				
	Cost Component		Non-Treatment Population Costs (€m)		
	Direct medical costs		31.9		
	Direct non-medical costs		15.2		
	Total Cost		114.6		
NICE 2023	Etranacogene dezaparvovec:				Etranacogene dezaparvovec was found to be cost-effective compared to all the comparators considered in the decision problem
Drug		Pack unit size (quantity)	Treatment dose	Treatment cost (List price)	
Etranacogene dezaparvovec		1	2 × 10 ¹³ GC/kg body weight	£2,600,000	
Healthcare resource use per cycle per health state:					
Health state		Items	Values		
Health state 1: No bleeds		Total	£0		
Health state 2: non-joint bleeds		Disease/bleed management costs per cycle	Alprolix: £26.54 BeneFix: £26.54 Idelvion: £26.54 Refixia: £26.54		

Study	Cost and resource use data presented			Study conclusion
		Cost of Factor IX treatment per non-joint bleed	Alprolix: £5,616.60 BeneFix: £2,066.91 Idelvion: £7,336.68 Refixia: £8,247.89	
		Administrative costs per bleed for non-joint bleed	Alprolix: £10.62 BeneFix: £4.41 Idelvion: £10.79 Refixia: £11.56	
		Total cost of health state 2 by comparator	Alprolix: £5,653.76 BeneFix: £2,097.86 Idelvion: £7,374.01 Refixia: £8,285.99	
	Health states 3: joint bleeds	Disease/bleed management costs per cycle	Alprolix: £26.54 BeneFix: £26.54 Idelvion: £26.54 Refixia: £26.54	
		Cost of Factor IX treatment per joint bleed	Alprolix: £5,616.60 BeneFix: £2,066.91 Idelvion: £7,336.68 Refixia: £8,247.86	
		Administrative costs per bleed for joint bleed	Alprolix: £10.62 BeneFix: £4.41 Idelvion: £10.79 Refixia: £11.56	
		Total cost of health state 3 by comparator	Alprolix: £5,653.76 BeneFix: £2,097.86 Idelvion: £7,374.01 Refixia: £8,285.99	
	Health state 4: death	Total	£0	

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Study	Cost and resource use data presented					Study conclusion
	Estimates of workdays lost due to bleeding:					
		Full-time (non-joint bleeds)	Full-time (joint bleeds)	Part-time (non-joint bleeds)	Part-time (joint bleeds)	
	Average workdays per week	5	5	2	2	
	Average workdays lost due to bleed per week	1.43	2.86	0.57	1.28	
	Percentage of the workdays lost per week	28.57%	57.14%	28.57%	64.29%	
	Resource		Resource use per year		Total cost per year (£)	
	Joint scans		0.5		198.23	
	Haematologist visit		6		1,949.84	
	Orthopaedist visit		1.5		188.51	
	Psychologist/psychiatrist visit		6		1,112.27	
	Physiotherapist		12		750.83	
	Abdominal ultrasound		1		397.47	
	Dental check-up		2		394	
	Nurse visit		18		705.07	
	Lab screening		2		85.91	
	Total		-		5,781.13	

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Cost and resource use data presented	Study conclusion																																
O'Hara 2017 (CHESS) Supplementary sources: O'Hara 2018	Total economic burden of severe haemophilia: <table><tr><th>Country</th><th>Total cost per country (EUR)</th><th>Total per-patient cost (EUR)</th><th>Percent of total healthcare expenditures in each country (%)</th></tr><tr><td>France</td><td>211,414,126</td><td>196,117</td><td>0.06</td></tr><tr><td>Germany</td><td>700,257,680</td><td>319,024</td><td>0.16</td></tr><tr><td>Italy</td><td>269,701,056</td><td>220,344</td><td>0.12</td></tr><tr><td>Spain</td><td>94,010,111</td><td>173,771</td><td>0.05</td></tr><tr><td>UK</td><td>271,278,405</td><td>129,365</td><td>0.10</td></tr><tr><td>All</td><td>1,423,725,035</td><td>199,541</td><td>—</td></tr></table>	Country	Total cost per country (EUR)	Total per-patient cost (EUR)	Percent of total healthcare expenditures in each country (%)	France	211,414,126	196,117	0.06	Germany	700,257,680	319,024	0.16	Italy	269,701,056	220,344	0.12	Spain	94,010,111	173,771	0.05	UK	271,278,405	129,365	0.10	All	1,423,725,035	199,541	—	The results of the CHESS study reflect previous research findings suggesting that the cost of CFRT accounts for the vast majority of the cost burden in severe haemophilia. While non drug-related direct medical costs in severe haemophilia are small in relation to the costs of replacement therapy, the analysis demonstrates that the majority of individuals with this disease experience medical complications requiring substantial follow-up in the hospital setting. Further, the presence of one or more target joint can have a major impact on medical resource utilisation and subsequent costs for patients with severe haemophilia				
	Country	Total cost per country (EUR)	Total per-patient cost (EUR)	Percent of total healthcare expenditures in each country (%)																														
	France	211,414,126	196,117	0.06																														
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	All	1,423,725,035	199,541	—																														
	Per-patient costs: <table><tr><th></th><th colspan="3">Per patient costs per year (EUR)</th></tr><tr><th>Country</th><th>CFRT</th><th>Other direct medical costs</th><th>Indirect costs</th></tr><tr><td>France</td><td>187,983</td><td>3,284</td><td>4,850</td></tr><tr><td>Germany</td><td>312,157</td><td>1,894</td><td>4,973</td></tr><tr><td>Italy</td><td>212,385</td><td>1,946</td><td>6,013</td></tr><tr><td>Spain</td><td>157,288</td><td>7,832</td><td>8,651</td></tr><tr><td>UK</td><td>117,709</td><td>5,949</td><td>5,707</td></tr><tr><td>All</td><td>189,285</td><td>4,181</td><td>6,075</td></tr></table>		Per patient costs per year (EUR)			Country	CFRT	Other direct medical costs	Indirect costs	France	187,983	3,284	4,850	Germany	312,157	1,894	4,973	Italy	212,385	1,946	6,013	Spain	157,288	7,832	8,651	UK	117,709	5,949	5,707		All	189,285	4,181	6,075
		Per patient costs per year (EUR)																																
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All	189,285	4,181	6,075																															
Resource use: <table><tr><th></th><th>No target joint (n=508)</th><th>1+ target joints (n=714)</th></tr><tr><td colspan="3">Outpatient haematologist consultations</td></tr><tr><td>Scheduled</td><td>4.71</td><td>5.48</td></tr></table>		No target joint (n=508)	1+ target joints (n=714)	Outpatient haematologist consultations			Scheduled	4.71	5.48																									
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Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Cost and resource use data presented			Study conclusion
	Unscheduled	1.15	1.84	
	Outpatient specialist nurse consultations			
	Scheduled	3.95	5.75	
	Unscheduled	1.13	1.93	
	Outpatient consultations – other specialties			
	General practice	1.35	1.91	
	General surgery	0.08	0.21	
	Pain management	0.11	0.68	
	Physiotherapy	0.89	3.14	
	Tests and examinations			
	Urinalysis	1.07	1.85	
	X-ray	0.61	1.24	
	Computed tomography	0.25	0.48	
	Magnetic resonance imaging	0.25	0.52	
	Radiography	0.36	1.05	
	Ultrasonography	0.41	1.00	
	Coagulation tests	1.82	3.11	
	Target joint surgeries	NA	0.70	
	Bleed event-related hospital admissions	0.36	0.97	
	Non drug-related direct costs:			
	Type and number of target joints		NDDC, mean (SD), EUR	
	No target joints		1,684 (NR)	
	≥1 target joint		5,046 (7,479)	

Company evidence submission template for marstacimab for the treatment of severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Study	Cost and resource use data presented			Study conclusion											
	Number of target joints														
	1	3,468 (5,595)													
	2	5,585 (7,980)													
	3	7,470 (9,396)													
	Location of ≥1 target joint														
	Upper body	5,610 (7,861)													
	Lower body	5,186 (7,594)													
	Both upper and lower body	6,696 (8,461)													
	Rodriguez-Santana 2022 (CHESS-PAEDS)	Data referring to direct costs* was available for 462 severe haemophilia patients; of that population, 162 patients had societal costs reported			Children with haemophilia and their caregivers displayed a significant economic burden; severe patients showed the highest direct medical and societal costs										
<table><tr><th>Severe Haemophilia</th><th>Direct costs Sample, n (%)</th><th>Societal costs Samples, n (%)</th></tr><tr><td>No treatment</td><td>1 (0.2)</td><td>0</td></tr><tr><td>On-demand</td><td>47 (10)</td><td>17 (10)</td></tr><tr><td>Prophylaxis</td><td>415 (90)</td><td>145 (90)</td></tr></table>			Severe Haemophilia	Direct costs Sample, n (%)		Societal costs Samples, n (%)	No treatment	1 (0.2)	0	On-demand	47 (10)	17 (10)	Prophylaxis	415 (90)	145 (90)
Severe Haemophilia	Direct costs Sample, n (%)	Societal costs Samples, n (%)													
No treatment	1 (0.2)	0													
On-demand	47 (10)	17 (10)													
Prophylaxis	415 (90)	145 (90)													
<table><tr><th>Severe Haemophilia</th><th>Mean costs over previous 12 months</th><th>Predicted mean annual costs</th></tr><tr><td>Direct costs (n=462)</td><td>€2,957</td><td>€3,065</td></tr><tr><td>Societal costs (n=162)</td><td>€6,376</td><td>€6,950</td></tr></table>			Severe Haemophilia	Mean costs over previous 12 months		Predicted mean annual costs	Direct costs (n=462)	€2,957	€3,065	Societal costs (n=162)	€6,376	€6,950			
Severe Haemophilia	Mean costs over previous 12 months	Predicted mean annual costs													
Direct costs (n=462)	€2,957	€3,065													
Societal costs (n=162)	€6,376	€6,950													
Summary of costs by treatment group:															
<table><tr><th>Severe Haemophilia</th><th>Direct costs, mean (SD)</th><th>Societal costs, mean (SD)</th></tr><tr><td>No treatment</td><td>—</td><td>—</td></tr><tr><td>On-demand</td><td>€3,518 (3,940)</td><td>€8,066 (10,736)</td></tr><tr><td>Prophylaxis</td><td>€2,821 (3,494)</td><td>€5,840 (8,562)</td></tr></table>			Severe Haemophilia	Direct costs, mean (SD)		Societal costs, mean (SD)	No treatment	—	—	On-demand	€3,518 (3,940)	€8,066 (10,736)	Prophylaxis	€2,821 (3,494)	€5,840 (8,562)
Severe Haemophilia	Direct costs, mean (SD)	Societal costs, mean (SD)													
No treatment	—	—													
On-demand	€3,518 (3,940)	€8,066 (10,736)													
Prophylaxis	€2,821 (3,494)	€5,840 (8,562)													
*excluding costs of factor replacement therapy															

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Study	Cost and resource use data presented	Study conclusion																																	
Rodriguez-Santana 2022 (CHES II)	Data referring to direct costs* was available for 333 severe haemophilia patients; of that population, 155 patients had societal costs reported <table> <tr> <th>Severe Haemophilia</th><th>Direct costs Sample, n (%)</th><th>Societal costs Samples, n (%)</th></tr> <tr> <td>No treatment</td><td>0</td><td>0</td></tr> <tr> <td>On-demand</td><td>55 (17)</td><td>24 (15)</td></tr> <tr> <td>Prophylaxis</td><td>278 (83)</td><td>131 (85)</td></tr> </table> <table> <tr> <th>Severe Haemophilia</th><th>Descriptive mean costs over previous 12 months</th><th>Predicted mean annual costs</th></tr> <tr> <td>Direct costs</td><td>€4,125</td><td>€3,949</td></tr> <tr> <td>Societal costs</td><td>€15,655</td><td>€14,216</td></tr> </table> Summary of costs by treatment group: <table> <tr> <th>Severe Haemophilia</th><th>Direct costs, mean (SD)</th><th>Societal costs, mean (SD)</th></tr> <tr> <td>No treatment</td><td>–</td><td>–</td></tr> <tr> <td>On-demand</td><td>€5,443 (4,723)</td><td>€17,765 (19,127)</td></tr> <tr> <td>Prophylaxis</td><td>€3,864 (4,025)</td><td>€15,269 (19,420)</td></tr> </table> *excluding costs of factor replacement therapy	Severe Haemophilia	Direct costs Sample, n (%)	Societal costs Samples, n (%)	No treatment	0	0	On-demand	55 (17)	24 (15)	Prophylaxis	278 (83)	131 (85)	Severe Haemophilia	Descriptive mean costs over previous 12 months	Predicted mean annual costs	Direct costs	€4,125	€3,949	Societal costs	€15,655	€14,216	Severe Haemophilia	Direct costs, mean (SD)	Societal costs, mean (SD)	No treatment	–	–	On-demand	€5,443 (4,723)	€17,765 (19,127)	Prophylaxis	€3,864 (4,025)	€15,269 (19,420)	This study illustrates the humanistic and economic burden of increasing levels of disease severity among European adults with haemophilia A and B without inhibitors
Severe Haemophilia	Direct costs Sample, n (%)	Societal costs Samples, n (%)																																	
No treatment	0	0																																	
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Thakkar 2023	<table> <tr> <th></th><th>SHA</th><th>SHB</th></tr> <tr> <td>Patients with ≥1 hospitalisation in the year prior to survey</td><td>17.4%</td><td>23.2%</td></tr> <tr> <td>Mean consultations with healthcare professional per patient</td><td>15.2</td><td>9.7</td></tr> <tr> <td>Mean consultations with haemophilia nurse per patient</td><td>13.0</td><td>6.5</td></tr> <tr> <td>Mean consultations with physiotherapists per patient</td><td>11.0</td><td>9.5</td></tr> </table>		SHA	SHB	Patients with ≥1 hospitalisation in the year prior to survey	17.4%	23.2%	Mean consultations with healthcare professional per patient	15.2	9.7	Mean consultations with haemophilia nurse per patient	13.0	6.5	Mean consultations with physiotherapists per patient	11.0	9.5	Despite receiving treatment, SHA and SHB patients had high hospitalisation and consultation rates, highlighting increased HCRU and potentially greater economic burden with increased severity																		
	SHA	SHB																																	
Patients with ≥1 hospitalisation in the year prior to survey	17.4%	23.2%																																	
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Study	Cost and resource use data presented				Study conclusion
	Patients who underwent joint surgery	18.5%	18.9%		

Abbreviations: CFRT: clotting factor replacement therapy; CHES: Cost of Haemophilia in Europe: A Socioeconomic Survey; CI: confidence interval; CRU: cost and resource use; EHL: extended half-life; ER: emergency room; EUR: Euro; FIX: Factor IX; FVIII: factor VIII; GC: genome copies; HA: haemophilia A; HCRU: healthcare resource utilisation; ICU: Intensive Care Unit; IU: international units; kg: kilogram; m: million; mHJHS: modified Haemophilia Joint Health Score; NA: not applicable; NDDC: non drug-related direct costs; NR: not reported; PJ: problem joints; PK: pharmacokinetic; QoL: quality of life; rFVIII-Fc: recombinant factor VIII Fc fusion protein; SD: standard deviation; SHA: severe haemophilia A; SHL: short half-life; SLR: systematic literature review; UK: United Kingdom.

Appendix J Clinical outcomes and disaggregated results from the model

J.1 Mean total expected lifetime outcomes from the base case incremental cost-effectiveness analysis

Table 90: Mean total expected lifetime outcomes versus haemophilia A comparators, per patient (undiscounted and discounted)

	Marstacimab	FVIII prophylaxis basket	Incremental (versus FVIII prophylaxis)	Emicizumab	Incremental (versus emicizumab)
Lys					
Undiscounted	43.68	43.68	-	43.68	-
Discounted	21.52	21.52	-	21.52	-
QALYs					
Undiscounted					
Discounted					

Abbreviations: FVIII: factor VIII; LYs: life years; QALYs: quality-adjusted life years.

Table 91: Mean total expected lifetime outcomes versus FIX prophylaxis, per patient (undiscounted and discounted)

	Marstacimab	FIX prophylaxis basket	Incremental
Lys			
Undiscounted	43.68	43.68	-
Discounted	21.52	21.52	-
QALYs			
Undiscounted			
Discounted			

Abbreviations: FIX: factor IX; LYs: life years; QALYs: quality-adjusted life years.

J.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 92: Summary of QALY gain by health state, marstacimab versus haemophilia A comparators

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	% absolute increment
Marstacimab versus FVIII prophylaxis					
Health State					
No Bleeds					

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Bleeds	■	■	■	■	■
Utility Decrement					
Non-Joint Bleeds	■	■	■	■	■
Joint Bleeds	■	■	■	■	■
Treatment administration	■	■	■	■	■
Marstacimab versus emicizumab					
Health State					
No Bleeds	■	■	■	■	■
Bleeds	■	■	■	■	■
Utility Decrement					
Non-Joint Bleeds	■	■	■	■	■
Joint Bleeds	■	■	■	■	■
Treatment administration	■	■	■	■	■

Abbreviations: FVIII: factor VIII; QALYs: quality-adjusted life years.

Table 93: Summary of QALY gain by health state, marstacimab versus haemophilia B comparators (FIX prophylaxis)

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	% absolute increment
Health State					
No Bleeds	■	■	■	■	■
Bleeds	■	■	■	■	■
Utility Decrement					
Non-Joint Bleeds	■	■	■	■	■
Joint Bleeds	■	■	■	■	■
Treatment administration	■	■	■	■	■

Abbreviations: FIX: factor IX; QALY: quality-adjusted life year.

Table 94: Summary of predicted resource use by category of cost, marstacimab versus haemophilia A comparators

Item	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Marstacimab versus FVIII prophylaxis					
Drug acquisition	██████	██████	██████	██████	████
Acute bleed management	██████	██████	██████	██████	████
Other disease medical resource utilisation	████	████	████	████	████
Marstacimab versus emicizumab					
Drug acquisition	██████	██████	██████	██████	████
Acute bleed management	██████	██████	██████	██████	████
Other disease medical resource utilisation	████	████	████	████	████

Abbreviations: FVIII: factor VIII.

Table 95: Summary of predicted resource use by category of cost, marstacimab versus haemophilia B comparators (FIX prophylaxis)

Item	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Drug acquisition	██████	██████	██████	██████	████
Acute bleed management	██████	██████	██████	██████	████
Other disease medical resource utilisation	████	████	████	████	████

Abbreviations: FIX: factor IX.

Appendix K Price details of treatments included in the submission

K.1 Price of intervention

Table 96: Details of intervention costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per administration	Pack size	List price	Patient access scheme price	Source
Marstacimab maintenance dose	SC	150 mg	1	£■■■■	£■■■■	Pfizer Data on File
Marstacimab maintenance dose	SC	300 mg (2 x 150 mg)	2	£■■■■	£■■■■	Pfizer Data on File
Marstacimab loading dose	SC	300 mg (2 x 150 mg)	2	£■■■■	£■■■■	Pfizer Data on File

Abbreviations: mg: milligram; SC: subcutaneous.

K.2 Price of comparators and subsequent treatments

Table 97: Details of comparators and subsequent treatment costs, including concomitant medicines, for each formulation used in the model

Treatment	Units per pack	Cost per vial	Cost per unit	Source
Haemophilia A				
Advate®	250 IU	£177.50	£0.71	BNF (2024) ¹⁸
	500 IU	£355.00	£0.71	
	1,000 IU	£710.00	£0.71	
	2,000 IU	£1,420.00	£0.71	
Refacto AF®	250 IU	£125.55	£0.50	
	500 IU	£251.10	£0.50	
	1,000 IU	£502.20	£0.50	
	2,000 IU	£1,004.40	£0.50	
	3,000 IU	£1,506.60	£0.50	
NovoEight®	250 IU	£138.59	£0.55	
	500 IU	£277.18	£0.55	
	1,000 IU	£554.37	£0.55	
	1,500 IU	£831.55	£0.55	
	2,000 IU	£1,108.74	£0.55	
	3,000 IU	£1,663.11	£0.55	
Nuwiq®	250 IU	£190.00	£0.76	

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	500 IU	£380.00	£0.76	
	1,000 IU	£760.00	£0.76	
	1,500 IU	£1,140.00	£0.76	
	2,000 IU	£1,520.00	£0.76	
Esperoct®	500 IU	£425.00	£0.85	
	1,000 IU	£850.00	£0.85	
	1,500 IU	£1,275.00	£0.85	
	2,000 IU	£1,700.00	£0.85	
	3,000 IU	£2,550.00	£0.85	
Elocta®	250 IU	£212.50	£0.85	
	500 IU	£425.00	£0.85	
	750 IU	£637.50	£0.85	
	1,000 IU	£850.00	£0.85	
	1,500 IU	£1,275.00	£0.85	
	2,000 IU	£1,700.00	£0.85	
	3,000 IU	£2,550.00	£0.85	
Adynovi®	250 IU	£212.50	£0.85	
	1,000 IU	£850.00	£0.85	
	2,000 IU	£1,700.00	£0.85	
Hemlibra®	30 IU	£2,415.30	£80.51	
	60 IU	£4,830.60	£80.51	
	105 IU	£8,453.55	£80.51	
	150 IU	£12,076.50	£80.51	
Haemophilia B				
BeneFIX®	3,000 IU	£1,821.60	£0.61	BNF (2024) ¹⁸
	2,000 IU	£1,214.40	£0.61	
	1,000 IU	£607.20	£0.61	
	500 IU	£303.60	£0.61	
	250 IU	£151.80	£0.61	
Alprolix®	3,000 IU	£3,600.00	£1.20	MIMS (2024) ¹⁹
	2,000 IU	£2,400.00	£1.20	
	1,000 IU	£1,200.00	£1.20	
	500 IU	£600.00	£1.20	
	250 IU	£300.00	£1.20	
Idelvion®	2,000 IU	£4,180.00	£2.09	
	1,000 IU	£2,090.00	£2.09	
	500 IU	£1,045.00	£2.09	
	250 IU	£522.50	£2.09	
Refixia®	2,000 IU	£4,886.00	£2.44	
	1,000 IU	£2,443.00	£2.44	

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	500 IU	£1,221.50	£2.44	

Abbreviations: BNF: British National Formulary; IU: international units; MIMS: Monthly Index of Medical Specialities.

Appendix L Checklist of confidential information

The checklist of confidential information is provided in a separate document.

Appendix M Additional information from the marstacimab Phase 3 clinical trial programme: BASIS and its OLE

M.1 Additional methodological details

M.1.1. Eligibility criteria

The majority of eligibility criteria for BASIS are presented in Document B, Section B.2.3.1.1. Additional specific lab-based exclusion criteria are presented in Table 98 below. The eligibility criteria for the OLE were identical to that for the BASIS trial.

Table 98: Additional details of the BASIS trial eligibility criteria

Eligibility criteria	Additional exclusion criteria: - Abnormal renal or hepatic function as defined by the following laboratory results at screening: - Alanine transaminase (ALT) $>2 \times$ upper limit of normal (ULN) - Bilirubin $>1.5 \times$ ULN (isolated bilirubin $>1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $<35\%$) - Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C -eg, presence of hepatitis B surface antigen [HBsAg] or positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention) is acceptable if the participant otherwise meets entry criteria - Serum albumin less than the lower limit of normal (LLN). - Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² - Abnormal haematology values as defined by the following laboratory tests at screening: - Platelet count $<100,000/\mu\text{L}$ - Hemoglobin level <10 g/dL - QTcF >450 msec for male participants or QTcF >480 msec in participants with bundle branch block.

Abbreviations: ALT: alanine transaminase; eGFR: estimated glomerular filtration rate; g/dL: grams per decilitre; HBsAg; hepatitis B surface antigen; LNL: lower limit of normal; msec: millisecond; QTcF: QT interval; μL : microlitres; ULN: upper limit of normal.

Source: Pfizer marstacimab Phase 3 BASIS trial protocol, 2022.²⁰

M.1.2. OLE Baseline characteristics

A total of 88 patients entered the treatment phase. Subsequently, two discontinued due to participant withdrawal and one entered the follow-up phase. All 29 participants in the on-demand group were included in the safety analysis set while 58 of 59 participants in the prior prophylaxis group were included in the safety analysis set; one enrolled participant from the non-inhibitor prior prophylaxis cohort is not included in the safety analysis set because their data were not available by the 10 March 2023 interim data cutoff.

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Baseline characteristics for patients in the OLE treated with prior factor prophylaxis in the OP of the BASIS trial are provided in Table 99 and Table 100. An updated version of Table 100 is presented in Table 101, showing data from the October 2023 data cut-off of the OLE.

Table 99: Baseline demographic characteristics in the OLE for patients treated with factor prophylaxis in the OP of the BASIS trial (10th March 2023 data cut-off; safety analysis set)

Characteristic	Patients treated with prior factor prophylaxis in the OP (N=58)
Age, years	
Mean (SD)	31.5 (14.65)
Median (Range)	29.0 (13.0, 66.0)
Sex, n (%)	
Male	58 (100.0)
Race, n (%)	
Asian	22 (37.9)
Black or African American	1 (1.7)
White	34 (58.6)
Not reported	1 (1.7)
Ethnicity, n (%)	
Hispanic or Latino or Spanish origin	9 (15.5)
Not Hispanic or Latino or Spanish origin	49 (84.5)
Estimated glomerular filtration rate	
≥ 90	41 (70.7)
≥ 60 to < 90	12 (20.7)
≥ 30 to < 60	0 (0.0)
<30	0 (0.0)
Missing	5 (8.6)
Weight, kg	
Mean (SD)	72.3 (16.11)
Median (Range)	72.6 (39.0, 128.8)
Height, cm	
Mean (SD)	172.2 (6.83)
Median (Range)	173.0 (156.3, 184.7)
Body mass index, kg/m²	
Mean (SD)	24.3 (4.86)
Median (Range)	24.1 (15.6, 38.9)

Abbreviations: OLE: open label extension; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 OLE CSR, 2023²¹

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Table 100: Baseline disease characteristics in the OLE for patients treated with factor prophylaxis in the OP of the BASIS trial (10th March 2023 data cut-off; safety analysis set)

Characteristic	Patients treated with prior factor prophylaxis in the OP (N=58)
Haemophilia Type, n (%)	
Haemophilia A	45 (77.6)
Haemophilia B	13 (22.4)
Age and Haemophilia Type	
Adolescents Hem A	10 (17.2)
Adolescents Hem B	3 (5.2)
Adults Hem A	35 (60.3)
Adults Hem B	10 (17.2)
ISTH Disease Severity, n (%)	
Mild	0
Moderate	0
Severe	58 (100.0)
Number of Target Joints at Baseline	
0	28 (48.3)
1	12 (20.7)
2	10 (17.2)
≥3	8 (13.8)

Abbreviations: ISTH: International Society on Thrombosis and Haemostasis; OLE: open label extension; OP: observational phase.

Source: Pfizer marstacimab Phase 3 OLE CSR, 2023²¹

Table 101: Baseline disease characteristics in the OLE for patients treated with factor prophylaxis in the OP of the BASIS trial (9th October 2023 data cut-off; safety analysis set)

Characteristic	Patients treated with prior factor prophylaxis in the OP (N=75)
Haemophilia Type, n (%)	
Haemophilia A	58 (77.3)
Haemophilia B	17 (22.7)
Age and Haemophilia Type	
Adolescents Hem A	12 (20.7)
Adolescents Hem B	4 (23.5)
Adults Hem A	46 (61.3)
Adults Hem B	13 (76.5)
ISTH Disease Severity, n (%)	
Mild	0
Moderate	0
Severe	75 (100.0)

Abbreviations: ISTH: International Society on Thrombosis and Haemostasis; OLE: open label extension; OP: observational phase.

Source: Kazani *et al.* EHA24 oral presentation.¹²

M.2 Additional efficacy and safety results from BASIS

M.2.1. ABR_{treat} in patients who had their marstacimab dose increased during the ATP

Eleven patients in the BASIS trial had their weekly marstacimab dose increased from 150 mg to 300 mg during the ATP. Treatment duration on each dose and ABR_{treat} before and after the dose increase are presented in Table 101.

Table 102: Comparison of ABR_{treat} and treatment duration before and after the dose increase for participants with a dose increase during the ATP and with routine factor prophylaxis during the OP (17th April 2023 data cut-off; mITT analysis set)

	Before dose increase (N=11)	On or after dose increase (N=11)
Treatment duration (Days)		
Mean (SD)	247.0 (56.71)	117.6 (57.36)
Median (Range)	251.0 (175.0, 315.0)	108.0 (52.0, 185.0)
ABR_{treat}		
Mean (SD)	14.03 (8.916)	3.42 (3.992)
Median (Range)	11.24 (2.32, 30.95)	2.02 (0.00, 11.24)

If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.

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Abbreviations: ABR: annualised bleeding rate; ATP: active treatment phase; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.
Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹¹

M.2.2. Factor consumption (exploratory endpoint)

In the BASIS trial, factor replacement consumption, as measured by IU/kg per month/year and total annualised IU, reduced from 248,871 IU (mean total annualised) during the OP to 16,246 IU during the ATP when patients were receiving marstacimab (Table 102). In addition, the total days requiring factor replacement treatment were also reduced during the ATP (median exposure: 3 days per patient) when compared with the OP (median exposure: 57 days per patient).

Table 103: Summary of factor replacement consumption during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set)

	Routine prophylaxis during OP (N=83)	Marstacimab prophylaxis during ATP (N=83)
Total IU/kg per year		
Mean (SD)	3,532 (1,370)	221 (339)
Median (range)	3,430 (626, 8,178)	61 (0, 1,517)
Total IU/kg per month		
Mean (SD)	294 (114)	18 (28)
Median (range)	286 (52, 682)	5 (0, 126)
Total IU (Annualised)		
Mean (SD)	248,871 (106,937)	16,246 (25,185)
Median (range)	232,913 (40,583, 542,657)	3,746 (0, 103,129)

Abbreviations: ATP: active treatment phase; IU: international units; kg: kilogram; mITT: Modified intention to treat; OP: observational phase; SD: standard deviation.
Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹¹

M.2.3. HLIQ

A detailed summary of HLIQ results for each of the items in the questionnaire at baseline and at Week 52 are presented in Table 103.

Table 104: Summary of HLIQ responses at OP baseline and ATP day 360 (17th April 2023 data cut-off; mITT analysis set)

HLIQ questions and answers						
Question 1. During the past week, how much was Haemophilia on your mind?						
Visit	N	Not at all, n (%)	A little, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Constantly, n (%)
OP Baseline	83	15 (18.1)	33 (39.8)	23 (27.7)	9 (10.8)	3 (3.6)
ATP Day 360	75	20 (26.7)	31 (41.3)	11 (14.7)	8 (10.7)	5 (6.7)
Question 2a/2b. During the past week, how much precaution did you take because of your haemophilia?						

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Visit	N	No precaution, n (%)	A little, n (%)	Some, n (%)	Quite a bit, n (%)	A lot, n (%)	
OP Baseline	83	15 (18.1)	9 (10.8)	32 (38.6)	19 (22.9)	7 (8.4)	
ATP Day 360	75	24 (32.0)	16 (21.3)	15 (20.0)	16 (21.3)	4 (5.3)	
Question 3. During the past week, how much did having haemophilia interfere with your ability to perform day to day activities?							
Visit	N	Not at all, n (%)	A little, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Extremely, n (%)	
OP Baseline	83	19 (22.9)	30 (36.1)	25 (30.1)	7 (8.4)	2 (2.4)	
ATP Day 360	75	27 (36.0)	22 (29.3)	17 (22.7)	7 (9.3)	2 (2.7)	
Question 4. During the past week, how much did having haemophilia limit your ability to live the life you want to live?							
Visit	N	Not at all, n (%)	A little, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Extremely, n (%)	
OP Baseline	83	20 (24.1)	28 (33.7)	20 (24.1)	11 (13.3)	4 (4.8)	
ATP Day 360	75	26 (34.7)	22 (29.3)	14 (18.7)	8 (10.7)	5 (6.7)	
Question 5a/5b. During the past week, did you participate in any social activities? (e.g. with friends and/or family)? - No							
Visit	N	No, n (%)		Due to having haemophilia, n (%)		Due to other reasons, n (%)	
OP Baseline	83	26 (31.3)		6 (7.2)		20 (24.1)	
ATP Day 360	75	20 (26.7)		4 (5.3)		16 (21.3)	
Question 5a/5c. During the past week, did you participate in any social activities (e.g. with friends and/or family)? - Yes; how much did having haemophilia interfere with your ability to participate in social activities (e.g. with friends and/or family)?							
Visit	N	Yes, n (%)	Not at all, n (%)	A little, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Extremely, n (%)
OP Baseline	83	57 (68.7)	27 (32.5)	16 (19.3)	9 (10.8)	5 (6.0)	0 (0.0)
ATP Day 360	75	55 (73.3)	30 (40.0)	9 (12.0)	12 (16.0)	4 (5.3)	0 (0.0)
Question 6a/6b. During the last week, did you participate in any hobbies or leisure activities? - No							
Visit	N	No, n (%)		Due to having haemophilia, n (%)		Due to other reasons, n (%)	
OP Baseline	83	31 (37.3)		7 (8.4)		24 (28.9)	
ATP Day 360	75	23 (30.7)		6 (8.0)		17 (22.7)	
Question 6a/6c. During the last week, did you participate in any hobbies or leisure activities? - Yes; how much did having haemophilia interfere with your ability to participate in hobbies or leisure activities?							
Visit	N	Yes, n (%)	Not at all, n (%)	A little, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Completely, n (%)
OP Baseline	83	52 (62.7)	19 (22.9)	20 (24.1)	10 (12.0)	3 (3.6)	0 (0)

ATP Day 360	75	52 (69.3)	21 (28.0)	18 (24.0)	9 (12.0)	4 (5.3)	0 (0)
Question 7a/7b. During the past week, did you participate in any physical activities (e.g. exercise or sports)? - No							
Visit	N	No, n (%)		Due to having haemophilia, n (%)		Due to other reasons, n (%)	
OP Baseline	83	50 (60.2)		23 (27.7)		27 (32.5)	
ATP Day 360	75	33 (44.0)		12 (16.0)		21 (28.0)	
Question 7a/7c. During the past week did you participate in any physical activities (e.g. exercise or sports)? - Yes; how much did having haemophilia interfere with your ability to participate in physical activities (e.g. exercise or sports)?							
Visit	N	Yes, n (%)	Not at all, n (%)	A little, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Completely, n (%)
OP Baseline	83	33 (39.8)	8 (9.6)	14 (16.9)	7 (8.4)	4 (4.8)	0 (0.0)
ATP Day 360	75	42 (56.0)	20 (26.7)	10 (13.3)	8 (10.7)	4 (5.3)	0 (0.0)
Question 8. During the past week, how difficult was it to fit haemophilia treatment into your life?							
Visit	N	Not at all, n (%)	A little, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Extremely, n (%)	
OP Baseline	83	29 (34.9)	33 (39.8)	14 (16.9)	7 (8.4)	0 (0.0)	
ATP Day 360	75	38 (50.7)	18 (24.0)	15 (20.0)	2 (2.7)	2 (2.7)	
Question 9. During the past week, how much did treating your haemophilia interfere with your ability to enjoy life?							
Visit	N	Not at all, n (%)	A little, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Extremely, n (%)	
OP Baseline	83	29 (34.9)	33 (39.8)	15 (18.1)	4 (4.8)	2 (2.4)	
ATP Day 360	75	34 (45.3)	22 (29.3)	11 (14.7)	5 (6.7)	3 (4.0)	

For cases with multiple observations in a single analysis visit window, the ceiling of the average value is used for the descriptive summary.

Abbreviations: ATP: active treatment phase; HLIQ: Haemophilia Life Impacts Questionnaire; mITT: Modified intention to treat; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial CSR, 2023¹¹

Appendix N BASIS trial data used to inform the model

The Phase 3 BASIS study represents the pivotal clinical trial demonstrating the efficacy and safety of marstacimab prophylaxis compared to factor prophylaxis. Data from the primary and secondary endpoints of the BASIS trial are presented in Section B.2.6. Additional post hoc analyses were conducted to inform the data used in the economic model. The trial patients considered in these post hoc analyses, along with the efficacy inputs for the cost effectiveness model base case, are presented in Document B Section B.2.9. Post hoc data informing scenario analyses are presented below.

N.1 Scenario analysis excluding dose escalation

Efficacy data for factor prophylaxis and marstacimab which informs the cost effectiveness model scenario where data from patients receiving marstacimab dose escalation are censored are presented in Table 104. The proportion of patients receiving factor prophylaxis or marstacimab with no bleeds or ≥ 1 bleed is the same as that used to inform the base case, presented in Table 104.

Table 105: Comparison of ABR_{treat} and $AJBR_{treat}$ after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set excluding patients with dose escalation of marstacimab)

	Routine prophylaxis and >0 bleeds during OP (N=50)	Marstacimab prophylaxis and >0 bleeds during ATP (N=52)
ABR_{treat}		
Mean (SD)	13.09 (14.478)	8.25 (8.834)
$AJBR_{treat}$		
Mean (SD)	9.43 (12.758)	6.71 (8.285)

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

N.2 Scenario analyses by type of haemophilia

N.2.1. Haemophilia A specific efficacy

Two scenarios considered in the model focus on patients with haemophilia A only. The proportion of haemophilia A patients distributed within the bleeds and no bleeds health state is the same for both scenarios, with data presented in Table 105. Efficacy data for factor prophylaxis and marstacimab in patients with haemophilia A only, which informs the cost effectiveness model scenario which includes data from patients receiving an escalated marstacimab dose are presented in Table 106. Efficacy data for the scenario where data from dose escalated patients are excluded are presented in Table 107.

