Medicinrådet

Bilag til direkte indplacering af marstacimab i Medicinrådets evidensgennemgang vedrørende lægemidler til hæmofili A og B

Vers. 1.0

Bilagsoversigt

1. Høringsbrev fra Pfizer vedr. marstacimab (Hympavzi)
2. Forhandlingsnotat fra Amgros vedr. marstacimab (Hympavzi)
3. Ansøgers endelige ansøgning vedr. marstacimab (Hympavzi) til patienter med hæmofili A uden inhibitor
4. Ansøgers endelige ansøgning vedr. marstacimab (Hympavzi) til patienter med hæmofili B uden inhibitor

Pfizer ApS
Lautrupvang 8
DK-2750 Ballerup
Tlf. 4420 1100
Fax 4420 1101

www.pfizer.dk
CVR.nr. 66351912

Pfizer Danmark

Til Medicinrådet

Ballerup, den 8. august 2025

Vi takker Medicinrådet for en konstruktiv proces i forbindelse med den igangværende vurdering af marstacimab og for det fremsendte udkast til tillæg til Medicinrådets evidensgennemgange vedrørende hæmofili A og B.

Vi står dog stadig uforstående over for Medicinrådets anbefaling. Ved gennemlæsning af rapporten har vi identificeret flere uklarheder og mener ikke, at man på baggrund af de fremførte argumenter kan konkludere, at marstacimab ikke bør ligestilles med komparator (emicizumab) til behandling af hæmofili A.

I det følgende vil vi redegøre for vores synspunkter:

Medicinrådets konklusioner vedrørende mindste klinisk relevante forskel er uklare

For de kritiske effektmål er det forholdsvis tydeligt angivet, at den mindste klinisk relevante forskel (MKRF) ikke er opnået, hvilket må betyde, at produkterne er ligeværdige. For de vigtige effektmål – tromboemboli og livskvalitet – er det dog uklart, hvad Medicinrådet konkluderer.

For hæmofili B står der specifikt, at der ikke er en klinisk relevant forskel mellem produkterne vedrørende tromboemboli, men herefter diskuteres tromboemboli uden henvisning til MKRF.

Resultatet er, at det er uklart, hvorvidt Medicinrådet mener, at der er en klinisk relevant forskel mellem produkterne, og hvordan de a priori opstillede effektmål vægtes i forhold til andre overvejelser. Udkastet indeholder ingen konklusion eller overvejelser omkring, om der samlet set kan anses at være en klinisk relevant forskel mellem marstacimab og komparator – hverken for hæmofili A eller B. I stedet lægges der vægt på et afsnit med ”andre overvejelser”, som ikke er en del af det formelle sammenligningsgrundlag.

Da metoden for direkte indplacering af nye lægemidler lægger vægt på sammenligning af lægemidler med hensyn til MKRF, er det vigtigt, at det er tydeligt, om Medicinrådet mener, der er forskel mellem produkterne i forhold til de a priori opstillede effektmål, og hvordan eventuelle andre faktorer vægtes i forhold til disse.

Samlet set mener Pfizer ikke, at disse forhold er nok til at konkludere, at marstacimab ikke er sammenlignelig med komparator (emicizumab) for hæmofili A.

Med venlig hilsen,

Sara Engstrand, Senior Market Access Manager,

Pfizer Danmark

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

08.08.25

MBA/LEJ/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	Pfizer
Lægemiddel	Hympavzi (marstacimab)
Ansøgt indikation	Rutineprofylakse mod blødningsepisoder hos patienter i alderen 12 år og derover med en vægt på mindst 35 kg, som har: • Svær hæmofili A (medfødt faktor VIII-mangel, FVIII < 1 %) uden faktor VIII-hæmmere eller • Svær hæmofili B (medfødt faktor IX-mangel, FIX < 1 %) uden faktor IX-hæmmere.
Nyt lægemiddel / indikationsudvidelse	Direkte indplacering af nyt lægemiddel i behandlingsvejledningen for hhv. hæmofili A og hæmofili B

Prisinformation

Amgros har forhandlet følgende pris på Hympavzi (marstacimab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Hympavzi	150 mg, 1 stk fyldt pen	[redacted]	[redacted]	[redacted]

[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.
[redacted]

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2 viser lægemiddeludgifter i relation til Hemlibra, som er relevant for sammenligningen ved Hæmofili A. Lægemiddeludgiften er opgjort pr. år for hhv. opstartsår og vedligeholdelsesår.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Hympavzi*	150 mg, 1 stk. fyldt pen.	Uge 1: Støddosis 300 mg én gang ugentligt. Efterfølgende uger: 150 mg én gang ugentligt Fast dosis, s.c.	[redacted]	Opstartsår: [redacted] Vedligeholdelsesår: [redacted]
Hemlibra*	Tilgængelig i 12, 30, 60, 105, 105 og 300 mg hætteglas	Opstartsdosis (3 mg/kg) en gang om ugen i de første 4 uger Vedligeholdelsesdosis fra uge 5 på enten 1,5 mg/kg en gang om ugen s.c.	[redacted]	Opstartsår: [redacted] Vedligeholdelsesår: [redacted]

* [redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til status
England	Hæmofili A: Ikke anbefalet Hæmofili B: Anbefalet		Link til vurdering
Sverige	Under vurdering	Link først tilgængeligt ved afgørelse	

Opsummering

[redacted]

Application for the assessment of Hympavzi® (marstacimab) by updating the treatment guidelines for haemophilia A

Contact information

Contact information	
Name	**Sara Engstrand / Pfizer**
Title	Senior Market Access Lead
Phone number	[redacted]
E-mail	[redacted]
Name (External representation)	**N/A**
Title	
Phone number	
E-mail	

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Tables and Figures

Abbreviations

ABR	Annualised Bleeding Rate
AE	Adverse Event
ATP	Active Treatment Phase
CENTRAL	Cochrane Central Registry of Controlled Trials
CI	Confidence Interval
CSR	Clinical Study Report
DMC	Danish Medicines Council
EC	European Commission
EHL	Extended Half-Life
EMA	European Medicines Authority
EQ-5D	EuroQol 5-Dimensional Quality of Life-Questionnaire
FVIII	Factor VIII
FIX	Factor IX
FX	Factor X
HAL	Hemophilia Activities List
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
Haemo-QoL	Haemophilia-specific health-related quality of life questionnaire
HIV	Human Immunodeficiency Virus
HJHS	Haemophilia Joint Health Score
IQR	Interquartile range
IU	International Unit
mITT	modified intention-to-treat (ITT)
NA	Not Applicable
NICE	National Institute for Health and Care Excellence
NIS	Non-Interventional Study
NR	Not Reported
OLE	Open Label Extension
OP	Observational Phase.
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SD	Standard Deviation
SLR	Systematic Literature Review
TEAE	Treatment Emergent Adverse Event
TFPI	Tissue Factor Pathway Inhibitor

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Hympavzi®
Generic name	Marstacimab
Therapeutic indication as defined by EMA	Marstacimab is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with: • severe haemophilia A (congenital factor VIII (FVIII) deficiency, FVIII < 1%) without factor VIII inhibitors, or • severe haemophilia B (congenital factor IX (FIX) deficiency, FIX < 1%) without factor IX inhibitors.
Marketing authorization holder in Denmark	Pfizer ApS
ATC code	B02BX11
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	18 November 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR

Overview of the pharmaceutical	
Packaging – types, sizes/number of units and concentrations	1 pre-filled pen with 150 mg solution for subcutaneous injection

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with: • severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors
Dosage regiment and administration:	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 subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, with a pre-filled auto injectable pen.
Choice of comparator [if any]	Emicizumab (Hemlibra®), the only other subcutaneous treatment for haemophilia A. The recommended dose of emicizumab is 3 mg/kg once weekly for the first 4 weeks (start-up dose) and then 1.5 mg/kg once weekly or 3 mg/kg every two weeks or 6 mg/kg every 4 weeks (maintenance dose). Emicizumab should be given as a subcutaneous injection.
Most important efficacy endpoints (Difference/gain compared to comparator)	Median ABR, all bleeds: -1.39 Median ABR, treated bleeds: -2.02 Median ABR treated bleeds long term: [redacted] Haem-A-QoL (adults): [redacted] Severe venous thromboembolism: 0 Discontinuations due to AE: -1.2%
Most important serious adverse events for the intervention and comparator	Marstacimab: 1 serious adverse event (SAE) considered by the investigator to be treatment **related but was diagnostically confirmed to be unrelated to a bleeding or thrombotic event.** **Emicizumab: No SAE related to emicizumab** were reported.

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

Haemophilia is a rare, genetic, non-progressive disease that mainly affects males. Untreated, severe disease results in repeated spontaneous bleeding episodes that leads to progressive joint damage, severe pain, impaired mobility, and an early death (1).

The severity of haemophilia is classified according to the relative plasma level of blood coagulation factor VIII (FVIII) or factor IX (FIX). This application is only concerned with patients with severe haemophilia, i.e. with patients with less than 1% of normal blood clotting activity, i.e. <1 International unit (IU)/dL (2-4).

The average life expectancy of a newborn person with severe haemophilia is approaching that of the background population in the Nordic countries, all which practice early and continuing prophylactic treatment. Furthermore, with modern prophylactic treatment from toddler age, young adult men with severe haemophilia are expected to live a normal life (1).

Despite this, prophylactic treatment with factor replacement products alone appears to be insufficient to normalise quality of life for all patients, leaving an unaddressed unmet need (5). Some patients still have bleeds (6, 7), due to a particularly severe bleeding phenotype or compliance issues, for example due to the mode of administration. The Danish treatment recommendations for haemophilia A and B are taking the burden of treatment into account, by making specific recommendations for the treatment of patients with difficult venous access, problems with compliance, and with breakthrough bleeds despite optimised prophylactic treatment (8), (9).

Even with today's prophylactic treatment, an unmet need exists for patients with severe haemophilia; a substantial psychological burden is associated with the disease; anxiety and depression are commonly reported due to the unpredictability of bleeding events, frustration with treatment, and issues with venous access (17, 16, (10). Further underlying reasons for psychological impacts of the condition are expected to include 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 infusions (11).

Furthermore, an 11-year Nordic registry study analysed longitudinal national data from 2007–2017 of people with haemophilia (n=3,246). The study showed a markedly higher use of pain medicine, antidepressants, and anxiety medications amongst patients with haemophilia compared with those without the disorder (10).

Current treatment and comparators

Danish patients with severe haemophilia A are currently treated with prophylactic treatment with Factor VIII replacement or non-factor replacement therapy (8). Factor replacement therapy is administered through intravenous injections, and is taken at varying intervals, depending on the product and on patients bleeding profiles. Most patients are well controlled and those who are not may be so due to a particularly severe bleeding phenotype or compliance issues, for example due to the mode of administration. In the Danish treatment guidelines, it is recommended to consider treatment with emicizumab for such patients (8). Pfizer expects that this patient population is the most likely to be treated with marstacimab.

The appropriate comparator is thus expected to be emicizumab, the only previously recommended subcutaneous treatment for haemophilia A. The recommended dose of emicizumab is 3 mg/kg once weekly for the first 4 weeks (start-up dose) and then 1.5 mg/kg once weekly or 3 mg/kg every two weeks or 6 mg/kg every 4 weeks (maintenance dose).

For more information regarding the burden of disease and the standard of care in Denmark, please see "Medicinrådets Behandlingsvejledning (version 1.1)", "Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til hæmofili A (version 1.1)", and"Medicinrådets gennemgang af terapiområdet for hæmofili B (ver. 1.1)".

Patient population

Globally, the incidence of severe haemophilia A is 9.5 out of 100,000 male births and 1.5 for severe haemophilia B (12), with haemophilia A comprising approximately 80% of these patients (13).

In Denmark, the treatment of haemophilia is handled by the two haemophilia centres in Aarhus and Copenhagen. During the summer of 2023, the centres reported approximately 158 patients 12 years or older with severe haemophilia A and 25 patients with severe haemophilia B on prophylactic treatment. Based on clinician input, approximately 12% of patients are estimated to be aged 12-17 years (14).

Table 1 shows the expected number of patients with haemophilia in the coming 5 years, counting 2025 as "year 1". 2024 was used as index year, using the numbers from the summer 2023. For the following years, the expected number of patients was estimated using data from Statistics Denmark (15).

Table 1. Estimated number of patients in Denmark aged ≥12 years with haemophilia A

Year	Year 1	Year 2	Year 3	Year 4	Year 5
No. of haemophilia A patients in Denmark ≥12 years	158	159	159	160	162

Source: Bassed on information received from haemophilia centres in Summer of 2023: haemophilia A:139 adults, 19 adolescents 12-17 years. Assuming numbers from the summer 2023 were accurate for 2024, 2024 was used as index year. The male population 12 years and older was calculated according to table FRDK 124 (15).

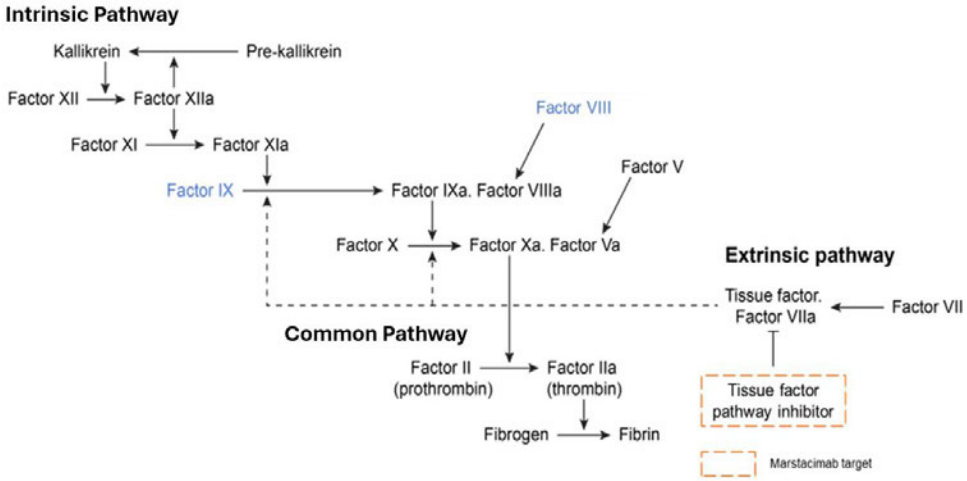
Most treatments for haemophilia are dosed based on patient weight. The average weight of adult men in Denmark was 81.9 kg, according to a national Danish health examination survey in 2007-2008 (16), however subsequent surveys from the Danish Health Authority (Den nationale sundhedsprofil), showing BMI indicate that the average weight of Danish men is increasing, which means that patients are heavier today.