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Table 106: The proportion of patients with 0 bleeds and ≥ 1 bleed after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set including haemophilia A patients)

	Routine prophylaxis during OP (N=65)	Marstacimab prophylaxis during ATP (N=65)
0 bleeds, n (%)		
≥ 1 bleed, n (%)		

Abbreviations: ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

Table 107: Comparison of ABR_{treat} and AJBR_{treat} after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set including haemophilia A patients with dose escalation of marstacimab included)

	Routine prophylaxis and >0 bleeds during OP (N=40)	Marstacimab prophylaxis and >0 bleeds during ATP (N=42)
ABR_{treat}		
Mean (SD)		
AJBR_{treat}		
Mean (SD)		

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

Table 108: Comparison of ABR_{treat} and AJBR_{treat} after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set including haemophilia A patients with dose escalation of marstacimab excluded)

	Routine prophylaxis and >0 bleeds during OP (N=40)	Marstacimab prophylaxis and >0 bleeds during ATP (N=42)
ABR_{treat}		
Mean (SD)		
AJBR_{treat}		
Mean (SD)		

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

N.2.2. Haemophilia B specific efficacy

Two scenarios considered in the model focus on patients with haemophilia B only. The proportion of haemophilia B patients distributed within the bleeds and no bleeds health state is the same for both scenarios, with data presented in Table 108. Efficacy data for factor prophylaxis and marstacimab in patients with haemophilia B only, which informs the cost effectiveness model scenario which includes data from patients receiving an escalated

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marstacimab dose are presented in Table 109. Efficacy data for the scenario where data from dose escalated patients are excluded are presented in Table 110.

Table 109: The proportion of patients with 0 bleeds and ≥ 1 bleed after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set including haemophilia B patients)

	Routine prophylaxis during OP (N=18)	Marstacimab prophylaxis during ATP (N=18)
0 bleeds, n (%)	██████	██████
≥ 1 bleed, n (%)	██████	██████

Abbreviations: ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

Table 110: Comparison of ABR_{treat} and $AJBR_{treat}$ after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set including haemophilia B patients with dose escalation of marstacimab included)

	Routine prophylaxis and >0 bleeds during OP (N=10)	Marstacimab prophylaxis and >0 bleeds during ATP (N=10)
ABR_{treat}		
Mean (SD)	██████	██████
$AJBR_{treat}$		
Mean (SD)	██████	██████

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

Table 111: Comparison of ABR_{treat} and $AJBR_{treat}$ after 6 months of routine factor prophylaxis during the OP and after 12 months of marstacimab prophylaxis in the ATP (17th April 2023 data cut-off; mITT analysis set including haemophilia B patients with dose escalation of marstacimab excluded)

	Routine prophylaxis and >0 bleeds during OP (N=10)	Marstacimab prophylaxis and >0 bleeds during ATP (N=10)
ABR_{treat}		
Mean (SD)	██████	██████
$AJBR_{treat}$		
Mean (SD)	██████	██████

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; ATP: active treatment phase; mITT: modified intention to treat; OP: observational phase; SD: standard deviation.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

N.2.3. Scenario analyses by EHL and SHL products

Data informing the distribution of patients receiving SHL or EHL factor prophylaxis into the bleeds and no bleeds health states are presented in Table 111. Efficacy data for factor prophylaxis,

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grouped by those receiving either SHL or EHL products, which informs a cost effectiveness model scenario, are presented in Table 112. The ABR_{treat} and $AJBR_{treat}$ efficacy values, as well as the proportion of patients with 0 bleeds and ≥ 1 bleed, for patients treated with marstacimab remained the same as in the base case.

Table 112: The proportion of patients with 0 bleeds and ≥ 1 bleed after 6 months of routine SHL or EHL factor prophylaxis during the OP (17th April 2023 data cut-off; mITT analysis set)

	Routine SHL prophylaxis during OP (N=67)	Routine EHL prophylaxis during OP (N=16)
0 bleeds, n (%)		
≥ 1 bleed, n (%)		

Abbreviations: EHL: extended half life; mITT: modified intention to treat; OP: observational phase; SD: standard deviation; SHL: standard half life.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

Table 113: ABR_{treat} and $AJBR_{treat}$ after 6 months of routine SHL or EHL factor prophylaxis during the OP (17th April 2023 data cut-off; mITT analysis set)

	Routine SHL prophylaxis and >0 bleeds during OP (N=40)	Routine EHL prophylaxis and >0 bleeds during OP (N=10)
ABR_{treat}		
Mean (SD)		
$AJBR_{treat}$		
Mean (SD)		

Abbreviations: ABR: annualised bleeding rate; AJBR: annualised joint bleeding rate; EHL: extended half life; mITT: modified intention to treat; OP: observational phase; SHL: standard half life.

Source: Pfizer marstacimab Phase 3 BASIS trial post hoc analyses, 2024²²

Appendix O Pairwise and fully incremental analysis results against individual FIX prophylaxis treatments

Table 114: Company base-case results, haemophilia A (deterministic with PAS)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Marstacimab	██████	21.52	████	–	–	–	–	–
Refacto AF	██████	21.52	████	██████	–	████	██████	Marstacimab is dominant
NovoEight	██████	21.52	████	██████	–	████	██████	Marstacimab is dominant
Advate	██████	21.52	████	██████	–	████	██████	Marstacimab is dominant
Nuwiq	██████	21.52	████	██████	–	████	██████	Marstacimab is dominant
Elocta	██████	21.52	████	██████	–	████	██████	Marstacimab is dominant
Esperoct	██████	21.52	████	██████	–	████	██████	Marstacimab is dominant
Adynovi	██████	21.52	████	██████	–	████	██████	Marstacimab is dominant
FVIII Basket	██████	21.52	████	██████	–	████	██████	Marstacimab is dominant
Hemlibra	██████	21.52	████	██████	–	████	██████	██████

^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: FVIII: Factor VIII; ICER: incremental cost-effectiveness ratio; LYG: life years gained; SW: south west; QALY: quality adjusted life year.

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Table 115: Company base-case results, haemophilia B (deterministic, with PAS)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Marstacimab	████████	21.52	████	–	–	–	–	–
BeneFix	████████	21.52	████	████████	-	████	████████	Marstacimab is dominant
Alprolix	████████	21.52	████	████████	-	████	████████	Marstacimab is dominant
Idelvion	████████	21.52	████	████████	-	████	████████	Marstacimab is dominant
Refixia	████████	21.52	████	████████	-	████	████████	Marstacimab is dominant
FIX Basket	████████	21.52	████	████████	-	████	████████	Marstacimab is dominant

Abbreviations: FIX: Factor IX; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality adjusted life year.

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Single Technology Appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	The Haemophilia Society
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Haemophilia Society (THS) is the only UK-wide charity and free membership organisation for everyone affected by a bleeding disorder. We have over 5,000 members. At THS we want to empower everyone affected by a bleeding disorder to live life to the full, whatever stage you are at. We offer free member events, a local group network and online communities to share advice and experiences, as well as the latest news and access to specialist resources. Many people with a bleeding disorder are undiagnosed or are diagnosed late, because of a lack of understanding about these rare conditions. Our community rallies together to raise awareness about bleeding disorders, giving hope to everyone affected. THS also campaigns and advocates for what matters to our community; lobbying government, the NHS and clinicians to demand excellent care and safe and effective treatment, which is available to everyone affected by a genetic bleeding disorder. The Haemophilia Society is predominately funded through donations, fundraising and legacies from our members and the general public. We also receive around a third of our income from corporate donors, details on our funding from the pharmaceutical industry is below.
4b. Has the organisation received any funding from the company bringing the	The Haemophilia Society (THS) receives funding from a range of organisations, as well as from members of our community. Like many charities working in the healthcare sector, including haemophilia societies across the UK and Europe, some of that funding comes from pharmaceutical companies. You can read more about how

treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	we are funded here: https://haemophilia.org.uk/our-funding/how-we-are-funded/ Listed below are the corporate partners who have contributed to the costs of our work in 2023/24. Events Talking Red – LFB, SOBI Newly Diagnosed Family Weekend – Roche/Chugai, SOBI Youth Ambassadors and Youth Activities – Pfizer, LFB Haemfest – LFB The Big Get Together – Pfizer, Takeda Advocacy SACRed Project – LFB, Octapharma, Roche/Chugai, Takeda Haemophilia Journal subscription – Roche/Chugai Dental Survey – Nordic Pharma Digital activities 3 Peaks Challenge video - CSL, SOBI Publications Ageing Booklet – Octapharma Paediatric Dental Booklet – Nordic Pharma Conference Attendance EAHAD – LFB WFH – Roche/Chugai, SOBI Core Activities CSL
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	The Haemophilia Society regularly speaks to and corresponds with its members collecting and amplifying their views and needs. We speak to people with bleeding disorders on the phone, by email and in person at our events. We have an active Facebook group where people share experiences of living with a bleeding disorder and their treatment and care. People also engage with us on other social media including Instagram and Twitter. We have a range of ambassadors, trustees and other patient experts who have contributed to or reviewed this submission. Our board of trustees is made up of people living with a bleeding disorder or the family member of someone with a bleeding disorder. Our members events include discussion of treatment options, and advice on living with their condition. Feedback and discussion from those events, focus groups, interviews and informal contact is incorporated into our submissions.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	In severe haemophilia the main problem is internal bleeding into joints and muscles. We all damage our tissues in small ways in the activities of everyday life and most people repair that damage automatically. With severe haemophilia, the tiny breaks in the blood vessels in joints and muscles may continue to bleed. These bleeds are sometimes described as ‘spontaneous’ because it’s impossible to identify an obvious reason such as a bump or a fall. Bleeding into the joint has a damaging effect on the joint. Once a joint becomes damaged bleeding may occur more frequently and damage can be permanent. This is why regular prophylaxis and prompt treatment of any bleeding is so important. When bleeding has affected a joint or muscle, physiotherapy is crucial for good recovery. Damage to a joint can be caused by one serious bleed, though normally it’s a result of repeated bleeding into the same joint over several years. The bleeding damages the synovium (the lining of the joint) as well as the cartilage and surrounding tendons and tissues. This leads to arthritic pain and loss of movement and strength in the joint. In general, the older someone is the more likely they are to have joint damage. Orthopaedic surgery, including joint replacement, can be required when a joint is badly damaged. People with haemophilia commonly have prolonged bleeding following larger cuts or minor surgery. This can last for several days. In most cases minor cuts and scratches aren’t a problem. Some types of bleeding are very serious, such as head, neck and face injury. These need immediate treatment and must be assessed at hospital. Haemophilia is classed as severe, moderate or mild depending on how much clotting factor is missing. The level of factor VIII or factor IX in the blood is measured by a specialist laboratory. In general, the lower the level, the more bleeding problems the affected person will have without treatment. Different types of treatments are available for managing haemophilia and may vary depending on how severe it is. Prompt, effective treatment and prevention of bleeding significantly reduces the risk of complications and disruptions to school, work and family life. Bleeding can be controlled or prevented by replacing the missing clotting factor in the blood through an infusion of clotting factor concentrate. The level of factor VIII or factor IX is increased temporarily so infusions need to be repeated. For some minor bleeding episodes one infusion may be enough to stop bleeding. For more serious bleeding or where the first infusion has been delayed, treatment may be needed once or twice a day until the

	bleeding stops. Recombinant factor VIII and factor IX concentrates are made using genetic technology and aren't made from blood. Treatment will be needed by everyone with haemophilia if they are bleeding. It will also be necessary to prevent bleeding if they need an operation or have an injury where there is a risk of bleeding. Clotting factor concentrate is given intravenously (into a vein) into the bloodstream through a needle. Children can have anaesthetic cream rubbed onto the skin before an injection to reduce any pain. Standard half-life factor concentrates stay in the blood for a relatively short time and require repeat injections for prophylaxis – every 2-3 days for haemophilia A and twice a week for haemophilia B. Extended half-life (EHL) treatments are factor VIII or FIX products that can stay in the bloodstream for longer. They mean people are able to have injections to prevent bleeds (prophylaxis) less often or may stay on the same dose/schedule and have higher trough levels. They are likely to need fewer injections to control any bleeds they have. Half-lives are shorter in children and young people than adults. Emicizumab is a subcutaneous (under the skin) treatment used to prevent or reduce bleeding in people with severe haemophilia A that is given weekly, two weekly or once a month. It is an antibody which mimics the action of factor VIII. Treatment with regular infusions of clotting factor aims to prevent the long-term damage caused by bleeding into joints and muscles. Prophylaxis works by stopping the bleeding that occurs without any obvious injury, often called spontaneous bleeding. It also reduces the risk of bleeding from minor injuries. Most people with severe haemophilia treat themselves or their children with clotting factor at home. Home treatment has many advantages including making regular treatment possible, treatment can be given as soon as possible after bleeding starts, there is less disruption to home, school and working life, greater independence and control for the parent/person with haemophilia, reduced need for hospital attendances and early treatment reduces recovery time and risk of permanent damage. A complication of haemophilia care is the development of an inhibitor. An inhibitor is an antibody that the immune system develops when it recognises the clotting factor being infused as something foreign. The inhibitor removes

	the clotting factor before it can work to stop any bleeding. Inhibitors usually affect people with severe haemophilia A in early childhood, but they can also occur later in life in milder forms of haemophilia. They are much more unusual in people with haemophilia B. People with inhibitors may not respond to treatment with factor products and will need bypassing agents such as FEIBA and rFVIIa to control bleeding. If they have haemophilia A and an inhibitor they will often use emicizumab to prevent bleeding. People with haemophilia can have any surgery they need but careful planning is essential. Good dental education and care is particularly important for people with haemophilia to prevent tooth decay and gum disease and avoid the need for dental surgery. Gum bleeding is caused by gum disease but will be worse for someone with haemophilia. Exercise and sport have many benefits for health and can improve self-esteem, learning and concentration. There are some particular benefits for children and adults with haemophilia as strong muscles, good balance and posture can help to protect joints from bleeding. Maintaining a healthy weight helps to reduce stress on joints that have already been damaged by bleeding. The choice of activity or sport will be individual and can be decided in consultation with a specialist haemophilia physiotherapist. There are risks and benefits of different sports taking account of the person's condition, treatment and disease severity. In general, sports involving a lot of physical contact and those where head and neck injuries occur carry the highest risk of injury and therefore risk of bleeding. Factor prophylaxis can be tailored around days of highest activity so that there is maximum protection from bleeding at these times. With modern treatment, haemophilia shouldn't have a serious impact on a child's education. There may be times when a child has to miss school while they recover after a bleed. Rarely, a child may temporarily need to use a wheelchair or crutches. For children with haemophilia who are on effective treatment, ordinary play activities aren't usually a problem beyond the occasional bruise. Cuts and grazes can generally be managed with standard first aid. Most young people with haemophilia will go through school much as the rest of their peer group. This means that choosing to go to college or out to work won't be any different either. If their haemophilia has been well-managed, people with severe haemophilia can reach adulthood with limited joint damage and will not be overly restricted in careers and lifestyle choices.

	However, in the past treatments were less effective and many adults with severe haemophilia have severe joint damage and will be less able to walk or stand for periods of time. They may have restricted movement in joints which may make household tasks, taking treatment and personal care much more difficult. Many older people with haemophilia will have been treated with contaminated blood products in the 70s and 80s and will be living with HIV or liver damage from hepatitis B and C.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Since the 90s people with severe haemophilia have moved from plasma-derived factor products to recombinant factor VIII and IX and most recently on to so-called extended or enhanced half-life products. In Haemophilia A there is commonly used non-factor product (emicizumab). In haemophilia B, while there is no currently used non-factor product, extended half-life products are more effective and can usually be administered weekly and they achieve higher trough levels than haemophilia A factor products. A haemophilia A product that could be comparable in effect to the best haemophilia B factor products is currently under consideration by NICE (Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]). NICE has recently approved a gene therapy for haemophilia B, and the first patients are expected to be dosed with this treatment in late 2024 or early 2025. Our members have described how currently, the treatments are better than they were even a few years ago and much better than in the past. However, they are not perfect and still leave a lot of unmet need. Treatments are still time consuming, awkward to travel with and not pleasant especially for younger people living with severe haemophilia or those with difficulty accessing veins due to joint damage causing restricted movement or damage to the veins. Non-factor treatments, like emicizumab, reduce the burden of treatment but at the cost of losing the peaks in factor levels that factor products provide making them less effective for more active people, particular those that take part in sport. More broadly, the way these treatments are provided and administered mean that people need to organise their lives around their treatment. We are often told of people at home waiting for deliveries. They are required to time factor use with physical activity to ensure they have more protection at those times but leaving them with lower levels at other points. If they want to leave the country or travel away from home, they must ensure that they have enough treatment for regular prophylaxis and additional factor for accidents. Additionally, there is the burden in detailed tracking of treatments and treatment outcomes in an app. Children learning to self-treat may find it easier to use a sub-cutaneous product such as this product or Emicizumab than learning to self-infuse a factor product intra-venously. However, for people on prophylaxis with non-factor products they will still need factor infusions following trauma and for major surgery. In general, the current treatments reduce spontaneity and require people with severe haemophilia to plan meticulously or risk having bleeds or missing out. For people on non-factor products, they have a steady state

	level of protection that cannot be tailored to individual bleeding tendency or lifestyle and so may not provide as much protection as high-dose highly optimised factor treatment.

8. Is there an unmet need for patients with this condition?	The inherited bleeding disorders patient survey first conducted in 2020 and repeated in 2022 showed that the majority of people with a bleeding disorder feel anxious because of their condition and up to 25% said they felt anxious “a lot” in the last 12 months. In both surveys almost half of respondents said that they had felt depressed in the last 12 months because of their condition. In the 2022 survey we asked a series of questions on pain which showed that only a third of people with bleeding disorders lived a life free from pain as a result of their condition. Around a quarter said this was chronic long-term pain that they felt every day. The Haemophilia Society provides its members with advice on pain management, and this is a common area of concern for clinicians managing the condition of people with haemophilia. Pain is highly prevalent in people with haemophilia with studies reporting acute pain being experienced by 20–68%. A detailed investigation on what impact pain in people in the UK with haemophilia has on their lives has shown that people make major changes to their life and that their experience of pain is a complex bio-medical and social construct. (P. McLaughlin, M. Hurley, P. Chowdary, D. Stephensen & K. Khair (2022) How does a lifetime of painful experiences influence sensations and beliefs about pain in adults with severe haemophilia? A qualitative study, <i>Disability and Rehabilitation</i>, 44:26, 8412-8419, https://www.tandfonline.com/doi/pdf/10.1080/09638288.2021.2018053) People with severe haemophilia still have painful bleeds requiring additional treatment and often rehabilitation. These bleeds mean that most people with severe haemophilia still develop joint damage impacting on their quality of life (O'Hara, J., Walsh, S., Camp, C. et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. <i>Health Qual Life Outcomes</i> 16, 84 (2018). https://doi.org/10.1186/s12955-018-0908-9) A number of people with haemophilia have spoken to us about how despite their current treatment they do not have full confidence to walk in crowds and will adapt their lives to avoid bumping into people and the risk of bleeds and bruising. For example, they will make changes to their plans to ensure they go to the supermarket at less busy times. People with haemophilia often do not have the confidence to take whatever career path they

	want or participate in all sports and social activities they want as they cannot rely on their protection from joint damage and bleeds at all times. Some people with haemophilia, particularly those affected by the scandal of contaminated blood products in the 70s and 80s, are put off by frequent attendance at hospital where they or their family members were prescribed or treated with blood products that gave them HIV and Hepatitis C leading to long-term health impacts including liver damage and premature death.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	People with haemophilia value convenience of administration of their treatment. There is a substantial burden to doing frequent intra-venous infusions and many patients with haemophilia A have chosen to move from factor products to emicizumab to reduce the burden of treatment and the complexities of managing peaks and troughs of factor levels. This product is delivered sub-cutaneously in fairly small doses and will offer people with haemophilia B a subcutaneous option for the first time and an alternative to emicizumab for people with haemophilia A. This product is delivered via an autoinjector which may make it even easier to use in adolescents who struggle with their treatment, people with joint mobility issues who struggle to self-infuse factor products or people in social care who require their treatment to be given to them by carers.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Due to a lack of comparative studies, it is unclear whether this product is as effective as emicizumab in preventing bleeds. For people with haemophilia A who are well-managed on their current treatment, they are unlikely to want to move to a product if it is less effective at preventing bleeds. The product, like emicizumab, is only suitable for prophylaxis so traumatic bleeds will still need to be treated at home or in hospital with factor products. Optimised, high dose treatment with EHL factor IX products, or gene therapy are the standard of care for people with haemophilia B. While some people will value the convenience of a sub-cutaneous weekly dosed product, it is unlikely that this product will provide as effective bleed prevention as the current standard of care.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This product is delivered sub-cutaneously in small doses and will offer people with haemophilia B a subcutaneous option for the first time and an alternative to emicizumab for people with haemophilia A. This product is delivered via an autoinjector which may make it even easier to use in children who struggle with their treatment, people with joint and mobility issues who struggle to self-infuse factor products or people in social care who require their treatment to be given to them by carers. In care settings social care staff and nurses are more likely to be able to give sub-cutaneous injections but may not be able to administer intravenous infusions. So this product may help people relying on care to get their treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	People will need to understand the benefits and disadvantages of this product compared to the current standard of care. NICE should be careful to avoid guidance which does not make clear that some products, particularly with optimised high dosing, are more effective in preventing and managing bleeds and reducing joint damage than others. With current products we have seen large regional variation in uptake of new treatments. NICE and NHS England should work to ensure there is equity of access across England and that patients in different centres are able to choose the best treatment option for them in well-informed shared decision-making.

Other issues

13. Are there any other issues that you would like the committee to consider?	No
14. What factors influence treatment decisions in haemophilia? Especially with regards to: • Frequency of administration? • Route of administration (subcutaneous vs. intravenous)?	The most important effects of good haemophilia treatment are the prevention of bleeds, swift resolution of bleeds, prevention of joint damage and the ability to take part in sport and other activities. The most valued treatments allow people to take part in whatever activities they wish without having to adapt or worry about their haemophilia. There is a substantial burden of treatment, particularly for people with severe haemophilia A who often need to do intravenous infusions 2-3 times a week. Through the rates of switching to emicizumab, particularly in children, we have seen that they highly value reduced frequency of administration and seem to prefer subcutaneous administration. People with severe haemophilia A who have remained on factor replacement tend to be people who have higher bleeding tendency or who require the peaks of factor levels to take part in sport and exercise. For people with severe haemophilia B, the standard dosing frequency is once weekly with EHL factor products so this treatment will not change the frequency of administration. However, we expect that some people will prefer subcutaneous administration, particularly children who would otherwise require a port-a-cath or people with range of movement or venous access issues that make intravenous infusions more difficult.

15. Please describe your experience, or that of the person you care for, of using on demand factor therapies for breakthrough bleeds whilst on prophylaxis? What aspects (e.g. bleed location) would influence the decision to treat with extra factor replacement therapies?	

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission.	• Bleed prevention and management, ability to take part in sport and activities and delay or prevention of joint damage are the most important outcomes for people with severe haemophilia A and B • Patients and carers do, however, also value ease of administration of treatments and a reduction in treatment burden • There is a substantial burden of treatment and anxiety in managing treatments which may be eased through steady state, subcutaneous treatments such as this product and emicizumab • Despite advances in treatment there is still unmet need among people with severe haemophilia

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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Single Technology Appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Friday 1 November**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Treating severe haemophilia A or severe haemophilia B and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Mary Mathias
2. Name of organisation	Great Ormond Street Hospital for Children NHS Foundation Trust
3. Job title or position	Haematology Consultant and Haemophilia Centre Director
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with severe haemophilia A or severe haemophilia B? ☒ A specialist in the clinical evidence base for severe haemophilia A or severe haemophilia B or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA

Clinical expert statement

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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8. What is the main aim of treatment for severe haemophilia A or severe haemophilia B? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment for severe haemophilia A and B is either to treat bleeding (on demand therapy) or to prevent bleeding (prophylaxis). The latter is the standard of care in the UK with the aim that people with haemophilia can lead normal lives and engage in the majority of physical activities. By preventing bleeds (which can be in any part of the body including within the brain, but are commonly within joints and muscles), mortality is reduced (intracerebral haemorrhage being a common cause of death in severe haemophilia patients in countries with no access to prophylaxis) and there is a preservation of joint and muscle health. The natural history of untreated severe haemophilia is bleed-related death or progressive joint deterioration leading to irreversible damage, chronic pain, significantly reduced mobility and poor quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Consideration must be given to what pre-existing treatment a patient has had access to: effective prophylactic treatment can result in an annualised bleed rate (ABR) in a person with severe haemophilia (PWSH) of zero, but given the appropriate involvement in physical activity which is made possible by prophylaxis, some individuals will inevitably have activity related bleeds requiring additional treatments. A PWSH who has not had access to prophylactic treatment may have an ABR of 20-40 on on-demand treatment. For a new treatment to demonstrate similar efficacy to existing haemophilia therapies, I would wish to see an ABR of <4 in patients coming from on demand treatment (who will have pre-existing joint disease with a consequent higher risk of further bleeds). Prophylactic treatment is the standard of care in most developed countries. The Marsticimab published studies describe the enrolled patient cohort as not having previous access to preventative haemophilia treatment. The majority of the cohort enrolled had significant joint damage, which means that they were more vulnerable to further bleeds into those joints with minimal or no trauma. Achieving an ABR of <4 would be more 'difficult' from the background of that clinical setting than if a patient was enrolled from a background of effective prophylaxis and no joint damage.

Clinical expert statement

10. In your view, is there an unmet need for patients and healthcare professionals in severe haemophilia A or severe haemophilia B?	Yes. There are 3 current strategies for treating severe haemophilia: -replacement therapy with either FVIII or FIX -non-replacement therapy with a monoclonal FVIII mimetic drug for haemophilia A only (emicizumab). -gene therapy in currently very limited numbers in developed countries and only currently in adults (over 18). Around 1 in 3 boys with severe haemophilia A develop antibodies against FVIII, making this treatment useless. If attempts to get rid of these antibodies (called inhibitors) are either not possible (there is a huge expense and high treatment burden associated) or not desired, this group have access to emicizumab which provides good bleed prevention, effectively converting the severe haemophilia A to a milder form of the condition. A much smaller proportion of boys with severe haemophilia B develop inhibitory antibodies against FIX. These are more difficult to remove and currently the only licensed treatment options (called bypassing agents) do not provide good bleed control. Children and men with this complication of severe haemophilia B typically have recurrent bleeds leading to disability (for example becoming wheelchair dependent in their second decade). Marstacimab therefore offers to meet the currently unmet needs of: 1) a subcutaneous treatment for severe haemophilia B and 2) effective prophylactic treatment for severe haemophilia B patients with inhibitors.
11. How is severe haemophilia A or severe haemophilia B currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The standard of care within the NHS for severe haemophilia is prophylaxis with either factor concentrate or the only currently licensed non factor treatment (for haemophilia A only), emicizumab. Gene therapy for severe haemophilia B will also be available shortly but only applies to patients over 18 years. Clinical guidelines on prophylaxis from the United Kingdom Haemophilia Centres Doctors Organisation (UKHCDO) are generally applied in the UK. There has been an evolution of choice of prophylaxis to treat haemophilia A since 2019 when emicizumab was commissioned for patients with and without FVIII inhibitory antibodies. Many adults use this treatment now and the parents of

Clinical expert statement

What impact would the technology have on the current pathway of care?	babies with severe haemophilia A are increasingly choosing this treatment option in order to avoid the need for a central venous access device, which requires a general anaesthetic. Some haemophilia centres use more emicizumab than others, but there is wide recognition that early and effective prophylaxis with either factor concentrate or emicizumab is appropriate and necessary. Marstacimab would add an additional subcutaneous prophylaxis strategy for severe haemophilia A and would be potentially the first available subcutaneous treatment for severe haemophilia B and potentially the first effective prophylaxis for severe haemophilia B with inhibitors.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? - How does healthcare resource use differ between the technology and current care? - In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) - What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	- Please see my comments about intravenous versus subcutaneous treatment for severe haemophilia. Marstacimab would be used as a treatment resource in a similar way to emicizumab. - This treatment would be prescribed and managed within specialist haemophilia centres (tertiary care) but administered at home by patients/their parents, as is the case for current prophylactic treatments. - No investment is needed to introduce this technology.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	- Marstacimab is likely to increase the life expectancy in patients with severe haemophilia B with inhibitors, for whom there is currently no licensed effective prophylaxis. - Marstacimab may be the first licensed/commissioned subcutaneous prophylactic treatment for severe haemophilia B. Based on the well recognised improvement in treatment burden provided by emicizumab for haemophilia A, it is highly likely that marstacimab will offer a similar improvement in quality of life for patients and families with severe haemophilia B.

Clinical expert statement

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	We do not have any information to suggest that marstacimab would be less effective for any group of patients with haemophilia, although the number of patients enrolled in the clinical trials with severe haemophilia B was very limited (<5 patients). The likely reason for this is competing clinical trials with other subcutaneous therapies effective for haemophilia B, and the very small pool of patients with severe haemophilia B being enrolled in these other studies, ahead of the marstacimab study recruitment. This particularly applies to the even smaller group of severe haemophilia B patients with inhibitors, who are likely to have been rapidly enrolled in competing studies as soon as they were available, given their previous lack of effective bleed prevention.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Marstacimab is given subcutaneously once weekly. This will be similar to administration of emicizumab (once weekly or every 2 week) but may be an improvement in treatment burden for patients with severe haemophilia B who have once or twice weekly intravenous injections.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	If a patient switching to marstacimab for prophylaxis experiences an increase in 'break-through' bleeding, advice from their treating team would be to switch to their previous or another treatment. In other words, reduced efficacy would not be tolerated because of increased convenience of administration. This would be a clinical decision rather than one based on additional testing.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	Marstacimab administration would be similar to that of emicizumab (non-factor treatment for haemophilia A), but it would offer an easier administration method than the current standard of care for severe haemophilia B (intravenous injection). QALY calculations may not pick this improvement up, but based on well documented improvements to treatment burden in haemophilia A with the introduction of emicizumab, I think marstacimab would offer a significant benefit in this respect. In many families only one parent gives the majority of FIX for boys with severe haemophilia B and the much easier administration of subcutaneous products means that other family members (including the

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may be more easily administered (such as an oral tablet or home treatment) than current standard of care	patients) can learn to give this treatment easily. Subcutaneous administration may lead to earlier independence of management of their own condition for adolescents and particularly for individuals with additional medical or social communication diagnoses, many of whom may never be able to administer their own intravenous treatment, but who can master subcutaneous treatment rapidly.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	- Please see above. This may be the first subcutaneous treatment for severe haemophilia B available outside of clinical trials in the UK and as such it does offer a step-change in management of severe haemophilia B, particularly for those patients with inhibitory antibodies against FIX, for whom there is currently no licensed effective prophylaxis. - For patients with severe haemophilia A (who do currently have access to a subcutaneous treatment), it would offer an alternative subcutaneous therapeutic choice with a different mechanism of action to emicizumab. For those patients who have developed anti-drug antibodies against emicizumab (very small numbers), or in whom emicizumab has not provided the best bleed prevention, marstacimab would offer an alternative subcutaneous prophylaxis option.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The treatment related adverse events for marstacimab described in the trial publications are predominantly injection site reactions. These have been common to all the subcutaneous haemophilia treatments (and all other s/c monoclonal antibodies) and in most instances a transient injection site reaction has not led to trial patients choosing to stop treatment. Although the number of patients enrolled in the marstacimab trials has been low, there were no thrombotic events reported, in contrast to emicizumab and the other subcutaneous severe haemophilia therapies in the trial pipeline. This may reflect the careful exclusion criteria for the marstacimab studies but should nonetheless be taken into consideration.
20. Do the clinical trials on the technology reflect current UK clinical practice? If not, how could the results be extrapolated to the UK setting?	The clinical trials for marstacimab were in patient populations previously without access to prophylactic treatment for their severe haemophilia with pre-trial annualised bleed rates in keeping with on-demand care. The improvement in ABR on marstacimab is equivalent to that seen for other haemophilia prophylaxis treatments following on-demand care, but the ABRs achieved in

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• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	study are also in keeping with effective prophylaxis in all severe haemophilia study settings. In other words, whilst it would not have been possible to recruit patients in the UK from on-demand treatment to prophylaxis with marstacimab, the ABR's they achieved are broadly in keeping with all current licensed treatments, with some patients experiencing no bleeds within the study window.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA989]?	No
23. How do data on real-world experience compare with the trial data?	I am not aware that any has been published yet.
24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	Haemophilia is an X linked disorder and its severe form almost universally affects boys and men. There are very rare situations where a girl/woman may have severe haemophilia and it is therefore important to recognise that marstacimab, as any other haemophilia treatment, must also be available to them.

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- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is no currently licensed and available subcutaneous treatment for severe haemophilia B in the UK.

Marstacimab would offer a weekly subcutaneous prophylaxis option for severe haemophilia B and A.

Marstacimab may be the first available effective prophylaxis for severe haemophilia B complicated by antibodies (inhibitors) to FIX (this is currently an unmet need, although there are several other potential treatments in the trial pipeline).

Marstacimab (and any other subcutaneous prophylaxis treatments for severe haemophilia B in the future) would offer a potential reduction in treatment burden for patients and their families in line with that observed when emicizumab was made available for treatment for haemophilia A.

Thank you for your time.

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Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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External Assessment Group's report

Title: *Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over: EAG Report [ID6342]*

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None

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Rider on responsibility for report

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Abbreviations

Abbreviation	Definition
AAS	All Analysis Set
ABR	Annualised bleeding rate
ABR _T	Annualised bleeding rate of treated bleeds
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
AJBR	Annualised joint bleeding rate
AJBR _T	Annualised joint bleeding rate of treated bleeds
ALT	Alanine transaminase
aPCC	Activated prothrombin complex concentrates
AS	Absolute shortfall
ASD	Absolute standardised difference
ATP	Active treatment phase
BMI	Body mass index

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Abbreviation	Definition
BNF	British National Formulary
BPI	Brief pain inventory
BSA	Business Services Authority
BSH	British Society for Haematology
BU	Bethesda units
CADTH	Canada's Drug and Health Technology Agency
CE	Conformité Européenne
CEA	Cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
DOT	Days of therapy
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
EHA	European Haematology Association
EHL	Extended half-life
EMA	European Medicines Agency
ES	Effective size
EU	European Union
FIX	Factor IX
FVIII	Factor VIII
FX	Factor X
GB	Great Britain
GBP	Great British Pounds
GEE	Generalised estimating equation
Haem-A-QoL	Haemophilia A Quality of Life for Adults
Haemo-QoL	Haemophilia Quality of Life Questionnaire for Children
HAL	Haemophilia Activities List
Hemo-TEM	Haemophilia Treatment Experience Measure
HIV	Human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
HLIQ	Haemophilia Life Impacts Questionnaire
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
IgG1	Immunoglobulin G1
IPD	Individual-level data
IQR	Interquartile range
ISTH	International Society on Thrombosis and Hemostasis
ITC	Indirect treatment comparison
IU	International units

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Abbreviation	Definition
IV	Intravenous
IVIG	Intravenous immunoglobulin
LPLV	Last patient last visit
LTE	Long-term extension
LTFU	Long term follow up
mAb	Monoclonal antibody
MAIC	Matching adjusted indirect comparison
MAR	Missing at random
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
mITT	Modified intention to treat
NA	Not applicable
nAb	Neutralising antibodies
NHB	Net health benefit
NHD	National Haemophilia Database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not recorded
OD	On demand
OLE	Open label extension
OP	Observational phase
OR	Odds ratios
PAS	Patient Access Scheme
PCC	Prothrombin complex concentrates
pedHAL	Paediatric Haemophilia Activities List
P-FIQ	Pain, functional impairment and quality of life
PFP	Pre-filled pen
PFS	Pre-filled syringe
PGIC-H	Patient global impression of change - haemophilia
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PS	Proportional shortfall
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QW	Once weekly
RCT	Randomised control trial
RP	Routine prophylaxis
RR	Rate ratios

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Abbreviation	Definition
RU	Resource use
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SHL	Standard half-life
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SOC	Standard of care
STA	Single technology appraisal
STC	Simulated treatment comparison
SW	South west
TBC	To be confirmed
TEAE	Treatment emergent adverse events
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TSD	Technical support document
Tx	Treatment
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centre Doctors' Organisation
US	United States
VAS	Visual analogue scale
WFH	World Federation of Hemophilia
WTP	Willingness-to-pay

Executive Summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: Summary of key issues

ID6342	Summary of issue	Report sections
1	Generalisability over the BASIS trial and its relevance to UK practice.	2.2.2
2	The source of information for baseline annualised bleed rates and treatment efficacy within the economic model.	2.2.2.2, 2.5.3
3	Dose-escalation of marstacimab	2.2.2.6, 5.3.1
4	Discontinuation of haemophilia treatments.	5.1.2
5	Dosing of factor prophylaxis	2.2.2.7, 5.3.2
6	Separate or pooled modelling of haemophilia types	2.2.2.3, 4.3.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the source of information used for the baseline annualised bleed rates, the estimates of relative efficacy, the mean IU dose for FVIII/FIX, whether clinical effectiveness estimates should be differentiated by haemophilia A and haemophilia B and whether marstacimab dose escalation during the open label extension should be included and extrapolated.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Having a different annualised treated bleed rate to other therapies
- Being subcutaneous rather than intravenous administration compared to FVIII/FIX, and having a different annual number of administrations compared to FVIII/FIX and emicizumab

Overall, the technology is modelled to affect costs by:

- Having a different purchase price to other therapies
- Affecting the mean number of bleeds and so the cost of treating these

The modelling assumptions that have the greatest effect on the ICER are:

- The mean FVIII/FIX dose, whether this should be based upon UKHCDO data or company assumptions, and if the latter whether wastage calculations should take into account some doses being rounded down.
- Whether marstacimab dose escalations during the open label extension are included and whether there will be further marstacimab dose escalations.
- Whether the clinical effectiveness estimates should be pooled across or differentiated by haemophilia A and haemophilia B, and within this whether dose escalation rates should be similarly differentiated.
- Whether clinical effectiveness estimates for the second year and beyond should be based upon the BASIS open label extension or upon the BASIS.

1.3 The decision problem: summary of the EAG's key issues

The EAG did not identify any key issues relating to the decision problem.

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 1: Generalisability over the BASIS trial and its relevance to UK practice.

Report section	2.2.2
Description of issue and why the EAG has identified it as important	The BASIS trial had no UK patients, had a much higher use of standard half-life factor therapies than used in UK practice. A naïve comparison of the baseline bleed rates to NHS data showed that bleed rates for the prophylactic period of BASIS were considerably higher than NHS patients. There is also a potential difference in dosing of factor therapies which could influence estimates of relative efficacy. Hence it is unclear whether it is appropriate to assume relative efficacy observed in BASIS can be applied to NHS data.
What alternative approach has the EAG suggested?	The EAG is not aware of any other sources to inform on the relative efficacy of marstacimab.
What is the expected effect on the cost-effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	The generation of new data relevant to NHS care.

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 2: The source of information for baseline annualised bleed rates and treatment efficacy within the economic model.

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Report section	2.2.2.2, 2.5.3
Description of issue and why the EAG has identified it as important	The company use inputs taken from the BASIS trial to inform the efficacy of factor therapy and marstacimab, however the numbers of bleeds per patient are much higher than those reported by UKHCDO for NHS care for factor therapy. Efficacy for emicizumab is estimated from an unanchored simulated treatment comparison
What alternative approach has the EAG suggested?	The EAG prefers to use estimates reported by UKHCDO to inform the efficacy of factor therapy and emicizumab, and to apply the rate ratios estimated in BASIS ATP and OLE to factor therapy to model efficacy of marstacimab. This avoids applying a highly uncertain estimate of relative effect between marstacimab and emicizumab, however does not account for potential differences between.
What is the expected effect on the cost-effectiveness estimates?	The UKHCDO data reduces bleed rates for emicizumab and FVIII/FIX. Combining with the BASIS ATP data worsens the relative effectiveness of marstacimab, particularly compared to FVIII/FIX. But extrapolating marstacimab effectiveness using the BASIS OLE data, which better reflects the effects of marstacimab dose escalation, increases the relative effectiveness of marstacimab.
What additional evidence or analyses might help to resolve this key issue?	A head-to-head study comparing marstacimab with emicizumab, or data from real-world use marstacimab in the NHS.

Issue 3: Dose-escalation of marstacimab

Report section	2.2.2.6, 5.3.1
Description of issue and why the EAG has identified it as important	The company models dose escalation of marstacimab to only occur within the first year of the economic model, based on the first 12 months of marstacimab follow-up in BASIS. However additional dose-escalation also occurs in the open-label extension, which is not captured in the model.
What alternative approach has the EAG suggested?	The EAG prefers to model this additional OLE dose-escalation whilst also decreasing the bleed rates for marstacimab to account for the additional benefit incurred from further dose-escalation using the open-label extension data. Due to the proportion of patients eligible for marstacimab dose escalation during BASIS the EAG also explores ongoing dose escalation subject to a maximum ceiling.
What is the expected effect on the cost-effectiveness estimates?	Dose escalation increases the patient benefits from marstacimab and the cost offsets from reduced bleeds. But it greatly increases costs in the marstacimab arm and the overall effect is to worsen the cost effectiveness of marstacimab. If dose escalation is likely to continue to occur beyond that recorded during the open-label extension October 2023 data cut this is likely to further considerably worsen the cost effectiveness of marstacimab.
What additional evidence or analyses might help to resolve this key issue?	Further follow-up from BASIS OLE would allow for better understanding of the extent and impact of dose-escalation.

Issue 4: Discontinuation of haemophilia treatments.

Report section	5.1.2
Description of issue and why the EAG has identified it as important	The economic model allows for people to discontinue marstacimab and switch to factor prophylaxis. Discontinuation is not applied to emicizumab, due to the absence of data. The EAG considers this to be a source of uncertainty and probable bias. This issue is complicated by the total annual drug costs of many of the treatments being above the NICE willingness to pay thresholds. This can introduce apparently perverse effects and the cost effectiveness of marstacimab improving if it has a higher discontinuation rate.
What alternative approach has the EAG suggested?	The EAG presents a scenario analysis that excludes marstacimab discontinuations. This may be the most reasonable basis for the comparison with emicizumab.
What is the expected effect on the cost-effectiveness estimates?	For the comparison to emicizumab, the cost effectiveness of marstacimab improves.
What additional evidence or analyses might help to resolve this key issue?	Information relating to discontinuation of emicizumab would allow for modelling of discontinuation to be applied to both marstacimab and emicizumab for their pairwise comparison. But as already noted this is complicated by the total annual drug costs of many of the treatments being above the NICE willingness to pay thresholds.

Issue 5: Dosing of factor prophylaxis

Report section	2.2.2.7, 5.3.2
Description of issue and why the EAG has identified it as important	The EAG is concerned about the potential bias in the analyses caused by uncertainty around the dosing of prophylaxis. The company uses relative efficacy estimates from BASIS however takes information of dosing from respective summaries of product characteristics documents. This inconsistency means that efficacy of factor may be underestimated or costs overestimated in the company analysis. The company approach assumes wastage and that all dosing is rounded up. Some patients may have their dosing rounded down. The UKHCDO annual report suggests somewhat lower total annual dosing for FVIII, and a confidential UKHCDO report for the company also suggests somewhat lower total annual FVIII/FIX dosing. The UKHCDO dosing appears to be better aligned with that of BASIS.
What alternative approach has the EAG suggested?	The EAG base case uses dosing estimates from UKHCDO data. It also explores the company dosing assumptions but with some patients rounding down their dose.
What is the expected effect on the cost-effectiveness estimates?	The EAG approach reduces the cost-effectiveness of marstacimab.
What additional evidence or analyses might help to resolve this key issue?	BASIS mean dosing data per unit time split by FVIII and FIX, these in turn being split by individual treatments or by standard half life and extended half life.

Issue 6: Separate or pooled modelling of haemophilia types

Report section	2.2.2.3, 4.3.1
Description of issue and why the EAG has identified it as important	The company presents data which suggests a possibly smaller effect among those with haemophilia B than haemophilia A, due in part to a lower bleed rate during BASIS when patients were receiving FVIII/FIX. Marstacimab dose escalation rates were also higher among those with haemophilia B, though BASIS was not powered to detect subgroup differences.
What alternative approach has the EAG suggested?	Applying haemophilia A and haemophilia B specific clinical effect estimates. The company supplies a scenario that performs this, though only for bleed rates.
What is the expected effect on the cost-effectiveness estimates?	The cost effectiveness among those with haemophilia A improves by a reasonable amount, but the cost effectiveness among those with haemophilia B worsens considerably. The effect of this is much less marked if it is assumed that haemophilia A and haemophilia B patients have the same marstacimab dose escalation, regardless of their clinical effect estimates.
What additional evidence or analyses might help to resolve this key issue?	None that readily present themselves. But it can be noted that there is more uncertainty around the estimates for haemophilia B patients due to small patients numbers in BASIS and that the UKHCDO bleed rate estimates for standard half-life FIX are also based on small patient numbers.

1.6 Other key issues: summary of the EAG's view

No further key issues were identified by the EAG.

1.7 Summary of EAG's preferred assumptions and resulting ICER

The EAG makes the following changes to the company base case.

- EAG01: Correct a number of model errors.
- EAG02: Adjust the ATP marstacimab dose escalation for those who discontinued not having dose escalated and apply the OLE dose escalation for year 2.
- EAG03: Based upon UKHCDO data for FVIII among adult patients revise the FVIII/FIX prophylaxis dosing to be 75% that of the company base case.
- EAG04: Based upon UKHCDO data increase the FVIII/FIX per bleed and assume FVIII/FIX used for bleeds is the same as for prophylaxis.

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- EAG05: Cap emicizumab dosing at the dose for a 100kg patients.
- EAG06: Assume that only 20% of bleeds incur the company hospital resource use estimate.
- EAG07: Assume a disutility for both joint and non-joint bleeds of 0.16, with this lasting an average 2.4 days
- EAG08: Revises the clinical effect estimates to be based upon UKHCDO ABRs coupled with the BASIS ABR rate ratios for marstacimab compared to FVIII/FIX, and for the haemophilia A and haemophilia B specific modelling compared to BASIS FVIII and BASIS FIX respectively.

The effect of these changes when using clinical effect estimates pooled across those with haemophilia A and haemophilia B is presented in Table 2 below, alongside results pooled across the comparison with emicizumab and the FVIII basket to provide estimates across haemophilia A patients and pooled across all patients, these each using UKHCDO market share data. The EAG also provides the equivalent of this using clinical effect estimates specific to those with haemophilia A and to those with haemophilia B in Table 59 in section 5.4.1.

Due to marstacimab being estimated to result in cost savings the cost effectiveness estimates are presented as net health benefits: the amount of additional QALYs that would result if these cost savings were reinvested in technologies with a cost effectiveness of £20,000 per QALY coupled with the direct QALY gains from marstacimab use.

Within this it should be noted that compared to emicizumab marstacimab at central estimates is [REDACTED] and also carries a slightly higher treatment burden due to its more frequent administration.

Table 2: EAG model changes - Pooled data - NHB QALYs at £20,000 / QALY

Comparator	Section	EMIC	FVIII	FIX	Ha	All
Company BC	4.2	*****	*****	*****	*****	*****
EAG01	4.5.1	*****	*****	*****	*****	*****
EAG02	5.3.1	*****	*****	*****	*****	*****
EAG03	5.3.2	*****	*****	*****	*****	*****
EAG04	5.3.6	*****	*****	*****	*****	*****

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EAG05	5.3.3	*****	*****	*****	*****	*****
EAG06	5.3.5	*****	*****	*****	*****	*****
EAG07	5.2.3	*****	*****	*****	*****	*****
	2.2.2.2,	*****	*****	*****	*****	*****
EAG08	2.5.3					
EAG01-EAG07		*****	*****	*****	*****	*****
EAG01-EAG08 ¹		*****	*****	*****	*****	*****

These results and those of Table 59 are most sensitive to:

- Whether marstacimab dose escalation increases beyond that which occurred during the ATP and the OLE October 2023 data cut and what is the final maximum proportion of marstacimab patients who would dose escalate.
- The mean FVIII/FIX dosing that is most reasonable to apply, and if based upon company estimates what the cut-off is for rounding down doses.
- Whether it is reasonable to differentiate clinical effect estimates by haemophilia A and haemophilia B, and if so whether it is reasonable to differentiate dose escalation rates between haemophilia A and haemophilia B.
- Whether the UKHCDO or BASIS should provide the ABR estimates for emicizumab and FVIII/FIX.

¹ These estimates are based upon the EAG pooling clarification data between haemophilia A and haemophilia B patients which resulted in an October 2023 OLE ABR for marstacimab of [REDACTED]. During FAC the company has pointed out that the pooled estimate is an OLE ABR of 2.880. This has minimal effect upon results. For instance, for the All Patient analysis EAG01-EAG08 the net costs change by -0.01%, the net QALYs by -0.07%, the NHB at £20,000 per QALY by -0.012% and the ICER in the NW quadrant by 0.06%. Due to the minimal effects of this correction and time constraints the EAG has not revised its OLE ABR estimate from [REDACTED] to 2.880. Note that this issue does not apply to the modelling where clinical effect estimates are differentiated by haemophilia type.

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 *Introduction*

1.1.1 Remit of this appraisal

To appraise the clinical and cost-effectiveness of marstacimab within its marketing authorisation for treating severe haemophilia A or severe haemophilia B in people 12 years and over.

1.1.2 Condition, epidemiology and symptoms, and economic burden

This section provides a summary and critique of the company overview of haemophilia, including symptoms and effects on quality of life. The CS provides a thorough examination of these factors in Section B.1.3.1 using a large number of citations. The EAG has focused the critique on key elements of relevance to the decision problem and selected references from primary studies only for checking. Overall the EAG considers that the CS provides an accurate summary of these factors.

Congenital haemophilia is a rare bleeding disease that follows an X-linked inheritance pattern and is characterised by a deficiency in clotting factors.¹ There are two main types of haemophilia: haemophilia A caused by a defect in factor VIII, and haemophilia B by a defect in factor IX (hereafter in the background referred to collectively as 'haemophilia' unless there are specific data by type).² Haemophilia predominately affects males.² Data from 60 UK haemophilia treatment centres show that in 2022-2023, there were 6,609 males living with haemophilia A and 1,305 males with haemophilia B in the UK.³ Although rarer, females may also be affected by haemophilia. In 2022-2023, 74 females with haemophilia A and 36 with haemophilia B were recorded in the UK.³

The CS describes the severity of haemophilia in Section B.1.3.1.2. Haemophilia can be mild, moderate or severe depending on the clotting factor levels in a patient's blood, which does not change over time.⁴ Clotting factor is either expressed as a

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percentage relative to normal human plasma or in international units (IU) relative to an international standard for FVIII or FIX in plasma.⁵ The normal level of clotting factor in the blood is 1 IU/mL / 100% (range 0.50–1.5 / 50%-150%).⁴ The focus of the current appraisal is on severe haemophilia. Patients with severe haemophilia have a clotting factor level of <1 IU/dL (less than 1%) and experience recurrent, often spontaneous, bleeding in muscles and joints.⁶ In 2022-2023, UK data show that there were 2,230 people (all ages) with severe haemophilia A and 374 people (all ages) with severe haemophilia B.³ The CS reports that in 2022/23 in the UK 2,128 people were treated for severe haemophilia A and 329 people were treated for severe haemophilia B;³ the EAG notes that these data include people of all ages. The EAG is unclear of the reasons why 5-8% of people with severe haemophilia are untreated. The focus of this appraisal is on those aged ≥ 12 years and the CS reports data from a bespoke analysis of the UKHCDO database conducted for Pfizer, which found that in 2022/23 [REDACTED] people aged 12 years or more were treated for severe haemophilia A and [REDACTED] were treated for severe haemophilia B.⁷

Severe haemophilia has a greater impact on people than mild or moderate haemophilia; repeated bleeding can lead to inflammation and pain, movement can be affected, and additionally people require regular access to treatment and healthcare services which impacts quality of life.^{5, 8} People with severe haemophilia can also suffer from other complications, such as increased fracture rates (due to a lower bone mineral density) and joint disease.^{9, 10} The CS reports the potential impact of severe haemophilia in Section B.1.3.1.5; much of the focus of this section is from analyses of the Cost of Haemophilia across Europe – a Socioeconomic Survey (CHESS)¹¹⁻¹³ and CHESS II^{10, 14} studies. These were real-world studies of people with severe haemophilia from five European countries (France, Germany, Italy, Spain and UK) between 2014 – 2015 and 2019 – 2020 respectively. Participants provided information on quality of life and adherence and also cost information such as work loss and out-of-pocket expenses. The EQ-5D-3L was used to assess health related quality of life. The EAG has checked the information reported in CS Section B.1.3.1.5 with the source data where possible and concurs with the CS that severe haemophilia, and in particular the recurrent bleeding episodes into joints, can lead to more pain and worse HRQoL.^{10, 11, 13} There is also the potential for an economic burden on an individual from greater likelihood of

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unemployment¹⁵ and from the direct and indirect costs of treatments.¹¹ Clinical advice to the EAG is that many people with haemophilia have significant musculoskeletal comorbidity and this is particularly the case for older people who have not received prophylaxis since childhood.

Despite improved treatments for haemophilia, the CS makes the case that haemophilia may still be associated with a lower life expectancy compared with the general population, citing data from an epidemiological study undertaken in the Netherlands. This study followed 1066 people with haemophilia between 2001 and 2018 and found mortality was increased compared with the general Dutch male population.¹⁶ The study data also suggested a higher risk of mortality in those with severe haemophilia, but study authors noted limitations including changes in treatments over time and not having data for all potential determinants of mortality and confounding variables which need to be considered.¹⁶ The CS also refers to data reporting the median life expectancy for people with severe haemophilia A and B, which were 77 and 79 years, respectively, in those registered between 1996 and 2023 in the UKHCDO database. The UKHCDO 2023 report states these values are 84 and 85 years, respectively, for individuals with mild haemophilia.³ The view of the EAG clinical advisers, however, is that life expectancy in the UK is very similar to the general population.

1.1.3 Current treatment pathway

The CS provides an overview of current clinical treatment options in Section B.1.3.2.1. Both haemophilia A and haemophilia B require lifelong treatment. Treatment aims to prevent bleeding episodes.²

The traditional standard-of-care for haemophilia A and B involves supplementing clotting factors through factor replacement therapy.² This therapy can be administered on-demand (in response to a bleeding episode) or prophylactically (to prevent bleeding episodes), or a combination of both. The EAG clinical advisers agree with the CS that on-demand treatment alone is only used by a minority of patients with severe haemophilia in the UK.¹⁷ Factor replacement is given through intravenous infusions of varying dosing regimens. Factor replacement therapies can

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be subdivided into standard half-life (SHL) and extended half-life (EHL) therapies, with the latter being longer-acting and therefore administered less frequently.²

Haemophilia A can also be treated with emicizumab, a non-factor replacement treatment which is available in the UK for people with severe haemophilia A following NHS Clinical Commissioning Policy approvals.^{18, 19} Emicizumab is used as a prophylaxis and is self-administered subcutaneously following a weight-based dosing regimen, either once weekly, once every two weeks or once every four weeks.²⁰ There is currently no equivalent treatment for people with haemophilia B.³

Figure 5 in the CS provides an overview of the available standard of care products for both haemophilia A and B respectively, and CS Tables 5 and 6 report the rates these products are used in the UK based on confidential sales data and data from the UKHCDO, reported as international units and days of therapy.³ The CS states that these rates are similar to those provided by UK clinical experts; that over 50% of severe haemophilia A patients received emicizumab, and that EHL products are used significantly more than SHL products in both severe haemophilia A and B. Clinical advice to the EAG concurs that generally around half of men with haemophilia A are treated with emicizumab, although in some centres now emicizumab is the standard of care and rates may be higher. Clinical advisers also noted that EHLs in general require less frequent dosing and most people would use an EHL for prophylaxis. One expert noted that SHLs are easier to use for managing breakthrough bleeds and for surgery, but for some minor procedures EHLs would be used to minimise the number of required doses.

Some people with haemophilia develop antibodies against the factor replacement therapies called inhibitors.² About 30% of patients with haemophilia A develop inhibitors to factor VIII, and up to 5% of people with haemophilia B develop inhibitors to factor VIII.⁵ Clinical advice to the EAG is that there are several risk factors that contribute to some people developing antibodies while others do not, including genetics, ethnicity, age, intensity of first treatment and environmental factors. Often linked to disease severity, inhibitors are more common among people with severe haemophilia.⁵ Inhibitors decrease the effectiveness of factor replacement therapy and pose a challenge in the management of bleeding episodes.²¹ Patients with

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inhibitors need specific monitoring and may require additional treatments called bypassing agents or alternatively treatment with emicizumab.^{5, 21}

Gene therapies are at various stages of development and approval and may offer life-long cures for haemophilia A or B in the near future.²² Etranacogene dezaparvovec for moderately severe or severe haemophilia B was recommended with managed access by NICE in July 2024.²³ NICE guidance on efanesoctocog alfa for haemophilia A and fidanacogene elaparvovec for haemophilia B are both currently in development (expected publication dates to be confirmed).^{24, 25}

1.1.4 Marstacimab mechanism of action

Marstacimab is a human monoclonal antibody, specifically immunoglobulin G isotope subtype 1 (IgG1), that targets the Kunitz 2 domain of the protein, tissue factor pathway inhibitor (TFPI).²⁶ TFPI is an anticoagulant protein that prevents blood clot formation by inhibiting tissue factor-activated FVII (FVIIa) and activated FX (FXa) (see CS, Figure 2). By binding to and neutralising TPFI, marstacimab alters the extrinsic clotting pathway to promote blood clotting.²⁶ Marstacimab's regimen involves an initial one-off loading dose followed by a weekly, flat dose, subcutaneous self-injection through a pre-filled syringe (PFS) or pre-filled pen (PFP) device.^{27, 28}

Marstacimab does not currently have marketing authorisation for any indication in the UK. The company has a submitted application for marketing authorisation to the European Medicines Agency (EMA) and a positive CHMP opinion was granted on 19th September 2024. The CS anticipates that following EMA review [REDACTED]

[REDACTED]. The anticipated date of GB marketing authorisation is [REDACTED].

1.1.5 Proposed placement of marstacimab in treatment pathway

The company states that marstacimab differs from factor replacement therapies as it is administered subcutaneously (as opposed to intravenously), which may improve patients' quality of life.²⁹ CS Section B.1.3.3.1 describes an unmet need for a treatment that is convenient and simple to administer, making the point that there is

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currently no self-administered subcutaneous treatment for haemophilia B available and that the self-administered subcutaneous treatment available for haemophilia A is complex to administer due to the weight-related dosing. The CS describes how the treatment burden on individuals has an additional emotional impact for individuals who already have a number of day-to-day challenges. The company considers that a more convenient method of administration could improve confidence in self-administration, adherence, and have a positive effect on patient outcomes, although no direct evidence was provided to support this and the EAG has not been able to identify any. The EAG clinical advisers commented that it is not a significant burden for patients to account for any changes in their dosage of haemophilia treatments due to weight changes as their weight is monitored in clinic and doses are adjusted accordingly. EAG experts also considered that compliance with emicizumab in haemophilia A is very good.

The CS proposes that in haemophilia A, marstacimab would be considered at the same line in the treatment pathway as emicizumab. The EAG clinical experts consider that while marstacimab would provide another treatment option, it would be unlikely a patient already receiving emicizumab would be switched from emicizumab to marstacimab unless emicizumab was found to be ineffective. If marstacimab is unlikely to displace any usage of emicizumab, then it raises the question of whether emicizumab is a relevant comparator, however the EAG considers this of low importance given that comparisons with FVIII are already provided. In the clinician's experience there is a very small number of people in whom emicizumab is less effective than FVIII and who have been switched back to FVIII. Clinical advice to the EAG was that for people with haemophilia B, the subcutaneous administration of marstacimab (as opposed to intravenous administration of factor) would be a benefit.

1.2 Critique of company's definition of decision problem

The EAG's comments on the company's decision problem can be seen in Table 3. There are some differences between the company decision problem and the final NICE scope, but the EAG has no major concerns. The evidence provided in the submission for marstacimab is aligned with the decision problem population.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with severe haemophilia A or severe haemophilia B aged 12 years and over	People with severe ^a haemophilia A, without FVIII inhibitors, or severe ^a haemophilia B, without FIX inhibitors, aged 12 years and over	As per the technology's full marketing authorisation	The EAG agrees that the population addressed in the company's decision problem is in line with anticipated marketing authorisation. However, the NICE scope did not limit the population to people without inhibitors, and it identified the development of inhibitors as a subgroup for consideration where evidence allows. This subgroup is not included in the CS.
Intervention	Marstacimab	Marstacimab	As per the final scope	The EAG agrees that the intervention is in line with the NICE scope. A positive EMA CHMP opinion was granted on 19 September 2024. Anticipated EU marketing authorisation is [REDACTED] and GB marketing authorisation is [REDACTED]. The anticipated marketing authorisation is for [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Comparator(s)	For people with severe haemophilia A: - Established clinical management, including: prophylaxis (with or without on-demand treatment) with FVIII replacement therapy (including efanesoctocog alfa – subject to NICE evaluation) emicizumab (in accordance with NHS England's clinical commissioning policies) For people with severe haemophilia B: - Established clinical management, including: prophylaxis (with or without on-demand treatment) with FIX	For people with severe haemophilia A: - Established clinical management, including: prophylaxis (with or without on-demand treatment) with FVIII replacement therapy emicizumab (in accordance with NHS England's clinical commissioning policies) For people with severe haemophilia B: - Established clinical management, including: prophylaxis (with or without on-demand	- The proposed comparators are in line with the NICE final scope - The NICE evaluations of efanesoctocog alfa and fidanacogene elaparvovec are still ongoing at the time of submission; these products are therefore not routinely used in clinical practice and as such, they are not considered relevant comparators in this evaluation^{24, 25, 30} - NICE have recently released final draft guidance recommending etranacogene dezaparvovec as	The EAG agrees that the relevant comparators are routine prophylaxis with FVIII replacement therapy (for haemophilia A) or FIX replacement therapy (for haemophilia B). The EAG also agrees that emicizumab should be considered as a comparator for haemophilia A, but notes the concerns of the clinical experts regarding the position of marstacimab in the treatment pathway (section 1.1.5). NICE guidance on efanesoctocog alfa for haemophilia A and fidanacogene elaparvovec for haemophilia B are both in development (expected publication dates to be confirmed).^{24, 25} Etranacogene dezaparvovec for haemophilia B was recommended with managed access by NICE in July 2024²³ and is therefore not considered established practice. The EAG agrees that recombinant activated coagulation factor VII (for people with inhibitors) is not an appropriate comparator for the population defined in the company's

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	replacement therapy Etranacogene dezaparvovec (subject to NICE evaluation) Fidanacogene elaparvovec (subject to NICE evaluation) Recombinant activated coagulation factor VII (for people with inhibitors)	treatment) with FIX replacement therapy	a treatment option for patients with moderately severe or severe haemophilia B but final guidance is yet to be published.³¹ Additionally, this recommendation included a managed access agreement. As per NICE guidelines, etranacogene dezaparvovec is therefore not considered established practice and is not a suitable comparator in this appraisal^{31, 32} • In line with the anticipated marketing authorisation for marstacimab, recombinant activated coagulation factor	decision problem (i.e. people without inhibitors). The EAG agrees that on-demand treatment on its own is not standard of care in the UK, and in line with the NICE scope is not a relevant comparator.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			VII is not a relevant comparator in this evaluation On-demand treatment on its own is not recommended for use in patients with severe haemophilia, as per WFH and BSH guidelines.^{5, 33} Therefore, the decision problem addressed in the submission will consider on-demand treatment only in the context of treating bleeding events on top of prophylactic treatment regimens	
Outcomes	The outcome measures to be considered include: • annualised bleeding rate (ABR) • need for on-demand treatment with FVIII or FIX injections • durability of response to treatment • complications of the disease (e.g. joint	Outcomes addressed in the submission include: • ABR (total bleeds and treated bleeds) • need for on-demand treatment with factor VIII or IX injections • durability of response to	As per the final scope	The EAG considers the following outcomes to be addressed in the submission: • ABR • joint health, but not joint surgeries specifically • mortality • health-related quality of life The need for on-demand treatment during the key trial was not reported but was included in the economic

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	problems and joint surgeries) • mortality • adverse effects of treatment • health-related quality of life	treatment • complications of the disease (e.g., joint health) • mortality • adverse effects of treatment • health-related quality of life		model in the form of acute bleed event management costs. Durability of response to treatment was not specifically addressed.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per the final scope	As per the final scope	The EAG considers that the model and analyses presented by the company adhere to the reference case.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	Costs will be considered from a NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups	If evidence allows subgroups will be considered based on: • Haemophilia type (A or B) Development of inhibitors	Subgroups considered in the submission include: Haemophilia type (A or B)	Pre-planned subgroup analyses of the BASIS trial by haemophilia type (A or B) have been presented in Section B.2.8. These data also informed scenario analyses in the cost-effectiveness analysis. The small sample sizes and lack of powering associated with these subgroup analyses mean these should be interpreted with caution.	The EAG acknowledges the subgroup analysis by haemophilia type (A or B) and agrees with the company's concerns regarding sample size. However, the EAG also notes that the indirect treatment comparison is limited to haemophilia A. This is appropriate since the marketing authorisation for the comparator (emicizumab) is limited to haemophilia A.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			The anticipated licensed indication is for 'people with severe haemophilia A, without FVIII inhibitors, or severe haemophilia B, without FIX inhibitors, aged 12 years and over'. Therefore, only data from the relevant population of patients in the BASIS trial without inhibitors are presented within this submission.	
Special considerations including issues related to equity or equality	None specified in the final scope.	This submission covers all people with severe haemophilia including females, people with HIV, or those with historical hepatitis B or hepatitis C infection	The Phase 3 BASIS trial did not include females. NICE should ensure that recommendations do not discriminate based on sex. Additionally, NICE should ensure that recommendations do not discriminate against people with HIV or historical hepatitis B or C infection	The EAG notes that females, people with HIV uncontrolled by antiretroviral drugs, active hepatitis B or active hepatitis C were excluded from the trial. The EAG clinical experts consider that the evidence is generalisable to females.

2 CLINICAL EFFECTIVENESS

2.1 Critique of the methods of review(s)

CS Appendix D reports a systematic literature review (SLR) to identify evidence on the efficacy and safety of marstacimab and relevant comparator therapies. Searches were originally undertaken in August 2020 (“original SLR”), then updates run in August 2023 and May 2024. The company’s response to clarification question A43 explains that the SLR undertaken in 2020 included both clinical and economic evidence, but separate clinical and cost effectiveness searches, screening and reporting were undertaken from 2023 onwards.

2.1.1 Search strategies

CS Appendix D.1.1 describes the literature search sources and strategies. A good, appropriate range of databases and other sources were searched, including clinical trials registries and proceedings of recent conferences. Some changes to the searches were made between the 2020 original SLR and the 2023 update (partly reflecting the splitting of clinical and economic SLRs); these are all sensible changes and would not have compromised the quality of the review.

The EAG has some concerns about the quality of the search strategies (Appendix D.1.1, Tables 1-14), including the use of the same search terms across both Embase and MEDLINE, which is not best practice as the databases have different controlled vocabularies (Emtree vs MeSH). Some important Emtree terms such as ‘Controlled clinical trial’ and ‘Double blind procedure’ were missed, and some MeSH terms (‘Randomized controlled trial’, ‘Clinical trial’) should have been exploded to include narrower terms like ‘Clinical Trial, Phase I/II/III/IV’. Additionally, in Embase (Tables 1-3) a limit to “article or article in press” is used (line 10); this limit did not work when tested by the EAG and, if functioning, would risk missing useful papers not yet indexed or defined as an ‘article’.

Despite the limitations identified, when the EAG ran a targeted MEDLINE search (see Appendix 7.2) for trials or systematic reviews on marstacimab or emicizumab, no additional studies that should have been included in the company’s SLR were identified.

2.1.2 SLR Methods

The methods of the company SLR were reviewed by the EAG using a modified ROBIS tool.³⁴ The full assessment can be found in Appendix 7.1. The EAG assessment of the overall risk of bias of the SLR was high concern. The initial SLR applied pre-defined eligibility criteria and the steps taken to select studies minimised the potential for errors. However, limited summary details of the 79 studies initially included in the SLR were reported in CS Appendix Table 17 and there was no synthesis or risk of bias assessment for these studies.

In addition, to determine eligibility of studies for the ITC the company undertook two feasibility assessments of potential studies. The EAG had concerns that not all eligibility criteria were pre-specified and for some criteria there was no justification reported. The steps taken to assess studies against the eligibility criteria were also not stated. However, the EAG generally agrees with the exclusion of most of these studies from the ITC. The exception is the exclusion of the HAVEN 4 study which the EAG considers relevant, see section 2.3 for more details.

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

2.2.1 Trial design

The source of evidence for the assessment of clinical effectiveness of marstacimab for treating severe haemophilia A or B in people 12 years or over is from a single study, BASIS (NCT03938792), and its open-label extension (OLE) study (NCT05145127). A Phase 2, dose-investigation study of marstacimab³⁵ is also cited by the CS, but results are not presented. The EAG agrees there are no data of relevance in this study.

BASIS is a Phase 3 open-label multicentre study conducted across 19 countries, including some sites in Europe, but none were in the UK. It is described as a one-way crossover study by the CS. All participants received their current treatment (on-demand therapy or prophylaxis factor replacement therapy) during a 6-month

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observational phase (OP), then received marstacimab for a 12-month active treatment phase (ATP). The study therefore provides a comparison of marstacimab and factor replacement therapy within the same participants. The population of BASIS is comprised of a number of cohorts of participants, some of which are not relevant to this appraisal, this is discussed further below. The cohort and comparison of relevance in BASIS is people without inhibitors receiving prophylaxis therapy during the OP.

Participants who did not require early termination in BASIS could enter the OLE and continue treatment for up to 16 additional months. Both BASIS and its OLE are ongoing. The CS presents analysis from the 17th April 2023 data-cut for BASIS, and interim analysis from the 10th March 2023 for the OLE (with an additional limited 4-month interim data-cut conducted in October 2023 and provided to the EAG at clarification). Results from BASIS³⁶ and the OLE³⁷ have been published as abstracts only. In clarification A32 the company confirmed that they are unable to provide a copy of the draft manuscript for the BASIS study but that updates on the status of the publication will be provided during the appraisal. The company also confirmed in clarification A14 that the final CSR of the BASIS OLE is anticipated in quarter four 2030 but that data for another interim analysis is anticipated to be available in October 2024.

CS Figure 6 summarises the study design of BASIS. A summary of BASIS methodology with cross-references to the relevant sections of the CS where more detail can be found is presented in Table 4. Areas that the EAG has identified for further consideration are described below.

Table 4: Summary of BASIS trial and OLE methodology

Method step	Summary details	Section(s) of CS of relevance or other source
Study enrolment	All participants entered the 6-month OP (receiving their current standard or care) followed by a 12-month ATP. Participants could then continue into the 16-month OLE.	B.2.2, Figure 6

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Eligibility criteria	Eligibility criteria were the same for BASIS and the OLE. For the cohort relevant to this appraisal (non-inhibitor cohort, on routine factor prophylaxis): • Male • Aged 12 to <75 years • Diagnosis of severe haemophilia A (FVIII <1%) or moderately severe to severe haemophilia B (FIX ≤2%) • Minimum weight of 35 kg at screening • No detectable or documented history of inhibitors (pre-defined in the trial protocol) • FVIII/FIX routine prophylaxis with ≥ 80% compliance during 6 months prior to enrolment and willing to continue during the OP Prior to receiving marstacimab in the ATP, participants must meet the following criteria: • confirmed fibrinogen level ≥LLN • confirmed prothrombin time ≤1.25 × ULN • remained on same treatment regimen throughout OP • at least 80% compliant during OP • no detectable or documented history of inhibitors during OP	B.2.3.1.1, Table 8, Appendix M.1.1.
Trial drugs by period of study	OP: continued with prior prophylactic factor replacement therapy ATP: marstacimab 300 mg SC loading dose followed by 150 mg once weekly. After 6 months, participants meeting dose-escalation criteria could receive 300 mg SC once weekly.	B.2.3.1.1, Table 7, Table 8
Primary endpoints of	Annualised bleeding rate for treated bleeds (ABR _{treat}) at 12 months post-marstacimab initiation	B.2.3.1.1, Table 8

relevance to the decision problem		
Key secondary endpoints of relevance to the decision problem	Annualised joint bleeding rate (AJBR), spontaneous bleeds, target joint bleeds and total bleeds (treated and untreated) Number of patients with no treated bleeds Change in joints as measured by HJHS Patient reported outcomes and HRQoL: • HAL/pedHAL • PGIC-H • Haem-A-QoL/Haemo-QoL • EQ-5D-5L	B.2.3.1.1, Table 8

ATP: active treatment phase; Haem-A-QoL: Haemophilia A Quality of Life for adults; Haemo-QoL: Haemophilia Quality of Life Questionnaire for Children; HAL: Haemophilia Activities List; HJHS: Haemophilia Joint Health Score; OP: observational phase; pedHAL: Pediatric Hemophilia Activities List; PGIC-H: patient global impression of change – haemophilia.

2.2.1.1 Population and eligibility

Men aged 12 to <75 years with severe haemophilia A (coagulation FVIII activity < 1%) or moderately severe to severe haemophilia B (coagulation FIX activity ≤2%) were eligible for BASIS. However, no patients with moderately severe haemophilia B were enrolled, so the population comprised only those with severe disease. The minimum age and severity of disease criteria in BASIS are in line with the NICE scope and anticipated marketing authorisation (MA), although limits on sex or upper age are not specified by NICE [REDACTED]

To be eligible for inclusion in BASIS, participants had to demonstrate at least 80% compliance with the scheduled prophylaxis regimen during 6 months prior to enrolment. To enter the ATP, participants had to demonstrate at least 80% compliance during the OP. In clarification A1, the company stated that compliance prior to enrolment was confirmed by the investigator, but did not explain how this was assessed. Compliance during the OP was monitored by sites and study teams and involved the use of an eDiary. The EAG has no concerns regarding the low numbers

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of participants who did not meet inclusion criteria or discontinued due to compliance (clarification A1).

People with active hepatitis B or C, or HIV uncontrolled by antiretroviral drugs were excluded from the study. The EAG clinical expert noted that this group of patients tend to be older, so may not have been on effective prophylaxis since childhood and may have more established joint disease and bleed more frequently.

Results are presented in the CS for a selected subgroup of participants from BASIS based on:

1. whether or not participants had inhibitors: only those without inhibitors were reported (*non-inhibitor cohort*);
2. whether participants were receiving on-demand therapy or factor prophylaxis therapy at OP entry and during the OP: only those receiving *prophylaxis therapy* were reported.

The patient cohorts were specified *a priori* in the BASIS protocol, see CS Figure 6. The CS and the submitted CSR do not present results for people who had inhibitors at OP entry. Inhibitor testing was conducted in the ATP at day 180 and study completion (day 360) and on days 180 and 360 or study completion of each year of the OLE. There were ■ participants in the prior prophylaxis cohort of BASIS who were identified as having a change in inhibitor status during the ATP (clarification A6). The EAG does not consider this ■■■■■ to be a concern

The CS also does not present results for people who received on-demand therapy at screening and during the OP (although these are available in the CSR). On-demand therapy is not specified as a comparator by the NICE scope, therefore this omission is appropriate. The cohort of participants without inhibitors is in line with the anticipated MA for marstacimab, and the comparison with routine factor prophylaxis therapy is appropriate.

2.2.1.2 Interventions

During the OP, participants continued with their routine factor FVIII or FIX replacement prophylaxis for 6 months. A breakdown of factor therapies used during

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the OP was provided by the company in clarification A23 and is presented in Table 5. It appears that none of the participants were receiving emicizumab, which the CS notes is considered standard of care for haemophilia A (CS B.1.3.2). In addition, [REDACTED] participants were receiving extended half-life agents than would be seen in the UK. The EAG clinical experts considered it likely that in general, the participants in BASIS were not on prophylaxis comparable to current UK standards of care.

Table 5: Factor therapies used during OP of BASIS

	Routine prophylaxis during OP (N=83)
[REDACTED]	[REDACTED]
Antihaemophilic factor (recombinant), pegylated AUCL	[REDACTED]
Jivi®	[REDACTED]
Elocta®	[REDACTED]
Alprolix®	[REDACTED]
Adynovi®	[REDACTED]
[REDACTED]	[REDACTED]
FIX	[REDACTED]
FIX Human	[REDACTED]
FVIII (Antihemophilic factor)	[REDACTED]
FVIII (Antihemophilic factor); Von Willebrand factor	[REDACTED]
FVIII, recombinant	[REDACTED]
ReFacto AF®	[REDACTED]
BeneFIX®	[REDACTED]
Advate®	[REDACTED]
NovoEight®	[REDACTED]

Source: Clarification A23 Table 3.