According to the growth curve for Danish boys, the average normal weight of Danish boys 12-17 years of age should be 57 kg[1] (17). However, even though the curve describes the ideal growth, it may not be indicative of actual weight. The 2024 survey for Danish school boys shows that the average weight for boys aged 13 to 16 years and 5 months is 63.97 kg (18). The higher weight compared to the growth curve may be explained by that 77.5% of boys were normal weight, while 15.5% were overweight, and 5.0% obese (18).

3.2 The intervention

Marstacimab is the first subcutaneous treatment available for both haemophilia A and B and is a human monoclonal IgG1 antibody targeting anti-tissue factor pathway inhibitor (anti-TFPI), which is the primary inhibitor of the extrinsic (external) coagulation pathway. Treatment with anti-TFPI is a novel mechanism of action and marstacimab can be used for the treatment of both haemophilia A and haemophilia B.

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



Haemophilia A and haemophilia B are caused by a lack of clotting factor VIII and clotting factor IX, respectively, both of which are part of the intrinsic (internal) clotting pathway.

In blood clotting, anticoagulants play a crucial role in preventing blood clots from forming by inhibiting various factors in the clotting cascade. By inhibiting specific clotting factors, anticoagulants disrupt the cascade and thus reduce the likelihood of clot

[1] The growth curve shows a mean weight for 12-year-olds of 42 kg, and 57 kg just when they turn 18. The average weight is 57 kg.

formation. TFPI is one of these natural anticoagulants that counteracts the extrinsic coagulation pathway by inhibiting TF-VIIa complex and activated factor X (factor Xa)(19).

The action of marstacimab to neutralise the inhibitory activity of TFPI may enhance the extrinsic coagulation pathway and compensate for deficiencies in the intrinsic coagulation pathway by increasing the available free factor Xa and thrombin formation (factor IIa) and thereby promote haemostasis (20), see Figure 1**Error! Reference source not found.**. Simply put, marstacimab is an inhibitor of the "break", TFPI, so that the extrinsic coagulation pathway is strengthened and thus also the common coagulation pathway.

As there is no difference in TFPI levels in patients with haemophilia A and haemophilia B, the mechanism of action is independent of the lack of FVIII or FIX in patients (21), (22). In other words, with this mechanism of action balance in haemostasis can be achieved for both patients with haemophilia A and B.

The marstacimab molecule has a lower binding affinity and exhibits slower clearance rates compared to factor replacement therapies, resulting in a longer steady-state half-life; therefore, marstacimab requires less frequent, fixed, once-weekly dosing (23), (24), (25). Additionally, this enables flat dosing and no monitoring of drug concentration is needed (20). Furthermore, a flat (fixed) dosing regimen is supported by comparable pharmacodynamics and annualized bleeding rates (ABRs) across weight ranges (26).

Table 2. Overview of the intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors
Method of administration	Subcutaneous administration with a pre-filled auto injecting pen
Dosing	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 subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, at any time of day. The dose is not weight based.
Should the pharmaceutical be administered with other medicines?	No. Before starting treatment, the patient should stop prophylaxis (preventive) treatment with clotting factors. Patients can initiate treatment with marstacimab at any time after discontinuing clotting factor concentrates.
Treatment duration / criteria for end of treatment	Life-long treatment

Overview of intervention	
Necessary monitoring, both during administration and during the treatment period	Not required
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	NA
Package size(s)	1 pre-filled pen with 150 mg solution

3.2.1 The intervention in relation to Danish clinical practice

In Danish clinical practice, marstacimab can be directly placed into the current treatment guidelines. Marstacimab is expected to be used for patients who have:

- Difficult venous access, where it is not possible to carry out prophylaxis treatment with an extended half-life (EHL) product.
- Compliance problems where it is not possible to carry out prophylaxis treatment with weekly intravenous injections.
- Breakthrough bleeds despite optimised prophylaxis with an EHL product

In the current treatment guidelines this is described in Table 2 (8).

4. Overview of literature

Table 3. Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
BASIS, NCT03938792 CSR, data on file (27)	One way, cross-over, open-label, multi-centre, phase 3 with an observational and an active treatment period	6-month observational phase followed by a 12-month open label period	Start: 9 March 2020 Data cut-off: 17 April 2023 (including the completion of non-inhibitor treatment arms) Estimated completion: 16 June 2025	Males 12-74 years with severe haemophilia A or moderately severe to severe haemophilia B (FIX activity ≤2%) with or without inhibitors, receiving episodic or prophylactic factor replacement therapy. Only patients without inhibitors, receiving prophylactic treatment during the observational period are included in the application (n=83).	Marstacimab initial loading dose of 300 mg subcutaneously followed thereafter by 150 mg by subcutaneously once weekly	Factor replacement therapy (or bypass therapy) during a 6-month observational period	Intervention, Outcomes	Outcomes at 12 months: ABR, treated bleeds, median ABR, all bleeds, median Haem-A-QoL, total score, adult Haemo-QoL, total score, adolescent Severe venous thromboembolism Discontinuation due to side effects
Open Label Extension OLE-study (BASIS-LTE) NCT05145127	Phase 3, interventional open-label extension study	7 years	Start: November 2021 Cut-off: 10 March 2023	Patients from the BASIS trial	Marstacimab 150 mg, once weekly.	None, open-label extension study	Intervention, Outcomes	ABR, treated bleeds, median ABR, total bleeds, median Haem-A-QoL, total score, adult Haemo-QoL, total score, adolescent

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
CSR (28), SmPC (20) ClinicalTrial.gov (29)			Expected completion date: July 2030					Severe venous thromboembolism Discontinuation due to side effects
HAVEN 3 NCT02847637 (30)	Open-label, multi-centre phase 3 trial. Treatment arm D: intra-individual compared to a non-interventional study	24 weeks	Start: September 2016 Data cutoff: September 2017 Completion May 2022	Males, ≥12 years with severe congenital haemophilia A without current factor VIII inhibitors receiving episodic or prophylactic factor VIII infusions. Treatment arm D: patients who had previously received prophylactic treatment, is relevant in this application.	Group D: Emicizumab, n=63, 3 mg/kg once weekly for the first 4 weeks (loading dose) followed by a maintenance dose in group D of 1.5 mg/kg weekly.	Group D: Intraindividual comparison to n=48 patients who had participated in the NIS	Comparator, Outcomes	Outcomes at least 24 weeks: ABR, treated bleeds, median ABR, all bleeds, median Haem-A-QoL, total score, adult Thromboembolic events Discontinuation due to side effects

5. Clinical question 4

Clinical question: *Which patients obtain a clinically relevant benefit by switching to prophylaxis treatment with marstacimab?*

5.1 Efficacy of marstacimab compared to emicizumab therapy for haemophilia A patients

5.1.1 Relevant studies

BASIS and its open label extension study (OLE) (NCT05145127) represent the pivotal clinical trials demonstrating the efficacy and safety of patients receiving weekly marstacimab prophylaxis compared with factor prophylaxis. Please note that neither BASIS nor the OLE are published yet. The BASIS study is expected to be published during, or very soon after the DMC process, therefore, unpublished data is submitted and marked as confidential, but references and markings will be updated as soon as possible. The OLE study is ongoing and not expected to be published within acceptable time for this application. Therefore, only information that may be published, i.e. data that is already public through the SmPC or clinicaltrials.gov is submitted.

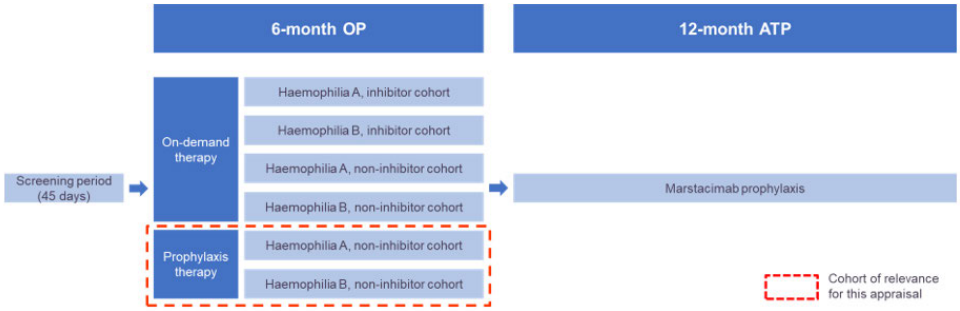
The **BASIS study** (NCT03938792) is a phase 3 study, one-way, cross-over, open-label, multi-centre, multi-country study planned in approximately 145 adolescent and adult participants aged 12 to <75 years. Included patients had severe haemophilia A or moderately severe to severe haemophilia B (defined as FVIII or FIX activity <1% or ≤2%, respectively) with and without inhibitors. The enrolment protocol included patients with moderately severe haemophilia B, but ultimately only patients with severe disease enrolled (31).

Patients who previously received on-demand or prophylactic treatment were included in separate treatment arms. The trial also has a still ongoing part, including patients with inhibitors, which in not included in this application (Figure 2) (31). As this application only concerns patients previously treated with prophylactic treatment, all data presented will be for this population only.

The study compared treatment with marstacimab in an active treatment phase to factor treatment during a 6-month observational phase. 91 patients who had previously received prophylactic treatment enrolled in the observational phase, of whom 84 (92.3%) completed and 83 of these patients progressed to the 12-month active treatment phase, during which participants received prophylactic treatment with marstacimab. Approximately 20% of participants were adolescents (32).

The modified Intention to Treat (mITT) Analysis Set consisted of participants who completed observational phase and received at least 1 dose of marstacimab in active treatment phase. The trial outcomes were measured at the end of the 12-month active treatment phase (27). Further information about the trial can be found in Appendix A.

Figure 2. BASIS study design



Source: Adapted from Clinical Study Report 2023 (27).

The Phase 3 open label extension (**OLE**) **study** (NCT05145127) is 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 study recruited patients from the BASIS trial which was haemophilia A and B patients ≥ 12 years, where patients remained on marstacimab treatment (29).

As of the interim data analysis cut-off at March 10th 2023, 88 patients had enrolled in the OLE (28). Of these, 29 patients had previously been treated with on-demand treatment, and 59 patients with prophylaxis treatment (32). One patient who received prior prophylaxis was not included in the safety analysis set, as their data was not available by the March 10th 2023 interim data cut-off (28). A total of 87 completing the 12-month treatment period had enrolled into the OLE study at the time of data cut-off on April 17th 2023. [redacted] of the patients who received prophylaxis in the BASIS trial were included in the OLE safety analysis set (28).

[redacted]

HAVEN 3 (NCT02847637) is a randomised, global, multi-centre open-label, phase 3 clinical study in participants with severe haemophilia A without inhibitors against factor VIII (FVIII), 12 years or older and who previously received on-demand or prophylactic FVIII treatment.

Participants were randomly assigned to one of three active treatment regimens based on previous episodic FVIII treatment: emicizumab once weekly (group A) or every 2 weeks (group B), or to receive no prophylaxis (group C). Participants who had previously received adequate prophylactic FVIII were assigned to emicizumab once weekly (group D). Participants in this group received emicizumab at a maintenance dose of 1.5 mg per kilogram per week.

Prior to initiating HAVEN 3, a non-intervention study (NIS) (NCT02476942) had been conducted to prospectively collect real-world data in patients with haemophilia to collect data on clinical practice, and to characterise the annualised bleeding rate (ABR),

haemophilia treatment practices, and adverse events (AEs) according to local practices. Eligible patients participating in the NIS could subsequently be enrolled in HAVEN 3. Intraindividual comparisons were performed in patients who had participated in the NIS study (30). As this application is only concerned with patients who have previously received prophylactic treatment, group D is the most relevant for the indirect comparison between marstacimab and emicizumab.

63 patients were assigned to group D, hereof 48 patients who also participated in the NIS study. The intra-individual comparison was only possible in the 48 patients who participated in the NIS study (30).

5.1.2 Comparability of studies

BASIS and HAVEN 3 both investigate the efficacy and safety of subcutaneous non-factor replacement therapies in patients with haemophilia. While BASIS includes patients with haemophilia A and B, HAVEN 3 includes patients with haemophilia A alone.

Both studies had separate treatment arms that included patients previously treated with prophylactic as well as with on-demand treatment. However, to be relevant to the Danish population, this application only considers the treatment arms including patients previously treated with prophylactic replacement therapy in both studies.

In the BASIS study, an observational period where the same patients who were treated with prophylactic factor replacement therapy was compared to an active treatment period with marstacimab. In HAVEN 3, patients on prophylactic treatment in arm D were compared to patients on prophylactic factor replacement treatment in a noninterventional treatment arm (30).

The primary endpoint in BASIS was mean ABR for treated bleeds, while the primary end point in HAVEN 3 was median ABR for treated bleeds, though both studies reported ABR for both all and treated bleeds.

The time frame of the measurements differed, as in BASIS the primary endpoint was measured at 12 months, while it was measured at 24 weeks in HAVEN 3 (median for treatment arm D was 33.14 (18.4-48.6) weeks). This means that the ABR for HAVEN 3 was annualized, but that ABR from BASIS was not. The different time frames may lead to different results. A way to handle this is to look at ABR for BASIS at different time points.