EHL: extended half-life; OP: observational phase; SHL: standard half-life.

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After the OP, participants who met additional criteria (Table 4) progressed to the ATP. Marstacimab was administered as a loading dose of 300 mg subcutaneous (SC) (as 2 x 150 mg injections) followed by 150 mg once weekly in a prefilled syringe for 12 months. After 6 months, participants who met protocol specified dose-escalation criteria could have their dose increased to 300 mg once weekly at the discretion of their clinician. The criteria were:

1. Weight at least 50kg
2. Two or more spontaneous bleeds (consisting of joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of coagulation FVIII or FIX over a 6-month period in the absence of a confirmed FVIII or FIX inhibitor, respectively. Significant spontaneous bleeds were defined as those that lead to a transient or persistent loss of function.²⁷

Breakthrough bleeding during the study was stabilized using the participant's standard haemostatic treatment regimen, which may include FVIII- or FIX replacement therapy.

The dose of marstacimab and the potential for dose escalation remained the same during the OLE, however the mode of administration changed from prefilled syringe to prefilled pen. This is discussed in section 2.5.4.

2.2.1.3 Outcomes

Measures of bleeding

The BASIS trial protocol adheres to the World Federation of Hemophilia (WFH) guidelines for the classification and documentation of bleeding events. The definitions in the BASIS study are as follows.

Bleed: a bleed was classified as either "spontaneous" or "traumatic," with specific criteria for each type outlined below. Any indication of a bleed, whether it led to the administration of medication or treatment, was documented as a "bleed" or "bleeding episode", see further definitions below.

Spontaneous bleeding episodes: a bleeding event without any known contributing factor, such as definite trauma, strenuous activity, or overuse. The determination of

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what constituted "strenuous" or "overuse" was left to the discretion of the participant, caregiver, or investigator.

Traumatic bleeding episodes: known or presumed contributing factor or reason for the bleed. For instance, if a participant exercised strenuously and subsequently experienced a bleed without any obvious injury. Bleeding episodes in target joints could be classified as traumatic if a specific action or event was known to have triggered the bleeding into the joint.

Treated bleed: treatment with factor replacement or bypassing agents within 48 hours of the onset, regardless of whether the treatment is preventive, prophylactic, or administered on-demand.

New treated bleed: occurred at the same location more than 72 hours after treatment for the initial bleed had stopped, or if it occurred at a different site, regardless of the time since the previous bleed.

New untreated bleed: occurred more than 48 hours after a previous untreated bleed at the same location, or more than 72 hours after the cessation of treatment for the original bleed for which treatment was initiated. An untreated bleed occurring at a different location was considered a new untreated bleed, regardless of the time since the previous bleed.

Bleed data were recorded in an electronic handheld device which was provided to each participant at baseline (if not available a paper copy was provided). Participants were given training which included the timing and the nature of information to be entered in the diary, including the location of the bleed. In the final protocol amendment (22nd March 2022) Section 6.4 was amended to state that the eDiary data must be reviewed at each study visit (telephone or in-person). This was to reinforce the need for the diary data review at each scheduled contact, to ensure data accuracy (the diary was also used to record dosing details and adverse events). Bleeding episodes from participant diaries were validated with medical records. The investigators also assisted in the classification of the bleed if necessary. Training materials and user guides were provided to study sites and to participants; no further details were available in the CS. All data were time-stamped and automatically uploaded to a database in real time. Investigators were responsible for informing

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participants of their data entry schedule and monitoring compliance via an electronic portal, with automatic notifications for any missed entries.

Measuring the ABR is an important indicator of patient outcomes. Bleed data were considered in the BASIS trial as annualised bleeding rates (ABR) according to two definitions. ABR_{treat} recorded the number of treated bleeding episodes during the 12-month ATP, this was the primary endpoint of the trial. ABR_{total} recorded the number of both treated and untreated bleeding during the 12-month ATP and was a secondary endpoint. ABR_{total} accounts for all bleeds, including those that, although not treated, still impose a burden on the patient. ABR_{treat} was also assessed for bleeding by type, such as spontaneous, joint, and target joint bleeds. Bleeding measured as ABR is the gold standard outcome measure in haemophilia, it is a clinically meaningful, valid, and reliable measure, although is partially subjective.^{5, 38} The ABRs calculated in the BASIS trial are in-line with the recommendations of the WFH.⁵ However, although ABRs are frequently used as a primary endpoint, they are subject to several biases, including the subjective nature of how patients and physicians define and report bleeding events.^{39, 40}

Joint health

An additional efficacy endpoint in the BASIS trial was the Hemophilia Joint Health Score (HJHS), which assesses joint health in the joints most frequently affected by haemophilia. The HJHS is a valuable tool in haemophilia management as it provides a standardised method to assess joint health, enabling clinicians to identify early signs of joint deterioration and to monitor the effectiveness of treatments over time.^{41,}

⁴² It evaluates various aspects of joint health across six joints (elbows, knees, ankles), with the following items being scored on scales ranging somewhere between 0-4: swelling, duration of swelling, muscle atrophy, crepitus during movement, flexion loss, extension loss, joint pain, and strength. Each joint can achieve a maximum score of 20. Gait is also assessed with a score ranging from 0-4. The tool has a maximum possible total score of 124 where higher scores indicate poorer joint health. The tool is designed to be used by physiotherapists, in BASIS training of the tool was provided. The HJHS is considered the best studied measure of joint health and has been validated in children and adults with

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haemophilia.^{5, 42} Its use in clinical practice, however, is limited owing to the time taken to administer the tool.³⁸

Patient reported outcomes

Patient-reported outcomes (PROs) were systematically recorded using an electronic device referred to as a 'site tablet' during study visits. Five measures were used: the EuroQoL 5 Dimensions 5 Level (EQ-5D-5L); the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) and for Children (Haemo-QoL); the Hemophilia Activities List (HAL); the Pediatric Hemophilia Activities List (pedHAL); the Patient Global Impression of change Hemophilia (PGIC-H) and the Hemophilia Life Impacts Questionnaire (HLIQ). Participants were asked to complete these measures at scheduled office visits before any other study activities (OP Baseline and ATP Visits 6, 7, 10, 12, 14, 16, and 20).

The EAG briefly summarises below the haemophilia specific PROs to provide more context about what they measure, how the scores are interpreted and their validity and reliability.

Haem-A-QoL and Haemo-QoL

These are disease-specific measures of health-related quality of life (HRQoL) for haemophilia patients, tailored by age. The Haem-A-QoL is used for participants aged 17 years and older, with 46 items across 10 domains, including physical health, feelings, and treatment. This measure provides insights into how haemophilia affects daily life and overall well-being.⁴³ The Haemo-QoL is for participants aged 12 to <17 years, comprising 77 items across 12 domains similar to the Haem A QoL. Items are rated as 'never', 'seldom', 'sometimes', 'often' or 'always' for a 4-week recall period. For both versions the scores can be calculated by domain and as a total, the CS presented data for the physical health domain and the total score only. Scores range from 0 to 100 with lower scores indicating better HRQoL. There is a risk of recall bias with these tools due to the need to remember events that occurred over an extended period in the past. It's also important to consider that cultural differences can influence how questions are interpreted, which may affect the accuracy of the

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results.⁴⁴ Nevertheless, this tool is generally regarded as reliable, consistently producing similar results when administered multiple times to the same individual.⁴⁵

HAL (version 2) and pedHAL

These are also disease-specific HRQoL measures for haemophilia, based on age. Both tools help in evaluating the physical impact of haemophilia on daily activities and can guide rehabilitation and physical therapy.⁴⁶ The HAL assesses the functional abilities of adults (aged 17 and older) with haemophilia by focusing on physical activities potentially limited due to joint damage or bleeding episodes. HAL evaluates functional impact through 42 items across seven domains:

Lying/Sitting/Kneeling/Standing, Lower Leg Functioning, Upper Arm Functioning, Self-care, and Sports/Leisure. Similar to HAL, pedHAL is for children (aged 12 to <17 years), focusing on age-appropriate activities, and assesses 53 items across the same seven domains.⁴⁷ Scoring can be by domain or total, additionally for HAL scores can be by components such as activities involving the upper extremities only. The CS only reported these measures total scores in BASIS. Scores range from 0 to 100 in both instruments, higher scores indicate better status. As discussed above, it's important to account for recall bias when evaluating these measures.⁴⁴

PGIC-H

This tool captures the patient's subjective assessment of overall change in health status due to treatment, providing a patient-centred outcome that is simple and quick to administer.⁴⁸ It is an assessment of the participant's overall impression of change in their life with haemophilia. This was used to measure the participant's impression during the two phases of the BASIS study (OP and ATP). The PGIC-H asks participants to reflect on changes "since the start of the study" or "since the infusion," using a 7-point categorical scale with three grades of improvement, three of worsening, and a central 'no change' option. It is noteworthy, that subjectivity can introduce variability in responses, as patients' perceptions may be influenced by factors unrelated to the treatment.⁴⁹ Additionally, as mentioned previously, recall bias may impact accuracy, particularly if patients are asked to remember how they felt before starting treatment.⁴⁴

HLIQ

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This tool is designed to evaluate the impact of haemophilia across various aspects of life, including physical, emotional, and social dimensions. By providing a comprehensive view of how haemophilia influences daily living, it helps researchers identify specific areas where intervention may be needed.⁵⁰ This is a 9-item measure evaluating the impacts of living with and being treated for haemophilia, with a recall period of the past week. It was an exploratory endpoint in BASIS. It includes four items rated on a 5-point ordinal verbal rating scale (VRS) from 0 to 4; four items that use a branching format where a 'yes' response leads to a 5-point VRS and where a 'no' response specifies reasons for not participating in the activity (due to haemophilia or other reasons), and one item rated on a 4-point ordinal VRS from 0 to 3. Questions include items such as 'how much was haemophilia on your mind', 'how much did haemophilia interfere with your ability to perform day to day activities' and 'did you participate in any social activities'. Higher scores on the VRS indicate a greater impact of haemophilia on daily life or treatment.

Each of these tools provides unique insights into the lives of individuals with haemophilia, focusing on quality of life, functional abilities, and perceived health changes. Although all are validated and reliable, potential issues such as recall bias, cultural differences, and subjectivity must be considered in the interpretation of results.

2.2.1.4 Risk of Bias

BASIS is described by the company as a one-way crossover study; the design is justified in the study protocol by a sample size advantage and to allow assessment of potential confounding factors in a rare disease. The company conducted a quality assessment of BASIS using a modified version of the Downs and Black checklist. The EAG agrees that this checklist is appropriate for the design of BASIS and that the modifications are acceptable. However, the company has focused on the overall summary score and has not discussed any of their responses that suggest a source of bias. The use of summary scores is no longer recommended.⁵¹ The EAG conducted an independent assessment of quality; a comparison of the company's and EAG's judgements is presented in Appendix 7.3. The first section of the tool

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focuses on reporting of the study, and as BASIS has not been published as a full article the EAG has based their judgements on the reporting of the study in the CS.

In contrast to the company, the EAG considers the external validity of BASIS (questions 11 to 13) to be unclear, because the CS does not identify the population that the participants were sourced from or describe how the patients were selected. It is unclear whether the population is representative of the target population in the UK and thus whether outcomes for the study population can be generalised to the UK population. The CS reports the number of participants screened but not the number of participants who were asked to participate, and does not demonstrate that the distribution of the main confounding factors was the same in the study sample and the source population. Additionally, the CS does not clearly demonstrate that location and delivery of the intervention was representative of that in use in the source population. The protocol states 'when necessary, the site staff may administer study intervention to the participant', but the impact of this is not clear. Question 21 also asks if all participants were recruited from the same source population, so this was also considered to be unclear by the EAG.

The EAG agrees with the company's judgement that principal confounders were not clearly described or adjusted for in the analysis, and that there was no blinding of outcome assessment, which is possible even in an open-label study. The bleed data outcomes were self-reported, and untreated bleeds are subjective. The EAG clinical expert considered that it is possible that not all recorded untreated bleeding episodes are bleeding events (for example, they may be musculoskeletal pain without bleeding).

The design of BASIS meant that patients receiving marstacimab were compared with the same patients who had previously been receiving factor prophylaxis and therefore each patient acts as their own control, with the potential for known and unknown factors changing between the time-periods. It is unclear whether there were any differences in the care participants received, either intentionally or unintentionally, during the OP and ATP. The company notes in section CS B.2.12.1 that many participants entered the ATP in early 2022 as COVID-19 rates were rising, and that 21.7% of participants experienced COVID-19 during the ATP. COVID-19 was designated as an adverse events of special interest (AESI) due to its potential to

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increase the risk of thrombotic events. Changes in activity levels during lockdown may also have had an impact on real-world haemophilia care; the EAG clinical expert considered that bleeds may have been less well treated, as patients may not have attended hospital for review. The EAG notes, however, that in TA989,²³ the committee concluded that the pandemic did not have a substantial impact on the magnitude of clinical benefits in the trial of etranacogene dezaparvovec for treating moderately severe or severe haemophilia. The company provided additional details of the impact of COVID-19 on the conduct of BASIS in clarification A24; the EAG has no concerns regarding this.

There was no washout-period between the OP and ATP, however sensitivity analyses were available in the CSR to assess the impact of a carryover effect from the OP.

2.2.1.5 Participant flow and analysis sets

Participant flow for the cohort without inhibitors through BASIS is presented in CS Appendix D.2, Figure 3. Of 179 patients, 47 (26.3%) failed screening and another four did not enter the OP (due to adverse event, withdrawn, or assignment after data cut off). The EAG considered this to be a high proportion of screening failures and requested reasons for failing screening in clarification A7. In response, the company stated that there was a typo in CS Appendix D.2, Figure 3 and that the wording “patients without inhibitors” was incorrect (i.e. the participant flow was for all patients entering BASIS). The company also stated that the 47 participants who failed screening includes both inhibitor and non-inhibitor cohort participants. A listing of screen failures and reasons was provided by the company in clarification A7, but the number of participants did not total 47 (only ■ unique Participant IDs were included). The EAG was unable to determine whether there is a generalisability issue due to the high proportion of screening failures.

Of the 128 patients without inhibitors entering the OP, 37 were receiving on-demand therapy and were not considered further in the CS. A total of 91 participants without inhibitors and with prior routine prophylaxis therapy entered the OP (all safety-set), and 83 of these entered the ATP (mITT and marstacimab safety set). Of the eight participants not entering the ATP, seven did not complete the OP (5 no longer met the eligibility criteria, 2 had protocol deviations), and one completed the OP but did

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not meet the criteria for the ATP (clarification A2). Compliance during the OP was at least 80% in ■■■ (n=91) of participants. Additional details on withdrawals and marstacimab discontinuations were provided by the company in clarification responses A3 to A5; the EAG has no concerns regarding these.

Analysis sets are described in CS B.2.3.1. The ATP was completed by 78 (85.6%) participants, and 59 entered the OLE. One participant withdrew from the OLE. One participant was not included in the safety analysis set of the OLE (n=58) as their data were not available by the March 2023 data-cut. At the more recent limited data-cut of October 2023, 75 prior prophylaxis participants had enrolled in the OLE (CS B.2.7.1).

2.2.2 Trial Results

2.2.2.1 Baseline characteristics

The baseline participant and disease characteristics of BASIS are shown in Table 6. A total of 83 male participants treated with prior factor prophylaxis in the OP entered the ATP of BASIS. The mean age was 32.6 years, and the study population was composed of 54.2% White and 43.4% Asian individuals. The participants had an average weight of 69.1 kg and mean body mass index (BMI) was 23.6. The company's clinical advisors considered that the population in BASIS was younger and lower weight compared with those in the UKHCDO dataset,³ with the latter being more reflective of patients in the UK. They also noted that patients in BASIS had more severe disease and that Asian patients were overrepresented, but they did not consider this to be a prognostic variable or treatment effect modifier. As noted above (2.2.1.2), it is likely that participants were not receiving optimal prophylaxis at enrolment and during the OP, therefore the appearance of more severe disease could relate to treatment rather than underlying phenotype. Only ■■■% of the safety set (data not available for the mITT set) were aged 65 years or older, with ■■■% aged 45 to 64 years. The EAG clinical expert noted that older participants are less likely to have had routine prophylaxis since childhood and as a result have more complications and are harder to treat.

Table 6: Baseline characteristics of participants – BASIS study

Characteristic	Patients treated with prior factor prophylaxis in the OP (N=83)
Age, years	
Mean (SD)	32.6 (14.81)
Median (Min, Max)	31.0 (13.0, 66.0)
Sex, n (%)	
Male	83 (100.0)
Race, n (%)	
Asian	36 (43.4)
Black or African American	1 (1.2)
White	45 (54.2)
Not reported	1 (1.2)
Weight, kg	
Mean (SD)	69.1 (15.32)
Median (Range)	69.0 (35.0, 120.0)
Height, cm	
Mean (SD)	170.5 (8.43)
Median (Range)	170.7 (141.0, 185.0)
Body mass index, kg/m²	
Mean (SD)	23.6 (4.25)
Median (Range)	23.5 (15.2, 36.0)
Haemophilia Type, n (%)	
Haemophilia A	65 (78.3)
Haemophilia B	18 (21.7)
Disease severity, n (%)	
Severe	83 (100)
Number of Target Joints at Baseline, n (%)	
0	36 (43.4)
1	19 (22.9)
2	15 (18.1)
≥3	13 (15.7)

2.2.2.2 Treatment Efficacy

Table 7 provides an overview of the main results from the BASIS trial. The company has presented results in terms of rate differences rather than rate ratios. In the original company analyses, patients are censored in the marstacimab arm if they experience dose escalation. Given that dose-escalation is expected to be included in NHS practice, the EAG requested additional analyses without this censoring.

In the company analyses, marstacimab demonstrating non-inferiority and superiority to routine prophylaxis across the bleed rate outcomes. Marstacimab was associated

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with slightly fewer people experiencing 0 bleeds, and more people experiencing ≥ 3 bleeds, however this could be attributable to the length of follow-up in each period (6 months vs 1 year) rather than the treatment received. The EAG was also concerned about the possibility of differences in compliance occurring across the OP and ATP, however insufficient information was provided by the company to resolve this concern. Compliance was $>80\%$ for 98.8% of people during the ATP and by design was for 100% for these people during the OP.

Table 7: Overview of results from BASIS (censored for dose escalation)

	Routine Prophylaxis during OP (N=83)	Marstacimab Prophylaxis during ATP (N=83)
Annualised Bleed Rate of Treated Bleeds (ABR_{treat})		
Mean (SD)	7.88 (12.91)	5.17 (8.04)
Median (Range)	2.16 (0.00, 59.51)	2.02 (0.00, 35.51)
Model derived estimate of difference	-2.77 (-5.37, -0.16) p = 0.0376	
Annualised Bleed Rate of Treated Joint Bleeds (ABJR_{treat})		
Mean (SD)	5.68 (10.90)	4.20 (7.30)
Median (Range)	1.89 (0.00, 55.89)	1.02 (0.00, 33.48)
Model derived estimate of difference	-1.53 (-3.70, 0.64) p = 0.1680	
Annualised Bleed Rate of Treated Target Joint Bleeds (AJBR_{target})		
Mean (SD)	3.38 (8.32)	2.55 (5.95)
Median (Range)	0.00 (0.00, 38.86)	0.00 (0.00, 27.24)
Model derived estimate of difference	-0.86 (-2.41, 0.70) p = 0.2811	
Annualised Bleed Rate of Spontaneous Bleeds (ABR_{spont})		
Mean (SD)	5.89 (10.87)	3.85 (7.26)
Median (Range)	1.94 (0.00, 53.89)	0.00 (0.00, 35.51)
Model derived estimate of difference	-2.09 (-4.23, 0.06) p = 0.0566	
Annualised Bleed Rate of Total Bleeds (ABR)		
Mean (SD)	8.87 (13.46)	6.06 (8.73)
Median (Range)	3.91 (0.00, 59.51)	2.89 (0.00, 37.54)
Model derived estimate of difference	-2.87 (-5.61, -0.12) p = 0.0406	

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Proportion of Bleeds		
Completed Phase	83 (100.0%)	78 (94.0%)
0 bleeds, n (%)	33 (39.8%)	29 (34.9%)
1 bleed, n (%)	9 (10.8%)	7 (8.4%)
2 bleeds, n (%)	11 (13.3%)	9 (10.8%)
≥ 3 bleeds, n (%)	30 (36.1%)	33 (39.8%)

The EAG requested the company perform analyses using information from the first 6 months of follow-up in the ATP to reduce potential for bias from the differing follow-up lengths when considering the proportion with zero bleeds (clarification question A33). The EAG present the results of these analyses in Table 8, where marstacimab [REDACTED] of people with zero bleeds. Whilst no hypothesis testing was performed, the EAG notes that the difference across the bleed rates has [REDACTED]. As dose escalation could only occur after 6 months, censoring is not an issue in these analyses.

Table 8: Results for BASIS analyses using first 6 months of data from ATP for marstacimab

		Routine Prophylaxis	Marstacimab Prophylaxis
All participants	Percentage with zero bleeds	[REDACTED]	[REDACTED]
	Mean ABR Treated (SE)	[REDACTED]	[REDACTED]
	Mean ABR Joint Treated (SE)	[REDACTED]	[REDACTED]
	Mean ABR Total (Treated)	[REDACTED]	[REDACTED]
Excluding those with zero bleeds	Mean ABR Treated (SE)	[REDACTED]	[REDACTED]
	Mean ABR Joint Treated (SE)	[REDACTED]	[REDACTED]
	Mean ABR Total (Treated)	[REDACTED]	[REDACTED]

The EAG also requested analyses that were not censored for dose-escalation, as these may better capture the relative efficacy of marstacimab. For analyses from ATP, the uncensored analyses show as expected that the relative benefit of

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marstacimab increases when the impact of the higher dosing is accounted for in the ABRs (clarification response A26-28).

However for the OLE analyses, there appears to be an unexpected result that the effect difference reduces when the impact of dose-escalation is included (Table 9). The EAG prefers to use uncensored estimates of efficacy as these are more representative of potential NHS use of marstacimab. The EAG combines these with other reported bleed rates (response A30) to derive an estimate of an ABR ratio between factor prophylaxis and marstacimab for the pooled population. Using the same approach, the EAG also derived haemophilia-specific estimates of efficacy for factor prophylaxis and marstacimab which are used in the economic modelling.

Table 9: Comparison of censored and uncensored analyses for treated ABR for all participants in BASIS

	ATP (n=83)	OLE (n=■)	Source
With censoring for dose escalation	■	■	Clarification response A26-28 Figure 2.5 and 3.6
Without censoring for dose escalation	■	■	Clarification response A26-28 Figure 2.6 and 3.5
Reported or estimated ABR for OP	7.88	■	CS Table 14 and derived from response A30 Table 6.2 and 6.4
Reported or estimated ABR for marstacimab	■	■	Combining response Figure 2.6 with Table 14 and derived from response A30 Table 6.2 and 6.4
Derived ABR ratio using censored	■	■	

estimates versus OP			

2.2.2.3 Subgroup analyses

Subgroup analyses are presented by the company in Figure 10 of the company submission. Whilst these results should be treated with caution due to the small number of people contributing information and lack of statistical power, the relative efficacy of marstacimab appeared worse for people with haemophilia B compared to the efficacy in the haemophilia A population. Hence, the EAG considers it reasonable to use haemophilia type-specific inputs for the economic model as they may be of interest to committee. The EAG is not aware that any models including interaction terms for treatment and haemophilia type have been fitted, or of any biological rationale for this difference.

2.2.2.4 Health Related Quality of Life

The BASIS trial collected information on patient quality of life using haemophilia specific tools (Haem-A-QoL and Haemo-QoL), and general quality of life tools (EQ-5D-5S). The EAG presents an overview of the results comparing the OP and ATP periods in Table 10. Dose-escalated patients were not censored in these analyses. Consistently with the primary clinical outcome, marstacimab did not show inferiority to routine prophylaxis within the BASIS population who provided data. The EAG is concerned over the potential for bias in these analyses. Whilst the extent of missing data has not been fully revealed, information in the CSR suggests that roughly █% of people from routine prophylactic cohort of BASIS failed to complete a PRO, with missing data replaced by imputed values.

Table 10: Overview of quality-of-life outcomes from BASIS

Measure	Routine Prophylaxis (6 months): change from baseline (95% CI)	Marstacimab (12 months): change from baseline (95% CI)	Median Difference (95% CI)
Haem-A-QoL total (adults, n = 63)	−1.2 (−3.5, 1.1)	−4.9 (−8.1, −1.7)	−3.7 (−8.3, 0.9)

[REDACTED]⁵² The CS states in section B.2.12.1 that TEAEs were mild or moderate with only one patient reporting a TEAE of Grade 3 severity. The EAG notes that [REDACTED] of patients had a Grade 3 TEAE during the ATP.

Adverse events of special interest (AESI) are presented in CS Table 45 and summarised in Table 13. The CS states that COVID-19 was designated as an AESI due to its potential to increase the risk of thrombotic events, and notes that COVID-19 rates were rising as patients entered the ATP (3.3% during OP, 21.7% during ATP). Injection site reactions occurred in 10.8% of patients with prior prophylaxis (and [REDACTED] of those with prior OD therapy) during the ATP. No participants

CS Table 46 presents AEs in participants who had dose escalation from 150 mg QW once weekly (QW) to 300 mg QW. None of these participants experienced an SAE or TEAE that led to discontinuation of the study intervention.

Clinical laboratory values are reported in CS Appendix F.1.2. The company states that none of the laboratory test anomalies were considered to be clinically significant or reported as AEs by the investigator. Among all participants without inhibitors regardless of prior treatment (n=116), 23 (19.8%) were positive for anti-drug (marstacimab) antibodies (ADA); this was transient in 14 participants and persistent in 9 participants. ADAs were resolved in 95.7% of participants by the end of the study.

Table 11: Overview of adverse events during 6 months of routine factor prophylaxis during OP, 12 months of marstacimab prophylaxis in ATP, and OLE

	People with prior routine factor prophylaxis		All patients regardless of prior treatment	
n (%)	Routine prophylaxis during OP (N=91)	Marstacimab during ATP (N=83)	Marstacimab during ATP (N=116)	Marstacimab during OLE (N=87)
All-cause AEs				
Patients with AEs	25 (27.5)	66 (79.5)		
Patients with SAEs	2 (2.2)	7 (8.4)		
Grade ≥3 AEs				
Discontinued from the study phase due to AEs ^a	0 (0)	1 (1.2)		
Discontinued from the study drug due to AEs ^b	0 (0)	0 (0)		
Dose reduced or temporary discontinuation due to AEs	0 (0)	14 (16.9)		
All-cause TEAEs, >5 % in either treatment phase				
Any TEAE	20 (22.0)	62 (74.7)		
Grade 3 TEAE				
COVID-19	3 (3.3)	18 (21.7)		
Headache	0 (0)	6 (7.2)		
Contusion	0 (0)	5 (6.0)		
Deaths	0 (0)	0 (0)	0 (0)	0 (0)

Source: Adapted from CS Table 39 and CSRs. ^a Patients who have an AE record that indicates that the AE caused the patient to be discontinued from the study. ^b Patients who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the patient to be discontinued from study.

Table 12: Summary of treatment-related TEAEs after 12 months of marstacimab ATP and during OLE

	Prior prophylaxis treatment	Prior OD treatment	All patients
	Marstacimab during ATP (N=83)	Marstacimab during ATP (N=33)	Marstacimab during OLE (N=87)
Number of patients, n (%)			
With any AE	19 (22.9)		
Gastrointestinal disorders			
Haemorrhoids			

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Haemorrhoids thrombosed			
General Disorders and Administration Site Conditions	11 (13.3)		
Fatigue	1 (1.2)		
Injection site bruising	1 (1.2)		
Injection site erythema	3 (3.6)		
Injection site induration	1 (1.2)		
Injection site oedema	1 (1.2)		
Injection site pain	1 (1.2)		
Injection site pruritus	4 (4.8)		
Injection site swelling	2 (2.4)		
Peripheral swelling	1 (1.2)		
Injury, Poisoning and Procedural Complications	1 (1.2)		
Contusion	1 (1.2)		
Investigations	3 (3.6)		
Fibrin D dimer increased	2 (2.4)		
Prothrombin fragment 1.2 increased	3 (3.6)		
Musculoskeletal and Connective Tissue Disorders	1 (1.2)		
Arthralgia	1 (1.2)		
Nervous System Disorders	1 (1.2)		
Headache	1 (1.2)		
Skin and Subcutaneous Tissue	2 (2.4)		
Pruritus	2 (2.4)		

Adapted from CS Table 41 and CSRs.

Table 13: AESIs during 6 months of routine factor prophylaxis during OP, 12 months of marstacimab prophylaxis in ATP, and OLE

	Prior prophylaxis therapy		Prior on-demand therapy	All patients regardless of prior treatment
n (%)	Routine prophylaxis during OP (N=91)	Marstacimab during ATP (N=83)	Marstacimab during ATP (N=33)	Marstacimab during OLE (N=87)
With any AESI	15 (16.5)	46 (55.5)		
COVID-19	3 (3.3)	18 (21.7)		
Haemorrhages	5 (5.5)	13 (15.7)	1	
Hypersensitivity	2 (2.2)	6 (7.2)		

Hypertension	2 (2.2)	5 (6.0)	■	■
Injection site reactions	0 (0.0)	9 (10.8)	■	■

Adapted from CS Table 43 and CSRs.

2.2.2.6 Marstacimab dose escalation

After 6 months in the ATP or anytime during the OLE, patients were eligible to move to a higher dose of marstacimab if they if they weighed $\geq 50\text{kg}$ and experienced at least two spontaneous bleeds over a 6 month period. Dose-escalated patients received 300mg of marstacimab weekly, rather than 150mg. Information on dose-escalation that occurred within BASIS is shown in Table 14.

Table 14: Overview of marstacimab dose-escalation within BASIS

	Proportion who dose escalated (%)
BASIS ATP	11/83 (13.25%) (though ■ were eligible)
BASIS OLE*	■ (though ■ were eligible and some were already on higher dose)

*Note OLE phase is ongoing and it is possible additional people may escalate doses with longer follow-up.

2.2.2.7 Prophylaxis received

The company provided details of treatment of breakthrough bleeds during both phases of the BASIS trial in clarification A12; these are presented in Table 15. The EAG's clinical experts commented that their use was higher than would be expected for people in the UK on prophylactic regimes.

Table 15: Summary of bleeding events and treatments during BASIS

	OP (n=83)	ATP (n=83)
Number of participants with bleeds n (%)		
Number of bleeds		
Number of treated bleeds		
<i>Treatments used</i>		
Blood coagulation factors		
Damoctocog alfa pegol		
Efmoroctocog alfa		
Eftrenonacog alfa		
Moroctocog alfa		
Nonacog alfa		
Octocog alfa		
Rurioctocog alfa pegol		
Turoctocog alfa		

Source: Clarification A12 Table 2.

2.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS considered studies for an indirect treatment comparison (ITC) to the BASIS study. Two potential comparator studies were identified in the CS SLR, HAVEN 3⁵³ and HAVEN 4.⁵⁴ The CS assessed the similarity of the study populations between the two HAVEN studies and the BASIS study in Section B.2.11.1, focusing on comparing with the subgroup of BASIS with haemophilia A, since HAVEN 3 and HAVEN 4 included only haemophilia A. The CS included data from Cohort D of the HAVEN 3 study in the indirect comparison; the population in this Cohort were without inhibitors and had received prior prophylaxis treatment, and were deemed similar enough for comparison to BASIS.

The HAVEN 4 study included both people with inhibitors and those without inhibitors at baseline; the CS excluded this study from the ITC as there were no baseline characteristics available for the relevant subgroup without inhibitors. Since submission there has been a publication of HAVEN 4 that includes details of participants without inhibitors.⁵⁵ HAVEN 4 included both prior episodic (on-demand)

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and prophylactic regimens, however the majority had prior prophylaxis (Table 17).

The EAG has compared the core study characteristics of BASIS, HAVEN 3 and HAVEN 4 in Table 16, and the baseline characteristics in Table 17. All studies included participants aged 12 years or older with severe haemophilia. All were multi-centre studies and data of relevance to an ITC were all from non-randomised cohorts. The duration of treatment varied between the three studies, with BASIS treating for 12 months, HAVEN 3 for at least 24 weeks and HAVEN 4 for 24 weeks. Similar to BASIS, the HAVEN trials followed the WFH guidelines for defining and categorizing bleeding episodes, ensuring consistency and standardization across studies. This includes the categorization of bleeds as either spontaneous or trauma-induced, and further classification into joint, muscle, or other types of bleeding.

Table 16: Comparison of study characteristics across BASIS, HAVEN 3 and HAVEN 4

Study characteristics	BASIS	HAVEN 3, Mahlangu 2018⁵³	HAVEN 4, Pipe 2019^{54, 55}
Study design	Non-RCT 6 months observation period followed by 12 months intervention	Open-label RCT (Cohorts A to C) with additional non-RCT cohort (Cohort D)	Non-RCT, two-stages: Run-in cohort (pharmacokinetics) Expansion cohort (efficacy)
Countries	19 countries (from Europe, North America, Asia, South America, South Africa)	14 countries (from Australia, Europe, North America, Asia, Central America, South Africa)	Run-in cohort 2 countries (Japan and Spain) Expansion cohort 6 countries (Australia, Europe, Asia, USA)
Dosage	Marstacimab; 300 mg SC loading dose followed by 150 mg once weekly. Possible dose escalation to 300 mg SC once	Cohort A: Emicizumab 1.5 mg/kg weekly Cohort B: Emicizumab 3 mg/kg every 2 weeks Cohort C: no prophylaxis)	Emicizumab 6 mg/kg every 4 weeks

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	weekly after 6 months	Cohort D: emicizumab 1.5 mg/kg weekly	
Key eligibility criteria	Males aged 12 to 74 years, severe haemophilia A (FVIII activity <1%) or moderately severe to severe haemophilia B (FIX activity ≤2% respectively) with or without inhibitors ^a	Males and females, ≥12 years, severe haemophilia A (FVIII activity < 1 IU/dL), without FVIII inhibitors	Males and females, ≥12 years, severe haemophilia A (<1% of normal FVIII activity in blood) or haemophilia A with FVIII inhibitors (reported separately)
Prior treatments	Only those with prophylaxis therapy during observation period were included by CS	Cohorts A to C: episodic factor VIII. Cohort D: prophylactic FVIII, this could continue until the 2 nd loading dose of emicizumab.	Episodic or prophylactic FVIII concentrates or bypassing agents for ≥ 24 weeks. Those on episodic treatment were required to have had ≥ 5 bleeds in the 24 weeks before entry
Treatment of breakthrough bleeds	Standard haemostatic treatment regimen which may include factor replacement therapy	Continued with usual episodic treatment with FVIII	Recombinant activated FVII (rFVIIa), FVIII concentrates or bypassing agents
No. of participants	Without inhibitors cohort: Enrolled: 91 All safety: 91 Marstacimab safety: 83 mITT: 83	Total 152 Cohorts A to C: 89 Cohort D: 63	Total: 48 With inhibitors: 8 Without inhibitors: 40 (run-in cohort + expansion cohort)

Length of treatment	12 month ATP	At least 24 weeks	24 weeks
Outcomes of relevance to ITC	ABR treated (primary outcome) ABR total ABR treated joint bleeds Number of patients with no treated bleeds Number of patients with no total bleeds	ABR for treated bleeds (primary outcome) ABR for all bleeds. ABR for treated joint bleeds Number of patients with no treated bleeds Number of patients with no total bleeds	Without inhibitor group: ABR for treated bleeds ABR total ABR treated joint bleeds Number of patients with no treated bleeds

^a Only those with haemophilia A were compared in the ITC.

2.3.1 Baseline characteristics

Table 17 presents the baseline characteristics of participants of relevance to the ITC from the BASIS, HAVEN 3 and HAVEN 4 studies. Comparisons are difficult to make for some characteristics because of reporting differences. The proportion of white participants was lower in the BASIS study compared with both of the HAVEN studies, and the participants in BASIS were slightly younger with a lower BMI than those in HAVEN 3 (not reported in HAVEN 4). The proportion with a target joint at baseline was higher in BASIS compared with HAVEN 3, but lower than in HAVEN 4, and prior total ABR was also higher in BASIS than HAVEN 3 (not reported in HAVEN 4). These factors lead the CS to commenting in Section B.2.11.3 that relative to the HAVEN 3 study, participants in BASIS had more severe disease. The treatment regimen at baseline was 100% prophylactic in BASIS and in HAVEN 3, but in HAVEN 4, 32.5% had only received prior episodic treatment. The EAG has concerns as to whether BASIS is similar enough to either of the HAVEN studies to be compared in an ITC.

Table 17: Comparison of baseline characteristics across BASIS, HAVEN 3 and HAVEN 4 (cohorts of relevance to the ITC)

Trial	BASIS	HAVEN 3 ^{53, 56}	HAVEN 4 ^{54, 55}

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	Haemophilia A subgroup^a		
Characteristic	N=65	N=63	N=40
Age, years			
Mean (SD)	31.63 (14.2)	36.4 (14.4 ^b)	NR
Median (Min, Max)	NR	36.0 (13-68)	40 (14, 66)
Sex, n (%)			
Male	65 (100.0)	63 (100)	40 (100)
Race, n (%)			
White	34 (52.3)	47 (74.6)	31 (77.5)
Hispanic/Latino (%)	13.85	11.1	NR
Body mass index, kg/m²			
Mean (SD)	23.91 (4.3)	25.6 (min 19.2, max 40.6)	NR
Treatment regimen at baseline, n (%)			
Episodic	0	5 (7.9) ^c	13 (32.5)
Prophylactic	65 (100)	63 (100)	27 (67.5)
Percent with target joints at baseline			
Yes	56.92	41.3	65.0
Mean (SD)	NR	NR	1.8 (1.9)
Annualised bleeding rate (ABR)			
Prior total ABR (mean, SD)	10.26 (14.8)	6.4 (NR) ^d	NR
Prior treated ABR (mean, SD)	9.2 (14.3)	NR	NR

^a Haemophilia A participants treated with factor prophylaxis during the OP, the EAG has not been able to verify these data in the CSR. ^b CS Table 32 reports this SD, the EAG has not been able to validate this in the HAVEN 3 publications. ^c Some participants received both episodic and prophylactic treatment. ^d From CS Table 32, which cites a published indirect treatment comparison of emicizumab, Astermark 2023⁵⁷ (data not in Mahlanhu 2018⁵³ or Kiialainen 2022⁵⁶).