Differences in endpoints and the clinical management of bleeding events across trials pose challenges in their direct comparison and interpretation. These variations can impact the comparability of studies. For instance, in the HAVEN-3 trial, only 23.9% of the bleeding events were treated (33), while in the BASIS study, [redacted] of total bleeds were managed with clotting factors (27). This discrepancy underscores the impact of methodological differences on the perception of ABRs between study populations. Therefore, it is crucial to acknowledge that variations in methodology can contribute to the appearance of higher ABRs in one study population compared to another. These differences in endpoints and clinical management should be considered when interpreting and comparing results across trials.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Both trials only included patients ≥12 years with severe haemophilia. While BASIS included patients with both haemophilia A (78%) and B (22%) (32), HAVEN 3 included only patients with haemophilia A. In the treatment arms relevant for the application, only patients without active inhibitors, and previously treated with prophylactic factor replacement therapy are included. Baseline characteristics for patients previously treated with prior factor prophylaxis are provided in Table 4.

Patients in BASIS who had previously received prophylactic treatment were slightly younger compared to equivalent patients in HAVEN 3 and a larger proportion were adolescents (20.% vs. 11.1%). Patients in BASIS consequently weighed notably less (mean [redacted] vs. 79.0 kg). Still, a third more BASIS-patients had target joints ([redacted] vs. 58.7%), and median ABR (treated bleeds) at baseline was slightly higher in BASIS compared in HAVEN 3 ([redacted] vs. 1.8). This tends to suggest that patients in BASIS were likely to have higher bleed rates compared to patients in HAVEN 3.

The BASIS trial had a higher proportion of Asian and a lower proportion of white patients compared to HAVEN 3.

Compared to the Danish haemophilia population, the relevant treatment arms in both BASIS and HAVEN were treated with prophylactic replacement therapy, in line with Danish patients. The main difference between the studies and Danish patients is expected to be that patients in both studies have more target joints and higher ABR at baseline.

Table 4. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	BASIS[a] (27) (Non-Inhibitor, prophylaxis population) Marstacimab (n=83)	BASIS[a] (27) (Non-Inhibitor, prophylaxis population, haemophilia A alone) Marstacimab (n=65)	HAVEN 3 (30) Arm D Emicizumab (n=63)
Number of patients previously treated with prophylaxis, n (%)	83 (100)	65 (100)	48 (76.2)
Age, years			
Mean (SD)	[redacted]	[redacted]	36.4 (14.4)
Median (Min, Max)	[redacted]	[redacted]	36.0 (13-68)
Sex, n (%)			
Male	83 (100.0)	65 (100)	63 (100)
Race, n (%)			
Asian	[redacted]	[redacted]	12 (19.0)
Black or African American	[redacted]	[redacted]	1 (1.6)

White	[redacted]	[redacted]	47 (74.6)
Not reported	[redacted]	[redacted]	3 (4.8)
Weight, kg			
Mean (SD)	[redacted]	[redacted]	79.0 (15.4)
Median (Range)	[redacted]	[redacted]	NA (52.8-139)
Body mass index, kg/m²			
Mean (SD)	[redacted]	[redacted]	25.6 (NR)[b]
Haemophilia Type, n (%)			
Haemophilia A	[redacted]	[redacted]	63 (100)
Haemophilia B	[redacted]	[redacted]	0
Age, n (%)			
Adolescents (≥12 to <18 years)	17 (20.5)	13 (20.0)	7 (11.1)
Adults (≥18 years)	66 (79.6)	52 (80.0)	56 (88.9)
ABR at baseline, median, n (Q1, Q3)			
ABR, all bleeds	3.91 (0.00, 11.66)	[redacted]	NA
ABR, treated bleeds	[redacted]	[redacted]	1.8 (0; 7.6)
Number of Target Joints, n (%)			
0	[redacted]	[redacted]	37 (58.7)
1	[redacted]	[redacted]	8 (12.7)
2	[redacted]	[redacted]	18 (28.6)
≥3	[redacted]	[redacted]	

	Definition of outcomes	
ABR, all bleeds	Any sign or symptom of a bleed, regardless of if medication/treatment is administered. Occurrences of bleeding episodes were obtained from participant diaries and medical records. No external monitoring of bleeds was necessary	All bleedings comprise both treated and non-treated bleeds. All bleeds are included, irrespective of treatment with coagulation factors, with the exception of bleeds due to surgery/procedure
ABR, treated bleeds	Bleeding episodes requiring treatment (intravenous coagulations factor products or bypass agents)	An event is considered a treated bleed if coagulation factors are administered to treat signs or symptoms of bleeding

[a]BASIS: 17th April 2023 data cut-off; mITT analysis set (27); Abbreviations: mITT= modified intention to treat, OP= observational phase, SD= standard deviation. [b]BMI was not available in the primary HAVEN 3 publication and was instead captured from Astermark et al 2023 (34).

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

BASIS, marstacimab efficacy and safety

Marstacimab was demonstrated to be an effective treatment option, providing significant reductions in mean ABR treated bleeds, the primary endpoint (32).

The median ABR for treated bleeds in patients previously treated with prophylaxis was 2.02 (0.00, 6.09 Interquartile range (IQR))(32) for marstacimab during the 12-month active treatment phase compared with [redacted] the 6-month observational phase (27) Table 5.

The median ABR for all bleeds was 2.89 (0.00, 7.06 IQR)[2] during the active treatment phase compared with 3.91 (0.00, 11.66 IQR) during the observational phase (32).

Table 5. Results at 12 months, BASIS for patients receiving prophylactic treatment

Outcome measure	Full population (Haemophilia A & B)		Haemophilia A subgroup	
	Observational phase (n=[redacted])	ATP (n=83)	Observational phase (n=65)	ATP (n=65)
ABR, all bleeds, median (IQR)	3.91 (0.00, 11.66)	2.89 (0.00, 7.06)	[redacted]	[redacted]
ABR treated bleeds, median (IQR)	[redacted]	2.02 (0.00, 6.09)	[redacted]	[redacted]
Haem-A QoL total score, adult patients (change from baseline) Mean (95% CI)		[redacted] n=63		NA
Haemo-QoL total score, adolescent patients (change from baseline) Mean (95% CI)		[redacted] n=20		NA

[2] During the publication process a discrepancy was found between the SPC and the Statistical Analysis Plan (SAP) in relation to how preventative factor treatment was treated in ABR calculations. The discrepancy only affects the 100th decimal and does not affect any conclusions or significances. ABR was recalculated to fit with the SAP and the numbers have been updated. The full description of how ABR is calculated can be found in Matino et al (2025) Supplementary Materials, Section 6.

Severe venous thromboembolism	1[a]	0	[redacted]	0
SAE	2 (2.2%)	7 (8.4%)	[redacted]	[redacted]
Treatment related SAE[b]	NA	1 (1.2%)[b]	NA	[redacted]
Permanent discontinuation due to adverse event (12 months)	0 (0%)	1 (1.2%)[c]	0 (0%)	[redacted]

Source: CSR, 2023 (27) for redacted information and Matino (2025) (32) for unblinded information. [a]SAE device occlusion reported observational phase [b]Grade 1 peripheral calf swelling considered to be treatment related but was diagnostically confirmed to be unrelated to a bleeding or thrombotic event. [c]Adverse Event (AE) not considered treatment-related, see Appendix E, Abbreviations: ATP= Active treatment phase, ABR= Annualised Bleeding Rate, CI=Confidence interval, SAE= Severe Adverse Event, IQR=Interquartile range

The *Haemophilia Quality of Life Questionnaire for Adults* (Haem-A-QoL) is a validated disease-specific tool for measuring quality of life, which assesses the physical and emotional limitations experienced by patients. The scale ranges from 0 to 100, with higher scores indicating a poorer health-related quality of life (35, 36, 37). In BASIS, the mean change from baseline to 12 months was [redacted] for marstacimab prophylaxis, see Table 5. For adolescents (12 to < 17 years; [redacted]) quality is measured via the Haemo-QoL total score. The mean change from baseline at 12 months was [redacted] for patients who had previously received prophylaxis (27).

[redacted] AEs occurred in 83 marstacimab patients (27). Of these, injection site reactions occurred in 9 (10.8%) patients during the active treatment phase (n=83), however reactions were generally mild and of short duration and did not cause dose adjustment or patient discontinuation (32).

Two SAEs (2.2%) were reported during the observational phase and 7 (8.4%) during the active treatment phase, with one SAE (Grade 1 peripheral calf swelling) considered by the investigator to be treatment related. However, the swelling was diagnostically confirmed to be unrelated to a bleeding or thrombotic events (32).

One patient (1.2%) discontinued marstacimab due to meningioma. The incident was not considered related to the study intervention (32).

No participants reported thromboembolic events during the marstacimab active treatment phase and no deaths occurred during the active treatment phase with marstacimab (32). For more information about safety data please see Appendix E.

BASIS long-term study (OLE) NCT05145127

In the marstacimab SPC, data is available for up to 16 months (mean 7 months) from the OLE study, i.e. additional data to the BASIS study, all in all a mean of 19 month follow up (20). The median ABR for all bleeds at that time was [redacted] (28).

HAVEN 3, emicizumab efficacy and safety

Data from HAVEN 3 arm D show that patients treated with emicizumab experienced a median ABR of 1.5 for all bleeds after a median follow up of 33.14 weeks. ABR for treated bleeds was 0.0 compared to 1.8 in the NIS study (see Table 6)

Table 6. HAVEN 3 study: Intra-patient comparison between emicizumab and the NIS study

Outcome measure	Arm D NIS n=48	Arm D N=63
ABR, All bleeds, median (IQR)	2.7 (0.0; 9.4)[a]	**1.5 (0.0; 4.3)[b]**
ABR treated bleeds, median, (IQR)	1.8 (0; 7.6)[c]	**0.0 (0; 2.2)[b]**
Heam-A QoL total score, adult patients (change from baseline) Mean (95% CI)	No data found	-3.02[b]
Heamo-QoL total score, adolescent patients (change from baseline at Median (95% CI)	No data found	No data found
Severe venous thromboembolism	0	0
SAE	5 (6.1)[d]	10
Treatment related	NR	0
Discontinuation due to adverse event	0	0 (0%)

[a]Note that the population in the prophylaxis arm is reported n=49 Table S5 (38). [b]DMC (39), [c]Mahlangu et al, ABR reported for a median of 33.14 weeks for Arm D in HAVEN 3 (30). [d]In the prophylactic group, 3 participants had a total of 5 SAEs (myocardial infarction [fatal], gastrointestinal polyp haemorrhage, pericoronitis, haemarthrosis and renal colic) Table S4 (38).

The Haem-A-QoL (patients ≥18 years) total score at week 25 for patients in treatment Arm D had a mean change (improvement) from baseline of -3.02.

236 AEs occurred in the 63 patients in HAVEN 3 group D. The most common event was injection-site reactions (grade 1 or 2) which occurred in 20 patients (32%). Bleeds occurred in 4 patients (6.3%) (30).

The number of treatment emergent SAEs was 10, and none of them were considered treatment related by the investigator. There were no thrombotic or thrombotic microangiopathy events, development of antidrug antibodies, or new development of factor VIII inhibitors and no patients from group arm discontinued due to adverse events (30), see Table 6.

5.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

For marstacimab, one SAE (Grade 1 peripheral calf swelling) was considered by the investigator to be treatment related but was diagnostically confirmed to be unrelated to a bleeding or thrombotic events. No SAE related to emicizumab were seen (30).

The main difference between the products was the occurrence of injection-site reactions, which occurred in 9 (10.8%) marstacimab patients previously treated with prophylaxis versus 20 (32%) emicizumab patients. No occurrence of injections site reactions led to a dose adjustment or drug discontinuation of marstacimab (27).

Furthermore, in neither study any thromboembolic events occurred (20), (40).[redacted]

The definition of outcomes is discussed in section 5.1.2 and 5.1.3. As noted there, there are important differences between the studies in relation to the definition of ABR.

5.2.3 Method of synthesis

There is no direct comparative evidence between marstacimab and emicizumab. In line with the protocol for developing the Danish treatment guidelines for haemophilia, we have conducted a naïve comparison.

Only the subsets of the studies including patients previously treated with prophylactic treatment and without inhibitors have been included in the comparison. The comparability of BASIS and HAVEN 3 was discussed in sections 5.1.2 and 5.1.3.

5.2.4 Results from the comparative analysis

The Danish Medicines Council has defined the minimal clinically relevant outcomes for each outcome measure as:

- ABR, median (critical): 3 bleeds per year per patient
- Haem-A-QoL(important): 0.5 SD or 5 points
- Severe venous thromboembolism (important): 2 events between each study
- Discontinuation due to side effects (% of patients who stop due to side effects) (important): 5%

There is no clinically relevant difference between the treatments for the critical outcome of ABR: marstacimab showed a median ABR for treated bleeds of 2.89 for patients previously treated with prophylaxis, compared to 1.5 for emicizumab. Long term data for marstacimab shows that [redacted] marstacimab as well, but no comparable long-term data has been found for emicizumab for patients previously treated with prophylaxis, please see Table 7.

There was an absolute difference in improvement in adult quality of life between marstacimab and emicizumab of 1.98 to the advantage of marstacimab, which in more than the minimally clinically relevant difference. However, no information was found on adolescent life quality for emicizumab, which means that the result concerns a subset of patients.

No incidences of venous thromboembolism were seen for either product.

Finally, one patient (1.2%) discontinued marstacimab due side effects (meningioma), an event that was not considered treatment related marstacimab, please see section 5.1.1. No discontinuations due to side effects were seen for emicizumab. The absolute difference between discontinuations (1.2%) is smaller than the clinically meaningful difference.

The minimal clinically relevant difference is reached for the quality-of-life outcome. However, only adult patients are considered, as quality of life is not reported for adolescents in HAVEN 3. For no other outcomes the minimal clinically relevant differences are reached. It is therefore concluded that no clinically relevant differences can be seen between marstacimab and emicizumab, according to this definition.

Table 7. Results from the comparative analysis of marstacimab vs. emicizumab for haemophilia

Outcome measure	Marstaciab weekly[1] mITT n=83	Emicizumab weekly[2] Arm D n=63	Result Absolut difference
ABR, All bleeds, median (IQR)[3]	2.89 (0.00, 7.04)	1.5 (0.0, 4.3)	-1.39
ABR treated bleeds, median (IQR)[3]	2.02 (0.00, 6.09)	0.0 (0.0, 2.2)	-2.02
ABR, Long term, all bleeds, median (IQR)	[redacted]	NR	NA
Haem-A QoL total score, mean, adult patients (change from baseline)	[redacted]	-3.02	[redacted]
Haemo-QoL total score, mean, adolescent patients (change from baseline at (12 months)	[redacted]	NR	NA
Severe venous thromboembolism[3]	0	0	0
Discontinuation due to adverse event[3]	1 (1.2%)	0	-1.2%

[1]BASIS CSR Data on file (27) for redacted information and Matino (32) for unblinded information; [2]Mahlangu et al (30); [3]ABR reported for 12 months of active treatment in BASIS vs. a median of 33.14 weeks for Arm D in HAVEN 3; [4]Data for up to 7 additional months, i.e. a total of 19 months (28).

Table 8. Results from the comparative analysis of marstacimab vs. emicizumab for haemophilia A subgroup

Outcome measure	Marstaciab weekly[1] mITT n=65	Emicizumab weekly[2] Arm D n=63	Result Absolut difference
ABR, All bleeds, median (IQR)[3]	[redacted]	1.5 (0.0, 4.3)	[redacted]
ABR treated bleeds, median (IQR)[3]	[redacted]	0.0 (0.0, 2.2)	[redacted]
ABR, Long term, all bleeds, median (IQR)	[redacted]	NR	NA
Severe venous thromboembolism[3]	[redacted]	0	[redacted]
Discontinuation due to adverse event[3]	[redacted]	0	[redacted]

[1]BASIS CSR Data on file (27); [2]Mahlangu et al (30); [3]ABR reported for 12 months of active treatment in BASIS vs. a median of 33.14 weeks for Arm D in HAVEN 3; [4]Data for up to 7 additional months, i.e. a total of 19 months (28).

6. Clinical question 3

Clinical question: *Which patients in prophylactic treatment gain a clinically relevant benefit from switching to an extended half-life FVIII preparation?*

As marstacimab is not a FVIII and the content of this clinical question is largely similar to that of clinical question 4, this clinical question has been included, as it contains one important feature not included in clinical question 4, i.e. an outcome concerning the product consumption.

6.1 Efficacy of marstacimab compared to emicizumab therapy for haemophilia A patients

The outcomes for clinical question 3 are to a large extent overlapping with question 4. Therefore, only the outcome that does not overlap, i.e. the dosing regimen, will be presented here. The clinical question answered in this section is thus: *What is the weekly dose needed for marstacimab in relation to emicizumab?*

6.1.1 Relevant studies

Please see section 5.1.1.

6.1.2 Comparability of studies

Please see section 5.1.2.

6.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Please see section 5.1.3.

6.2 Comparative analyses of efficacy and safety

6.2.1 Efficacy and safety – results per study

The recommended dose of marstacimab for patients 12 years of age and older, weighing at least 35 kg, is an initial loading dose of 300 mg by subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, at any time of day (20).

The recommended dose of emicizumab is 3 mg/kg subcutaneously once weekly for the first 4 weeks (loading dose) followed by a maintenance dose 1.5 mg/kg once weekly or 3 mg/kg every two weeks or 6 mg/kg every 4 weeks (maintenance dose) (40).

However, the BASIS study allowed patients weighing at least 50 kg to be dose escalated after 6-months on active treatment if they had experienced 2 or more spontaneous bleeds that had been treated with coagulation factor. However, if patients fulfilled the requirement it was fully up to the physician to decide on dose escalation (27).

[redacted] with haemophilia A and [redacted] with haemophilia B met the criteria, and 11 of these [redacted] were dose escalated from 150 mg marstacimab weekly to 300 mg weekly during the active treatment phase (27). This corresponds to [redacted] of prophylaxis patients in the BASIS study.

Patients who dose escalated are almost [redacted] However, two issues should be considered: the small sample size, especially in the haemophilia B population, and that dose escalations were at the discretion of patient and physician. This meant that some treatment centres may have used the opportunity to dose escalate frequently, while others may not have used it at all.

6.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

Please see section 5.2.2

6.2.3 Method of synthesis

Please see section 5.2.3.

6.2.4 Results from the comparative analysis

In contrast to marstacimab, emicizumab dosed based on patient weight. Therefore, the absolute weight of patients is of importance to calculate product consumption. As noted in section 3.1, the average weight of adult men in Denmark is at least 81.9 kg (16), while the average weight of Danish boys 12-17 years of age may be estimated to 63.97 kg (18).

Approximately 12% of the patients are expected to be aged 12-17, based on the Danish haemophilia population, described in section 3.1. Adjusting for the proportion of adolescents, the average weight of all patients indicated for treatment with marstacimab is expected to be 79.75 kg.[3]

Thus 150 mg of marstacimab weekly is comparable to 119.62 mg with emicizumab, please see Table 9. When taking the available package sizes into account, this corresponds to 0.80 mL of 150 mg/mL Hemlibra® (emicizumab) concentration[4] (41).

Table 9. Results from the comparative analysis of marstacimab vs. emicizumab for a patient weighing 79.75 kg

Outcome measure	marstacimab	emicizumab
Loading dose	300 mg flat dose once	3 mg/kg body weight once weekly for the first 4 weeks
Total dose for the first 4 weeks	750 mg	956.98 mg
Maintenance dose, weekly	150 mg flat dose	1,5 mg/kg body weight
Total weekly maintenance dose	150 mg	119.62 mg
Total weekly maintenance dose taking available package sizes into account	150 mg	150 mg/1 mL

Based on feedback from the dialogue meeting, dose escalations will be rare in Danish clinical practice. However, in case that dose escalations would occur at the rate seen in BASIS, [redacted] of patients could be expected to be dose escalated. This corresponds to an overall [redacted] increase in consumption. If so, the average maintenance dose of marstacimab would [redacted].

No dosage adjustments of emicizumab are recommended (40). As dose escalations are expected to be rare, it is relevant to compare the standard doses for both products, i.e. 150 mg of marstacimab equating 150 mg/1 mL of emicizumab.

[3] 0.12 * 63.97 kg + 0.88 * 81.9kg = 79.75 kg

[4] To calculate the volume to be administered divide calculated dose (119.62 mg) by 150 mg/mL: 119.62 mg of emicizumab ÷ 150 mg/mL = 0.78 mL of 150 mg/mL Hemlibra concentration to be injected.

7. References

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Appendix A. Main characteristics of studies included

Table 10. Main characteristic of studies BASIS

Trial name: BASIS	NCT number: (NCT03938792)
Objective	To demonstrate the efficacy and safety of marstacimab for routine prophylaxis in severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) participants 12 to <75 years of age with or without inhibitors.
Publications – title, author, journal, year	Matino at al. (2025) (32).
Study type and design	One-way, cross-over, open-label, multi-centre, multi-country, Phase 3 study
Sample size (n)	All patients in non-inhibitor population: 128 patients were included in the 6-month, lead-in, OP and 116 of these progressed to the 12-month ATP. 91 patients who previously received prophylactic treatment included in the observational phase; 83 patients progressed to the ATP.
Main inclusion criteria	Non-inhibitor cohort • Males, 12 years of age or older • Severe haemophilia A or moderately severe to severe haemophilia B with a minimum weight of 35 kg at screening. • Signed informed consent (or minor assent, when applicable). • No detectable or documented history of inhibitors • 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 Observational Phase. • 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 observational phase.
Main 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.

Trial name: BASIS	NCT number: (NCT03938792)
	• 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 • Regular, concomitant therapy with immunomodulatory drugs • Previous exposure to PF 06741086 during participation in studies B7841002 and B7841003. • Participation in other studies involving investigational drug(s) or investigational vaccines within 30 days 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 ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results. • Individuals with hypersensitivity or an allergic reaction to hamster protein or other components of the study intervention.
Intervention	Initial loading dose of 300 mg by subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, at any time of day.
Comparator(s)	Intra-individual comparison to prior factor replacement therapy during the 6-month observation phase with either prophylactic or on-demand factor replacement therapy.
Follow-up time	12 months ATP and 1 month follow-up after end of study for safety monitoring. Long term study (NCT05145127) “OLE Study” planned 7 years follow-up.
Primary, secondary and exploratory endpoints	All endpoints are measured at 12 months, unless otherwise stated. **Primary**

Trial name: BASIS	NCT number: (NCT03938792)

	ABR for treated bleeds at 12 months post-marstacimab initiation versus factor replacement therapy use in the OP
	
	Primary Safety
	
	• Incidence of AEs and SAEs
	• Incidence and severity of thrombotic events
	• Incidence and severity of injection site reaction
	• 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
	
	Secondary
	
	• ABR for joint bleeds, spontaneous bleeds, target joint bleeds and total bleeds (treated and untreated) at 12 months post-marstacimab initiation (ATP) versus factor replacement therapy use in the OP
	• Number of patients with no treated bleeds
	• Change in joints as measured by Haemophilia Joint Health Score (HJHS) at 12 months post-marstacimab initiation versus factor replacement therapy use in the OP
	• Patient reported outcomes and quality of life assessments at 12 months post-marstacimab initiation versus factor replacement therapy use in the OP:
	  • HAL/pedHAL
	  • PGIC-H
	  • Haem-A-QoL/Haemo-QoL
	  • EQ-5D-5L
	
	Exploratory
	
	• Analysis of PF-06741086 (marstacimab) concentrations (trough as well as post-dose)
	• Analysis of changes in biomarkers: TFPI (total and free), PKT, PF1+2, D-dimer, and dilute prothrombin time over duration of the study
	  • Hemophilia Life Impacts Questionnaire

Method of analysis	Marstacimab was compared with prior routine prophylaxis in the same individuals for various bleeding count endpoints, using a repeated measure negative binomial regression model via generalised estimating

Trial name: BASIS	NCT number: (NCT03938792)
	equation (GEE) approach with identity link function. If the non-inferiority on treated ABR was established, subsequent testing for superiority was conducted. The estimated mean treated ABR 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 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. Trial outcomes in the 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.
Subgroup analyses	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.
Other relevant information	NA

Abberviations: ATP= Active Treatment Phase, OP =Observational Phase, mITT= modified Intention To Treat

Table 11. Main characteristics of NCT05145127 (OLE)

Trial name: NCT05145127 "OLE"	NCT number: (NCT05145127)
Objective	To evaluate the long-term safety, tolerability, and efficacy of marstacimab prophylaxis in severe (coagulation factor activity <1%) heamophilia A participants with or without inhibitors or moderate severe to severe haemophilia B participants (coagulation factor activity ≤2%) with or without inhibitors.
Publications – title, author, journal, year	The study is not yet published.
Study type and design	Phase 3, interventional, multi-centre, multi-country, open-label extension study
Sample size (n)	Patients from the BASIS trial (NCT03938792) and from the Phase 3 study BASIS-KIDS (NCT05611801). From the BASIS trial 88 patients continued to the long-term extension study (OLE), of these, 29 patients had previously been treated with on-demand treatment, and 59 patients with prophylaxis treatment.
Main inclusion criteria	• Minimum body weight as defined by parent studies • Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

Trial name: NCT05145127 "OLE"	NCT number: (NCT05145127)
	• Participants have successfully completed participation in parent studies, defined as did not require "Early Termination".
Main exclusion criteria	• Previous or current treatment for or history of coronary artery disease, venous or arterial thrombosis (CTCAE Grade >3), or ischemic disease (except catheter-associated thrombosis) • Abnormal renal function as defined by eGFR <30 mL.min/1.73 m^2 • Known planned surgical procedure during the planned study period • Unstable hepatic function which would make the participant inappropriate for the study • Regular, concomitant therapy with immunomodulatory drugs (eg, IVIG, and routine systemic corticosteroids, rituximab) • Ongoing or planned use of immune tolerance induction or prophylaxis with FVIII or FIX replacement during the study • Participation in other studies involving investigational drug(s) or investigational vaccines within 30 days or 5 half-lives prior to study entry and/or during study participation.
Intervention	For participants aged ≥12 years 150 mg marstacimab subcutaneously once weekly. 300 mg subcutaneously once weekly for participants who were dose escalated. For participants aged ≥6 to <12 years is marstacimab 75 mg subcutaneously once weekly. 150 mg subcutaneously once weekly for participants who were dose escalated.
Comparator(s)	NA
Follow-up time	Up to an additional 7 years of participation beyond BASIS. There is currently up to 16 months (mean 7 months) of data available in this study, i.e. all in all a mean of 19 month follow up data in BASIS and OLE combined.
Primary, secondary and exploratory endpoints	All endpoints are measured form baseline up to 7 years, unless otherwise stated. **Primary** • Number of subject reporting adverse events • Number of subjects reporting serious adverse events • Incidence and severity of thrombotic events • Incidence and severity of thrombotic microangiopathy • Number of subjects reporting disseminated intravascular coagulopathy/consumption coagulopathy

Trial name: NCT05145127 "OLE"	NCT number: (NCT05145127)
	• Incidence of clinically significant persistent NAb against marstacimab • Incidence and severity of injection site reaction • Clinically significant changes in vital signs from baseline • Incidence of clinically significant laboratory value abnormalities • Incidence of severe hypersensitivity and anaphylactic reactions **Secondary** • ABR • Total coagulation factor product consumption • Incidence of joint bleeds • Incidence of spontaneous bleeds • Incidence of target joint bleeds • Incidence of total bleeds (treated and untreated) • Change in joints measured by the HJHS • Change in joints as measured by the HJHS for participants ≥4 years of age • Change in number of target joints per subject from baseline • Changes in Health Utilities Measure questionnaire data • Changes in Haem-A-QoL questionnaire data for participants ≥17 years of age • Changes in Haemo-QoL questionnaire data: Haemo-QoL CII (Ages 8 to <12 years), Haemo-QoL (Ages 12 to <17), • Total bypass product consumption • Changes in EQ-5D questionnaire data: EQ-5D-Y Proxy (Ages ≥ 4 to ≤ 6 years), EQ-5D-Y Self (Ages ≥ 7 to ≤ 11 years), EQ-5D-5L (Ages ≥12)
Method of analysis	Based on a repeated measure negative binomial regression model via generalised estimation 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.
Subgroup analyses	NA
Other relevant information	NA