2.3.2 Quality assessment

The company's quality assessment of HAVEN 3 using the Downs and Black checklist is reported in CS Appendix D.1.8. HAVEN 4 was excluded by the company therefore they did not assess it for quality. The company focuses on the overall summary score

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and does not discuss any of their responses that suggest a source of bias. The summary score is described as falling within the “poor” category. There is no explicit use of the quality assessment in the evidence synthesis. The EAG has conducted an independent quality assessment of both HAVEN 3 (the relevant non-interventional Cohort D only) and HAVEN 4, and presents this alongside the company’s judgements of HAVEN 3 in Appendix 7.4.

There are several differences between the company’s and EAG’s judgements of HAVEN 3; in most of these cases the company has responded with a ‘No’ or ‘Unclear’ response and the EAG has responded with a ‘Yes’ (Appendix 7.4). While the EAG has concerns regarding a number of items on the checklist, these are fewer than the company’s.

The EAG’s responses for HAVEN 4 are identical to those for HAVEN 3 (non-interventional Cohort D), reflecting the similarity in study design and reporting. The HAVEN studies do not describe the source population or how patients were selected, therefore the external validity of the studies is unclear. The principal confounding factors were not clearly described or adjusted for in the analysis, and there was no blinding of outcome assessment. It is unclear whether there are any differences in care between the treatment periods. Compliance was not reported in the HAVEN studies. The EAG considers the overall quality of HAVEN 3 and 4 to be similar to that of BASIS, with similar limitations of study design (section 2.2.1.4).

2.4 Critique of the indirect comparison and/or multiple treatment comparison

2.4.1 Overview

In the absence of a head-to-head comparison between marstacimab and emicizumab, an unanchored simulated treatment comparison (STC) was conducted. The STC compared the control of bleeding events among adult and adolescent patients with severe haemophilia A without inhibitors who had previously received routine prophylaxis therapy. The company compared five efficacy outcomes between the haemophilia A subpopulation of the marstacimab BASIS trial and a subgroup of group D of the emicizumab HAVEN 3 trial. The STC accounted for a range of effect

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modifiers and prognostic variables between the two studies. Overall, emicizumab is favoured numerically across the five efficacy outcomes, however the STC found none of these differences between marstacimab and emicizumab to be statistically significant.

2.4.2 Methods

The company ruled out conducting an anchored ITC such as a network meta-analysis due to the single-arm crossover design of the BASIS study. Additionally, the company deemed it infeasible to conduct an anchored ITC using the inpatient comparison data between the lead-in observational phase and active trial phases due to the differences in disease management, differences in sample size between HAVEN 3 subgroup of group D (N=48) and BASIS haemophilia A subgroup (N=65) and an absence of baseline characteristics data for the HAVEN 3 group D subgroup inpatient comparison population. Hence, the company opt for an unanchored approach.

Note that HAVEN 3 recruited 4 groups of patients, but only group D (n=63) is of interest as they received previous prophylactic factor therapy. This unanchored STC uses baseline characteristics and efficacy estimates for the entire group D population. For the BASIS clinical trial, the STC used data from the haemophilia A patient subgroup only, since emicizumab is used in haemophilia A patients only. The EAG notes the company uses rate ratios to compare efficacy of emicizumab and marstacimab, and not rate differences as it has reported in the company submission for the BASIS trial.

The STC used individual-level patient data (IPD) from the BASIS trial and aggregate-level data from the HAVEN 3 trial. Analyses are based on bleed rates for all participants, and do not distinguish between people who do and not experience bleeds. The effect modifiers and prognostic variables accounted for were: prior ABR_{total} (rate), target joints (yes/no), age (years), body mass index (BMI; kg/m²), percent white, and percent Hispanic/Latino.

The EAG requested additional analyses based on those published by Astermark et al.⁵⁷ who included covariates for age, % white, BMI, baseline ABR, proportion with <9 bleeds in prior 24 weeks, and proportion receiving SHL FVIII (clarification question A35). The company conducted this analysis also including target joints in

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their STC adjustment. Note this analysis used only the first 33 weeks of follow-up from BASIS for consistency with the reported follow-up available for HAVEN 3. The EAG considers this analysis to be an improvement over the company's preferred analysis based on the choice of covariates.

The EAG also asked for a MAIC analysis to be run, to compare to the STC analyses (A36), however the company declined this opportunity for reasons based on anchored comparisons, which do not necessarily apply to unanchored analyses as presented by the company.

Within group D, results are reported for the subgroup who received prior prophylaxis as part of a non-interventional study (n=48) by Mahlangu (2018).⁵³ The EAG notes that an anchored comparison is possible using this information.

The EAG also requested that the company perform an indirect comparison to the HAVEN 4 study, to avoid reliance on comparisons of a single pair of studies (clarification question A34). The main limitation of this approach is that the information available for the HAVEN 4 study and used in the indirect comparison includes groups of people who did and did not receive prior prophylaxis, reducing the generalisability to UK patients. To reduce potential bias within the comparison, the company included information from the patients who did not receive prior prophylaxis from the BASIS study. These analyses included adjustments for age (% <18), race (% white), number of bleeds in prior 24 weeks, target joints (%), record of ≥ 1 CV risk factor (%) and prior on demand therapy (%).

2.4.3 STC Results

Overall, the STC found no statistically significant differences between marstacimab and emicizumab at a $p = 0.05$ threshold. Emicizumab has numerical improvements in ABRs (total, treated and joint treated) and numerically lower proportions of patients experiencing bleeds (total and treated) when compared to marstacimab (Table 18). For the STC using covariates based on Astermark et al. the bleed rate ratios is closer to one, however the proportion with zero bleeds is further from one. The EAG considers that neither study was designed to be compared this way, and it is possible that differences in treatment effect may exist that have not been detected in these analyses.

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Table 18: Company STC results comparing marstacimab to emicizumab using information from HAVEN 3

	Naïve rate ratio	Company Preferred STC adjusted rate ratio	STC using Astermark ⁵⁷ covariates + Target Joints
ABR total			
ABR treated			
AJBR treated			
Proportion Zero Treated Bleeds (odds ratio)			

The results from the STC using HAVEN 4 and including people without previous routine prophylaxis are shown in Table 19. The results are generally consistent with the other STCs where the point estimates suggest a

[REDACTED]. Note that the ratios estimated by the company relate to the whole population, including people with zero bleeds, however in the company base case, the ratio is applied to the baseline ABR for people with bleeds only, excluding those without bleeds. The EAG does not consider this appropriate and is a potential source of bias.

Table 19: Marstacimab (BASIS) vs emicizumab (HAVEN 4) - STC results (adapted from Table 9 company clarification response)

Outcome	Trial Arm	n	Outcome ^a (95% CI)	Effect Estimate ^b (95% CI)	p-value
<i>With censoring for dose-escalation</i>					
Total ABR (1-24 week)	BASIS: STC ^c	■	██████████	██████████	████
	HAVEN-4 ^d	40	4.38 (1.31 to 10.80)	N/A	N/A
Total ABR (25-48 week)	BASIS: STC ^c	■	██████████	██████████	████
	HAVEN-4 ^d	38	3.07 (0.67 to 8.85)	N/A	N/A
Treated ABR	BASIS: STC ^c	■	██████████	██████████	████
	HAVEN-4 ^d	40	2.41 (0.39 to 7.79)	N/A	N/A

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(1-24 week)					
Treated ABR (25-48 week)	BASIS: STC ^c	■	██████████	██████████	■
	HAVEN-4 ^d	38	1.80 (0.19 to 6.82)	N/A	N/A
Without censoring for dose-escalation					
Total ABR (25-48 week)	BASIS: STC ^c	■	██████████	██████████	■
	HAVEN-4 ^d	38	3.07 (0.67 to 8.85)	N/A	N/A
Treated ABR (25-48 week)	BASIS: STC ^c	■	██████████	██████████	■
	HAVEN-4 ^d	38	1.80 (0.19 to 6.82)	N/A	N/A

^aRefers to the negative binomial model-derived rate for total ABR and treated ABR

^bRefers to the estimated rate ratio (RR) for total ABR and treated ABR

^cAdjusted for age (% under 18), race (% white), mean number of bleeds in prior 24 weeks, % with target joints, % with a record of one or more CV risk factors, and % with prior on-demand therapy

^dData digitized from Figure 2 in Mahlangu, J. et al. (2024)

Abbreviations: ABR: annualised bleed rate; AJBR: annualised joint bleed rate; CI: confidence interval; n: number of individuals; STC: simulated treated comparison.

2.5 Additional work on clinical effectiveness undertaken by the EAG

2.5.1 Adverse events in HAVEN 3 and HAVEN 4

The CS does not compare adverse events between marstacimab and emicizumab in the ITC or narratively. Whilst acknowledging the limitations of a simple comparison between adverse events in BASIS and the HAVEN studies, Table 20 presents a summary of adverse events occurring in the HAVEN studies for information. For HAVEN 3, all four cohorts are combined. Only participants without inhibitors are reported. SAEs, Grade >3 AEs and injection site reactions appear to be more common with emicizumab than with marstacimab.

Table 20: Summary of adverse events in participants without inhibitors from HAVEN 3, HAVEN 4 and BASIS ATP

n (%)	HAVEN 3 (N=151)	HAVEN 4 (N=40)	HAVEN 3 + 4 (N=191)	BASIS ATP (N=83)
Any AE	148 (98.0)	40 (100)	188 (98.4)	66 (79.5)
SAE	35 (23.2)	9 (22.5)	44 (23.0)	7 (8.4)
AE with fatal outcome	0	0	0	0

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AE leading to withdrawal from treatment	1 (0.7)	0	1 (0.5)	0 (0)
AE leading to dose modification/ interruption	2(1.3)	1 (2.5)	3 (1.6)	14 (16.9)
Grade ≥3 AE	38 (25.2)	8 (20.0)	46 (24.1)	██████
Treatment-related AE	57 (37.7)	14 (35.0)	71 (37.2)	19 (22.9)
Injection-site reaction	47 (31.1)	8 (20.0)	55 (28.8)	9 (10.8)
AESI				
Systemic hypersensitivity /anaphylactic / anaphylactoid reaction	0	0	0	Not an AESI
Thromboembolic event	2 ^a (1.3)	0	2 (1.0)	Not an AESI
Thrombotic microangiopathy	0	0	0	Not an AESI

Source: Mahlangu 2024,⁵⁵ CS Table 39, CS Table 41. ^a In one participant, a subsequent medical review revealed no evidence of thrombosis. AESI; adverse event of special interest.

2.5.2 Network Meta-Analysis

The EAG conducted a network meta-analysis (NMA) combining information from the BASIS and HAVEN 3 studies. An overview is shown in Table 21. As inputs, the EAG used information Mahlangu 2018 which reports relative effects for n=48 participants who were previously enrolled in a non-interventional study whilst receiving routine prophylaxis. For BASIS, the EAG opted to use information from clarification response A33, where the follow-up for both the OP and ATP are limited to 6 months. Whilst the point estimates from the NMA differ slightly, they are consistent with the other STCs.

Table 21: Summary of inputs and outputs from EAG NMA

Inputs	Proportion of people without bleed	Treated ABR
BASIS - factor prophylaxis	N of No Bleed = 33 N total = 83	Mean = [REDACTED] SE = [REDACTED]
BASIS - marstacimab	N of No Bleed = [REDACTED] N total = 83	Mean = [REDACTED] SE = [REDACTED]
HAVEN 3 – factor	N of No Bleed = 19 N total = 48	Rate ratio vs factor: 0.32 (95% CI: 0.20, 0.51)
HAVEN 3 - emicizumab	N of No Bleed = 26 N total = 48	
Output		
	Odds Ratio for Zero Bleeds = [REDACTED]	ABR Treated Ratio = [REDACTED]

2.5.3 Treatment patterns and outcomes in the UK

The EAG was provided with unpublished information from the UKHCDO National Haemophilia Database (NHD), a real-world UK database, relating to treatments used in NHS care. The analysis included people with severe haemophilia aged 12 years and over, registered between 1st October 2022 and 30th September 2023. The NHD report also included data from Haemtrack, a patient self-reporting system. Data were presented separately for those aged 12-17 years and 18 years plus for severe haemophilia A and B. The EAG has summarised these in Table 22.

[REDACTED] It is important to note that some people could be issued with more than one product. Limitations of the data include it being self-reported and there may be some selection bias as participants involved are likely to have an interest and be more motivated.

Table 22 also presents data on annualised bleed rates from Haemtrack, a subset of the NHD cohort.

[REDACTED]

The EAG considers this information the best source to inform efficacy of factor prophylaxis and emicizumab and has calculated estimates combining SHL and EHL efficacy across adult and adolescent age groups through weighted averages. This approach avoids reliance on the highly uncertain indirect comparisons. The main limitation of this approach is the potential for differences between the FVIII and emicizumab populations within the UKHCDO, which could affect the comparisons of marstacimab and emicizumab. Potential differences in effect-modifying variables may also introduce confounding.

The EAG also calculated a baseline treated ABR combining the reported ABR from the UKHCDO report with the balance of SHL and EHL received in BASIS, to derive a real-world UK specific baseline ABR for the BASIS population. This estimate (ABR=[REDACTED]) was used when applying the relative effects as estimated from the BASIS study to derive the efficacy of marstacimab.

Table 22: Bleed data for haemophilia A and B^a registered on Haemtrack and The UK National Haemophilia Database October 2022 – September 2023 inclusive plus EAG calculations used in economic model

Diagnosis	Age Group, years	Product Group	N	ABR Mean, Median, (IQR)	ABR Mean, Median, (IQR) HA / B	ABR Mean, Median, (IQR) Total cohort	AJBR Mean, Median, (IQR)	ASBR Mean, Median, (IQR)	% with no Bleeds
HA	12-17	Emicizumab							
		EHL							
		SHL							
	18 +	Emicizumab							
		EHL							
		SHL							
HB	12-17	EHL							
	18+	EHL							
		SHL							
HA ^b	All	Emicizumab			N/A	N/A		N/A	N/A
HA ^b + HB ^b	All	SHL/EHL			N/A	N/A		N/A	N/A
HA ^b + HB ^b using BASIS SHL/EHL weighting		SHL/EHL	N/A		N/A	N/A		N/A	N/A

^abaseline factor VIII < 1 IU/dL; ^bEAG calculations from UKHCDO data provided earlier in table. ABR: Annualised bleeding rate; AJBR: Annualised Joint Bleeding Rate; ASBR: Annualised Spontaneous bleeding rate; EHL: Extended Half life; IQR: Interquartile range; HA: Haemophilia A; HB: Haemophilia B; SHL: Standard Half life.

2.5.4 Marstacimab Administration

In the BASIS Clinical Trial, marstacimab was administered using a prefilled syringe (PFS).⁵⁸ In the BASIS OLE, marstacimab was administered using a prefilled pen (PFP).⁵⁹ The company's economic model was informed by administration-related utility decrements based on the PFP.⁵⁸

The company conducted a phase 1, randomised, cross-over study (NCT04832139) to investigate bioequivalence.⁶⁰ The company established bioequivalence between the PFS and PFP devices for 300 mg marstacimab administered as two single injections of 150 mg marstacimab subcutaneously in a cohort of 22 healthy adult male participants.^{59, 60}

The EAG questions the generalisability of this cohort to the UK haemophilia population and whether PFP and PFS have equal efficacy among haemophilia patients. The EAG raises the concern that the BASIS trial used an administrative device that was not the intended administrative device for marstacimab in real-world use and that PFP and PFS could differ in safety/adverse event frequency, pharmacodynamics, pharmacokinetics, frequency of dosing/administration errors and impact on quality of life.⁶¹

There is the potential that PFPs could be preferable and medically equivalent, among haemophilia patients compared to syringes – and literature comparing the two among different biological medicines suggests that to be the case.⁶¹⁻⁶³ However, the EAG would prefer to err on the side of caution and suggest further investigation into the efficacy and safety profile of marstacimab administered through the PFP.

The clinical expert consulted by the EAG suggests they have little/no concern over this generalisability of PFS to PFP and that the pen form may be preferable to patients - highlighting the recent research in a similar medicine, concizumab, that is also administered as a PFP.⁶²

2.5.5 Immunogenicity

Biologics, such as monoclonal antibody-based therapies like marstacimab and emicizumab, are immunogenic.⁶⁴ Drug immunogenicity occurs when a patient's immune system produces anti-drug antibodies (ADAs).⁶⁴ ADAs can be neutralising

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(NAb) – whereby they inhibit the biological activity of the drug by blocking or altering the active part; or non-neutralising (non-NAb) – whereby they bind to the drug but do not affect the drug-target interaction.⁶⁴ Both NAb and non-NAb form antibody-drug complexes that the immune system clears and therefore may affect the efficacy, safety, pharmacodynamics and pharmacokinetics of a medicine.⁶⁵

The company conducted immunogenicity testing during the BASIS clinical trial to evaluate the incidence and effect of ADAs against marstacimab. Of the 116 ADA-evaluable participants, 23 (19.8% incidence) were positive for treatment-induced ADAs. Of the 23 treatment-induced ADA-positive participants, 6 produced NAb. The company states that immunogenicity testing results showed ADA were of “low incidence”, low titre with a relatively early onset, and mostly transient.⁵⁸ A concern of the EAG is that patients with haemophilia A who produce ADAs against emicizumab – a patient subgroup of potentially good candidates for marstacimab – could be at greater risk of developing ADAs against marstacimab. Scientific literature, to the knowledge of the EAG, does not support or oppose this suggestion. Additionally, the link between emicizumab inefficacy among patients and ADAs remains under investigation; with most evidence being individual case study data.⁶⁶⁻⁶⁹ Indeed, emicizumab discontinuation due to lack of efficacy with a proven ADA is a very rare event.⁷⁰

2.5.6 Review of recent relevant appraisals

The EAG examined the key issues raised in the recent NICE technology appraisals of efanesoctog alfa for treating and preventing bleeding episodes in haemophilia A and etranacogene dezaparvovec for moderately severe or severe haemophilia B, to investigate their relevance to the appraisal of marstacimab. Only issues already raised by the current EAG were identified, including uncertainties around the indirect comparisons, the source of ABR information and the treatment of bleeding events.

2.6 *Conclusions of the clinical effectiveness section*

The BASIS trial demonstrates that marstacimab is non-inferior to routine prophylaxis for people with severe haemophilia. However, the BASIS trial has limited generalisability to NHS practice given the differences in baseline bleed rates, in the proportion of people receiving EHL factor prophylaxis, and potentially the dosing of factor prophylaxis. These may also effect estimates of relative efficacy coming from BASIS, in addition to the dose-escalation of marstacimab.

The EAG is concerned about the potential for marstacimab to be inferior to routine prophylaxis for people with severe haemophilia B. The relative efficacy of marstacimab to emicizumab for haemophilia A comes from indirect comparisons which have very high uncertainty but consistently suggest that marstacimab is [REDACTED] to emicizumab. The EAG considers UKHCDO to be a valuable source for informing efficacy of current NHS treatments.

3 COST EFFECTIVENESS

3.1 EAG comment on company's review of cost-effectiveness evidence

The company's SLR "to identify economic evidence in the field of haemophilia" (CS Document B.3.1) comprised three "evidence streams"; economic evaluations, utilities/health-related quality of life and healthcare costs/resource use (reported in CS Appendices G, H and I respectively). The original SLR undertaken in August 2020 included both clinical and economic evidence, then in May 2024 update searches and screening for the three economic evidence streams were undertaken separately to the clinical SLR. As a result, 123 publications from the original SLR were excluded from the SLR in 2024 because they did not report relevant economic outcomes (Company clarification responses A45 and A46).

Due to a large number of included studies, a process of evidence prioritisation for each evidence stream was undertaken. The prioritisation criteria are described in CS Appendices G.1.2, H.1.2 and I.1.2, and deprioritised studies are listed in CS Appendices Tables 75, 81 and 86. The prioritisation criteria include UK relevance and recent publication. However, as stated in CS Appendix G.1.3: "included records were prioritised for extraction if they were key studies informing the structure of the economic model in this submission, or informed utilities or costs in the economic model", which leads the EAG to conclude that some studies may have been selected for the SLR based on prior use to build the economic model, rather than the literature review informing the building of the model in an unbiased manner based on *a priori* eligibility criteria.

3.1.1 Search strategies

CS Appendix G.1.1 describes the various literature search sources and strategies for the economic SLR's three evidence streams. A good, appropriate range of databases and other sources were searched, including recent conference proceedings, HTA agency websites and the CEA Registry and EQ-5D Publications databases. The electronic database search strategies (Appendix G.1.1, Tables 26-68) are good and comprehensive. The 2024 update searches (Tables 52-68) are limited by publication year (2020-current), however use of the date a record is *added* to the database is best practice, as sometimes database records can be added, or

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significantly changed, long after an article is published. The same search terms were used across Embase and MEDLINE, which can mean useful terms are missed, as the databases have different controlled vocabularies (Emtree vs Mesh), however the EAG does not consider this to have affected the sensitivity of the searches for this review.

Due to the SLR not identifying any cost effectiveness analyses of marstacimab the company developed a de novo model. This model is informed by the previous NICE assessments in the area. The EAG critique of the company modelling tries to bring in the evidence and ACD/FAD conclusions of the previous NICE assessments. The EAG review of the company identified cost effectiveness literature is limited, and may require further work depending upon which elements Committee identifies as key model drivers.

3.2 Summary and critique of the company's submitted economic evaluation by the EAG

3.2.1 NICE reference case checklist

Table 23: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes. But note that the model does not contain long term sequelae from bleeds, such as joint replacement. The company base case does not include possible mortality effects from bleeds.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. The 64 year time horizon is a lifetime horizon for the assumed baseline age of 36 years. But note that BASIS included adolescents.

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Element of health technology assessment	Reference case	EAG comment
Synthesis of evidence on health effects	Based on systematic review	The comparison of marstacimab with FVIII/FIX is based upon the BASIS OP versus ATP. The comparison of marstacimab with emicizumab is based upon the ITC as reported in the clinical effectiveness section above.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs are used. The main QALY differences arise from patient preference for subcutaneous administration over intravenous infusion. The disutilities for these are based upon a Canadian Time Trade Off (TTO) study. The disutilities of bleeds are source from two studies both of which used the EQ-5D, one addressing bleeds and the other joint involvement which was used as a proxy for joint bleeds.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The treatment preference TTO study was among members of the Canadian general public. The bleeds study was among patients and their care givers, as was the joint involvement study
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The treatment preference TTO study was among a sample of the Canadian general public. The bleeds study used the US EQ-5D tariff. The joint involvement study was across a number of European countries with relatively few UK participants. The EAG has not been able to source the valuation function(s) used.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.

Element of health technology assessment	Reference case	EAG comment
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company model structure is most easily thought of as a partitioned health state model² with an annual cycle, a 64 year time horizon and 3.5% discounting of costs and benefits.

Individual treatments are modelled, marstacimab, emicizumab, 7 FVIIIs and 4 FIXs. The outcomes for the 7 FVIIIs and 4 FIXs can be subsequently pooled weighted by UK market shares.

For each cycle patients are split into three categories, those with:

- No bleeds
- Joint bleeds requiring treatment
- Non-joint bleeds requiring treatment

A 6.02% discontinuation rate from marstacimab to a pooled FVIII basket for those with haemophilia A and to a pooled FIX basket for those with haemophilia B is applied during the first cycle for the company base case. The model contains the facility to apply marstacimab discontinuations in every model cycle.

Mortality is applied through standard UK life table estimates. A scenario analysis applies an SMR of 2.4 for those with bleeds requiring treatment.

The BASIS baseline EQ-5D quality of life is applied to all patients.

QALY decrements specific to joint bleeds and to non-joint bleeds are applied.

² There is one transition probability, that of discontinuing from marstacimab to FVIII

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QALY decrements per administration for subcutaneous treatments, marstacimab and emicizumab, and for intravenous treatments, FVIII and FIX, are applied. These QALY decrements are the main source of the estimated QALY gains from marstacimab over FVIII and to a lesser extent over FIX.

All routine treatments, marstacimab, emicizumab, FVIII and FIX are assumed to be home administered and incur no administration costs.

A one-off dose escalation of 13.25% from 150mg to 300mg marstacimab is applied based upon the BASIS ATP.

Emicizumab is assumed to be dosed fortnightly as 3.0 IU/kg. There are no discontinuations from emicizumab to FVIII.

Dosing for FVIII/FIX is based upon the centre of the ranges of the dose and frequency specified in each FVIII/FIX SmPC.

There is no vial sharing and wastage is assumed for emicizumab and FVIII/FIX.

The base case assumes that bleeds require one additional FVIII/FIX treatment at the same dose as routine prophylaxis. The large majority of treated bleeds also require a haematology outpatient visit, and an A&E visit or something similar with some patients being admitted as inpatients.

The company presents a range of scenario and sensitivity analyses. The two main company scenario analyses split the bleed rate estimates by:

- Scenario 1: haemophilia A and haemophilia B
- Scenario 2: SHL and EHL FVIII/FIX.

Note that the company presents estimates for analyses that censor marstacimab estimates for dose escalation and analyses that do not. Throughout this chapter all inputs and results are from the analyses that do not censor marstacimab estimates for dose escalation.

3.2.3 Population

All patients are male. The baseline characteristics of the modelled population are taken from the UKHCDO 2023 report, undifferentiated by haemophilia type. The model also contains the facility to apply the BASIS baseline characteristics

Table 24: Baseline patient characteristics

	Mean (s.d.)
UKHCDO 2023 Report	
Age (years)	████
Weight (kg)	██████
BASIS	
Age (years)	<u>33 (15)</u>
Weight (kg)	<u>69.1 (15.3)</u>

3.2.4 Interventions and comparators

For haemophilia A patients the company compares marstacimab with emicizumab and the individual FVIII treatments.

The modelled outcomes for the FVIII treatments are also combined into a market share weighted FVIII basket to yield a single comparator. The company base case applies IQVIA market shares, the UKHCDO 2023 report providing an alternative set of weights.

Table 25: Market shares: FVIII

	iQVIA	UKHCDO
Advate	████%	28%
Refacto AF	████%	17%
NovoEight	██%	8%
Nuwiq	██%	3%
Esperoct	████%	23%
Elocta	████%	20%
Adynovi	██%	2%

For Haemophilia B patients the company compares marstacimab with the individual FIX treatments. The modelled outcomes for the FIX treatments are also combined into a market share weighted FIX basket to yield a single comparator.

Table 26: Market shares: FIX

	iQVIA	UKHCDO
BeneFIX	████%	23%
Alprolix	████%	47%
Idelvion	████%	15%

Refixia	■%	15%

3.2.5 Perspective, time horizon and discounting

These are largely aligned with the NICE reference case, though the time horizon of 64 year can be argued as being less than lifetime for any younger patients being modelled.

After the first model cycle the company base case is essentially static, making the time horizon relatively unimportant³. Only the scenarios of an ongoing annual discontinuation from marstacimab and an SMR for those with bleeds change this.

3.2.6 Treatment effectiveness and extrapolation

The main effect estimates are the proportion of patients with bleeds that require treatment, and the treated ABR (ABR_T) and treated joint ABR ($AJBR_T$) conditional upon having a treated bleed. The treated non-joint ABR is the residual: $AnJBR_T = ABR_T - AJBR_T$.

The estimates for emicizumab are derived by applying the ITC odds ratio of no bleeding of ■ to the marstacimab odds of no bleeding, and the rate ratios of ■ for ABR_T and ■ for $AJBR_T$.

The EAG presents the implied unconditional ABRs in the last two columns of Table 27 for ease of comparison with the clinical effectiveness section. These are all that are needed for the company base case and most analyses, the proportion with bleeds only being required for the scenario that applies a mortality effect.

Table 27: Main clinical effect estimates

	Bleeds	Conditional			Unconditional		
		ABR _T	AJBR _T	AnJBR _T	ABR _T	AJBR _T	AnJBR _T
Base case							
Marstacimab	62.6%	7.53	6.09	1.44	4.72	3.82	0.9
FVIII/FIX	60.2%	13.09	9.43	3.66	7.89	5.68	2.2
Emicizumab	■	■	■	■	■	■	■
Scenario 1 – Differentiated by Haemophilia A and Haemophilia B							
Haem. A							

³ The ICER will be little affected though total NHB QALYs will increase with a longer time horizon

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Marstacimab	■%	■	■	■	■	■	■
FVIII	■%	■	■	■	■	■	■
Emicizumab	■%	■	■	■	■	■	■
Haem. B							
Marstacimab	■%	■	■	■	■	■	■
FIX	■%	■	■	■	■	■	■
Scenario 2 – Differentiated by SHL and EHL FVIII/FIX							
Marstacimab	■%	■	■	■	■	■	■
SHL FVIII/FIX	■%	■	■	■	■	■	■
EHL FVIII/FIX	■%	■	■	■	■	■	■
Emicizumab	■%	■	■	■	■	■	■

3.2.7 Marstacimab dose escalation

A one-off dose escalation rate for 13.25% from 150mg to 300mg marstacimab is applied in the first cycle of the model, based upon the ATP of BASIS.

3.2.8 Treatment discontinuations

A one-off treatment discontinuation rate of 6.02% for marstacimab is applied in the first cycle of the model, based upon the ATP of BASIS. The company presents a scenario analysis that applies this for each annual model cycle.

Haemophilia A patients discontinuing from marstacimab are assumed to have the costs and efficacy of the market weighted FVIII basket. It is assumed that none discontinue to emicizumab.

Haemophilia B patients discontinuing from marstacimab are assumed to have the costs and efficacy of the market weighted FIX basket.

It is assumed that there are no discontinuations from emicizumab.

3.2.9 Adverse events

Adverse events have minimal effects upon model outputs and are not included in the company base case. If included, they occur during each model cycle for marstacimab and emicizumab, rates being taken from BASIS for marstacimab and from HAVEN 3 for emicizumab. The rates for marstacimab are a constant 1.2% across all adverse events, but with there being no epistaxis as shown in Table 28.

Table 28: Adverse events rates

	Marstacimab	Emicizumab
Chest Pain	1.2%	
Haemarthrosis	1.2%	
Haemorrhage (vascular disorder)	1.2%	
Meningioma	1.2%	
Peripheral Swelling	1.2%	
Tonsillitis	1.2%	
Traumatic Haemorrhage	1.2%	
Tympanic Membrane Perforation	1.2%	
Epistaxis		2.9%

3.2.10 Mortality

The company base case applies standard UK life table values.

The model also contains the facility to apply an SMR for those with bleeds. The company uses the relatively recent study of 1,031 Dutch patients with data between 2001 and 2018,¹⁶ of whom 421 had severe haemophilia with a reported SMR of 2.4 (1.8-3.0).

3.2.11 Health related quality of life

3.2.11.1 Base quality of life value

The baseline quality of life value of 0.726 is taken from the BASIS trial baseline EQ-5D value.

3.2.11.2 Bleed quality of life values

Quality of life decrements of 0.280 for joint bleeds and 0.160 for non-joint bleeds are taken from the literature.^{13, 71} These are assumed to apply in full for 2 days and at 50% for a further 5 days yielding a loss of 0.0034 QALYs per joint bleed and 0.0020 QALYs per non-joint bleed. This yields the QALY losses per model cycle for the company base case of Table 29, the last column reporting the net QALY gain from marstacimab. Due to the company base case assuming equal effect for all FVIII treatments and all FIX treatments these all have the same bleed QALY losses.

Table 29: Company Base Case: QALYs per year from bleeds

	Unconditional		QALY loss per annual cycle			
	AJBR _T	AnJBR _T	AJBR _T	AnJBR _T	Total	Net
Marstacimab	■	■	■	■	■	-
FVIII/FIX	■	■	■	■	■	■

Emicizumab						

Lower bleed rates for marstacimab compared to FVIII/FIX are estimated to result in an annual QALY gain. Higher bleed rates for marstacimab compared to emicizumab are estimated to result in an annual QALY loss.

3.2.11.3 Treatment modality quality of life values

Losses of 0.0003 QALYs per IV administration and 0.0002 per SC administration are taken from the literature.⁷²

Table 30: Company Base Case: Ha: QALYs per year from treatment modality

	QALY	Number of treatments		QALYs	
	Per admin	Weekly	Annual	Total	Net
Marstacimab	-0.0002	1.00	52.2	-0.0104	..
Advate	-0.0003	2.80	146.1	-0.0438	0.0334
Refacto AF		2.80	146.1	-0.0438	0.0334
NovoEight		3.50	182.6	-0.0548	0.0444
Nuwiq		2.80	146.1	-0.0438	0.0334
Esperoct		1.75	91.3	-0.0274	0.0170
Elocta		1.75	91.3	-0.0274	0.0170
Adynovi		2.00	104.4	-0.0313	0.0209
FVIII Basket	..	..	..		
Emicizumab	-0.0002	0.50	26.1	-0.0078	-0.0026

Table 31: Company Base Case: Hb: QALYs per year from treatment modality

	QALY	Number of treatments		QALYs	
	Per admin	Weekly	Annual	Total	Net
Marstacimab	-0.0002	1.00	52.2	-0.01044	..
BeneFIX	-0.0003	2.00	104.4	-0.0313	0.0209
Alprolix		1.00	52.2	-0.0157	0.0052
Idelvion		1.00	52.2	-0.0157	0.0052
Refixia		1.00	52.2	-0.0157	0.0052
FVIII Basket	..	..	..		

Marstacimab being subcutaneous rather than intravenous yields an annual gain of between 0.017 QALYs and 0.044 QALYs over FVIII, depending upon the frequency

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of FVIII administration. The weighted average QALY gain of [REDACTED] can be compared with the [REDACTED] QALY gain from avoiding bleeds, illustrating that around 75% of the modelled QALY gain arises from treatment modality benefits rather than the avoidance of bleeds for those with haemophilia A.

Marstacimab being weekly and emicizumab being fortnightly results in a net 0.0026 QALY loss. This can be compared with the [REDACTED] net QALY loss from additional bleeds, illustrating that around 25% of the modelled QALY loss arises from treatment modality losses rather than the additional bleeds for the comparison with emicizumab.

Marstacimab being subcutaneous yields an annual gain of [REDACTED] QALYs over FIX. This can be compared with the [REDACTED] QALY gain from avoiding bleeds, illustrating that around 50% of the modelled QALY gain arises from treatment modality benefits rather than the avoidance of bleeds for those with haemophilia B.

3.2.11.4 Adverse events quality of life

Adverse event quality of life decrements are taken from the literature, largely from Doyle et al.,⁷³ and are typically between 0.030 and 0.070, though epistaxis is an outlier with a decrement of only 0.003. All are assumed to last for 7 days, resulting in an annual loss of -0.000083 QALYs for marstacimab and -0.00001 QALYs for emicizumab.

3.2.12 Resources and costs

3.2.12.1 Direct drug costs

For marstacimab the weekly cost of [REDACTED] for 150mg results in an annual cost of [REDACTED] for 150mg and [REDACTED] for those dose escalating to 300mg. Marstacimab is costed assuming 86.75% receive 150mg and 13.25% receive 300mg, based upon the dose escalation percentage of the BASIS ATP which yields an average annual cost of [REDACTED]. An additional one-off [REDACTED] for a 300mg loading dose is added to this.

For FVIII/FIX the company assumes around the midpoint of the SmPC dosing frequencies and IU per kg. The base case assumes treatment wastage, but the model has the facility to assume no wastage. Wastage calculations are based upon

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the UKHCDO mean weight of [REDACTED] kg and standard deviation of [REDACTED] kg; i.e. it reflects the patients' weight distribution rather than being evaluated at the mean value.

Table 32: FVIII treatment costs

	Per administration			Tx per week	Annual cost	
	IU/kg	Waste	No waste		Waste	No waste
Advate	30	[REDACTED]	[REDACTED]	2.80	[REDACTED]	[REDACTED]
Refacto AF	30	[REDACTED]	[REDACTED]	2.80	[REDACTED]	[REDACTED]
NovoEight	30	[REDACTED]	[REDACTED]	3.50	[REDACTED]	[REDACTED]
Nuwiq	30	[REDACTED]	[REDACTED]	2.80	[REDACTED]	[REDACTED]
Esperoct	50	[REDACTED]	[REDACTED]	1.75	[REDACTED]	[REDACTED]
Elocta	50	[REDACTED]	[REDACTED]	1.75	[REDACTED]	[REDACTED]
Adynovi	45	[REDACTED]	[REDACTED]	2.00	[REDACTED]	[REDACTED]
FVIII Basket	..	[REDACTED]	[REDACTED]	..	[REDACTED]	[REDACTED]

Table 33: FIX treatment costs

	Per administration			Tx per week	Annual cost	
	IU/kg	Waste	No waste		Waste	No waste
BeneFIX	40	[REDACTED]	[REDACTED]	2.00	[REDACTED]	[REDACTED]
Alprolix	50	[REDACTED]	[REDACTED]	1.00	[REDACTED]	[REDACTED]
Idelvion	42.5	[REDACTED]	[REDACTED]	1.00	[REDACTED]	[REDACTED]
Refixia	40	[REDACTED]	[REDACTED]	1.00	[REDACTED]	[REDACTED]
FIX Basket	..	[REDACTED]	[REDACTED]	..	[REDACTED]	[REDACTED]

Emicizumab is costed assuming fortnightly 3.0 IU/kg dosing which results in an annual cost of £[REDACTED] with wastage, or £[REDACTED] without wastage. An additional one-off £[REDACTED], or £[REDACTED] without wastage, for four weekly loading doses is added to this.

Wastage adds around 5% to the cost of the FVIII basket, 6% to the cost of emicizumab and 4% to the cost of the FIX basket.

3.2.12.2 Administration and monitoring costs

All routine prophylaxis is assumed to be patient administered and there are no administration costs.

There are no monitoring costs within the model. For the base case which assumes no difference in overall survival provided that monitoring costs do not differ by

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treatment these would net out between the arms. For scenarios which model a difference in overall survival monitoring costs would not net out between the arms.