Table 12. Main characteristics of HAVEN 3

Trial name: HAVEN 3	NCT number: (NCT02847637)
Objective	To evaluate two prophylactic emicizumab regimens versus no prophylaxis in this population with emphasis on efficacy, safety, and pharmacokinetics.
Publications – title, author, journal, year	Mahlangu, J., Oldenburg, J., Paz-Priel, I., Negrier, C., Niggli, M., Mancuso, M. E., Schmitt, C., Jiménez-Yuste, V., Kempton, C. & Dhalluin, C. 2018. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. New England Journal of Medicine, 379, 811-822.
Study type and design	HAVEN 3 is a randomised, global, multi-centre, open-label, Phase 3 clinical study. It is composed of a randomised controlled trial recruiting patients previously treated with on-demand regimen, and a non-randomised study assessing patients, who received prophylactic factor replacement therapy before enrolment. Participants of the RCT were allocated to 2 different prophylactic regimens (1.5 mg/kg/week or 3.0 mg/kg every 2 weeks) and an on-demand treatment. Those, allocated to non-RCT arm were receiving prophylaxis with 1.5 mg/kg/week regimen.
Sample size (n)	63 patients who received prophylactic treatment (Group D)
Main inclusion criteria	• 12 years of ages or older • Body weight ≥ 40 kilogram (kg) at the time of screening • Diagnosis of severe congenital haemophilia A • Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks • Adequate hematologic function • Adequate hepatic function • Adequate renal function
Main exclusion criteria	• Bleeding disorder other than haemophilia A • Previous or current treatment for thromboembolic disease or signs of thromboembolic disease • Conditions that may increase risk of bleeding or thrombosis • History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection • Known human immunodeficiency virus (HIV) infection with. Participants with HIV infection who has CD4 greater than (>) 200 and meet all other criteria are eligible • Use of systemic immunomodulators at enrolment or planned use during the study, with the exception of anti-retroviral therapy • Participants who are at high risk for thrombotic microangiopathy

Trial name: HAVEN 3	NCT number: (NCT02847637)
	• Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the participant's safe participation in and completion of the study • Planned surgery (excluding minor procedures) during the study • Receipt of emicizumab in a prior investigational study; an investigational drug to treat or reduce the risk of haemophilic bleeds within 5 half-lives of last drug administration; a non-haemophilia-related investigational drug concurrently, within last 30 days or 5 half-lives, whichever is shorter
Intervention	Patients previously on on-demand treatment: Group A: 1.5 mg/kg emicizumab once weekly, Group B: 3 mg/kg emicizumab every 2 weeks, Group C: no prophylactic treatment Patients previously on prophylactic treatment: Group D: 1.5 mg/kg emicizumab once weekly
Comparator(s)	Prior prophylactic treatment
Follow-up time	Median follow-up: 33.7 weeks
Primary, secondary and exploratory endpoints	**All endpoints are measured at least 24 weeks, unless otherwise stated.** **Primary** • ABR for treated bleeds. **Secondary** • ABR for All Bleeds. • ABR for Treated Joint Bleeds. • Intra-Participant Comparison on Study Versus Pre-Study in Participants Previously Treated With Factor VIII (FVIII) Prophylaxis (NISP): Treated bleeds and all Bleeds • Intra-Participant Comparison on Study Versus Pre-Study in Participants Previously Treated With Episodic FVIII (NISE): Treated bleeds and all Bleeds • Hemophilia A Quality of Life (Haem-A-QoL) Questionnaire Physical Health Sub score for Adult Participants (≥18 Years of Age) in the Randomized Population at Week 25. • Haem-A-QoL Questionnaire Total Score for Adult Participants (≥18 Years of Age) in the Randomised Population at Week 25. • European Quality of Life 5-Dimensions-5 Levels (EQ-5D-5L) Questionnaire Visual Analogue Scale (VAS) Score in the Randomised Population at Week 25. • EQ-5D-5L Questionnaire Index Utility Score in the Randomised Population at Week 25.

Trial name: HAVEN 3	NCT number: (NCT02847637)

- Haemophilia-Specific Quality of Life - Short Form (Haemo-QoL-SF) Questionnaire Score in Adolescent Participants (12 to 17 Years of Age) in the Randomised Population at Week 25.
- Percentage of Participants With at Least One Adverse Event
- Percentage of Participants With at Least One Grade ≥3 Adverse Event
- Percentage of Participants With at Least One Adverse Event Leading to Withdrawal From
- of Participants With at Least One Adverse Event of Changes
- Percentage of Participants With at Least One Adverse Event of Changes
- Percentage of Participants With at Least One Adverse Event of Abnormal Laboratory Values
- Percentage of Participants With at Least One Local Injection-Site Reaction
- Percentage of Participants With at Least One Thromboembolic Event
- Percentage of Participants With at Least One Thrombotic Microangiopathy
- Percentage of Participants With at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction
- Safety Summary of the Percentage of Emicizumab-Treated Participants With at least one adverse event
- Model-Based ABR for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants.
- Mean Calculated ABR for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants.
- Median Calculated ABR for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants.
- Mean Calculated ABR for Treated Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants.
- Median Calculated ABR for Treated Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants.
- Mean Calculated ABR for All Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants.
- Median Calculated ABR for All Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants.
- Mean Calculated ABR for Treated Spontaneous Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants.

Trial name: HAVEN 3	NCT number: (NCT02847637)
	• Median Calculated ABR for Treated Spontaneous Bleeds Per 12-Week Intervals Over Time, All Emicizumab Participants. • Percentage of Participants with Anti-Emicizumab Antibodies at Any Time Post-Baseline During the Study. • Percentage of Participants With De Novo Development of Factor VIII (FVIII) Inhibitors. • Trough Plasma Concentration of Emicizumab.
Method of analysis	For bleeding-related end points, comparisons of bleeding rate (which were calculated over the entire efficacy period) were performed with the use of a negative binomial-regression model. The model included the stratification factor (<9 or ≥9 bleeding events in the previous 24 weeks) and accounted for various follow-up times to determine the bleeding rate per day, which was converted to an ABR. The intraindividual comparison (without stratification as a covariate) included the participant component in the model.
Subgroup analyses	NA
Other relevant information	NA

Appendix B. Efficacy results per study

Table 13. Results of BASIS – patients previously treated with prophylactic factor replacement therapy

Results of BASIS (NCT03938792)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ABR (IQR), Median, all bleeds (12 month)	Marstacimab	83	2.89 (0.00, 7.06*)	1.02	NA	NA	NA	NA	NA	Counts, single arm versus baseline	(32)
	Routine prophylaxis	83	3.91 (0.00, 11.66)								
ABR Median, treated bleeds (12 month)	Marstacimab	83	2.02 (0.00, 6.09)	[redacted]	NA	NA	NA	NA	NA	Counts, single arm versus baseline	Table 24 (27)
	Routine prophylaxis	83	[redacted]								
Heam-A QoL total score, **adult** patients (12 months)	Marstacimab	63		[redacted]	[redacted]	NA	NA	NA	NA	Non-parametric analysis 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	Data on file
	Routine prophylaxis	63									
	Marstacimab	20		[redacted]		NA	NA	NA	NA	Non-parametric analysis	Table 34 (27)

Results of BASIS (NCT03938792)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Heamo- QoL total score, **adolescent** patients ((12 months)	Routine prophylaxis	20			[redacted]					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	
Severe venous thromboembolis (12 months)	Marstacimab	83	0	1	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	(32)
	Routine prophylaxis	91	1								
SAE	Marstacimab	83	7 (8.4) Treatment related: 1	-5 Treatment related: -1	NA	NA	NA	NA	NA	One considered by the investigator to be treatment related that was diagnostically confirmed to be unrelated to a bleeding or thrombotic event. (32)	
	Routine prophylaxis	91	2 (2.2%)								
Discontinuation due to adverse event (12 months)	Marstacimab	83	1 (1.2%)	-1	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	(32)
	Routine prophylaxis during OP	91	0 (0%)								

* During the publication process a discrepancy was found between the SPC and the Statistical Analysis Plan (SAP) in relation to how preventative factor treatment was treated in ABR calculations. The discrepancy only affects the 100th decimal and does not affect any conclusions or significances. ABR was recalculated to fit with the SAP and the numbers have been updated. The full description of how ABR is calculated can be found in Matino et al (2025) Supplementary Materials, Section 6.

Table 14. Results of BASIS – patients previously treated with prophylactic factor replacement therapy, for haemophilia A subgroup

Results of BASIS (NCT03938792)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ABR (IQR), Median, all bleeds (12 month)	Marstacimab	65	[redacted]	[redacted]	NA	NA	NA	NA	NA	Counts, single arm versus baseline	CSR Table 22a 5
	Routine prophylaxis	65	[redacted]								
ABR Median, treated bleeds (12 month)	Marstacimab	65	[redacted]	[redacted]	NA	NA	NA	NA	NA	Counts, single arm versus baseline	Table 14.2.2.1.7 (27)
	Routine prophylaxis	65	[redacted]								
Severe venous thromboembolism (12 months)	Marstacimab	65	0	0	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	Data on file
	Routine prophylaxis	65	0								
SAE	Marstacimab	65	[redacted]	[redacted]	NA	NA	NA	NA	NA	[redacted]	Data on file
	Routine prophylaxis	65	[redacted]								

Results of BASIS (NCT03938792)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										[redacted]	
Discontinuation due to adverse event (12 months)	Marstacimab	65	[redacted]	[redacted]	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	Data on file
	Routine prophylaxis during OP	65	0								

Table 15. Results of (NCT 05145127) "OLE"

Results of OLE (NCT 05145127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Long-term ABR Median, all bleeds	Marstacimab	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA	Counts, single arm versus baseline	(28)
	Baseline of OLE study	[redacted]	[redacted]								

Table 16. Results of HAVEN 3 - patients previously treated with prophylactic factor replacement therapy

Results of HAVEN-3 (NCT02847637)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ABR, all bleeds, (IQR), median (33 weeks)	Emicizumab, Arm D	63	1.5 (0.0, 4.3)	0.3	NA	NA	NA	NA	NA	ABR was calculated with the use of a negative binomial-regression model	Table S2 (30)
	NIS FVIII Prophylaxis	49	2.7 (0,0; 9.4)								Table 3 (38)
ABR, treated bleeds (IQR), Median	Emicizumab, Arm D	63	0.0 (0.0, 2.2)	1.8	NA	NA	NA	NA	NA	ABR was calculated with the use of a negative binomial regression model	Table 2 (30)
	NIS F VIII Prophylaxis	48	1.8 (0.0-7.6)								Table 2 (30)
Heam-A QoL total score, mean, adult patients (change from baseline	Emicizumab, Arm D	NR	NR	-3.02	NA	NA	NA	NA	NA	NA	(8)
	NIS FVIII Prophylaxis	NR	NR								
Severe venous thromboembolism (12 months)	Emicizumab		0	NA	NA	NA	NA	NA	NA	NA	(30)
	NIS FVIII Prophylaxis		NR								

Results of HAVEN-3 (NCT02847637)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
SAE	Emicizumab		TESAE: 10 Treatment related: 0	NA	NA	NA	NA	NA	NA	NA	(39)
Discontinuation due to adverse event (12 months)	Emicizumab	63	0 (0%)	NA	NA	NA	NA	NA	NA	NA	Table 3 (30)

Appendix C. Comparative analysis of efficacy

Table 17. Comparative analysis of studies comparing marstacimab to emicizumab for patients with haemophilia A

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
ABR Median, all bleeds (12 month)	BASIS HAVEN 3	-1.39	NA	NA	NA	NA	NA	Indirect naive comparison	No
ABR Median, treated bleeds (12 month)	BASIS HAVEN 3	-2.02	NA	NA	NA	NA	NA	Indirect naive comparison	No
ABR Median Long term	BASIS HAVEN 3	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Quality of Life: Heam-A QoL total score, mean **adult** patients (change from baseline at 12 months)	BASIS HAVEN 3 all arms	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Quality of Life: Heamo- QoL total score, adolescent patients (change from baseline at (12 months)	BASIS HAVEN 3	NA	NA	NA	NA	NA	NA	Indirect naive comparison	No
Severe venous thromboembolism (12 months)	BASIS HAVEN 3	0	NA	NA	NA	NA	NA	Indirect naive comparison	No

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
SAE	BASIS HAVEN 3	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Discontinuation due to adverse event (33 weeks)	BASIS HAVEN 3	[redacted]	NA	NA	-1.2%	NA	NA	Indirect naive comparison	No

Table 18. Comparative analysis of studies comparing marstacimab to emicizumab for patients with haemophilia A subgroup

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
ABR Median, all bleeds (12 month)	BASIS HAVEN 3	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
ABR Median, treated bleeds (12 month)	BASIS HAVEN 3	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
ABR Median Long term	BASIS HAVEN 3	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Severe venous thromboembolism (12 months)	BASIS HAVEN 3	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
SAE	BASIS HAVEN 3	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Discontinuation due to adverse event (33 weeks)	BASIS HAVEN 3	[redacted]	NA	NA	-1.2%	NA	NA	Indirect naive comparison	No

Appendix D. Literature searches for the clinical assessment

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

A systematic literature review (SLR) was conducted on August 4th 2020 (original SLR) and subsequently updated on August 21st 2023 and May 17th 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 detailed in the Cochrane Handbook for Systematic Reviews of Interventions, guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the National Institute for Health and Care Excellence (NICE) (42), (43).

Table 19: Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
Medline		From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
CENTRAL	Wiley platform	From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
CDSR		From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
DARE		From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)

Abbreviations: CDSR: Cochrane Database of Systematic Reviews, DARE: Database of Abstracts of Reviews of Effects

Table 20: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	ClinicalTrials.gov	Electronic search	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)

Source name	Location/source	Search strategy	Date of search
WHO ICTRP	www.who.int/clinical-trials-registry-platform	Electronic search	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
EMA EPARs	www.ema.europa.eu	Electronic search	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)

Table 21: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ISTH	Congress of the International Society on Thrombosis and Haemostasis	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
EAHAD	Annual Congress of the European Association for Haemophilia and Allied Disorders	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
WFH	World Congress of the World Federation of Hemophilia	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
ASH	Annual Meeting of the American Society of Hematology	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
EHA	Annual Congress of European Hematology Association	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)

D.1.2 Search strategies

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 22-

Table 22

- Table 35). 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.
- The searches were modified from the August 4th 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 as the database was discontinued in 2015

Table 22: Search strategy table for EMBASE in the clinical SLR updates, searches 21.08.2023 and 17.05.2024

No.	Query	Results (2023)	Results (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

No.	Query	Results (2023)	Results (2024)
#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
#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	1,498
#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

Table 23: Search strategy table for EMBASE in the 2020 original clinical SLR (clinical outcomes for haemophilia A), search date 04.08.2020

No.	Query	Results (2020)[a]
#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$).ti,ab.	25,601
#2	Randomized controlled trials as Topic/ or Randomized controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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
#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

No.	Query	Results (2020)[a]
#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

Table 24: Search strategy table for EMBASE in the 2020 original clinical SLR (clinical outcomes for haemophilia B), search date 04.08.2020

No.	Query	Results (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$).ti,ab.	9,169
#2	Randomized controlled trials as Topic/ or Randomized controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ adj trial$1) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3))).tw. or Placebos/ or Placebo$.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.	4,031,923
#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

No.	Query	Results (2020)
#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

Table 25: Search strategy table in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conduced 21.08.2023 and 17.05.2024 (clinical outcomes for haemophilia A and B)

No.	Query	Results (2023)	Results (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	3,569,469	3,719,063

No.	Query	Results (2023)	Results (2024)
	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	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

Table 26: Search terms used in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conduced 04.08.2020 (clinical outcomes for haemophilia A)

No.	Query	Results (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	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	3,008,333

No.	Query	Results (2020)
	random).tw. or (single arm trial or singl* or singlearm).tw. or (non-random* or single group assign*).tw.	
#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

Table 27: Search terms used in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conduced 04.08.2020 (clinical outcomes for haemophilia B)

No.	Query	Results (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$).ti,ab.	5,593
#2	Randomized controlled trials as Topic/ or Randomized controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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

No.	Query	Results (2020)
#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

Table 28: Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted 21.08.2023 and 17.05.2024 (clinical outcomes for haemophilia A and B)

No.	Query	Results (2023)	Results (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.	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
#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

No.	Query	Results (2023)	Results (2024)
#6	1 not 5	496	1,119
#7	limit 6 to (english language and yr="2020 -Current")	88	215

Table 29. Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted 04.08.2020 (clinical outcomes for haemophilia A)

No.	Query	Results (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 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
#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

Table 30: Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted 04.08.2020 (clinical outcomes for haemophilia B)

No.	Query	Results (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$).ti,ab.	371
#2	Randomized controlled trials as Topic/ or Randomized controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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
#10	limit 8 to english language	92

Abbreviations: SLR: systematic literature review

Table 31: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted 21.08.2023 and 17.05.2024 (clinical outcomes for haemophilia A and B)

No.	Query	Results (2023)	Results (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	19	19

No.	Query	Results (2023)	Results (2024)
	hemophilic a or haemophilic a or factor 8 deficienc$ or classical hemophilia or classical haemophilia).ti,ab.		
#2	limit 1 to yr="2020-Current"	10	3

Table 32: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted 04.08.2020 (clinical outcomes for haemophilia A)

No.	Query	Results (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

Table 33: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted 04.08.2020 (clinical outcomes for haemophilia B)

No.	Query	Results (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"	14

Table 34: Search terms used for the DARE; searches conduced on the 04.08.2020 (clinical outcomes for haemophilia A)

No.	Query	Results (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

Table 35: Search terms used for the DARE; searches conduced on the 04.08.2020 (clinical outcomes for haemophilia B)

No.	Query	Results (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$).af.	3
#2	((clinic$ 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

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.1.3 Systematic selection of studies

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.

The eligibility criteria for the clinical SLR are listed in Table 36. 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.

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 36). 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 36: Eligibility criteria for the clinical SLR

Clinical effectiveness	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 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	• 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 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: octocog alfa (Advate®), moroctocog alfa (ReFacto AF®), turoctocog alfa (NovoEight®), simoctocog alfa (Nuwiq®)	Studies on interventions not intended for the treatment of haemophilia (e.g., pre or postsurgery protocols)

	- Extended half-life FVIII replacement therapy: turoctocog alfa pegol (Esperoct®), efmoroctocog alfa (Eloctate®), rurioctocog alfa pegol (Adynovi®), lonoctocog alfa (Afstyla®), efanesoctocog alfa (Altuviiio®), damoctocog alfa pegol (Jivi®) - Standard half-life FIX replacement therapy,: nonacog alfa (BeneFIX®), nonacog gamma (Rixubis®) - Extended half-life FIX replacement therapy: eftrenonacog alfa (Alprolix®), albutrepenonacog alfa (Idelvion®), nonacog beta pegol (Refixia®), dalcinonacog alfa • Emicizumab (Hemlibra®) • Rebalancing agents: Marstacimab, Fitusiran, Concizumab (Alhemo®), • Gene therapies: Valoctocogene roxaparvovec (Roctavian®), Giroctocogene fitelparvovec, Etranacogene dezaparvovec (Hemgenix®), Fidanacogene elaparvovec (Beqvez®, Durveqtix®)	
Comparators	Any of the above interventions or none (no comparison is required)	NA
Outcomes	• Total 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	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

	titre), thromboembolic events and infusion related reactions	
Study design/publication type	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 may not have been identified during search or screening	• 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
Geographical limits	No restrictions	N/A
Language restrictions	• 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.

Figure 3 shows the PRISMA diagram for the study selection for the combined SLR data cuts. Of the 8,034 unique records identified in literature search in databases and trial registries, 4,797 were screened using title/abstract for relevance according to the eligibility criteria, and 3,802 were excluded. A total of 995 citations went through full-text screening to assess for potential relevance. A total of 79 publications met the inclusion criteria corresponding to 79 unique trials, which were extracted to undergo full-text review.

Among the 80 trials included in the SLR, two investigated marstacimab (BASIS and a phase 2 trial), of which the BASIS trial was selected as the reference for the intervention and 78 investigated comparator treatments were selected for the comparator. The justification for excluding the comparator studies is presented in Table 37.

From the 78 studies, 47 were excluded based on the following reasons: Population= 7; Outcome=8; No baseline characteristics=6; Not reported at least one primary or secondary outcome assessed in the BASIS-1 trial =14; early phase trial in which phase 3 or 4 trial data were available = 10; Historical plasma-derived product that is not widely used within clinical practice =2; experimental treatments for which the manufacturer has terminated development =1.

Of the remaining 30 studies evaluating 22 different interventions, 29 were subsequently excluded because they did not report on a relevant comparator of interest to the Danish evaluation of haemophilia A, where the comparator of relevance is emicizumab. Furthermore, HAVEN 4 evaluating emicizumab was excluded, as this trial includes patients with inhibitors. Thus HAVEN-3 alone, was included in addition to the BASIS-1 marstacimab studies, see Table 37 for included studies.

Additionally, one reference was included as a data source in application: the marstacimab (NCT05145127) open-label long term extension "OLE" study CSR report. See Table 38 and Table 39 for included studies.

Table 37: List of studies included in the clinical SLR

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
BASIS, NCT03938792	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) n=128	Include	Matino D., Palladino A., Taylor C. T., et al. Marstacimab Prophylaxis in Hemophilia A/B Without Inhibitors: Results from the Phase 3 BASIS Trial. Blood. 2025 Jul 3:blood.2024027468. doi: 10.1182/blood.2024027468. Epub ahead of print. PMID: 40608864. Clinical Study Report, 2024
NCT03363321	A and B	Phase 2 open label, non-RCT	Brazil, Chile, Croatia, Poland, South Africa, Switzerland, US	Marstacimab (PF-06741086), Different dosing, n=20	Exclude, later phase results available	Mahlangu J, Luis Lamas J, Cristobal Morales J, et al. Long-term safety and efficacy of the anti-tissue factor pathway inhibitor marstacimab in participants with severe haemophilia: Phase II study results. Br J Haematol. 2023 Jan;200(2):240-248. doi: 10.1111/bjh.18495. Epub 2022 Oct 11. PMID: 36220152; PMCID: PMC10092220.
Atlas-PPX, NCT03549871	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), n=80	Exclude, not relevant comparator	Kenet G, Nolan B, Zulfikar B, et al. Fitusiran prophylaxis in people with hemophilia A or B who switched from prior BPA/CFC prophylaxis: the ATLAS-PPX trial. Blood. 2024 May 30;143(22):2256-2269. doi: 10.1182/blood.2023021864. PMID: 38452197; PMCID: PMC11181353.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
ATLAS-A/B, NCT03417245	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, n=120	Exclude, not relevant comparator	Srivastava A, Rangarajan S, Kavakli K, et al. Fitusiran prophylaxis in people with severe haemophilia A or haemophilia B without inhibitors (ATLAS-A/B): a multicentre, open-label, randomised, phase 3 trial. Lancet Haematol. 2023 May;10(5):e322-e332. doi: 10.1016/S2352-3026(23)00037-6. Epub 2023 Mar 29. PMID: 37003278.
Explorer 8, NCT04082429	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, n=148	Exclude, baseline data not available	Chowdary P, Angchaisuksiri P, Apte S, et al. Concizumab prophylaxis in people with haemophilia A or haemophilia B without inhibitors (explorer8): a prospective, multicentre, open-label, randomised, phase 3a trial. Lancet Haematol. 2024 Dec;11(12):e891-e904. doi: 10.1016/S2352-3026(24)00307-7. Epub 2024 Nov 6. Erratum in: Lancet Haematol. 2024 Dec;11(12):e886. doi: 10.1016/S2352-3026(24)00353-3. PMID: 39521008.
NR	A and B	Crossover RCT (Phase NR)	Sweden	FVIII and FIX products, Different regimens, prophylaxis, on-demand n=13	Exclude, not relevant comparator	Lindvall K, Astermark J, Björkman S, et al. Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy. Haemophilia. 2012 Nov;18(6):855-9. doi: 10.1111/j.1365-2516.2012.02879.x. Epub 2012 Jun 11. PMID: 22681244

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
Explorer 5, NCT03196297	A only	Phase 2 open-label, single-arm trial	France, Germany, Italy, Japan, Spain, Sweden, Thailand, Turkey, UK, Ukraine, US	Concizumab (Alhemo™), NA n=36	Exclude, later phase results available	Shapiro AD, Angchaisuksiri P, Astermark J, et. Al. Subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results. Blood. 2019 Nov 28;134(22):1973-1982. doi: 10.1182/blood.2019001542. PMID: 31444162; PMCID: PMC6895373.
GENEr8-1, NCT03370913	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 n=134	Exclude, not relevant comparator	Mahlangu J, Kaczmarek R, von Drygalski A, et al. GENEr8-1 Trial Group. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. N Engl J Med. 2023 Feb 23;388(8):694-705. doi: 10.1056/NEJMoa2211075. PMID: 36812433.
GENEr8-3, NCT04323098	A only	Phase 3 open-label, single-arm trial	Australia, Brazil, Taiwan, US	Valoctocogene roxaparvovec (ROCTAVIAN™), NA n=22	Exclude, not relevant comparator	**Ozelo MC, Mason J, Dunn AL, et. Al. Safety and efficacy of valoctocogene roxaparvovec with prophylactic glucocorticoids: 1-year results from the phase 3b, single-arm, open-label GENEr8-3 study. Thromb Haemost. 2025 Jan 10:S1538-7836(25)00002-9. doi: 10.1016/j.jtha.2024.12.038. PMID: 39800255**
BMN 270-201, NCT02576795, EudraCT number, 2014-003880-38	A only	Phase 1/2 open-label, dose-escalation, single-arm	UK	Valoctocogene roxaparvovec (ROCTAVIAN™), Different dosing n=9	Exclude, later phase results available	Rangarajan S, Walsh L, Lester W, et al. AAV5-Factor VIII Gene Transfer in Severe Hemophilia A. N Engl J Med. 2017 Dec 28;377(26):2519-2530. doi: 10.1056/NEJMoa1708483. Epub 2017 Dec 9. PMID: 29224506.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
Alta study, NCT03061201	A only	Phase 2 open-label, dose ranging, non-RCT	US	Giroctocogene fitelparvovec (PF-07055480), Different dosing n=11	Exclude, later phase results available	Leavitt AD, Konkle BA, Stine KC, et al. Giroctocogene fitelparvovec gene therapy for severe hemophilia A: 104-week analysis of the phase 1/2 Alta study. Blood. 2024 Feb 29;143(9):796-806. doi: 10.1182/blood.2022018971. PMID: 37871576; PMCID: PMC10933705.
GO-8, NCT03001830	A only	Phase 1/2 open-label, single-arm trial	UK, US	Factor VIII variant (AAV-HLP-hFVIII-V3), NA n=12	Exclude, baseline data not available	Pratima Chowdary, Ulrike M. Reiss, et al. GO-8: Stable Expression of Factor VIII over 5 Years Following Adeno-Associated Gene Transfer in Subjects with Hemophilia a Using a Novel Human Factor VIII Variant. *Blood* 2023; 142 (Supplement 1): 3624. doi.10.1182/blood-2023-190803
SPK-8011-101/ SPK-8011/8016-LTFU, NCT03003533 / NCT03432520	A only	Phase 1/2 open-label, non-RCT	Australia, Canada, Israel, Thailand, US	SPK-8011, Different dosing n=18	Exclude, baseline data not available	George LA, Monahan PE, Eyster ME, et al. Factor VIII Expression after AAV Gene Transfer for Hemophilia A. N Engl J Med. 2021 Nov 18;385(21):1961-1973. doi: 10.1056/NEJMoa2104205. PMID: 34788507; PMCID: PMC8672712.
NCT03588299	A only	Phase 1/2 open-label, single-arm trial	France, Germany, the Netherlands, Bulgaria, UK, US	Peboctocogene camaparvovec (BAY 2599023;	Exclude, baseline data not available	Pipe SW, Ferrante F, Reis M, et al. First-in-Human Gene Therapy Study of AAVhu37 Capsid Vector Technology in Severe Hemophilia A - BAY 2599023 has Broad Patient Eligibility and Stable and Sustained Long-Term Expression