3.2.12.3 Bleed FVIII/FIX costs

Bleeds are assumed to be treated with an FVIII basket or a FIX basket depending upon whether the patient has haemophilia A or haemophilia B. This applies not only to bleeds among patients on marstacimab or emicizumab prophylaxis. It also applies to bleeds for those receiving a specific FVIII or FIX; e.g. patients using BeneFIX for prophylaxis do not have their bleeds treated with BeneFIX but with a weighted average of FIX treatments.

The dosing required for treating bleeds is assumed to be the same as a routine prophylactic dose, hence FVIII and FIX costs per bleed are as per Table 32 and Table 33, [REDACTED] and [REDACTED] respectively with wastage and [REDACTED] and [REDACTED] without wastage. The model also allows for a doubling in the dose and hence the cost per bleed for joint bleeds.

3.2.12.4 Bleed hospital visit costs

The proportions of patients requiring hospital visits per bleed are taken from O'Hara et al.,¹³ and coupled with 2021/22 NHS reference costs.

Table 34: Bleed hospital visit costs

	Proportion	Unit Cost
Haematologist OP	97%	£203
Orthopaedist OP	97%	£129
A&E visit	18%	£56
Inpatient stay	29%	£157
Total		£545

3.2.12.5 Adverse event costs

All adverse events are costed at £53.74 based upon a Community Health Services District Nurse face to face visit, costed using 2021/22 NHS reference costs and reportedly inflated to 2025 costs. This results in annual adverse event costs of £5.16 for marstacimab and £1.56 for emicizumab.

4 COST EFFECTIVENESS RESULTS

4.1 Cost basis

There are commercial agreements in place for all comparators with the exception of NovoEight which is no longer a part of the MPSC framework. The results of this report only include the PAS for marstacimab. Other treatments are costed using list prices as per Table 32 and Table 33 above. A confidential cPAS appendix that summarises and applies the comparator price discounts has been supplied.

4.2 Company base case cost effectiveness results

For those with haemophilia A the company base case estimates are presented in Table 35 to Table 39.

Marstacimab treatment costs are split into the costs of marstacimab and the costs of the FVIII basket among those who discontinue marstacimab treatment.

Table 35: Comp. BC: Ha: Disaggregate costs

	Treatment	Bleed costs		Total	Net
		FVIII	Visits		
Marstacimab				*****	1
2 nd line FVIII					
Advate				*****	*****
Refacto AF				*****	*****
NovoEight				*****	*****
Nuwiq				*****	*****
Esperoct				*****	*****
Elocta				*****	*****
Adynovi				*****	*****
Emicizumab				*****	*****
FVIII Basket				*****	*****

The disaggregate QALYs are presented in Table 36. Note that within this the treatment disutilities, Tx Disutil, are the QALYs lost due to the mode of treatment, subcutaneous or intravenous. They are not related to the treatment of bleeds.

Table 36: Comp. BC: Ha: Disaggregate QALYs

	Base	Non-joint	Joint	Tx Disutil	Total	Net

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Marstacimab						
Advate						
Refacto AF						
NovoEight						
Nuwiq						
Esperoct						
Elocta						
Adynovi						
Emicizumab						
FVIII Basket						

In Table 36 the QALY gains from marstacimab over the FVIII treatments occur mainly due to the mode of treatment, not from the avoidance of bleeds. The mode of treatment accounts for between 65% and 84% of the net QALY gain from marstacimab over the FVIII treatments, and 73% of the net gain compared to the FVIII basket.

Table 37 presents the cost effectiveness of marstacimab relative to the individual comparators, and at the foot of the table relative to the FVIII basket weighted by market share. Due to marstacimab generally being estimated to dominate FVIII the QALY net health benefits are also reported. These infer the amount of QALYs that the NHS could purchase by spending the estimated net savings on other interventions with an ICER of £20,000 per QALY and an ICER of £30,000 per QALY respectively. These inferred QALYs are added to the direct Δ QALY estimate to give the total QALY net health benefit.

Table 37: Comp. BC: Ha: Pairwise marstacimab vs individual comparators

	Δ Cost	Δ QALY	ICER	NHB £20k	NHB £30k
Advate					
Refacto AF					
NovoEight					
Nuwiq					
Esperoct					
Elocta					
Adynovi					
Emicizumab					

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FVIII Basket					

Table 38: Comp. BC: Ha: Fully incremental with individual comparators

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab	*****	*****	-	-	-
Refacto AF	*****	*****	-	-	
NovoEight	*****	*****	-	-	
Advate	*****	*****	-	-	
Nuwiq	*****	*****	-	-	
Elocta	*****	*****	-	-	
Esperoct	*****	*****	-	-	
Adynovi	*****	*****	-	-	
Emicizumab	*****	*****	*****	*****	

Table 39: Comp. BC: Ha: Fully incremental with FVIII basket

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab	*****	*****	-	-	-
FVIII Basket	*****	*****	-	-	
Emicizumab	*****	*****	*****	*****	

For those with Haemophilia B the company base case estimates are presented in Table 40 to Table 43 below.

Table 40: Comp. BC: Hb: Disaggregate costs

	Treatment	Bleed costs		Total	Net
		FIX	Visits		
Marstacimab				*****	-
2 nd line FIX					
BeneFIX				*****	*****
Alprolix				*****	*****
Idelvion				*****	*****
Refixia				*****	*****
FIX Basket				*****	*****

Table 41: Comp. BC: Hb: Disaggregate QALYs

	Base	Non-joint	Joint	Tx Disutil	Total	Net
Marstacimab						-

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BeneFIX						
Alprolix						
Idelvion						
Refixia						
FIX Basket						

As with the Haemophilia A results, for the Haemophilia B modelling while less marked the net QALY gain is still mainly attributable to the mode of administration rather than the avoidance of bleeds.

Table 42: Comp. BC: Hb: Pairwise marstacimab vs individual comparators

	Δ Cost	Δ QALY	ICER	NHB £20k	NHB £30k
BeneFIX					
Alprolix					
Idelvion					
Refixia					
FIX Basket					

Table 43: Comp. BC: Hb: Fully incremental with individual comparators

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab			-	-	-
BeneFIX			-	-	
Alprolix			-	-	
Idelvion			-	-	
Refixia			-	-	

For Haemophilia A the PSA estimates that for low willingness to pay values marstacimab has a probability of being the most cost effective of around 94% with Refacto AF accounting for the residual probability. The probability of marstacimab being the most cost effective gradually rises to 98% at a willingness to pay of £100k per QALY, again with Refacto AF accounting for the residual probability. The other comparators, including emicizumab, have no probability of being cost effective.

If only marstacimab, emicizumab and the FVIII basket are considered, the probability of marstacimab being the most cost effective over the willingness to pay range of £0 to £100k per QALY is 100%.

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For Haemophilia B the probability of marstacimab being the most cost effective over the willingness to pay range of £0 to £100k per QALY is 100% regardless of whether the comparators are disaggregated or aggregated into the FIX basket.

4.3 Company scenario analyses

The company presents two main scenario analyses.

- haemophilia A specific and haemophilia B specific estimates for the proportion with bleeds, the ABR and the AJBR.
- SHL and EHL specific estimates for the proportion with bleeds, the ABR and the AJBR.

4.3.1 Company Scen01: Haemophilia A and B specific effect estimates

For those with haemophilia A the pairwise comparisons for the scenario that applies haemophilia A specific estimates for the proportion with bleeds, the ABR and the AJBR are presented in Table 44 with the fully incremental analysis in Table 45 and the fully incremental analysis for marstacimab, emicizumab and the FVIII basket in Table 46.

Table 44: Comp. Scen01: Ha: Pairwise marstacimab vs individual comparators

	Δ Cost	Δ QALY	ICER	NHB £20k	NHB £30k
Advate	*****	*****	██████	*****	*****
Refacto AF	*****	*****	██████	*****	*****
NovoEight	*****	*****	██████	*****	*****
Nuwiq	*****	*****	██████	*****	*****
Esperoct	*****	*****	██████	*****	*****
Elocta	*****	*****	██████	*****	*****
Adynovi	*****	*****	██████	*****	*****
Emicizumab	*****	*****	██████	*****	*****
FVIII Basket	*****	*****	██████	*****	*****

Table 45: Comp. Scen01: Ha: Fully incremental with individual comparators

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab	*****	*****	-	-	-
Refacto AF	*****	*****	-	-	██████
NovoEight	*****	*****	-	-	██████
Advate	*****	*****	-	-	██████

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Nuwiq	*****	*****	-	-	
Elocta	*****	*****	-	-	
Esperoct	*****	*****	-	-	
Adynovi	*****	*****	-	-	
Emicizumab	*****	*****	*****	*****	

Table 46: Comp. Scen01: Ha: Fully incremental with FVIII basket

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab	*****	*****	-	-	-
FVIII Basket	*****	*****	-	-	
Emicizumab	*****	*****	*****	*****	

For those with haemophilia B the pairwise comparisons for the scenario that applies haemophilia B specific estimates for the proportion with bleeds, the ABR and the AJBR are presented in Table 47 with the fully incremental analysis in Table 48.

Table 47: Comp. Scen01: Hb: Pairwise marstacimab vs individual comparators

	Δ Cost	Δ QALY	ICER	NHB £20k	NHB £30k
BeneFIX	*****	*****		*****	*****
Alprolix	*****	*****		*****	*****
Idelvion	*****	*****		*****	*****
Refixia	*****	*****		*****	*****
FIX Basket	*****	*****		*****	*****

Table 48: Comp. Scen01: Hb: Fully incremental with individual comparators

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab	*****	*****	-	-	-
BeneFIX	*****	*****	-	-	
Alprolix	*****	*****	-	-	
Idelvion	*****	*****	-	-	
Refixia	*****	*****	-	-	

For those with haemophilia A the PSA estimates that at low willingness to pay values the probability of marstacimab being the most cost effective is 96%, the residual probability applying to Refacto AF. This rises to 99% at a willingness to pay of £100k per QALY. When compared to the FVIII basket and emicizumab, the probability of marstacimab being the most cost effective is 100% across the willingness to pay range.

For those with haemophilia B the PSA estimates that at low willingness to pay values the probability of marstacimab being the most cost effective is 93%, the residual probability applying to BeneFIX. This rises to 98% at a willingness to pay of £100k per QALY. When compared to the FIX basket, the probability of marstacimab being the most cost effective is 100% across the willingness to pay range.

4.3.2 Company Scen02: SHL and EHL specific effect estimates

For those with haemophilia A the pairwise comparisons for the scenario that applies SHL and EHL specific estimates for the proportion with bleeds, the ABR and the AJBR are presented in Table 49 with the fully incremental analysis in Table 50 and the fully incremental analysis for marstacimab, emicizumab and the FVIII basket in Table 51.

Table 49: Comp. Scen02: Ha: Pairwise marstacimab vs individual comparators

	Δ Cost	Δ QALY	ICER	NHB £20k	NHB £30k
Advate	*****	*****	████████	*****	*****
Refacto AF	*****	*****	████████	*****	*****
NovoEight	*****	*****	████████	*****	*****
Nuwiq	*****	*****	████████	*****	*****
Esperoct	*****	*****	████████	*****	*****
Elocta	*****	*****	████████	*****	*****
Adynovi	*****	*****	████████	*****	*****
Emicizumab	*****	*****	████████	*****	*****
FVIII Basket	*****	*****	████████	*****	*****

Table 50: Comp. Scen02: Ha: Fully incremental with individual comparators

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab	*****	*****	-	-	-
Refacto AF	*****	*****	-	-	████████
NovoEight	*****	*****	-	-	████████
Advate	*****	*****	-	-	████████
Nuwiq	*****	*****	-	-	████████
Elocta	*****	*****	-	-	████████
Esperoct	*****	*****	-	-	████████
Adynovi	*****	*****	-	-	████████
Emicizumab	*****	*****	*****	*****	████████

Table 51: Comp. Scen02: Ha: Fully incremental with FVIII basket

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab	*****	*****	■	■	■
FVIII Basket	*****	*****	■	■	■
Emicizumab	*****	*****	*****	*****	■

For those with haemophilia B the pairwise comparisons for the scenario that applies haemophilia B specific estimates for the proportion with bleeds, the ABR and the AJBR are presented in Table 52 with the fully incremental analysis in Table 53.

Table 52: Comp. Scen02: Hb: Pairwise marstacimab vs individual comparators

	Δ Cost	Δ QALY	ICER	NHB £20k	NHB £30k
BeneFIX	*****	*****	*****	*****	*****
Alprolix	*****	*****	*****	*****	*****
Idelvion	*****	*****	*****	*****	*****
Refixia	*****	*****	*****	*****	*****
FIX Basket	*****	*****	*****	*****	*****

Table 53: Comp. Scen02: Hb: Fully incremental with individual comparators

	Cost	QALY	Δ Cost	Δ QALY	ICER
Marstacimab	*****	■	-	-	■
Alprolix	*****	■	-	-	*****
BeneFIX	*****	■	-	-	*****
Idelvion	*****	■	-	-	*****
Refixia	*****	■	-	-	*****

For those with haemophilia A the PSA estimates that at low willingness to pay values the probability of marstacimab being the most cost effective is 97% with the residual probability applying to Refacto AF. This rises to 99% at a willingness to pay of £100k per QALY. When compared to the FVIII basket and emicizumab, the probability of marstacimab being the most cost effective is 100% across the willingness to pay range.

For those with haemophilia B the PSA estimates that marstacimab has a 100% probability of being the most cost effective across the £0 to £100k per QALY willingness to pay range, whether compared to the individual FIX or to the FIX basket.

4.4 *Company sensitivity analyses*

The company presents a wide range of sensitivity analyses in Document B, Section B.3.10.2 (Page 134) of the effects of various inputs upon the estimated net health benefits. The four inputs that the company reports the model being most sensitive to for the comparison with the FVIII basket, across the ranges explored, are:

- Baseline weight
- Baseline age
- The proportion of marstacimab patients who dose escalate
- The proportion of marstacimab patients who discontinue to FVIII

The estimated proportions with bleeds also have some effect.

The results for the baseline age need to be interpreted with some caution as the analyses are reporting net health benefits. A given annual net health benefit will result in a larger total net health benefit for a younger patient.

As would be expected, for the comparison with emicizumab results are also sensitive to the odds ratio of bleeds and the rate ratio of bleeds.

The pattern for the comparison with the FIX basket is similar to that for the FVIII basket, but the proportions with bleeds for marstacimab and the individual FIX treatments matter more. This is due at least in part due to the lesser importance of administration route for the QALY gains for the comparison with the FIX basket due to less frequent administrations within the FIX basket, whereas as summarised in Section 3.2.11.3 above these are more important for the comparison with the FVIII basket.

Further scenario analyses, as reported in Document B, Table 74 (Page 138) suggest a reasonable sensitivity as to whether:

- The UKHCDO market shares should be applied or the iQVIA estimates
- The UKHCDO emicizumab dosing should be applied
- Wastage is applied
- Double FVIII/FIX dosing for joint bleeds is applied

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Results are also sensitivity as to whether a 2.4 SMR is applied for those with bleeds. Applying this worsens the net health benefits for marstacimab compared to both the FVIII basket and the FIX basket, but improves them for marstacimab compared to emicizumab. This apparently perverse result is due to annual treatment costs being substantially more than the £30,000 per QALY willingness to pay threshold for all treatments, meaning that a superior net survival worsens the cost effectiveness estimate.

4.5 *Model validation and face validity check*

4.5.1 EAG cross check model rebuild

The EAG has fully rebuilt the company model and gets good agreement with it. There are minor disagreements in terms of the total discounted bleeds that are modelled. The largest discrepancy for the discounted sum of any outcome is 0.2%, with the discrepancies for the discounted total costs and QALYs being 0.004% and 0.002% respectively.

Based upon the EAG model rebuild the EAG provides a simplified model cross check within the EAG revised company model to highlight the main structural errors.

- The marstacimab versus emicizumab rate ratios for ABR_T and $AJBR_T$ are for the entire population. They are applied to the ABR_T and $AJBR_T$ of those who have had a bleed. This causes the modelled ABR_T and $AJBR_T$ risk ratios to be overstated by the relative risk of having a bleed, ■■■, which in turn causes the bleed rates of emicizumab to be understated by a similar amount.
- The FVIII/FIX costs for treatment of bleeds are double counted. This error favours the more effective treatment.
- The weekly loading doses for the first 4 weeks of emicizumab are assumed to be in addition to the Q2W dosing.
- Those who dose escalate with marstacimab require two subcutaneous administrations. The model assumes only one disutility for these administrations. The EAG thinks that the most reasonable interpretation of the administrative disutilities paper is that dose escalation should involve two administration disutilities.

- Wastage calculations are based upon the smallest vial available. The cost per IU is identical across all vial sizes for the factor VIII/FIX and for emicizumab. Given this, if the smallest vial is a factor of all other larger vials the company wastage calculation is correct, but not if not. Emicizumab is available as 30 IU, 60 IU, 105 IU and 150 IU so the company wastage calculations for it are incorrect. Basing wastage on the 30 IU vial means that for doses between 90 IU and 120 IU four 30 IU vials and so 120 IU are required. But the 105 IU vial is available which saves 15 IU for doses between 90 IU and 105 IU. This 15 IU saving recurs at various higher doses. For the company base case weight distribution the company method estimates an annual cost for emicizumab with wastage of [REDACTED]. Correcting this results in an annual cost for emicizumab of [REDACTED], an annual [REDACTED] less.
- For the modelling of haemophilia B to estimate the FIX direct drug costs the proportion surviving during the first cycle is applied to the annual direct drug cost for both the first cycle and the second cycle. The proportion surviving during the second cycle is applied to the annual direct drug cost for the third cycle, the third cycle proportion to the fourth cycle, and so on. This inflates the FIX direct drug costs by a little over 1%.

4.5.2 Validation: Bleed rates

The modelled ABR and AJBR cross check with the model inputs, subject to the possible error in terms of implementation of the emicizumab bleed rates as per the section above.

4.5.3 Validation: Quality of life

The company provides non-parametric estimates for the BASIS mITT median EQ-5D tariff change from baseline at 6 months and net effect, and the change from baseline at 12 months and net effect. These can be compared with the modelled values for the first cycle⁴.

Table 54: Validation: Quality of life

	OP	ATP	Net effect
Basis mITT median at 6 months	[REDACTED]	[REDACTED]	[REDACTED]

⁴ Setting the model time horizon to 1 year

Basis mITT median at 12 months	████	████	████
Model 1 st cycle: Ha	████	████	████
Model 1 st cycle: Hb	████	████	████
Model 1 st cycle: Ha and Hb pooled	████	████	████

It can be argued that the effect of bleeds upon quality of life is transient. Some patients in BASIS will not have had a bleed within the EQ-5D recall period, but will have had prior to it. The effect of bleeds on these patients may not be reflected in their EQ-5D. But others will have had a bleed during the recall period and the effect of their bleeds will be reflected in their EQ-5D. Given a large enough sample these effects would be expected to cancel out, with the correct overall effect of bleeds on quality of life being reflected in the EQ-5D responses. But the relatively small sample size of BASIS increases the uncertainty around this.

The model simulates a loss from baseline due to bleeds and administration effects upon QoL, in contrast to a gain from baseline during BASIS. The EAG thinks that this could argue for adjusting the baseline value within the model, but this would be inconsequential for the net effect estimates.

The main result appears to be that the net quality of life gains are not particularly large. The modelled absolute net gains are reasonably aligned with the modelled net gain being only 0.0045 larger than the company reported BASIS net gain, but this small absolute value is an increase of 20% compared to the medians. Assessing this is complicated by the company reporting medians rather than means. If nothing else it illustrates that small absolute changes in the quality of life inputs to the model may cause large changes in the ICERs.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 *EAG critique of elements of the company model*

5.1.1 FVIII/FIX treatment of bleeds

The company model assumes that those requiring additional FVIII for the treatment of a bleed have the average cost of the market share weighted FVIII basket. The parallel assumption applies for FIX.

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It may be more reasonable to assume that those requiring additional FVIII for the treatment of a bleed have the same FVIII as their routine prophylaxis, and likewise for FIX.

5.1.2 Discontinuations

The model applies an annual discontinuation rate from marstacimab to a basket of FVIII/FIX of 6.02% for the first cycle of the company base case, and for all cycles in a sensitivity analyses. The model assumes no discontinuations from emicizumab.

The effect of this is most obvious for the comparison with emicizumab. Emicizumab is in effect being compared with a basket of marstacimab and FVIII. If the cost effectiveness of emicizumab against marstacimab is worse than the cost effectiveness of emicizumab against the FVIII basket a higher discontinuation rate for marstacimab improves the cost effectiveness of emicizumab against the basket of marstacimab and FVIII.

The estimates of the company base case of a discontinuation from marstacimab during the first cycle of 6.02% can be compared with this discontinuation rate being applied every cycle and set to 0.00% for marstacimab.

Table 55: The effect of marstacimab discontinuation rates upon the NHB @ £30k/QALY vs main comparators

	Emicizumab	FVIII Basket	FIX Basket
Base case: One off 6.02%	■	■	■
6.02% each cycle	■	■	■
0.00%	■	■	■

A lower discontinuation rate improves the estimated cost effectiveness of marstacimab. This also suggests that at comparator list prices the model structure may be biased against marstacimab due to it assuming that emicizumab has in effect a 0.00% discontinuation rate.

5.1.3 Longer term effects of bleeds: Complications and Mortality

5.1.3.1 Complications

In common with other NICE STAs in the area, the downstream complications of bleeds such as a higher likelihood of joint replacement are not modelled.

The EAG undertook a literature search of the relationship between bleeds and joint arthropathy and possible replacement. The initial search found 9 possibly relevant papers. Kubes et al. analysed time to arthropathy and joint replacement by age but with no other contributory factors such as bleed rates or treatment.⁷⁴ Lin et al. provide some estimates of joint replacement and associated clotting factor frequency among on demand US patients but it is difficult to see how this data could be used for modelling purposes.⁷⁵

Tobase et al. estimated the risks of arthrodesis or arthroplasty to be 40% less with continuous prophylaxis.⁷⁶ They also reported the odds ratio of arthrodesis or arthroplasty by the number of joint bleeds in the previous 6 months compared to none: 1.1 for 1 joint bleed, 2.9 for 2 to 3 joint bleeds and 4.4 for 4 or more joint bleeds, the latter two odds ratios being statistically significant.

The most promising paper for modelling purposes is Fischer et al⁷⁷ who analysed the data of 117 Dutch patients with severe haemophilia A or B and found that the Petterson score, a measure of arthropathy, increased slowly over time even in the absence of joint bleeds, but that it increased by 1 point per 13.5 joint bleeds over a mean period of 10.3 years between first and last Petterson score. This relationship was used by Zhou et al. in the cost effectiveness modelling of emicizumab, with an assumption of joint replacement when the Petterson score reached 28.⁷⁸

In short, it may be possible to explore the effects of joint bleeds on the likelihood of joint replacement surgery. This might be quite speculative and would require a fair number of additional assumptions which may not be uncontroversial. It would also require an entirely new modelling approach. Also note that the EAG exploratory base case applies rather lower baseline bleed rates than the company base case which would reduce the impact of any modelling of joint replacement. Nevertheless, not including it biases the model against the more effective treatment.

5.1.3.2 Mortality

EAG expert opinion suggests that with better modern treatments haemophilia patients may in time have similar life expectancy as the general population. Issues that may affect this for the currently prevalent population are adherence to older therapies such as SHLs. New patients are more likely to use the more modern treatments so this is becoming less of an issue over time.

As the company notes, within Hassan et al.¹⁶ most bleed related deaths were due to intracranial bleeds with a crude death rate of 2.33 per 1,000 patient years. But it can also be noted that non-hepatic cancers had a non-trivial crude death rate within this data as well. Not all the mortality within Hassan et al. was directly bleed related and the SMR may similarly not be directly attributable to differences in treated bleeds.

It is credible that reducing treated bleeds will improve life expectancy. It can be argued that the base case should include this. But due to the high direct drug costs of treating haemophilia the situation could arise where a treatment that is less effective with a higher cost is estimated to be cost effective due to the shorter survival and the shorter duration of expensive treatment. The EAG thinks that this may mean it is better not to differentiate haemophilia treatments by mortality for the assessment of cost effectiveness.

5.2 EAG critique of the handling of quality of life within the model

5.2.1 Baseline quality of life value and age weighting

The baseline quality of life value and age weighting have no effect upon net effects or the base case ICERs due to all utility decrements being absolute rather than proportional and there being no mortality effects.

It does affect the scenario with mortality effects but as reviewed in Section 5.1.3.2 the EAG questions the desirability of this scenario for decision making purposes. It also affects the severity calculation as reviewed in Section 6 but the baseline quality of life would need to be hugely lower for the severity multipliers to be applicable.

For these reasons the EAG does not further consider the baseline quality of life value.

5.2.2 Disutilities per administration

The disutilities of 0.0003 QALYs per IV administration and 0.0002 QALYs per subcutaneous (SC) administration are central to the company cost effectiveness estimates. For the company base case and as outlined in greater detail in section 3.2.11.3 above, they provide around 75% of the modelled QALY gain over FVIII and 50% of the modelled QALY gain over FIX. Due to the EAG exploratory base case reducing the baseline number of bleeds for FVIII/FIX it is likely to be even more central to the modelled QALY gains.

The company draws these disutilities from Johnston et al.,⁷² a paper sponsored by Hoffman-La Roche, the manufacturer of emicizumab which is administered subcutaneously.

Johnston et al. performed a time trade-off (TTO) study among 82 members of the Canadian general public. Vignettes were presented for six possible health states:

- On demand routine treatment with an ABR of 36
- IV prophylaxis 2-3 times per weeks with an ABR of 4 to 5
- IV prophylaxis 2-3 times per weeks with an ABR of 10
- IV prophylaxis 7 times per weeks with an ABR of 4 to 5
- SC prophylaxis weekly with an ABR of 1 to 2
- SC prophylaxis 4 weekly with an ABR of 1 to 2

The vignettes summarise an IV administration as you *“have to go to a clinic/hospital to receive an intravenous infusion of medication. Over time you may be able to do this yourself”* which is *“administered through vein in arm, wait up to 30 minutes for full dose”*. This is augmented with *“Challenges: pain, burning or scarring may be experienced at the injection site, making it difficult to find a suitable vein, infusion may take several tries to complete”*, and *“Risks: Significant risk of complications, including injury, infections and internal bleeding”*. For child patients the vignettes note *“Challenges: Parents administering painful treatment to their children can be a difficult experience. Pain or scarring may occur at the injection site so infusion may take several tries to complete”*.

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The vignettes describe SC administration as “*This involves inserting a needle under your skin and administering a dose*” and that “*the process is completed in less than two minutes*”. This is augmented with “*Challenges: You might experience a burning sensation while the medication is injected*”. There are no risks.

The TTO study was among members of the general public so the EAG thinks that their awareness of what is involved with haemophilia and its treatment is likely to be very limited and no better than that of the EAG economist. Due to this the EAG has a number of concerns around the vignettes.

- IV administration is initially at a clinic or hospital. Admittedly the vignette says you may in time be able to do this yourself, but given the significant risks of injury, infection and internal bleeding it is an open question how many respondents thought they would be likely to be able to or want to do IV administrations by themselves at home. This is not aligned with usual UK practice where EAG expert opinion is that after a few administrations, perhaps 1-2, almost all patients will perform IV administrations themselves or have their parents/carers do it at home, significantly lessening the treatment burden.
- The significant risks including of internal bleeding with IV administration are not quantified or placed in any real context. Where is the internal bleeding, how serious is it, how often does this occur, etc? Members of the Committee may be more familiar with the IV administration associated with haemophilia, but the EAG economist would have been quite concerned by the significant risk of internal bleeding and that this might seemingly occur in e.g. the chest cavity. EAG expert opinion is that internal bleeding from IV administration does not happen, with the worst that is seen being bruising or haematoma at the infusion site
- SC administration has no risks.

The EAG thinks that the design of the TTO study may be biased against IV administrations.

The disutilities are based upon a random-intercept analysis of the TTO data but very little further explanation or data is provided. There are no confidence intervals

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around the estimates or any indication of the statistical separation between the two estimates.

The estimates are provided at 4 decimal places. This means that the actual mean for the IV administration disutility could have been anything from 0.00025 to 0.00035, while the mean for the SC administration disutility could have been anything from 0.00015 to 0.00025. There may have been little to no actual difference between the two central estimates, the apparent difference simply being a function of rounding.

During FAC the company has pointed out that the paper estimates a statistically significant preference for subcutaneous treatment. To the EAG it is unclear whether this preference arises in part or in whole due to the subcutaneous vignettes having ABRs of 1-2 compared to intravenous ABRs of 4-5 and 10. Given the health state descriptors the EAG cannot see how a preference for subcutaneous administration can be estimated without other unwritten assumptions; e.g. a constant disutility per administration and a constant disutility per bleed. The study might have been more reliable if there were common dimensions; e.g. a vignette for IV with ABRs of 1-2 and perhaps also weekly administration, as per some EHLs, and a vignette for subcutaneous with ABRs of 4-5, and again perhaps with an administration frequency of 2-3 times per week to square the circle. By construction the data will have a high degree of collinearity between administration frequency and ABRs.

This also does not address the main point in terms of rounding and the point estimates for the disutilities per administration only being reported at one significant figure, which the EAG finds unusual. It can also be noted that the p-values for the disutilities per administration are 0.22 for subcutaneous and < 0.001 for intravenous. This suggests that the disutility per administration for subcutaneous may be zero, or it may be somewhat greater than zero. The EAG thinks that this means that the point estimates per administration are probably not statistically significantly different from one another; i.e. the confidence interval for the subcutaneous estimate is likely to encompass -0.0003.

EAG expert opinion is that SC administration compared to IV administration provides a patient benefit in and of itself, with less frequent administration at least compared to SHL providing a further benefit.

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Due to the apparent bias of Johnston et al⁷² and the uncertainty around the estimated mean disutilities, the EAG will supply scenarios which (a) halve the disutilities and (b) do not apply them.

5.2.3 Disutilities per bleed

The company sources disutilities of 0.16 for a non-joint bleed from Neufeld et al⁷¹ and 0.28 for a joint bleed from O'Hara et al.¹³

Neufeld et al., funded by Novo Nordisk, surveyed 52 US haemophilia patients with inhibitors who had frequent bleeds, at least 4 bleeds requiring treatment with factor in the previous quarter. Patients or their caregivers were asked to complete daily diaries for at least 90 days or until 4 bleeding episodes had been experienced. The EQ-5D was also completed daily, this being valued using the US dataset. Daily diary completion rates were around 80%. Across 36 patients who did complete daily EQ-5D diaries the mean (s.e.) EQ-5D index was 0.82 (0.03) during non-bleed days and 0.66 (0.04) during bleed days, yielding a net effect of 0.16. There may be some concerns that this analysis may not capture any overall effect of the patients' high bleed rates upon their quality of life such as fear of bleeding, but rather captures how the patients' day to day quality of life varies with bleeds. That said, the average quality of life on non-bleed days of 0.82 is above the baseline quality of life of BASIS so this may not be a concern. The more immediate point is that Neufeld et al. was not limited to non-joint bleeds.

O'Hara et al., funded by Novo Nordisk, explored the effect of target joints on quality of life among 515 European patients with severe haemophilia including 37 UK patients, the 515 being the 42% of the sample who returned EQ-5D responses in the CHES study. They used a general linear model to estimate the effect of the presence of one or more target joints, defined as chronic synovitis: 30% with 0, 30% with 1, 25% with 2, 8% with 3, 3% with 4 and a few patients with more than this. The EAG has not been able to source the 0.28 utility decrement, which may be due to incorrect referencing. But regardless of this the key point is that O'Hara et al. is a study of target joints, not of joint bleeds. The two will be linked but there is not an obviously linear 1:1 relationship with the number of joint bleeds and the number of joints with chronic synovitis.

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The EAG will apply the disutility of Neufeld et al. to both joint and non-joint bleeds. This is not to say that they have the same disutility, only that the data from Neufeld et al. encompasses both types of bleeds so it should be a reasonable average value for them.

The direct effects of bleeds from Neufeld et al. were specifically estimated for bleed days and non-bleed days, additional information on bleeds being recorded both during the bleed and during any treatment follow-up period after the bleed had ended. Of the 52 patients enrolled 39 completed diaries and 38 of these experienced bleeds with a total of 194 bleeds being reported. Among the 37 patients who complied with daily diary entries, these having a 99.8% completion rate, 472 days were bleed days. While the N=38 and N=37 are not perfectly aligned this suggests an average bleed duration of 2.4 days.

It can be argued that the quality of life effects of bleeds might extend beyond the post bleed treatment period. If this applied this data would be available to Neufeld et al. and it would be strongly in the interests of the sponsor, Novo Nordisk, to have this aspect of the data also investigated and reported. The EAG thinks that the most likely explanation is that the data showed that this did not apply or at least not to the extent that it was worth reporting. The alternative explanation is that the authors were incompetent.

The company assumes that the bleed disutilities apply in full for 2 days and at 50% for a further 5 days, so in effect for 4.5 days. The EAG will apply the 2.4 day duration implied by the Neufeld data and provide a scenario of the company assumed 4.5 days.

5.3 *EAG critique of the handling of costs within the model*

5.3.1 Marstacimab dose escalation

Dose escalation drives the costs of marstacimab, and as a consequence of the cost effectiveness of marstacimab.

The company applies the proportion who dose escalated from 150mg to 300mg marstacimab during the ATP of 13.25% alongside the proportion who discontinued marstacimab, 6.02%.

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Data supplied at clarification indicates that none of those who dose escalated during the ATP discontinued during the ATP or the OLE. The EAG will adjust the ATP dose escalation percentage to 13.25% / [REDACTED].

At clarification the company presented more detailed dose escalation data, including for the OLE October 2023 data cut. For the OLE there is some ambiguity in terms of the appropriate denominator and whether this includes or excludes those who dose escalated during the ATP. The EAG assumes it excludes these patients, but would be grateful if the company could clarify this during FAC.

Table 56: Marstacimab dose escalation: Eligible and actual

	Eligible			Actual		
	N	N	%	n	N	%
ATP						
haemophilia A	■	■	■	■	■	■
haemophilia B	■	■	■	■	■	■
All patients	■	■	■	■	■	■
OLE – Oct 2023						
haemophilia A	■	■	■	■	■	■
haemophilia B	■	■	■	■	■	■
All patients	■	■	■	■	■	■
OLE – Oct 2023 adjusted for ATP dose escalators						
haemophilia A	■	■	■	■	■	■
haemophilia B	■	■	■	■	■	■
All patients	■	■	■	■	■	■

It is possible that some adolescent patients were ineligible due the 50kg weight criterion, which would in time cease to apply. This may imply a higher eligibility proportion and possibly a higher actual proportion over time but it seems likely to be a minor issue.

The average duration of marstacimab 150mg treatment among dose escalators during the ATP was ■ days, while the average duration for those dose escalating during the OLE was the 12 months of the ATP plus ■ days. What is clear is that additional patients dose escalated during the OLE. It may also be a concern that

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despite the proportion who dose escalated during the ATP, the proportion eligible to dose escalate among those who did not dose escalate during the ATP continued to increase.

Unfortunately, the EAG does not know the mean duration of treatment during the OLE but notes that among those who dose escalated it was █ days. The EAG thinks that this argues for either a one off additional dose escalation during the 2nd year of █ or an annual ongoing dose escalation rate subsequent to the ATP of █. If the latter the remaining question is how long it should be applied for. Given the increase in eligibility during the OLE despite some patients already having dose escalated and presumably not being part of this eligible group the EAG thinks a reasonable ceiling to this is 50%.

The company base case includes the effect of dose escalation during the ATP. Any consideration of dose escalation during the OLE may also need to consider the possible effects of this dose escalation during the OLE. At clarification the company presented the following data for those who dose escalated.

Table 57: Marstacimab dose escalation: ABR_T before and after escalation

	150mg period			300mg period		
	n	Days	ABR _T	n	N	ABR _T
ATP escalators: ATP data (N=83)						
haemophilia A	█	█	█	█	█	█
haemophilia B	█	█	█	█	█	█
All patients	█	█	█	█	█	█
ATP escalators: OLE data October 2023 data cut (N=75)						
haemophilia A	-	-	-	█	█	█
haemophilia B	-	-	-	█	█	█
All patients	-	-	-	█	█	█
OLE escalators: OLE data October 2023 data cut (N=75)						
haemophilia A	█	█	█	█	█	█
haemophilia B	█	█	█	█	█	█
All patients	█	█	█	█	█	█

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If patients who dose escalated during the ATP retained their lower ABRs during the OLE phase, extrapolating using the ATP ABR will not include these longer term benefits. There is some evidence of their ABRs partially bouncing back during the OLE particularly among the haemophilia A patients, though patient numbers are small. A similar argument can be made for those who dose escalated during the OLE, though this dose escalation may have been due to a worsening ABR during the OLE. The EAG will explore application of the OLE ABR for year 2 and beyond within the modelling.

5.3.2 FVIII/FIX dosing compared to BASIS and UKHDCO data

At clarification the company supplied dosing data that showed a mean total of [REDACTED] IU/kg/year for routine prophylaxis during the BASIS OP.

The model applies a mean total of [REDACTED] IU/kg/year for routine prophylaxis when the company base case iQVIA market shares are applied, 15% higher than that of BASIS.

The EAG asked the company to provide data on the proportions of patients receiving the individual FVIII/FIX during the OP of BASIS. Unfortunately only the proportions receiving SHL and EHL split by haemophilia A and haemophilia B were provided. Applying these weights while retaining the iQVIA market shares balance within these categories results in a mean total of [REDACTED] IU/kg/year for routine prophylaxis, 17% higher than that of BASIS.

This raises two possibilities.

- Dosing during BASIS was less than would occur in the NHS which may imply suboptimal treatment during the OP and that BASIS is biased in favour of marstacimab within the NHS context.
- The FVIII/FIX dosing for routine prophylaxis in the model is too high.

The first bullet cannot be formally addressed by the EAG, the second can be explored by adjusting the dosing within the model.