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
				AAVhu37FVIII), NA, n=2		of FVIII 6. Blood (2020) 136 (Supplement 1): 44. http://doi.org/10.1182/blood-2020-139803
HAVEN 3, NCT02847637	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, n=152	Include	Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018 Aug 30;379(9):811-822. doi: 10.1056/NEJMoa1803550. PMID: 30157389.
HAVEN 4, NCT03020160	A only	Phase 3 open-label, single-arm trial	Australia, Belgium, Japan, Poland, Spain, US	Emicizumab (HEMLIBRA®), NA, n=48	Exclude, only inhibitor patients	Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol. 2019 Jun;6(6):e295-e305. doi: 10.1016/S2352-3026(19)30054-7. Epub 2019 Apr 16. PMID: 31003963.
HAVEN 5, NCT03315455	A only	Phase 3 open-label, RCT	China, Malaysia, Thailand	Emicizumab (HEMLIBRA®), Different dosing n=70	Exclude, conducted outside of North America, UK, Europe	Yang R, Wang S, Wang X, et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN 5). Res Pract Thromb Haemost. 2022 Mar 7;6(2):e12670. doi: 10.1002/rth2.12670. PMID: 35284778; PMCID: PMC8902287.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
CTRI/2018/05/013790	A only	Single-arm trial (Phase NR)	India	Antihemophilic factor human (HemoRel-A®), prophylaxis, NA, n=44	Exclude, outcomes from BASIS not reported	Mewada M, Sanyal S, Rangarajan Set al. A prospective, multicenter, clinical Study to evaluate the Safety, Pharmacokinetics, and Efficacy of Bleed Outcomes, with HemoRel-A® in severe Hemophilia A Patients. J Assoc Physicians India. 2022 Jul;70(7):11-12. doi: 10.5005/japi-11001-0039. PMID: 35833399.
CTTQ-NXBYZ-02, NCT04061109	A only	Phase 3 open-label, single-arm trial	China	B-domain-deleted recombinant factor VIII (TQG202), prophylaxis, NA, n=81	Exclude, conducted outside of North America, UK, Europe	Xi Y, Jin C, Liu W, et al. Efficacy, safety and bioequivalence of the human-derived B-domain-deleted recombinant factor VIII TQG202 for prophylaxis in severe haemophilia A patients. Haemophilia. 2022 Nov;28(6):e219-e227. doi: 10.1111/hae.14652. Epub 2022 Aug 22. PMID: 35996199; PMCID: PMC9805152.
GC8AIII, NCT01568580	A only	Phase 3 open-label, single-arm trial	Korea	Beroctocog Alfa (ALPHANATE®), on-demand, NA, n=88	Exclude, conducted outside of North America, UK, Europe	Hyun SY, Park SY, Lee SY, et al. Efficacy, Safety, and Pharmacokinetics of Beroctocog Alfa in Patients Previously Treated for Hemophilia A. Yonsei Med J. 2015 Jun 5;56(4):935–943. doi: **10.3349/ymj.2015.56.4.935. PMCID: PMC4479860. PMID: 26069114**
Study 310, NR	A only	Study 1: Double blind, RCT cross-over	Italy, New Zealand, Poland, UK, US	Moroctocog alfa (Xyntha®), prophylaxis and on-demand Full-length rFVIII	Exclude, not relevant comparator	Recht M, Nemes L, Matysiak M, et al. Haemophilia. Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of haemophilia A: demonstration of safety,

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		followed by open-label Study 2: open-label single-arm (Phase NR)		concentrate (FLrFVIII, Advate, Baxter), on-demand, n=204		efficacy, and pharmacokinetic equivalence to full-length recombinant factor VIII 2009 Jul;15(4):869-80. doi: 10.1111/j.1365-2516.2009.02027.x. Epub 2009 Apr 9.
SPINART, NCT00623480	A only	Phase 3b/4 randomised, controlled, parallel-group, open-label	Argentina, Bulgaria, Romania, US	Octocog alfa (Kogenate® FS), Prophylaxis and on-demand, n=84	Exclude, not relevant comparator	Manco-Johnson MJ, Kempton CL, Reding MT, et al. Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). J Thromb Haemost. 2013 Jun;11(6):1119-27. doi: 10.1111/jth.12202. Erratum in: J Thromb Haemost. 2014 Jan;12(1):119-22. PMID: 23528101.
LIPLONG, NR	A only	Phase 2 active-controlled, double-blind	Israel, US	Octocog alfa (Kogenate® FS), prophylaxis rFVIII-FS, prohylaxis, n=143	Exclude, later phase results available	Powell J, Martinowitz U, Windyga J, et al. Efficacy and safety of prophylaxis with once-weekly BAY 79-4980 compared with thrice-weekly rFVIII-FS in haemophilia A patients. A randomised, active-controlled, double-blind study. Thromb Haemost. 2012 Nov;108(5):913-22. doi: 10.1160/TH12-03-0188. PMID: 23014711. DOI: 10.1160/TH12-03-0188
NR	A only	Open-label, single-arm	Europe, US	Octocog alfa (Kogenate® FS), on-	Exclude, later phase	Collins P, Faradji A, Morfini M et al. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		trial (Phase NR)		demand followed by prophylaxis Different regimen, n=20	results available	formulated recombinant factor VIII treatment in adults with severe hemophilia A: results from a 13-month crossover study. Journal of Thrombosis and Haemostasis, 2010. 8 (1): 83-89, doi: 10.1111/j.1538-7836.2009.03650.x.
NR	A only	Single-arm trial (Phase NR)	France, Germany	Octocog alfa (Kogenate® FS), prophylaxis NA, n=33	Exclude, later phase results available	Rothschild C, Scharrer I, Brackmann HH, et al. European data of a clinical trial with a sucrose formulated recombinant factor VIII in previously treated haemophilia A patients. Haemophilia. 2002 Mar;8 Suppl 2:10-4. doi: 10.1046/j.1351-8216.2001.00131.x. PMID: 11966846
NR	A only	Cross-over RCT (Phase NR)	North America, Europe	Octocog alfa (Kogenate® FS), prophylaxis, Different formulation, n=71	Exclude, outcomes from BASIS not reported	Abshire TC, Brackmann HH, Scharrer I, et al. Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy--International Kogenate-FS Study Group. Thromb Haemost. 2000 Jun;83(6):811-6. PMID: 10896230
NCT00717626	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	Exclude, later phase results available	No publication: https://clinicaltrials.gov/study/NCT00717626

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
				n=14		
LEOPOLD I, NCT01029340	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®) prophylaxis Octocog Alfa (Kogenate), prophylaxis Octocog alfa (Kovaltry®), n=62	Exclude, not relevant comparator	Saxena K, Lalezari S, Oldenburg J, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Haemophilia. 2016 Sep;22(5):706-12. doi: 10.1111/hae.12952. Epub 2016 Jun 24. PMID: 27339736.
LEOPOLD II, NCT01233258	A only	Phase 2/3 cross-over, open-label	Europe, North America, South America, South Africa, Asia (11 countries)	Octocog alfa (Kovaltry®), On-demand, Octocog alfa (Kovaltry®), FVIII Prophylaxis, n=97	Exclude, not relevant comparator	Kavakli K, Yang R, Rusen L, et al. LEOPOLD II Study Investigators. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). J Thromb Haemost. 2015 Mar;13(3):360-9. doi: 10.1111/jth.12828. PMID: 25546368; PMCID: PMC4671268.
SCT800-A401, NCT03947567	A only	Phase 4 open-label, single-arm trial	China	Omfiloctocog alfa (Ancain®), prophylaxis and/or on-demand NA, n=69	Exclude, baseline data not reported	Xue F, Zhao X, Sun J, et al. P1670: Long term safety and efficacy of recombinant human coagulation factr VIII (SCT800) in previously treated patients with severe hemophilia A, Hemasphere. 2022 Jun 23;6(Suppl):1551-

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
						1552. doi: **10.1097/01.HS9.0000849536.75261.f1** PMCID: PMC9430633
SCT800-A302, NCT03815318	A only	Phase 3 open-label, single-arm trial	China	Omfiloctocog alfa (Ancain®), prophylaxis, NA, n=73	Exclude, conducted outside of North America, UK, Europe	Xue F, Zhao X, Sun J, et al. **Pharmacokinetic, efficacy and safety evaluation of B-domain-deleted recombinant FVIII (SCT800) for prophylactic treatment in adolescent and adult patients with severe haemophilia A.** Haemophilia. 2021 Sep;27(5):814-822. doi: 10.1111/hae.14350. Epub 2021 Jun 5.PMID: 34089210
NR	A only	Open-label, single-arm trial (Phase NR)	Poland	pdFVIII (Haemoctin® SDH), prophylaxis, on-demand, NA, n=61	Exclude, historical product not widely used in clinical practice	**Wolf DM, Rokicka-Milewska R, Lopaciuk S,** et al. **Clinical efficacy, safety and pharmacokinetic properties of the factor VIII concentrate Haemoctin SDH in previously treated patients with severe haemophilia A. Haemophilia. 2004 Sep;10(5):438-48. DOI: 10.1111/j.1365-2516.2004.00947.x PMID: 15357768.**
NR	A only	Randomized, four-way cross-over, subject-blinded trial (Phase NR)	Russia	PEGLip-rFVIII-FS (sucrose-formulated FVIII noncovalently bound to pegylated liposomes), prophylaxis, Different dosing, n=16	Exclude, outcomes from BASIS not reported	**Spira J, Plyushch OP, Andreeva TA,** et al. **Evaluation of liposomal dose in recombinant factor VIII reconstituted with pegylated liposomes for the treatment of patients with severe haemophilia A. Thromb Haemost. 2008 Sep;100(3):429-34. PMID: 18766258**

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
NR	A only	Controlled, cross-over, patient-blinded trial (Phase NR)	The Netherlands, Russia	PEGylated liposome–reconstituted rFVIII, prophylaxis Different dosing, n=24	Exclude, outcomes from BASIS not reported	**Spira J, Plyushch OP, Andreeva TA,** et al. **Prolonged bleeding-free period following prophylactic infusion of recombinant factor VIII reconstituted with pegylated liposomes. Blood. 2006 Dec 1;108(12):3668-73. DOI: 10.1182/blood-2006-03-008276. PMID: 16888098**
GENA-21b, NCT02256917	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, n=58	Exclude, not relevant comparator	Midori S, Masashi T, Rie S, Tadashi M, et al. Efficacy and Safety of Personalized Prophylaxis with Simoctocog Alfa in Adult Japanese Previously Treated Patients with Severe Hemophilia a. *Blood* 2022; 140 (Supplement 1): 11304–11305. doi10.1182/blood-2022-167449
GENA-21, NCT01863758	A only	Phase 3b open-label, single-arm trial	Austria, Bulgaria, France, Germany, Poland, Romania, Switzerland	Simoctocog alfa (Nuwiq®), prophylaxis, Different dosing, n=66	Exclude, not relevant comparator	**Dargaud Y, Negrier C, Rusen L,** et al. **Individual thrombin generation and spontaneous bleeding rate during personalized prophylaxis with Nuwiq (human-cl rhFVIII) in previously treated patients with severe haemophilia A. Haemophilia. 2018 Jul;24(4):619-627. doi: 10.1111/hae.13493. Epub 2018 May 31.**
Guardian 1, NCT00840086	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, n=150	Exclude, not relevant comparator	Lentz SR, Misgav M, Ozelo M, et al. Results from a large multinational clinical trial (guardian™1) using prophylactic treatment with turoctocog alfa in adolescent and adult patients with severe haemophilia A: safety and efficacy. Haemophilia. 2013 Sep;19(5):691-7. doi: 10.1111/hae.12159. Epub 2013 May 7. PMID: 23647704.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
Guardian 2, NCT00984126	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 regimen n=158	Exclude, no outcome data 6-24 months	Lentz SR, Janic D, Kavakli K, et al. Long-term safety and efficacy of turoctocog alfa in prophylaxis and treatment of bleeding episodes in severe haemophilia A: Final results from the guardian 2 extension trial. *Haemophilia*. 2018; 24: e391–e394. https://doi.org/10.1111/hae.13617
Guardian 7, NCT02938585	A only	Phase 3 open-label, non-RCT	China	Turoctocog alfa (NovoEight®) prophylaxis, on-demand, n=26	Exclude, conducted outside of North America, UK, Europe	**Wu R, Sun J, Xu W,** et al. **Safety and Efficacy of Turoctocog Alfa in the Prevention and Treatment of Bleeding Episodes in Previously Treated Patients from China with Severe Hemophilia A: Results from the Guardian 7 Trial. Ther Clin Risk Manag. 2020 Jun 23;16:567–578. doi: 10.2147/TCRM.S243146. PMCID: PMC7320881. PMID: 32606716**
NCT04085458	A only	Phase 4 open-label, single-arm trial	Bulgaria, Denmark, Greece, Italy, Norway, Poland, Spain	Damoctocog alfa pegol (Jivi®), prophylaxis, Different dosing, n=32	Exclude, not relevant comparator	Holme PA, Poulsen LH, Tueckmantel C, et al. Safety and efficacy of damoctocog alfa pegol prophylaxis in patients with severe haemophilia A: Results of an interventional, post-marketing study. Haemophilia. 2024 Mar;30(2):388-394. doi: 10.1111/hae.14930. Epub 2024 Jan 16. PMID: 38229269.
PROTECT VIII, NCT01580293	A only	Phase 2/3 open-label, RCT	Austria, Belgium, Canada, Colombia, Denmark, France, Germany, Israel, Italy, Japan, the Netherlands,	Damoctocog alfa pegol (Jivi®) prophylaxis every 5 or	Exclude, not relevant comparator	**Reding MT, Ng HJ, Poulsen LH,** et al. **Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII. Journal of Thrombosis and Haemostasis. 5: 411–419. https://doi.org/10.1111/jth.13597**