The 2023 UKHDCO annual report Tables 8a and 8b note that among 483 with severe haemophilia A and without inhibitors receiving FVIII SHL a total of 259,574 IU per person during 2022/23 was issued, and 271,697 IU per person among those receiving FVIII EHL. Adolescents were around 28% of those contributing data and

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were issued with an average of 242,094 IU for SHL and 187,836 IU for EHL. Adults were issued with more, 266,217 IU for SHL and 305,174 IU for EHL. This appears to include both routine prophylaxis and IU issued for the treatment of bleeds, but excludes those not registered for the full treatment period, those issued with emicizumab and those using gene therapy. The company base case assumes routine prophylaxis requires an annual [REDACTED] IU of FVIII SHL and an annual [REDACTED] IU of FVIII EHL, [REDACTED] and [REDACTED] more than the UKHCDO data. It can be argued that adolescents form too large a proportion given the lifetime modelling, but even compared to the adult UKHCDO dosing the company base case dosing estimates are [REDACTED] and [REDACTED] higher. Figure 10 of the report also suggests a mean of around 3,500 IU/kg/year which is reasonably aligned with BASIS.

The confidential UKHCDO report commissioned by the company suggests lower dosing than is assumed in the company base case, though for those with haemophilia B the average annual dose is around [REDACTED] of that of the company base case.

The EAG base case will reduce the FVIII/FIX dosing to 75% that of the company base case. It will supply scenarios that set it to 85% and 100% of the company base case.

5.3.3 Emicizumab dosing: maximum weight applied

The company assumes that as patients' weight increases beyond 100kg, their dose of emicizumab continues to increase. EAG expert opinion is that the emicizumab dose is capped at that for a weight of 100kg: i.e. 300 IU Q2W. The EAG will apply this cap in its exploratory base case.

5.3.4 FVIII/FIX dosing: vial rounding

The company assumes that all patients whose calculated optimal dose fall above a given number of vials round up the number of vials required, resulting in wastage.

EAG expert opinion is that no product is unused due to patient doses being rounded up or rounded down to whole vials. This rounding is more often up than down, but there is rounding down. The ACD of ID6170 for efanesoctocog alfa for severe haemophilia A reports Committee notes much the same.

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The EAG will explore vial rounding down for FVIII/FIX at 50%, 40% and 30% cuts for rounding down.

5.3.5 Hospital visits per bleed

The company base case assumes the same hospital visit resource use per bleed as the company submission for the ID6170 efanesoctocog alfa STA: an average of 2.12 non-IP visits and 0.29 IP admissions, based upon O'Hara et al.⁸ yielding an average cost of £545 per bleed. This is the same source as cited in the company submission for ID3812 etranagogene for moderate or severe haemophilia B with the same resource use being reported in Table 37 of the company submission, though with a somewhat higher cost per bleed of £1,384 due mainly to a higher inpatient unit cost of £3,081 compared to the current £157 being assumed.

O'Hara et al. reported results from the Novartis funded CHESS study of resource use among those with severe haemophilia A, with resource use and EQ-5D data gathered from a range of European countries through patient completed questionnaires.¹³ Another publication with O'Hara as lead author suggests very different PCS completion rates by country, this ranging from a high of 73% in France to a low of 12% in the UK, the UK contributing only 37 responses out of the overall CHESS PCS responses of 552 and its average 43% response rate.¹²

As previously noted, O'Hara et al. explore the relationship between the presence or absence of joints with chronic synovitis, target joints, and resource use.¹³ O'Hara et al. estimate higher costs for those with target joints compared to those without target joints. But the EAG has not been able to source the company reported resource use from O'Hara et al., and also notes that this paper explores target joints' effects upon resource use and not bleeds. The company may be able to address this during FAC.

O'Hara et al. appear to report non-drug direct costs and drug related direct costs of major and minor bleeds.¹¹ CHESS defined major bleeds as moderate to severe pain, effusion, limitation of motion and failure to improve within 24 hours, while minor bleeds were associated with minor pain, minimal joint swelling, minimal restriction of movement and resolution within 24 hours.

The paper is poorly documented and provides minimal information on input data. After controlling for age and number of target joints they report an additional annual non-drug direct cost per bleed of €2,489 (± €671) for major bleeds and a non-

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statistically significant €145 ($\pm$ €114) for minor bleeds. The drug costs are reported as being in 2015 prices. Assuming that non-drug costs are also in 2015 prices these can be converted to sterling using the mid-year exchange rate of €1.40/£ and inflated to 2021/22 prices using the PSSRU NHS Cost Inflation Index uplift of 12.8% so as to be aligned with model inputs results. This results in estimates for non-drug annual direct costs of bleeds of £2,005 ($\pm$ £472) for major bleeds and £117 ($\pm$ £80) for minor bleeds.

Drug related direct cost estimates of €8,092 for major bleeds and €11,944 for minor bleeds were based upon an average cost per IU of €0.61, suggesting a mean dose of 13,266 IU per major bleed and 19,580 IU per minor bleed. These are both somewhat larger than the company base case mean dose per bleed of 3,474 IU, 3.8 times as large for major bleeds and 5.6 times as large for minor bleeds.

Unfortunately, the EAG has not been able to find the balance between major and minor bleeds within O'Hara et al. PCS completion rates are a concern, particularly the UK 12% reporting rate. All reported bleeds seem likely to classify as treated bleeds given the estimated mean IU per minor bleed. The markedly higher mean IU for minor bleeds is also a concern, even though this does not appear to be limited to the treatment of bleeds but may include changes to routine prophylaxis.

The ACD of ID6170 efanesoctocog alfa for bleeding episodes in haemophilia A noted that mild to moderate bleeds would be managed over the phone, often by specialist nurses instead of doctors.

EAG expert opinion is that most bleeds are managed at home without the need for a hospital visit, and that very few bleeds now require hospital admission or inpatient treatment.

In the absence of other data, the EAG base case will assume that 20% of treated bleeds require the resource use outlined in Table 34 above. It will present scenarios of 10% and 100%.

5.3.6 FVIII/FIX administered for bleeds

The company model assumes that FVIII/FIX treatment of bleeds is the weighted average basket of FVIII/FIX. EAG expert opinion suggests that home managed bleeds will be managed with the same FVIII/FIX that the patient uses for prophylaxis,

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and that this is also often aimed for within hospital treated bleeds. The EAG will assume this, though it is mainly likely to affect the pairwise comparisons with the individual FVIII and FIXs rather than the comparisons with the market weighted baskets.

The dosing for bleeds is assumed to be the same as that required for one routine prophylaxis dose, around [REDACTED] IU for SHL and [REDACTED] IU for EHL among those with haemophilia A and around [REDACTED] IU for both SHL EHL among those with haemophilia B.

UKHCDO data, while having a degree of uncertainty around it due to the need to link different databases and the data being incomplete, suggests an average for those with haemophilia A of around [REDACTED] IU for treating a breakthrough bleed and another [REDACTED] IU for follow-up treatment. Figures for those with haemophilia B involved a quite small number of patients with bleeds, N=42, so need to be treated with some caution, but suggest around [REDACTED] IU for breakthrough and another [REDACTED] IU for follow-up.

Additional data supplied by the UKHCDO restricting the data to those reporting having had at least one joint bleed increases the proportion of bleeds that are joint bleeds, though some bleeds within this data are still be non-joint bleeds. Among these patients it suggests if anything slightly lower dosing per bleed than among the patient group as a whole. This may warrant further examination if the EAG base case assumption of 66% of bleeds being joint bleeds for all treatments is thought unreasonable.

The EAG will increase the FVIII/FIX dosing for the treatment of bleeds to reflect the UKHCDO figures for the patient group as a whole.

5.3.7 FVIII treatments available

NICE in its comparator cost spreadsheet notes that NovoEight is no longer a part of the NHS FVIII commissioning process. As a consequence, within the EAG cPAS appendix it is costed at its list price and so is considerably more expensive than the other FVIII. This may raise questions about how representative the market share data is, whether current patients are being switched from Novo Eight to another similar FVIII and whether new patients are starting Novo Eight. It can be noted that the IQVIA market share data already suggests a lower market share for NovoEight

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compared to the 2022/23 UKHCDO market shares. EAG expert opinion has indicated that due to a pegylated version now being marketed, NovoEight use is in decline.

The EAG cPAS appendix will explore excluding Novo Eight from the FVIII basket.

5.3.8 Treatment Efficacy

The EAG models pooled and haemophilia-type specific efficacies for marstacimab and the comparators, similar to the company. The specific EAG inputs for treatment efficacy are described in sections 2.2.2.2 and 2.5.3 of the EAG report. The evidence whether bleed rates and efficacy differs by haemophilia type remains unclear.

5.4 *Exploratory and sensitivity analyses undertaken by the EAG*

5.4.1 EAG model revisions

The EAG makes the following model changes.

- EAG01: Correct the model errors outlined in section 4.5.1 above.
- EAG02: Adjust the ATP marstacimab dose escalation for those who discontinued not having dose escalated and apply the OLE dose escalation for year 2.
- EAG03: Based upon UKHCDO data for FVIII among adult patients revise the FVIII/FIX prophylaxis dosing to be 75% that of the company base case.
- EAG04: Based upon UKHCDO data increase the FVIII/FIX per bleed and assume FVIII/FIX used for bleeds is the same as for prophylaxis.
- EAG05: Cap emicizumab dosing at the dose for a 100kg patients.
- EAG06: Assume that only 20% of bleeds incur the company hospital resource use estimate.
- EAG07: Assume a disutility for both joint and non-joint bleeds of 0.16, with this lasting an average 2.4 days
- EAG08: Revises the clinical effect estimates to be based upon UKHCDO ABRs coupled with the BASIS ABR rate ratios for marstacimab compared to FVIII/FIX, and for the haemophilia A and haemophilia B specific modelling

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compared to BASIS FVIII and BASIS FIX respectively as outlined in greater detail in sections 2.2.2.2 and 2.5.3 above⁵.

These changes result in the following changes to the company base case results that apply the company pooled clinical effectiveness estimates. Due to marstacimab being estimated to result in cost savings the cost effectiveness estimates are presented as net health benefits. The EAG also present results for the cost effectiveness of marstacimab against the pooled emicizumab and FVIII basket using UKHCDO weights 51:49 and pooled across haemophilia A and haemophilia B patients using UKHCDO weights 83:17.

Table 58: EAG model changes: Pooled data: NHB QALYs at £20,000 / QALY

Comparator	Section	EMIC	FVIII	FIX	Ha	All
Company BC	4.2	*****	*****	*****	*****	*****
EAG01	4.5.1	*****	*****	*****	*****	*****
EAG02	5.3.1	*****	*****	*****	*****	*****
EAG03	5.3.2	*****	*****	*****	*****	*****
EAG04	5.3.6	*****	*****	*****	*****	*****
EAG05	5.3.3	*****	*****	*****	*****	*****
EAG06	5.3.5	*****	*****	*****	*****	*****
EAG07	5.2.3	*****	*****	*****	*****	*****
EAG08	2.2.2.2, 2.5.3	*****	*****	*****	*****	*****
EAG01-EAG07		*****	*****	*****	*****	*****
EAG01-EAG08 ⁶		*****	*****	*****	*****	*****

⁵ Note that due to the UKHCDO FIX SHL ABR being based upon only 5 patients the EAG has applied the UKHCDO all patient SHL ABR to EHL ABR ratio to the UKHCDO FIX EHL ABR to estimate the UKHCDO FIX SHL ABR.

⁶ These estimates are based upon the EAG pooling clarification data between haemophilia A and haemophilia B patients which resulted in an October 2023 OLE ABR for marstacimab of [REDACTED]. During FAC the company has pointed out that the pooled estimate is an OLE ABR of 2.880. This has minimal effect upon results. For instance, for the All Patient analysis EAG01-EAG08 the net costs change by -0.01%, the net QALYs by -0.07%, the NHB at £20,000 per QALY by -0.012% and the ICER in the NW quadrant by 0.06%. Due to the minimal effects of this correction and time constraints the EAG has not revised its OLE ABR estimate from [REDACTED] to 2.880. Note that this issue does not apply to the modelling where clinical effect estimates are differentiated by haemophilia type.

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For the modelling that applies the company haemophilia A and haemophilia B specific clinical effectiveness estimates the EAG changes results in the following.

Table 59: EAG model changes: Haemophilia type specific data: NHB QALYs at £20,000 / QALY

Comparator	Section	EMIC	FVIII	FIX	Ha	All
Company BC	4.3.1	*****	*****	*****	*****	*****
EAG01	4.5.1	*****	*****	*****	*****	*****
EAG02	5.3.1	*****	*****	*****	*****	*****
EAG03	5.3.2	*****	*****	*****	*****	*****
EAG04	5.3.6	*****	*****	*****	*****	*****
EAG05	5.3.3	*****	*****	*****	*****	*****
EAG06	5.3.5	*****	*****	*****	*****	*****
EAG07	5.2.3	*****	*****	*****	*****	*****
EAG08	2.2.2.2,	*****	*****	*****	*****	*****
	2.5.3	*****	*****	*****	*****	*****
EAG01-EAG07		*****	*****	*****	*****	*****
EAG01-EAG08		*****	*****	*****	*****	*****

The EAG changes that have the most effects upon results are:

- EAG02: Adjust the ATP marstacimab dose escalation for those who discontinued not having dose escalated and apply the OLE dose escalation for year 2, the latter being by far the more important aspect of this.
- EAG03: Based upon UKHCDO data for FVIII among adult patients revise the FVIII/FIX prophylaxis dosing to be 75% that of the company base case.
- EAG04: Based upon UKHCDO data increase the FVIII/FIX per bleed and assume FVIII/FIX used for bleeds is the same as for prophylaxis.
- EAG05: Cap emicizumab dosing at the dose for a 100kg patients.
- EAG08: Revise the clinical effect estimates to be based upon UKHCDO ABRs coupled with the BASIS ABR rate ratios.

Note that EAG08 which extrapolates for years 2+ using the UKHCDO ABRs for emicizumab and FVIII/FIX and the BASIS OLE ABR ratio between marstacimab and

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FVIII/FIX involves two effects. Firstly, it tends to reduce the ABRs compared to the company base case. Secondly, it increases the effectiveness of marstacimab compared to FVIII/FIX and by implication relative to emicizumab.

The EAG does not present disaggregate results for the above because these estimates are not relevant for decision making. Note also that the EAG is not suggesting that the appropriate willingness to pay threshold is £20,000 per QALY rather than £30,000 per QALY. The above results are presented mainly for the company factual accuracy check of the EAG assessment.

The EAG presents more disaggregate results in the cPAS appendix.

5.4.2 EAG scenario analyses

The EAG supplies the following scenario analyses:

- SA01: Halving the administration disutilities, and not applying them
- SA02: Assuming a bleed duration of 4.5 days
- SA03: Applying the annualised OLE dose escalation to a maximum total dose escalation proportion of 50%
- SA04: FVIII/FIX dosing at 85% and 100% of the company base case
- SA05: Company FVIII/FIX dosing and vial rounding down at 50%, 30% and 20%
- SA06: The company hospital resource use for bleeds applying to 10% and 100% of bleeds
- SA07: Not differentiating marstacimab dose escalations by haemophilia type in the haemophilia type specific modelling
- SA08: Applying the BASIS FVIII/FIX ABRs of the ATP for year 1 and of the OLE for years 2+ and the company ITC results for the comparison with emicizumab
- SA09: No discontinuations for marstacimab, mainly to provide a more reasonable comparison with emicizumab.

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- SA10: Assuming no marstacimab dose escalations and effectiveness based upon censoring for dose escalations, coupled with (a) 100%, (b) 50% and (c) 0% of the administrative disutilities.

Table 60: EAG scenarios: Pooled data: NHB QALYs at £20,000 / QALY

Comparator	EMIC	FVIII	FIX	Ha	All
EAG BC	*****	*****	*****	*****	*****
SA01a: Admin disutility 50%	*****	*****	*****	*****	*****
SA01b: Admin disutility 0%	*****	*****	*****	*****	*****
SA02: Bleed 4.5 days	*****	*****	*****	*****	*****
SA03: Max Mars. dose escal. 50%	*****	*****	*****	*****	*****
SA04a: FVIII/FIX dose 85%	*****	*****	*****	*****	*****
SA04b: FVIII/FIX dose 100%	*****	*****	*****	*****	*****
SA05a: Vial round down at 50%	*****	*****	*****	*****	*****
SA05b: Vial round down at 30%	*****	*****	*****	*****	*****
SA05c: Vial round down at 20%	*****	*****	*****	*****	*****
SA06a: Bleed hosp RU 10%	*****	*****	*****	*****	*****
SA06b: Bleed hosp RU 100%	*****	*****	*****	*****	*****
SA07: Pool dose escalation	-	-	-	-	-
SA08: BASIS ATP and OLE ABRs	*****	*****	*****	*****	*****
SA09: Mars. discontinuation 0%	*****	*****	*****	*****	*****
SA10a: Mars. dose escal. 0%	*****	*****	*****	*****	*****
SA10b: SA10a + 50% admin QoL	*****	*****	*****	*****	*****
SA10c: SA10a + 0% admin QoL	*****	*****	*****	*****	*****

Table 61: EAG scenarios: Haemophilia type specific data: NHB QALYs at £20,000 / QALY

Comparator	EMIC	FVIII	FIX	Ha	All
EAG BC	*****	*****	*****	*****	*****
SA01a: Admin disutility 50%	*****	*****	*****	*****	*****
SA01b: Admin disutility 0%	*****	*****	*****	*****	*****
SA02: Bleed 4.5 days	*****	*****	*****	*****	*****

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SA03: Max Mars. dose escal. 50%	*****	***	***	*****	*****
SA04a: FVIII/FIX dose 85%	*****	*****	*****	*****	*****
SA04b: FVIII/FIX dose 100%	*****	*****	*****	*****	*****
SA05a: Vial round down at 50%	*****	*****	*****	*****	*****
SA05b: Vial round down at 30%	*****	*****	*****	*****	*****
SA05c: Vial round down at 20%	*****	*****	*****	*****	*****
SA06a: Bleed hosp RU 10%	*****	*****	***	*****	*****
SA06b: Bleed hosp RU 100%	*****	*****	***	*****	*****
SA07: Pool dose escalation	*****	*****	*****	*****	*****
SA08: BASIS ATP and OLE ABRs	*****	*****	*****	*****	*****
SA09: Mars. discontinuation 0%	*****	*****	*****	*****	*****
SA10a: Mars. dose escal. 0%	*****	*****	*****	*****	*****
SA10b: SA10a + 50% admin QoL	*****	*****	*****	*****	*****
SA10c: SA10a + 0% admin QoL	*****	*****	*****	*****	*****

The EAG exploratory base cases are sensitive to:

- Whether marstacimab dose escalation increases beyond that which occurred during the ATP and the OLE October 2023 data cut and what is the final maximum proportion of marstacimab patients dose escalating.
- The mean FVIII/FIX dosing that is most reasonable to apply, and if based upon company estimates what the cut-off is for rounding down doses.
- Whether it is reasonable to differentiate clinical effect estimates by haemophilia A and haemophilia B, and if so whether it is reasonable to differentiate dose escalation rates between haemophilia A and haemophilia B.
- Whether the UKHCDO or BASIS should provide the ABR estimates for emicizumab and FVIII/FIX.

Unfortunately, due to the nature of the revised clinical effectiveness data, the available data and time constraints the EAG has been unable to characterise the uncertainty around these parameters and so does not provide probabilistic scenario analyses. The EAG is unable to adequately capture the uncertainty around the estimates derived from BASIS and UKHCDO, however the company may be able to provide the former.

6 SEVERITY MODIFIERS

While there are arguments for not including (a) long term complications due to the probably speculative nature of such modelling or (b) mortality effects due to possible perverse results for the assessment of cost effectiveness, this is less warranted for the assessment of severity modifiers.

The EAG presents the results of the company base case severity modelling that does not include the 2.4 SMR for those with bleeds, and modelling that does include it in Table 62. The EAG estimates are based upon the inputs to the model, including the mortality and general population quality of life values, in order to ensure consistency between the various estimates. The reasons for the discrepancy between the EAG estimated 18.7 discounted QALYs and the company 19.4 discounted QALYs for the general population is unclear but may be due to alternative inputs being used by the company or to EAG errors⁷.

Table 62: EAG severity modelling using Company model: QALYs

	QALYs	Shortfall	% Shortfall
Population	18.704	-	-
No SMR for those with bleeds			
FVIII basket	■	■	■
Emicizumab	■	■	■
FIX basket	■	■	■
2.4 SMR for those with bleeds			
FVIII basket	■	■	■
Emicizumab	■	■	■
FIX basket	■	■	■

The inclusion of the 2.4 SMR for those with bleeds increases the shortfall, but the absolute shortfall remains well below 12 QALYs and the proportionate shortfall remains well below 85%. Even with the 2.4 SMR for those with bleeds the long term effects of complications such as joint replacement would have to more than double the absolute QALY shortfall for severity multipliers to apply.

⁷ To derive the population QALYs the EAG has set all disutilities to zero and the baseline utility to the value for the mean age as taken from Utilities E45:E134.

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8 Appendices

8.1 ROBIS of Company SLR

Table 63: EAG assessment of risk of bias of the company's systematic review of clinical effectiveness

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	No	The SLR was part of a wider review with eligibility criteria presented, however, it is unclear if these were pre-defined. Further sets of criteria were applied to consider relevance to the decision problem and these were not predefined.
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The criteria were appropriate for the wider SLR and the additional criteria used for applicability to the decision problem were also appropriate.

1.3 Were eligibility criteria unambiguous?	Probably yes	The criteria were generally unambiguous but it was not clear how the distinction was made between case series studies (which were excluded) and single arm non-randomised studies (which were included).
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably no	Studies published before 2000 were excluded, although no reason provided this is likely reasonable. Restrictions based on the types of study design were reasonable. There were no restrictions on the basis of the geographic region of a study in the wider SLR but this was subsequently restricted in the ITC without justification.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably no	There were restrictions to English language publications and there were restrictions in the ITC based on the availability of outcome data but a justification was provided
Concerns regarding specification of study eligibility criteria	Unclear concern	Not all eligibility criteria were specified a priori for the ITC and some criteria were not fully justified.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of	Yes	An appropriate range of databases and other sources

databases/ electronic sources for published and unpublished reports?		were searched, including clinical trials registries and proceedings of recent conferences.
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	In addition to the database searches the reference lists of relevant published reviews were checked to identify any other potentially relevant studies.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably yes	The same search terms were used across both Embase and MEDLINE, which is not best practice as the databases have different controlled vocabularies, and some MeSH terms were not exploded, however, no additional relevant studies were identified by the EAG.
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes	No concerns
2.5 Were efforts made to minimise errors in selection of studies?	Probably yes	For the wider SLR the selection of studies at titles and abstracts and full texts was conducted with two independent reviewers. It was not reported how the feasibility criteria for the ITC were applied to the studies.
Concerns regarding methods used to identify and/or select studies	Low concern	The search strategy and selection of studies was appropriate to identify relevant studies and to minimise errors in

		the selection of studies for the SLR.
3: Data collection and study appraisal		
3.1 Were efforts made to minimise error in data collection?	Probably yes	The data to be extracted was reported and one reviewer performed the data extraction with another reviewer checking. It was unclear if the second reviewer checked only the accuracy of extracted data or also checked nothing had been missed with the CS reporting only that the second reviewer 'verified 100% of the data extraction'.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	No	Limited summary data were presented for the 79 studies included in the wider SLR.
3.3 Were all relevant study results collected for use in the synthesis?	Yes	For the studies included in the ITC the relevant results were extracted.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes	Study quality was formally assessed with recognised tools, however the narrative focussed on the overall summary score rather than individual items of bias. No data were presented for the assessments of quality for

		the majority of studies included in the SLR
3.5 Were efforts made to minimise error in risk of bias assessment?	Probably no	No details were provided of the processes used to assess the ROB of the included studies.
Concerns regarding methods used to collect data and appraise studies	Unclear concern	Data collection methods and processes were not clearly reported.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	Probably no	One study was excluded which the EAG considered met the inclusion criteria (HAVEN 4) ^{54, 55}
4.2 Were all predefined analyses followed or departures explained?	No information	No discussion of predefined analyses reported
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably yes	There was only one study included in the narrative synthesis. The CS undertook an unanchored simulated treatment comparison of two studies because of data limitations, this focused on subgroups which they considered most similar. However, there were some missing covariates in the CS base analysis.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	No information	There was no discussion of statistical heterogeneity being formally assessed in the synthesis.

4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably no	The CS includes only two studies in the comparison.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	There was no explicit use of the risk of bias assessments in the synthesis
Concerns regarding the synthesis and findings	High	Potential bias was not accounted for in the synthesis, there was no assessment of heterogeneity in the analysis, and findings were not demonstrated to be robust
Summary of concerns identified (Overall risk of bias) in the review		
Risk of bias	High	One domain has a high risk of bias

8.2 Additional Searches undertaken by EAG

Ovid MEDLINE(R) ALL <1946 to August 12, 2024>

Date searched: 12/08/24

- 1 (marstacimab or PF-06741086 or emicizumab or hemlibra).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 687
- 2 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt. 717409
- 3 (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt. 620433
- 4 Multicenter Study.pt. 351994
- 5 Clinical Studies as Topic/ 839
- 6 exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/ 1317381

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7      Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
      373416
8      Randomization/      107496
9      Random Allocation/  107496
10     Double-Blind Method/      179804
11     Double Blind Procedure/    0
12     Double-Blind Studies/179804
13     Single-Blind Method/ 33831
14     Single Blind Procedure/    0
15     Single-Blind Studies/ 33831
16     Placebos/      35982
17     Placebo/      0
18     Control Groups/      2131
19     Control Group/      2131
20     Cross-Over Studies/ or Crossover Procedure/      57236
21     (random* or sham or placebo*).ti,ab,hw,kf. 1935499
22     ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. 277879
23     ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. 1889
24     (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf. 2032000
25     (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf. 1504741
26     (Nonrandom* or non random* or non-random* or quasi-random* or
      quasirandom*).ti,ab,hw,kf. 58900
27     (phase adj6 (study or studies or trial*)).ti,ab,hw,kf. 226965
28     ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf. 79859
29     ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf. 433194
30     allocated.ti,ab,hw. 90552
31     ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. 48738
32     ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies
      or trial*)).ti,ab,hw,kf. 13738
33     (pragmatic study or pragmatic studies).ti,ab,hw,kf. 666
34     ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. 8644
35     ((quasiexperimental or quasi-experimental) adj3 (study or studies or
      trial*)).ti,ab,hw,kf. 14178
36     trial.ti,kf. 339446
37     or/2-364055704
38     exp animals/ 27403703
39     exp animal experimentation/ 10543
40     exp models animal/ 658078
41     exp animal experiment/ 10543
42     nonhuman/ 0
43     exp vertebrate/26634666
44     or/38-43 27405682
45     exp humans/ 22155324
46     exp human experiment/ 0
47     or/45-46 22155324
48     44 not 47 5250358
49     37 not 48 [CADTH filter: All Clinical Trials - MEDLINE, Embase] 3639329
50     (systematic review or meta-analysis).pt. 357694

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- 51 meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/ 399959
- 52 ((systematic* adj3 (review* or overview*))) or (methodologic* adj3 (review* or overview*))).ti,ab,kf. 375694
- 53 ((quantitative adj3 (review* or overview* or syntheses*)) or (research adj3 (integrati* or overview*))).ti,ab,kf. 17902
- 54 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf. 43500
- 55 (data syntheses* or data extraction* or data abstraction*).ti,ab,kf. 46511
- 56 (handsearch* or hand search*).ti,ab,kf. 11704
- 57 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf. 39129
- 58 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf. 13302
- 59 (meta regression* or metaregression*).ti,ab,kf. 16876
- 60 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. 532891
- 61 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. 392232
- 62 (cochrane or (health adj2 technology assessment) or evidence report).jw. 22007
- 63 (comparative adj3 (efficacy or effectiveness)).ti,ab,kf. 19460
- 64 (outcomes research or relative effectiveness).ti,ab,kf. 11866
- 65 ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf. 4717
- 66 (multi* adj3 treatment adj3 comparison*).ti,ab,kf. 314
- 67 (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf. 181
- 68 umbrella review*.ti,ab,kf. 2164
- 69 (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf. 14
- 70 (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf. 19
- 71 (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf. 12
- 72 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 [Filter for Systematic Reviews HTAs meta analyses CADTH <https://searchfilters.cadth.ca/link/33>. Accessed 2023-05-10.] 771974
- 73 1 and (49 or 72) 211

8.3 Quality assessment of BASIS

Table 64 Quality assessment of BASIS

Item		Response	Company Judgement	EAG judgement
Reporting				
Q1	Hypothesis/aim/objective clearly described	Yes = 1, No = 0	1	1
Q2	Main outcomes in Introduction or Methods	Yes = 1, No = 0	1	1
Q3	Patient characteristics clearly described	Yes = 1, No = 0	1	1

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Item		Response	Company Judgement	EAG judgement
Q4	Interventions of interest clearly described	Yes = 1, No = 0	1	1
Q5	Principal confounders clearly described	Yes = 2, Partially = 1, No = 0	0	0
Q6	Main findings clearly described	Yes = 1, No = 0	1	1
Q7	Estimates of random variability provided for main outcomes	Yes = 1, No = 0	1	1
Q8	All adverse events of intervention reported	Yes = 1, No = 0	1	1
Q9	Characteristics of patients lost to follow-up described	Yes = 1, No = 0	1	1
Q10	Probability values reported for main outcomes	Yes = 1, No = 0	1	1
External Validity				
Q11	Subjects asked to participate were representative of source population	Yes = 1, No = 0, Unclear = 0	1	Unclear
Q12	Subjects prepared to participate were representative of source population	Yes = 1, No = 0, Unclear = 0	1	Unclear
Q13	Location and delivery of study treatment was representative of source population	Yes = 1, No = 0, Unclear = 0	1	Unclear
Internal Validity – Bias and Confounding				
Q14	Study participants blinded to treatment	Yes = 1, No = 0, Unclear = 0	0	0
Q15	Blinded outcome assessment	Yes = 1, No = 0, Unclear = 0	0	0
Q16	Any data dredging clearly described	Yes = 1, No = 0, Unclear = 0	1	1
Q17	Analyses adjust for differing lengths of follow-up	Yes = 1, No = 0, Unclear = 0	1	1
Q18	Appropriate statistical tests performed	Yes = 1, No = 0, Unclear = 0	1	1
Q19	Compliance with interventions was reliable	Yes = 1, No = 0, Unclear = 0	1	1
Q20	Outcome measures were reliable and valid	Yes = 1, No = 0, Unclear = 0	1	1
Q21	All participants recruited from the same source population	Yes = 1, No = 0, Unclear = 0	1	Unclear
Q22	All participants recruited over the same time period	Yes = 1, No = 0, Unclear = 0	1	0
Q23	Participants randomised to treatment(s)	Yes = 1, No = 0, Unclear = 0	0	0
Q24	Allocation of treatment concealed from investigators and participants	Yes = 1, No = 0, Unclear = 0	0	0
Q25	Adequate adjustment for confounding	Yes = 1, No = 0, Unclear = 0	0	0
Q26	Losses to follow-up taken into account	Yes = 1, No = 0, Unclear = 0	1	1
Power				

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Item		Response	Company Judgement	EAG judgement
Q27	Sample size calculation was reported	Yes = 1, No = 0, Unclear = 0	1	1
Total			21	

8.4 *Quality assessment of HAVEN 3 and HAVEN 4*

Table 65 Quality assessment of HAVEN 3 and HAVEN 4

Item		Response	HAVEN 3 company judgement	HAVEN 3 EAG judgement	HAVEN 4 EAG judgement
	Reporting				
Q1	Hypothesis/aim/objective clearly described	Yes = 1, No = 0	1	1	1
Q2	Main outcomes in Introduction or Methods	Yes = 1, No = 0	1	1	1
Q3	Patient characteristics clearly described	Yes = 1, No = 0	1	1	1
Q4	Interventions of interest clearly described	Yes = 1, No = 0	1	1	1
Q5	Principal confounders clearly described	Yes = 2, Partially = 1, No = 0	0	0	0
Q6	Main findings clearly described	Yes = 1, No = 0	1	1	1
Q7	Estimates of random variability provided for main outcomes	Yes = 1, No = 0	1	1	1
Q8	All adverse events of intervention reported	Yes = 1, No = 0	1	1	1
Q9	Characteristics of patients lost to follow-up described	Yes = 1, No = 0	0	1 ^a	1
Q10	Probability values reported for main outcomes	Yes = 1, No = 0	0	1 ^b	1
	External Validity				
Q11	Subjects asked to participate were representative of source population	Yes = 1, No = 0, Unclear = 0	1	0 ^c Unclear	0 Unclear
Q12	Subjects prepared to participate were representative of source population	Yes = 1, No = 0, Unclear = 0	0	0 Unclear	0 Unclear
Q13	Location and delivery of study treatment was representative of source population	Yes = 1, No = 0, Unclear = 0	1	0 ^d Unclear	0 Unclear
	Internal Validity – Bias and Confounding				
Q14	Study participants blinded to treatment	Yes = 1, No = 0, Unclear = 0	0	0 No	0 No
Q15	Blinded outcome assessment	Yes = 1, No = 0, Unclear = 0	0	0 No	0 No
Q16	Any data dredging clearly described	Yes = 1, No = 0, Unclear = 0	1	1	1

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Item		Response	HAVEN 3 company judgement	HAVEN 3 EAG judgement	HAVEN 4 EAG judgement
Q17	Analyses adjust for differing lengths of follow-up	Yes = 1, No = 0, Unclear = 0	0	1 ^e	1
Q18	Appropriate statistical tests performed	Yes = 1, No = 0, Unclear = 0	1	1	1
Q19	Compliance with interventions was reliable	Yes = 1, No = 0, Unclear = 0	0	0 Unclear	0 Unclear
Q20	Outcome measures were reliable and valid	Yes = 1, No = 0, Unclear = 0	1	1	1
Q21	All participants recruited from the same source population	Yes = 1, No = 0, Unclear = 0	1	0 ^f Unclear	0 Unclear
Q22	All participants recruited over the same time period	Yes = 1, No = 0, Unclear = 0	0	1 ^g	1
Q23	Participants randomised to treatment(s)	Yes = 1, No = 0, Unclear = 0	0	0 (not for cohort of relevance)	0 No
Q24	Allocation of treatment concealed from investigators and participants	Yes = 1, No = 0, Unclear = 0	0	0 No	0 No
Q25	Adequate adjustment for confounding	Yes = 1, No = 0, Unclear = 0	0	0	0
Q26	Losses to follow-up taken into account	Yes = 1, No = 0, Unclear = 0	0	1 ^h	1
Power					
Q27	Sample size calculation was reported	Yes = 1, No = 0, Unclear = 0	0	1 ⁱ	1
Total			13	16	16

^a Participant flow reported, the small number of patients lost to follow-up is unlikely to affect the overall findings. ^b P-values reported for primary outcome. ^c Study states recruitment was from university hospitals, hospitals and clinics, but unable to determine if participants comprised the entire source population, an unselected sample of consecutive patients, or a random sample. ^d The study does not clearly demonstrate that location and delivery of the intervention was representative of that in use in the source population. ^e To adjust for varying follow-up periods, the analysis employed negative binomial regression, enhancing the robustness of the results.

The study does not describe the source population, therefore it is unclear whether all participants were recruited from the same source population. ^f The study does not described the source population, therefore it is unclear whether all participants were recruited from the same source population. ^g Recruitment was conducted within a defined period (September 2016 to September 2017), ensuring consistency in participant inclusion. ^h Losses to follow-up were too small to affect the main findings. ⁱ Sample size calculations reported.

8.5 Source of prices used in EAG confidential appendix

Name	Source
Marstacimab	PAS
Octocog alfa (Advate)	MPSC
Moroctocog alfa (ReFacto)	MPSC
Turoctocog alfa (NovoEight)	BNF
Simoctocog alfa (Nuwiq)	MPSC
Turoctocog alfa pegol (Esperoct)	MPSC
Efmoroctocog alfa (Elocta)	MPSC
Rurioctocog alfa pegol (Adynovi)	MPSC
Emicizumab (Hemlibra)	MPSC
Nonacog alfa (recomb coag factor ix) [BeneFIX]	MPSC
Eftrenonacog alfa (Alprolix)	MPSC
Albutrepenonacog alfa (recomb coag factor ix) [Idelvion]	MPSC
Nonacog beta pegol (recomb coag factor ix) [Refixia]	MPSC

Single Technology Appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

EAG report – factual accuracy check and confidential information check [Redacted]

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 3 October** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Any information highlighted with black highlight was information marked as confidential

Section 1: Factual inaccuracies related to EAG's key issues

Issue 1 Factual inaccuracies related to Key Issue 1: Generalisability over the BASIS trial and its relevance to UK practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 12, Section 1.4: Limitation of alternative sources of data is not included. “...the baseline bleed rates for the prophylactic period were considerably higher than NHS patients.”	Please consider amending the text as follows: “...the baseline bleed rates for the prophylactic period were considerably higher than NHS patients, although this is based on a naïve comparison to UK registry data which does not control for confounding variables and has different reporting conditions to the BASIS trial.”	The report states that baseline bleed rates during the prophylactic period of BASIS were considerably higher than NHS patients. However, it should be caveated that this is based on a naïve comparison between a clinical trial dataset and a real-world dataset. As it stands, the EAG's statement could be misleading to a reader as it suggests a fair direct comparison can be made between the two datasets. This is important because, unlike the intra-patient comparison design of the BASIS trial, such a comparison does not control for confounding variables which may impact the interpretation of the different bleed rates.	The EAG has amended the text to make it clear the comments are based on a naïve comparison.

		Additionally, there are considerable limitations to consider when comparing clinical trials to UK registry data. Since bleed rates are self-reported by patients, the different conditions, definitions and reporting requirements between the BASIS trial dataset and a real-world dataset may prevent a fair comparison being made. Participants in the BASIS trial were closely monitored and sent regular reminders to complete their eDiary. In contrast, bleeding data reported from the UK registry is reliant on the Haemtrack system and patient compliance with reporting.	

Issue 2 Factual inaccuracies related to Key Issue 2: The source of information for baseline annualised bleed rates and treatment efficacy within the economic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Limitations and uncertainties associated with the use of alternative sources of data are	Please consider amending the text as follows:	Whilst the company acknowledge that the EAG may wish to explore different assumptions or sources of	Not a factual error. The current text provides a

not acknowledged or described fully. Page 13, Section 1.5: “The EAG prefers to use estimates reported by UKHCDO to inform the efficacy of factor therapy and emicizumab, and to apply the rate ratios estimated in BASIS ATP and OLE to factor therapy to model efficacy of marstacimab. This avoids applying a highly uncertain estimate of relative effect between marstacimab and emicizumab.”	“The EAG prefers to use naïve unadjusted estimates reported by UKHCDO to inform the efficacy of factor therapy and emicizumab, and to apply the rate ratios estimated in BASIS ATP and OLE to factor therapy to model efficacy of marstacimab. This avoids applying a highly uncertain estimate of relative effect between marstacimab and emicizumab derived using population-adjustment methods. However, this approach relies on naïve estimates and does not attempt to adjust for any potential confounding due to important imbalances in either prognostic or effect modification variables.”	data, there are several caveats and limitations associated with using these naïve unadjusted estimates of efficacy that should be presented for factual accuracy. Additionally, as noted in response to Key Issue 1 above, there are challenges with comparing unadjusted bleed rates between clinical trials and UK registry data. Since bleed rates are self-reported by patients, the different conditions, definitions and reporting requirements between the BASIS trial dataset and a real-world dataset may prevent a fair comparison being made.	clear description of the EAG preferred analysis.
Limitations and uncertainties associated with the use of alternative sources of data are not acknowledged or described fully. Page 13, Section 1.5: “The UKHCDO data reduces bleed rates for emicizumab and FVIII/FIX. Combining	Please consider amending the text as follows: “The UKHCDO data reduces bleed rates for emicizumab and FVIII/FIX. Combining with the BASIS ATP data worsens the relative effectiveness of marstacimab, particularly compared to FVIII/FIX. However, the magnitude and direction of any possible bias introduced from the	It is important to note that the data used for this comparison is unadjusted and based on naïve estimates from the UK registry. Therefore, without controlling for potential confounders between the registry and trial data, it is important to highlight the potential bias that may have	Not a factual error. The EAG analysis models a treatment effect between factor therapy and marstacimab that is estimated from the BASIS trial. Hence, it is not appropriate to call this naïve comparison.

with the BASIS ATP data worsens the relative effectiveness of marstacimab, particularly compared to FVIII/FIX.”	use of naïve comparisons is not possible to quantify.”	been introduced, although the direction is uncertain.	
Limitations and uncertainties associated with the use of alternative sources of data are not acknowledged or described fully. Page 19, Section 1.7: “Whether the UKHCDO or BASIS should provide the ABR estimates for emicizumab and FVIII/FIX.”	Please consider amending the text as follows: Whether naïve unadjusted estimates from UKHCDO or the population-adjusted and intra-patient comparisons from BASIS, should provide the ABR estimates for emicizumab and FVIII/FIX.”	Provides clarity on the sources of data available to inform the ABR estimates.	Not a factual error.
Important limitations or assumptions associated with the use of UKHCDO data are missing. Page 71, Section 2.5.3:	Please consider amending the text as follows: This approach avoids reliance on the highly uncertain indirect comparisons. However, several limitations should be acknowledged. The use of the UKHCDO data relies on naïve estimates and does not attempt to adjust for any potential confounding due to important	The company acknowledges that the EAG may wish to explore alternative sources of data or assumptions. However, when using alternative sources of data or assumptions, the full implications and limitations of the alternative should also be presented for clarity and factual accuracy.	The EAG has added text to clarify the main limitations of their analysis.

	imbalances in either prognostic or effect modification variables.		

Issue 3 Factual inaccuracies related to Key Issue 3: Dose-escalation of marstacimab

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
If the EAG's preferred scenario of applying bleeding estimates from UKHCDO (Key Issue 2) is applied, continuing to apply rates of dose escalation from BASIS lacks face validity. Since the application of the UKHCDO ABR data results in fewer bleeds for marstacimab patients compared to the BASIS trial, it is expected that fewer patients would also require dose escalations. This comment links in with comments raised in issue 1 and 2 regarding consistency of decisions/assumptions.	Other plausible alternatives should be considered where the rates of dose escalation are lower than those seen in the clinical trials for marstacimab.	The EAG prefers to use estimates reported by UKHCDO to inform the baseline bleed rates resulting in lower baseline bleed rates compared to the company base case (Key Issue 2). One of the criteria for dose escalation in BASIS was two or more spontaneous bleeds over a 6-month period. Therefore, because dose escalation is dependent on experiencing two or more bleeds, and marstacimab patients experience fewer bleeds in the EAG's preferred approach, then it can be reasonably expected that fewer marstacimab patients	The EAG has amended the EAG report to reflect the company concerns and will provide additional scenario analyses. The EAG note that the estimate of relative treatment effect is based on data that permitted marstacimab dose-escalation, so it is not clear that reducing the marstacimab dose-escalation is appropriate. The EAG consider the most reasonable scenario is to assume no

		will require dose escalation compared to the BASIS trial. Therefore, to ensure consistency and face validity with the alternative set of inputs, the company considers it reasonable to explore a lower proportion of dose escalation in the economic model than observed in the clinical trials to accurately reflect the use of alternative sources of data.	marstacimab dose escalation and to apply the ATP censored effect estimates, coupled with the EAG scenarios around the administrative quality of life effects (SA01)
Page 118, SA03 scenario: This scenario analysis which assumes a 50% dose escalation proportion for marstacimab is not supported by evidence or data.	Given the observed dose escalation in BASIS and the limitations with this scenario, it is recommended that scenario analysis SA03 is removed from the list of scenarios.	The company acknowledges that the EAG may wish to explore alternative assumptions regarding dose escalation. However, the company have several concerns with SA03 which is not supported by available evidence and provides only an extreme scenario. The EAG presented scenario analysis SA03 based on the interpretation that there was an increase in eligibility for dose	Not a factual error. The EAG considers that the dose-escalation of marstacimab in real-world care to be a source of uncertainty, and that a range of scenarios should be explored.

		escalation during the OLE despite some patients already having dose escalated. However, as acknowledged by the company further down in this document, this interpretation is incorrect. Therefore, this scenario may be based on an overestimation of eligibility for dose escalation. Additionally, as demonstrated by Table 56, only a small proportion of participants eligible to dose escalate actually received the dose escalation. Therefore, basing the ceiling for this scenario on eligibility rather than actual proportions of dose escalations observed in the trial is considered inappropriate and unreflective of the available evidence. Finally, as mentioned in the row above, the application of the UKHCDO ABR data in EAG08 results in fewer	

		bleeds for marstacimab patients compared to the BASIS trial, and bleeding rate was one of the criterions for dose escalation. Therefore, rather than increasing the proportion of dose escalation compared to the results from BASIS, it may be more appropriate to consider scenarios in which a smaller proportion of patients require dose escalation.																																																																																																			
Pages 108-109: The EAG ask for clarity from the company regarding the proportion of patients who met eligibility criteria for dose escalation during the OLE.	Page 108, Table 56: Remove ‘Eligible’ data for the results ‘adjusted for ATP dose escalators’: <table><tr><td></td><td colspan="3">Eligible</td><td colspan="3">Actual</td></tr><tr><td></td><td>N</td><td>N</td><td>%</td><td>n</td><td>N</td><td>%</td></tr><tr><td>ATP</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>haemophilia A</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>haemophilia B</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>All patients</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>OLE – Oct 2023</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>haemophilia A</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>haemophilia B</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>All patients</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>OLE – Oct 2023 adjusted for ATP dose escalators</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>haemophilia A</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>haemophilia B</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>All patients</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table> Page 109:		Eligible			Actual				N	N	%	n	N	%	ATP							haemophilia A							haemophilia B							All patients							OLE – Oct 2023							haemophilia A							haemophilia B							All patients							OLE – Oct 2023 adjusted for ATP dose escalators							haemophilia A							haemophilia B							All patients							Within the report, the EAG note there is some ambiguity in terms of the OLE data and whether this includes or excludes those who dose escalated during the ATP. On page 108, the EAG assumes it excludes these patients, but asks if the company could clarify this during FAC. The company acknowledges the ambiguity with the data and thanks the EAG for raising this for FAC.	The EAG does not consider that the table requires updating based on the company’s response.
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	~~“It may also be a concern that despite the proportion who dose escalated during the ATP, the proportion eligible to dose escalate among those who did not dose escalate during the ATP continued to increase.”~~ ~~“Given the increase in eligibility during the OLE despite some patients already having dose escalated and presumably not being part of this eligible group the EAG thinks a reasonable ceiling to this is 50%.”~~	Upon reviewing Table 56, the company can clarify that, for the data provided on the proportion of participants who met eligibility criteria for dose-escalation during the OLE, this data includes those who dose escalated during the ATP. In contrast, the EAG had assumed this data excluded participants who had dose escalated during the ATP. Therefore, changes are required to Table 56 and statements within the report.	
Page 40 and 58: Inaccurate description of the dose-escalation decisions. Dose escalation will be at the clinician’s discretion.	Pg 40: After 6 months, participants who met protocol specified dose-escalation criteria could have their dose increased to 300 mg once weekly. Even if these criteria were met, dose escalation was at the clinician discretion. Pg 58: After 6 months in the ATP or anytime during the OLE, patients were eligible to move to a higher dose of marstacimab if they weighed ≥50kg and experienced at least two spontaneous bleeds over a 6 month period. Dose-escalated patients received 300mg of	Dose escalation will be at the clinician’s discretion. A patient may have met the dose escalation criteria in the trial but not actually dose escalated.	Not a factual error, but text on page 40 was amended for clarity

	marstacimab weekly, rather than 150mg. Even if these criteria were met, dose escalation was at the clinician discretion.		
Page 58 Table 14, footnote: Inaccurate description of the dose-escalation	Table 14 footnote: ~~*Note OLE phase is on-going and it is possible additional people may escalate doses with longer follow-up.~~	Additional people may or may not escalate doses with long term follow-up, this is currently unknown. Once patients are stable on treatment, it is expected that changes in dose will become less common.	Not a factual error.
Page 14, Section 1.5: “If dose escalation is likely to continue to occur beyond that recorded during the open-label extension October 2023 data cut this is likely to further considerably worsen the cost effectiveness of emicizumab.”	Please consider rewriting the text as follows: “There remains uncertainty about whether further dose escalation will continue to occur beyond the October 2023 data cut of the open-label extension trial, leading to uncertainty about the potential impact of this on the net benefit of marstacimab.”	Correction of typo of “emicizumab” to “marstacimab” and adjustment of the statement to highlight the uncertainty regarding further dose escalation, rather than suggesting dose escalation is likely to continue, which is currently unknown.	The EAG has amended the treatment name but left the other text unchanged.

Issue 4 Factual inaccuracies related to Key Issue 4: Discontinuation of haemophilia treatments

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 15:	Discontinuation is not applied to emicizumab, due to the absence of data	The proposed wording more accurately describes the potential	The EAG revised the text to “ <i>Discontinuation is not</i>

Inaccurate description of discontinuation assumptions used.	~~to inform this, which~~ The EAG considers to be a source of uncertainty bias .	uncertainty and the rationale for not modelling discontinuation from emicizumab.	<i>applied to emicizumab, due to the absence of data. The EAG considers this to be a source of uncertainty and probable bias."</i>

Issue 5 Factual inaccuracies related to Key Issue 5: Dosing of factor prophylaxis

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 16, Section 1.5: Inaccurate description of bias	Please consider amending the text as follows: "The EAG is concerned about the potential bias in the analyses uncertainty in the results caused by uncertainty around the dosing of prophylaxis."	The proposed wording more accurately describes the potential uncertainty introduced.	Not a factual error.
Pages 110-111, Section 5.3.2: The report does not mention several important limitations of considering data from UKHCDO to adjust factor prophylaxis dosing calculations.	It is recommended that the following limitations are added to the report: • On-demand treatment regimen. The UKHCDO data includes a proportion of patients receiving on-demand regimens. These patients are not relevant for the current decision-problem and their inclusion in the UKHCDO data can be expected to reduce the average IU per person per year when compared to an average person receiving routine prophylaxis.	The company have concerns with the EAG scenario EAG03 which adjusts factor prophylaxis dosing in an attempt to reflect real-world dosing. Currently, the report omits several important limitations with this approach when considering the interpretation of UKHCDO dosing data for factual accuracy. Additionally, UK clinical experts consulted as part of this submission stated that they prescribe factor products in line with SmPC dosing	The UKHCDO dosing is aligned with current UK dosing. EAG expert opinion suggests that relatively few UK patients remain on "on demand" dosing and would have negligible impact on the UKHCDO data. The EAG notes that the CIC UKHCDO report commissioned by the company provides haemophilia A and

	• Data for haemophilia A only. The 2023 UKHCDO annual report presents data on factor issued (FVIII) for people with severe haemophilia A. However, the report does not present comparable data for people with severe haemophilia B.	recommendations. Clinical experts also stated that clinicians may even prescribe higher doses than SmPC recommendations to try and get fewer bleeds. Therefore, there exists an unexplained discrepancy between UK clinical validation and the real-world data.	haemophilia B specific dosing. The EAG has added text to section 5.3.2 exploring the effects of this, though notes that for haemophilia A the company commissioned report may suggest lower dosing.
EAG03: For this change to the economic model, there is an inconsistency in the calculation of dosing whereby the dosing of factor prophylaxis is reduced in an attempt to reflect real-world usage, but the dosing of marstacimab remains based on anticipated SmPC dosing recommendations.	Due to inconsistency in the assumptions regarding factor prophylaxis and marstacimab dosing calculations, it is recommended that EAG03 is revised to ensure consistency in dosing assumptions used.	EAG03: The EAG implemented this scenario to test their possibility that the FVIII/FIX dosing for routine prophylaxis in the model is too high. For this change to the economic model, the dosing of factor prophylaxis is adjusted to be 75% of the company base case, in an attempt to reflect real-world usage. For context, the company base case instead used dosing based on each product's SmPC to match the regulatory labels. However, within EAG03, the dosing of marstacimab is not similarly adjusted to reflect potential real-world dosing of marstacimab. In other words, this scenario does not consider that the dosing for marstacimab	No factual error. No revision required. The FVIII/FIX SmPCs do not specify an exact dose or frequency of administration. Marstacimab dosing is specified as 150mg or 300mg weekly. As a consequence, that EAG does not think that this consideration applies to marstacimab, unless the company anticipates prolonged treatment holidays or poor compliance with marstacimab into the long term. The company is free to supply additional data on

		prophylaxis in the model may also be too high. Therefore, there is an inconsistency in the calculation of dosing whereby the dosing of factor prophylaxis is reduced in an attempt to reflect real-world usage, but the dosing of marstacimab remains based on anticipated SmPC dosing recommendations. This inconsistency is likely to result in incorrect dosing calculations that artificially reduce factor prophylaxis dosing costs, and result in lower NHB estimates for marstacimab.	this, separately for the ATP and the OLE phase of BASIS. If provided the EAG will endeavour to incorporate either in its main report or an addendum to it.

Issue 6 Factual inaccuracies related to Key Issue 6: Separate or pooled modelling of haemophilia types

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
General comment: The limitations of relying on data from subgroup analyses should be highlighted where relevant throughout the report.	Where relevant in the report, the company proposes that the following statement be added to highlight the limitations of the subgroup analyses: “The BASIS study was not powered to detect differences within subgroups. The lack of powering, small sample sizes associated with the subgroup analyses, and the absence of any clear biological	The company believes it is important to highlight the limitations associated with subgroup analyses where these are presented. Without such wording, the reader may not fully understand the context of the data.	The EAG has amended the text to clarify that BASIS was not designed to detect subgroup differences.

	rationale for differences in treatment effect between haemophilia types mean these data should be interpreted with caution.”	The report does briefly touch on these limitations. For example, on page 31, the EAG agrees with the company’s concerns regarding sample size and, on page 53, the report states that results from subgroup analyses should be treated with caution due to the small number of people contributing information. However, there are instances in the report where subgroup analyses are presented or discussed without this important caveat. The company suggest it would be helpful to add the proposed amendment throughout the report, where relevant.	
Page 17, Section 1.5: “The company presents data which suggests a possibly smaller effect among those with haemophilia B than haemophilia A, due in part to a lower bleed rate during BASIS when	Please consider amending the text as follows: “The company presents subgroup analyses of the BASIS trial which show differences in the point estimates of marstacimab’s relative treatment effect compared to factor prophylaxis, for haemophilia A and haemophilia B subgroups. However, these results should be interpreted with caution because of the small patient numbers, lack of	The company believes it is important to highlight the limitations associated with subgroup analyses. Additionally, since the trial was not powered to detect differences between haemophilia types, the interpretation of a smaller effect among those with haemophilia B may not be factually accurate.	Not a factual error. This has been accounted for in the previous point.

patients were receiving FVIII/FIX.”	statistical powering for subgroups, and feedback from clinicians who could identify no biological reason for the differences between haemophilia type.”		
Page 17, Section 1.5: “But it can be noted that there is more uncertainty around the estimates for haemophilia B patients due to small patient numbers in BASIS and that the UKHCDO bleed rate estimates for standard half-life FIX are also based on small patient numbers.”	Please consider amending the text as follows: “But it can be noted that there is more uncertainty around the estimates for haemophilia B patients due to small patient numbers in BASIS, the lack of biological plausibility for differences in marstacimab treatment effect between haemophilia types, and that the UKHCDO bleed rate estimates for standard half-life FIX are also based on small patient numbers.”	Whilst the small patient numbers are important to acknowledge, the company believes it is also important for the reader to be aware of the lack of biological plausibility for differences in treatment effect between haemophilia types.	Not a factual error. This sentence is referring only to people with haemophilia B.
Page 19, Section 1.7: “Whether it is reasonable to differentiate clinical effect estimates by haemophilia A and haemophilia B, and if so whether it is	Please consider amending the text as follows: “In light of the challenges due to small numbers, lack of statistical powering, and the absence of any clear biological rationale for differences in treatment effect between haemophilia types, whether it is reasonable to	The proposed wording more accurately describes the full context for whether this approach can be considered reasonable.	Not a factual error.

reasonable to differentiate dose escalation rates between haemophilia A and haemophilia B.”	differentiate clinical effect estimates by haemophilia A and haemophilia B, and if so whether it is reasonable to differentiate dose escalation rates between haemophilia A and haemophilia B.”		
Page 53, Section 2.2.2.3: “Whilst these results should be treated with caution due to the small number of people contributing information, the relative efficacy of marstacimab appeared worse for people with haemophilia B compared to the efficacy in the haemophilia A population.”	Please consider amending the text as follows: “Whilst these results should be treated with caution due to the small number of people contributing information, the lack of statistical powering, and the absence of any clear biological rationale for differences in treatment effect between haemophilia types, the relative efficacy of marstacimab appeared worse for people with haemophilia B compared to the efficacy in the haemophilia A population.”	The proposed wording more accurately describes the full context for why the subgroup results should be treated with caution.	The EAG has amended the text to include these points.
Page 75, Section 2.6: “The EAG is concerned about the potential for marstacimab to be inferior to routine	Please consider amending the text as follows: “The EAG is concerned about the potential for marstacimab to be inferior to routine prophylaxis for people with severe haemophilia B, although acknowledges that results from	The proposed wording more accurately provides important context for why the subgroup results should be treated with	Not a factual error. The EAG has only described this as a possibility.

prophylaxis for people with severe haemophilia B.”	subgroup analyses should be treated with caution, in part due to the small number of people contributing information.”	caution and uses the EAG’s wording from page 53. The company believes it is important to highlight the limitations associated with these subgroup analyses where these are presented or discussed.	
Page 116, Section 5.4.1: The EAG have presented results against emicizumab, FVIII basket, FIX basket, and a blended comparator of FVIII and FIX weighted by UKHCDO patient proportions. The blended comparator approach should include emicizumab to reflect current UK clinical practice.	Since the blended comparator is weighted using the prevalence of haemophilia A and haemophilia B patients in the UKHCDO data, the inclusion of emicizumab in this comparator is needed to represent UK clinical practice.	The EAG present results tables comparing marstacimab against emicizumab, FVIII basket, and FIX basket. However, the EAG also present results for the cost effectiveness of marstacimab against the pooled FVIII and FIX baskets weighted by UKHCDO proportions of 83% and 17%. However, emicizumab is not included in this comparator. Importantly, emicizumab makes up over 50% of the market share in haemophilia A and therefore makes up a significant proportion of the 83% haemophilia A patients upon which this FVIII/FIX comparator is based. Therefore, this approach should be updated to include emicizumab to more accurately reflect UK clinical practice.	The EAG has added an overall blended comparator. This usefulness of this is complicated by marstacimab being superior to FVIII/FIX in terms QALYs derived from both a reduced ABR and a SC rather than IV administration and lower dosing frequency. The opposite applies for the comparison with emicizumab, marstacimab being inferior to emicizumab on both counts.

Section 2: Other Factual Inaccuracies

Issue 7 Clarification on clinical trial design

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 45 – inaccurate description of the BASIS trial design: “It could alternatively be described as a before and after study, or a non-randomised comparison with historical data.”	Please consider amending the text as follows: “The study design allows for intra-patient comparisons in which each patient acts as their own control. ~~It could alternatively be described as a before and after study, or a non-randomised comparison with historical data.~~”	The proposed wording more accurately reflects the design of the trial. The alternative definitions are not considered to be factually correct. For example, a historical control study refers to a study that has no control group and therefore uses data from past studies to create a historical control group. Since BASIS was designed as a prospective study with both an observational phase (OP) and an active treatment phase (ATP) following the same patients, it cannot be considered a historical control study.	The EAG has amended the text as suggested.
Page 46 – inaccurate description of the BASIS trial design: “The design of BASIS meant that marstacimab was compared with a historical control...”	Please consider amending the text as follows: “The design of BASIS meant that patients receiving marstacimab were compared with the same patients who had previously been receiving factor	The proposed wording more accurately reflects the design of the trial. The alternative definitions are not considered to be factually correct. For example, a historical control study refers to a study that has no control group and therefore uses data from past studies to	The EAG has amended the text as suggested.

	prophylaxis and therefore each patient acts as their own control ...”	create a historical control group. Since BASIS was designed as a prospective study with both an observational phase (OP) and an active treatment phase (ATP) following the same patients, it cannot be considered a historical control study.	
Page 51: “The EAG requested the company perform analyses using information from the first 6 months of follow-up in the ATP to reduce potential for bias from the differing follow-up lengths (clarification question A33).”	The EAG requested the company perform analyses using information from the first 6 months of follow-up in the ATP to reduce potential for bias from the differing follow-up lengths when considering the proportion with zero bleeds (clarification question A33).	It is not factually correct to state that comparing the first 6 months of the ATP phase with the OP phase will reduce the potential for bias for all bleeding outcomes. Although participants receiving routine prophylaxis during the OP were only followed for 6 months, routine prophylaxis is considered standard of care, and it is likely these participants were receiving prophylactic treatment for a period of time before enrolment in the OP. In contrast, participants receiving marstacimab in the ATP were new to marstacimab and therefore follow-up is required to observe clinical outcomes once steady-state concentrations are reached. Furthermore, the majority of bleeding endpoints are annualised bleeding rates and therefore are	The EAG has amended the text as suggested.

		already adjusted for the follow-up time period. Therefore, the company believe that utilising the entirety of the 12-month ATP follow-up for analysis is most appropriate. The possible exception is the outcome: proportion with zero bleeds. Since this is not an annualised rate, the company acknowledge that the different follow-up periods between the OP and ATP may influence the interpretation of these results.	

Issue 8 Clarification on reporting of clinical trial data

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 47 - Incorrect interpretation of a clarification response regarding the listing of screening failures, the report states the number of participants did not total 47 because only ten unique Participant IDs were categorised as 'Exclusion'. However, this interpretation of the listing is incorrect.	A listing of screen failures and reasons was provided by the company in clarification A7, ~~but the number of participants did not total 47 (only ■ unique Participant IDs were categorised as 'Exclusion')~~. The EAG was unable to determine whether there is a generalisability issue due to the high proportion of screening failures.	Participants could fail screening due to not meeting either 'Exclusion' or 'Inclusion' criteria and therefore the provided listing is correct.	This text has been amended however, an issue still remains.

Page 49, Section 2.2.2.2: "In the company analyses, marstacimab did not show inferiority to routine prophylaxis across the bleed rate outcomes."	Please consider amending the text as follows: "In the pre-specified primary endpoint of the BASIS trial, marstacimab demonstrated non-inferiority and superiority over routine prophylaxis as measured by ABR_{treat}. Marstacimab also demonstrated non-inferiority to factor prophylaxis in all bleed-related secondary efficacy outcomes. In the company analyses, marstacimab did not show inferiority to routine prophylaxis across the bleed rate outcomes."	The current statement could be misleading to a reader as it implies marstacimab only met non-inferiority and omits the superiority demonstrated for the primary endpoint of the BASIS trial. It is important to include the result for the pre-specified primary endpoint, pooled across haemophilia A and B, for which the BASIS trial was powered for; for this primary endpoint, marstacimab met both non-inferiority and superiority over routine prophylaxis.	The text has been amended, however the company's suggestion is incorrect as it implies that the testing for superiority was the primary endpoint, however from table 4 of the SAP the EAG understands all superiority testing was a secondary endpoint.
Page 53, Section 2.2.2.4: "Consistently with the clinical outcomes, marstacimab did not show inferiority to routine prophylaxis within the BASIS population who provided data."	Please consider amending the text as follows: "Demonstrating consistency with the primary bleeding endpoint which met non-inferiority and superiority and the bleed-related secondary efficacy endpoints which met non-inferiority, marstacimab did not show inferiority to routine prophylaxis within the BASIS population who provided data."	This statement refers to health related quality of life collected during the BASIS trial. The current statement could be misleading to a reader as it implies marstacimab only met non-inferiority for all clinical outcomes and omits the superiority demonstrated for the primary endpoint of the BASIS trial. Therefore, the proposed wording ensures this statement is factually accurate.	Not a factual error, however a minor textual change has been made.

Page 118: ABR data from the October 2023 OLE period, pooled across all patients (haemophilia A and haemophilia B).	At clarification, the pooled data (haemophilia A and haemophilia B) for the October 2023 OLE was presented within the updated version of Document B. This updated version of Document B was dated 28AUG2024 and the October 2023 OLE data is presented from page 71.	On page 118, the EAG mention that they had ABRs from the OLE for the haemophilia A and haemophilia B subgroups, but not pooled across all patients. The EAG asked if the company could clarify the correct ABR value for the OLE during the FAC.	The EAG notes the information was provided in Table 29 of the updated company submission, however the impact of this change has minimal impact of the efficacy of marstacimab in the relevant scenario analysis (from ABR of ■■■ to 2.880) and has not updated the economic model due to time-constraints and prioritisation of other analyses. The EAG will provide a footnote in the results section about the effect of this input change upon the EAG revised pooled effects base case, also doing likewise within the cPAS appendix.
Page 50, Section 2.2.2.2: Inaccurate description of marstacimab compliance: "Compliance was >80% for 98.8% of people during the	Please consider amending the text as follows: "Compliance was >80% for 98.8% of people during the ATP ~~and for 100% of people who completed OP.~~"	Since marstacimab was not dosed in the OP, the company is unsure what is meant here by 100% of people who completed OP. This statement could be removed to ensure factual accuracy.	This text has been amended for clarity.

ATP and for 100% of people who completed OP."			

Issue 9 Clarification on the company's economic model and its inputs

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 49, Section 2.2.2.2: "Given that dose-escalation is expected to be included in NHS practice, the EAG requested alternative analyses without this censoring."	Please consider amending the text as follows: "To inform the cost-effectiveness model in the CS, post-hoc analyses were conducted which did not censor data on or after dose escalation. Given that dose-escalation is expected to be included in NHS practice, the EAG requested additional alternative analyses to those already presented by the company without this censoring."	The current statement implies that analyses without censoring were not provided in the original CS. The proposed wording clarifies that the original CS did present analyses without censoring (post-hoc analyses without this censoring were presented in Section B.2.9, Document B and these were the preferred analyses used in the company's economic model).	Not a factual error, however the EAG has made a minor amendment to the text.
Page 75: In the context of comparing marstacimab to routine prophylaxis in the BASIS trial, the report states that the company removed dose-escalation of marstacimab from their preferred analyses. However, this is incorrect.	Page 75: These may also affect estimates of relative efficacy coming from BASIS, in addition to the dose-escalation of marstacimab which the company have removed from their preferred analyses.	In the context of the company's economic model base case, the company utilised efficacy data from the BASIS trial which did include efficacy data following dose-escalation of marstacimab.	The EAG has amended this text.

Page 98: The report suggests the company could confirm a potential error related to implementation of the emicizumab indirect treatment comparison results in the economic model.	N/A The company agrees with the EAG that by applying the STC-derived treatment effect on both the bleed rates (for participants with ≥ 1 bleeds only) and the proportion who have had a bleed, the company's economic model underestimates the bleed rates for participants receiving emicizumab. This means the company's model provides a conservative estimate of the cost-effectiveness of marstacimab. As demonstrated by the EAG revisions to the economic model, correcting this error results in a more favourable estimate of cost-effectiveness for marstacimab.	N/A	Not a factual error.
Page 105, Section 5.2.2: "The estimates are provided at 4 decimal places. This means that the actual mean for the IV administration disutility could have been anything from 0.00025 to 0.00035, while the mean for the SC administration disutility could have been anything from 0.00015 to 0.00025. There may have been little to no actual difference between the two central estimates, the apparent	Please consider removing this paragraph.	This paragraph speculates that the difference in disutility between IV and SC administration may be a function of rounding, but this is not supported by the evidence in the published paper. The evidence in the paper indicates a clear preference for subcutaneous administration as demonstrated in Table 2 where subcutaneous treatment health states were associated with a utility increment of 0.11 vs.	The EAG has revised the text for this section.

difference simply being a function of rounding."		intravenous infusions with a p-value of <0.001.	
CEM: Column EB on the Engine Haem- A sheet and Column DV on the Engine Haem-B sheet; connected to Cell B70 on the EAG sheet: Based on the company's interpretation of the EAG calculations, administration-related disutilities are doubled for the proportion of marstacimab dose-escalated patients in each cycle.	Please consider removing this adjustment to the administration-based disutilities as part of the EAG02 revision.	This adjustment to the administration-based disutility does not seem to be further described or justified as part of the EAG report.	The EAG report contains text describing this adjustment in section 4.5.1.

Issue 10 Clarification on regulatory information

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 24, 26: Since the original company submission, further regulatory information is now available. The CHMP granted a positive opinion for marstacimab on 19 th September 2024.	To add in CHMP opinion information: Page 24 'Marstacimab does not currently have marketing authorisation for any indication in the UK. The company has a submitted application for marketing authorisation to the European Medicines Agency (EMA) and a positive CHMP opinion was granted on 19th September 2024.	The CHMP opinion was granted on 19 th September. Please see the press release link: Hympavzi European Medicines Agency (EMA) (europa.eu)	This was not a factual error at time of writing, however this has been updated.

	Page 26: The EAG agrees that the intervention is in line with the NICE scope. The anticipated dates of positive EMA CHMP opinion was granted on 19th September 2024. is [REDACTED]		
Page 37: Not specifying that the marketing authorisation is anticipated	The minimum age and severity of disease criteria in BASIS are in line with the NICE scope and anticipated marketing authorisation (MA), although limits on sex or upper age are not specified by NICE [REDACTED]	Clarification on the marketing authorisation status.	Text has been amended as suggested.

Section 3: Typographical and data errors

Issue 11 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Typo using the incorrect treatment name of emicizumab instead of marstacimab	<i>Page 79:</i> 6.02% discontinuation rate from marstacimab emicizumab to a pooled FVIII basket for those with haemophilia A and to a pooled FIX basket for those with haemophilia B is applied during the first cycle for the company base case. <i>Page 83 (last sentence):</i>	Incorrect treatment name used.	Text has been amended.

	The rates for marstacimab emicizumab are a constant 1.2% across all adverse events, but with there being no epistaxis as shown in Table 28. <i>Pg 101 (3rd paragraph):</i> The estimates of the company base case of a discontinuation from marstacimab emicizumab during the first cycle of 6.02% can be compared with this discontinuation rate being applied every cycle and to 0.00% emicizumab marstacimab discontinuations being assumed.		
Page 101, Table 55: Clarity required on the threshold (£20,000 or £30,000) used for the NHB results.	It is suggested that the title of Table 55 be updated to reflect the threshold (£20,000 or £30,000) that is being used for the NHB results.	Clarity on the NHB results within Table 55.	Text has been amended for clarity.
Page 44, Section 2.2.1.3: Clarification that the measure used was the HAL version 2. “HAL and pedHAL”	Please amend the wording as follows: “HAL version 2 and pedHAL”	Clarity on the version of the HAL.	Text has been amended for clarity.
Page 44, Section 2.2.1.3: Clarification on the number of items included in the pedHAL: “Similar to HAL, pedHAL is for children (aged 12	Please amend the wording as follows: “Similar to HAL, pedHAL is for children (aged 12 to <17 years), focusing on age-appropriate	Correction that the numbers of items in the pedHAL is 53 items, not 40.	Text has been amended.

to <17 years), focusing on age-appropriate activities, and assesses 40 items across the same seven domains”	activities, and assesses 53 40 items across the same seven domains”		
Page 101, Section 5.1.2: “This also suggests that at comparator list prices the model structure may be biased against marstacimab due to it assuming that emicizumab has in effect a 0.00% discount rate.”	Please amend the wording as follows: “This also suggests that at comparator list prices the model structure may be biased against marstacimab due to it assuming that emicizumab has in effect a 0.00% discontinuation discount rate.”	Correction of ‘discount rate’ to ‘discontinuation rate’.	Text has been amended.

Issue 12 Data errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 2 and Table 58: These tables appear to be reporting the same information for EAG model changes (pooled data), but the NHB numbers do not match.	It is currently unclear which table is showing the correct NHB results. The company would be grateful if the EAG can cross-check these tables and correct the relevant table if necessary.	Both Table 2 and Table 58 appear to be presenting EAG model changes (pooled data). However, the NHB numbers do not exactly match. The discrepancy appears to be coming from EAG04 which results in a higher NHB in Table 58 but a significantly lower NHB in Table 2.	The EAG has amended Table 2 to match Table 58.

		This causes the results for EAG01-EAG07 and EAG01-EAG08 to also differ between Table 2 and Table 58. The company believe the results presented in Table 58 to be correct as they appear to match the results generated in the EAG model.	
Page 47, Section 2.2.1.5: Minor error for the proportion of patients that failed screening. “Of 179 patients, 47 (26.5%) failed screening...”	Please amend the data as follows: “Of 179 patients, 47 (26.3% ~~26.5%~~) failed screening...”	Correction of minor calculation error.	This has been amended.
Page 67, Table 18: Minor error in the reporting of ratio for company STC results.	Please amend the data in Table 18 as follows for the naïve rate ratio for AJBR treated: [REDACTED] [REDACTED]	Correction of minor error in reporting of rate ratio for company STC results (please see Table 37 in Document B of CS, Section B.2.11.3).	This has been amended.
Page 81, Table 25: Minor rounding error for market share.	Please amend the market share value in Table 25, column ‘UKHCDO’ for Refacto AF: 17% ~~16%~~	Correction of minor rounding error.	This has been amended.
Page 86, Section 3.2.12.1:	Please amend the data as follows:	Correction of percentage.	This has been amended.

There is a minor error in the proportion of marstacimab patients receiving 150 mg.	"Marstacimab is costed assuming 86.75% ~~87.75%~~ receive 150mg..."		

Section 4: Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response														
Incorrect confidentiality marking in Table 24, page 81	Incorrect data marked as CIC in Table 24	CIC marking for the UKHCDO data and not the BASIS trial <table><tr><td></td><td>Mean (s.d.)</td></tr><tr><td colspan="2">UKHCDO 2023 Report</td></tr><tr><td>Age (years)</td><td>██████</td></tr><tr><td>Weight (kg)</td><td>████████</td></tr><tr><td colspan="2">BASIS</td></tr><tr><td>Age (years)</td><td><u>33 (15)</u></td></tr><tr><td>Weight (kg)</td><td><u>69.1 (15.3)</u></td></tr></table>		Mean (s.d.)	UKHCDO 2023 Report		Age (years)	██████	Weight (kg)	████████	BASIS		Age (years)	<u>33 (15)</u>	Weight (kg)	<u>69.1 (15.3)</u>	Thank you, this has been amended in the EAG report.
	Mean (s.d.)																
UKHCDO 2023 Report																	
Age (years)	██████																
Weight (kg)	████████																
BASIS																	
Age (years)	<u>33 (15)</u>																
Weight (kg)	<u>69.1 (15.3)</u>																

Missing confidential marking on Page 54, Section 2.2.2.5.	Missing confidential marking for adverse event data.	"During the OLE, *** of all participants experienced an AE and [REDACTED] had an SAE."	Thank you, this has been amended in the EAG report.
Incorrect confidentiality marking regarding % of discontinuation. Page 79, Section 3.2.2. Page 83, Section 3.2.8.	Confidentiality marking is not required.	Page 79, Section 3.2.2: "A 6.02% discontinuation rate from marstacimab to a pooled FVIII basket for those with haemophilia A and to a pooled FIX basket for those with haemophilia B is applied during the first cycle for the company base case." Page 83, Section 3.2.8: "A one-off treatment discontinuation rate of 6.02% for marstacimab is applied in the first cycle of the model..."	Thank you, this has been amended in the EAG report.
Missing confidentiality marking on Page 87, Section 3.2.12.1.	Missing confidential marking for UKHCDO mean weight data.	"Wastage calculations are based upon the UKHCDO mean weight of [REDACTED] and standard deviation of [REDACTED]"	Thank you, this has been amended in the EAG report.
Missing confidentiality marking within Table 32 and Table 33.	In the CS (Document B, Section B.3.4.1), acquisition cost per administration and annual acquisition cost are marked as CIC in Table 61 and Table 62. Therefore, the equivalent data in Table 32 and Table 33 should also be marked as confidentiality.	Within Table 32 and 33, please mark all costs (including both waste and no waste for per administration and annual costs) as confidential.	Thank you, this has been amended in the EAG report.

Missing confidentiality marking on Page 87, Section 3.2.12.1.	Missing confidential marking for annual costs of emicizumab.	“Emicizumab is costed assuming fortnightly 3.0 IU/kg dosing which results in an annual cost of [REDACTED] with wastage, or [REDACTED] without wastage. An additional one-off [REDACTED] or [REDACTED] without wastage, for four weekly loading doses is added to this.”	Thank you, this has been amended in the EAG report.