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
			Norway, Poland, Singapore, South Korea, Taiwan, Turkey, UK, US	7 days, On-demand, n=134		
XTEND-1, NCT04161495	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 (ALTUVIIIO® or ALTUVOCT®) prophylaxis, On-demand, n=159	Exclude, not relevant comparator	von Drygalski A, Chowdary P, Kulkarni R, et al. XTEND-1 Trial Group. Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A. N Engl J Med. 2023 Jan 26;388(4):310-318. doi: 10.1056/NEJMoa2209226. PMID: 36720133.
ASPIRE, NCT01454739	A only	Open-label, non-RCT (Phase NR)	Europe (Ireland, the Netherlands, Poland, and the United Kingdom), North America (US), Australia, Hong Kong, South Africa	Efmoroctocog alfa (Eloctate®), Prophylaxis, On-demand Different dosing, n=211	Exclude, no outcome data 6-24 months	Nolan B, Mahlangu J, Perry D, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A. Haemophilia. 2016 Jan;22(1):72-80. doi: 10.1111/hae.12766. Epub 2015 Jul 27. PMID: 26218032.
A-LONG, NCT01181128	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, n=165	Exclude, not relevant comparator	Mahlangu J, Powell JS, Ragni MV, et al. A-LONG Investigators. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014 Jan 16;123(3):317-25. doi: 10.1182/blood-2013-10-529974. Epub 2013 Nov 13. PMID: 24227821; PMCID: PMC3894491.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
CSL627_1001, NCT01486927	A only	Phase 1/3 open-label, non-RCT	Europe, Japan, US	Lonoctocog alfa (Afstyla®), prophylaxis, on-demand, n=175	Exclude, not relevant comparator	Mahlangu J, Kuliczkowski K, Karim FA, et al.; AFFINITY Investigators. Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A. Blood. 2016 Aug 4;128(5):630-7. doi: 10.1182/blood-2016-01-687434. Epub 2016 Jun 21. PMID: 27330001; PMCID: PMC4974198.
CTR20201212, NCT04456387	A only	Phase 3 open-label, non-RCT	China	Recombinant Factor VIII-Fc Fusion Protein (FRSW107), prophylaxis, on-demand, n=119	Exclude, baseline data not available	Feng X, Hu Z, Yun C, et al.; Pharmacokinetics, Efficacy and Safety Evaluation of FRSW107 in Previously Treated Hemophilia a Patients: A Multicentre, Open-Label, Non-Randomized Phase III Study. *Blood* 2022; 140 (Supplement 1): 8468–8469. doi: https://doi.org/10.1182/blood-2022-158760
PROPEL, NCT02585960, EudraCT: 2014-005477-37	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 n=115	Exclude, not relevant comparator	Klamroth R, Windyga J, Radulescu V, et al. Rurioctocog alfa pegol PK-guided prophylaxis in hemophilia A: results from the phase 3 PROPEL study. Blood. 2021 Apr 1;137(13):1818-1827. doi: 10.1182/blood.2020005673. PMID: 33150384; PMCID: PMC8039905.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
NCT01945593	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 n=216	Exclude, no outcome data 6-24 months	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. Haemophilia. 2020 Jul;26(4):e168-e178. doi: 10.1111/hae.14052. Epub 2020 Jun 28. PMID: 32597029.
EXTEN-A, NCT03205163	A only	Phase 1–2a open-label, sequential, non-RCT	Japan, US	Rurioctocog alfa pegol (Adynovate®/ Adynovi®) followed by Efanesoctocog alfa (Altuviiio; BIVV001), prophylaxis, Different dosing, n=16	Exclude, outcomes from BASIS not reported	Konkle BA, Shapiro AD, Quon DV, et al. BIVV001 Fusion Protein as Factor VIII Replacement Therapy for Hemophilia A. N Engl J Med. 2020 Sep 10;383(11):1018-1027. doi: 10.1056/NEJMoa2002699. PMID: 32905674.
PROLONGATE, NCT01736475	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, n=137	Exclude, not relevant comparator	Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. Blood. 2015 Aug 27;126(9):1078-85. doi: 10.1182/blood-2015-03-630897. Epub 2015 Jul 8. PMID: 26157075; PMCID: PMC4551361.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
Pathfinder 10, NCT05082116	A only	Phase 3 open-label, single-arm trial	China	Turoctocog alfa pegol (Esperoct®) prophylaxis NA, n=36	Exclude, conducted outside of North America, UK, Europe	Matsushita T, Mangles S. An overview of the pathfinder clinical trials program: Long-term efficacy and safety of N8-GP in patients with hemophilia A. J Thromb Haemost. 2020 Sep;18 Suppl 1(Suppl 1):26-33. doi: 10.1111/jth.14958. PMID: 32558236. PMCID: PMC7540506
Pathfinder 2, NCT01480180	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 n=186	Exclude, not relevant comparator	Giangrande P, Abdul Karim F, Nemes L, et al. Long-term safety and efficacy of N8-GP in previously treated adults and adolescents with hemophilia A: Final results from pathfinder2. J Thromb Haemost. 2020 Sep;18 Suppl 1(Suppl 1):5-14. doi: 10.1111/jth.14959. PMID: 32544297; PMCID: PMC7540590.
HOPE-B, NCT03569891	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), n=54	Exclude, not relevant comparator	Pipe SW, Leebeek FWG, Recht M, et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. N Engl J Med. 2023 Feb 23;388(8):706-718. doi: 10.1056/NEJMoa2211644. PMID: 36812434.
AMT-061, NCT03489291	B only	Phase 2 open label, single-arm trial	Germany, the Netherlands, US	Etranacogene dezaparvovec (HEMGENIX®), NA, n=3	Exclude, later phase trial available	Von Drygalski A, Giermasz A, Castaman G, et al. Etranacogene dezaparvovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in hemophilia B. Blood Adv. 2019 Nov 12;3(21):3241-3247.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
						doi: 10.1182/bloodadvances.2019000811. Erratum in: Blood Adv. 2020 Aug 11;4(15):3668. doi: 10.1182/bloodadvances.2020002987. PMID: 31698454; PMCID: PMC6855101.
AMT-060, NCT02396342	B only	Phase 1/2 open label, non-RCT	Denmark, Germany, the Netherlands	AAV5-hFIX (AMT-060), Different dosing, n=10	Exclude, manufacturer terminated product development	Miesbach W, Meijer K, Coppens M, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. Blood. 2018 Mar 1;131(9):1022-1031. doi: 10.1182/blood-2017-09-804419. Epub 2017 Dec 15. PMID: 29246900; PMCID: PMC5833265.
BENEGENE-2, NCT03861273	B only	Phase 3 open label, single-arm trial	Australia, Brazil, Canada, France, Germany, Greece, Japan, Korea, Republic of, Saudi Arabia, Sweden, Taiwan, Turkey, UK, US	Fidanacogene elaparvovec (BEQVEZ), FIX prophylaxis (lead-in phase), n=45	Exclude, not relevant comparator	Cuker A, Kavakli K, Frenzel L, et al. Gene Therapy with Fidanacogene Elaparvovec in Adults with Hemophilia B. N Engl J Med. 2024 Sep 26;391(12):1108-1118. doi: 10.1056/NEJMoa2302982. PMID: 39321362
SPK-9001-101, NCT02484092	B only	Phase 1/2a open label, single-arm trial	Australia, US	Fidanacogene elaparvovec (BEQVEZ), NA, n=15	Exclude, later phase results available	George LA, Sullivan SK, Giermasz A, et al. Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant. N Engl J Med. 2017 Dec 7;377(23):2215-2227. doi: 10.1056/NEJMoa1708538. PMID: 29211678; PMCID: PMC6029626.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
AskBio009-101, NCT01687608	B only	Phase 1/2 open label, non-RCT	US	BAX 335 (AskBio009), Different dosing, n=8	Exclude, outcomes from BASIS not reported	Konkle BA, Walsh CE, Escobar MA, et al. BAX 335 hemophilia B gene therapy clinical trial results: potential impact of CpG sequences on gene expression. Blood. 2021 Feb 11;137(6):763-774. doi: 10.1182/blood.2019004625. PMID: 33067633; PMCID: PMC7885820.
B-AMAZE, NCT03369444, NCT03641703 EdudraCT: 2017-000852-24, 2017-005080-40	B only	Phase 1/2 open label, non-RCT	UK	Verbrinacogene setparvovec (FLT180a), Different dosing, n=10	Exclude, later phase results available	Chowdary P, Shapiro S, Makris M, et al. Phase 1-2 Trial of AAVS3 Gene Therapy in Patients with Hemophilia B. N Engl J Med. 2022 Jul 21;387(3):237-247. doi: 10.1056/NEJMoa2119913. PMID: 35857660.
NR	B only	Open label, single-arm trial (Phase NR)	Bulgaria, Poland, Spain	Factor IX Grifols (AlphaNine® SD), prophylaxis, NA, n=25	Exclude, outcomes from BASIS not reported	**Lissitchkov T, Matysiak M, Zawilska K,** et al. **Haemophilia. 2010 Mar;16(2):240-6. An open clinical study assessing the efficacy and safety of Factor IX Grifols, a high-purity Factor IX concentrate, in patients with severe haemophilia B. doi: 10.1111/j.1365-2516.2009.02090.x. Epub 2009 Dec 14. PMID: 20015218**
NR	B only	Phase 3/4 open label,	The Netherlands, Poland	Human coagulation Factor IX (Nonafact®),	**Exclude, no outcome**	**Mauser-Bunschoten EP, Budde IK, et al. An ultrapure plasma-derived monoclonal antibody-purified factor IX concentrate (Nonafact®), results of phase 3 and 4 clinical**

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		single-arm trial		prophylaxis, on-demand, n=60	data 6-24 months	studies. Haemophilia, Vol 17, Issue 3: 439-445. https://doi.org/10.1111/j.1365-2516.2010.02453.x
B1821010, NCT01335061	B only	Phase 3 open label, non-RCT	Bulgaria, Canada, Croatia, Korea, Malaysia, Mexico, Poland, Singapore, Turkey	Nonacog alfa (BeneFIX®), prophylaxis, on-demand, n=25	Exclude, not relevant comparator	Kavakli K, Smith L, Kuliczkowski K, et al. Haemophilia. Once-weekly prophylactic treatment vs. on-demand treatment with nonacog alfa in patients with moderately severe to severe haemophilia B. Haemophilia. 2016 May;22(3):381-8. doi: 10.1111/hae.12878. Epub 2016 Jan 29.PMID:26823276
B1821059, NCT04286412	B only	Phase 4 open label, single-arm trial	India	Nonacog alfa (BeneFIX®) prophylaxis, NA, n=25	Exclude, conducted outside of North America, UK, Europe	Choraria N, Rangarajan S, John MJ, et al. Nonacog Alfa for Prophylaxis and Treatment of Bleeding Episodes in Previously Treated Patients with Moderately Severe or Severe Hemophilia B in India. Indian J Hematol Blood Transfus. 2022 Nov 27;39(4):630–634. doi: 10.1007/s12288-022-01588-0. PMCID: PMC10542435.PMID: 37790744
NR	B only	Open label, non-RCT (Phase NR)	Spain	Nonacog alfa (BeneFIX®), prophylaxis, on-demand,Different regimen. n=23	Exclude, outcomes from BASIS not reported	Korth-Bradley JM, Rendo P, Smith L, et al. Pharmacokinetics, Efficacy, and Safety of Nonacog Alfa in Previously Treated Patients with Moderately Severe to Severe Hemophilia B. Clin Ther. 2016 Apr;38(4):936-44. doi: 10.1016/j.clinthera.2016.02.015. PMID: 26969334
NR	B only	Double-blind crossover	France, Spain, UK, US	Nonacog alfa (BeneFIX®),	Exclude, later phase	Lambert T, Recht M, Valentino LA, et al. Reformulated BeneFix: efficacy and safety in previously treated patients

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		RCT (Phase NR)		prophylaxis, on-demand, Different regimen, n=34	results available	with moderately severe to severe haemophilia B. Haemophilia.. 2007 May;13(3):233-43. DOI: 10.1111/j.1365-2516.2007.01458.x. PMID: 17498071.
NCT01286779	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, n=117	Exclude, not relevant comparator	Windyga J, Stasyshyn O, Lissitchkov T, et al. Safety, Immunogenicity, and Hemostatic Efficacy of Nonacog Gamma in Patients With Severe or Moderately Severe Hemophilia B: A Continuation Study. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620950836. doi: 10.1177/1076029620950836. PMID: 32866032; PMCID: PMC7469725.
NCT01174446	B only	Phase 1/3 double-blind crossover RCT and open label single-arm	Argentina, Brazil, Bulgaria, Chile, Columbia, Czechia, Japan, Poland, Romania, Russian Federation, Spain, Sweden, Ukraine, UK	Nonacog gamma (RIXUBIS™), prophylaxis, on-demand, n=86	Exclude, not relevant comparator	Windyga J, Lissitchkov T, Stasyshyn O, et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B. Haemophilia. 2014 Jan;20(1):15-24. doi: 10.1111/hae.12228. Epub 2013 Jul 9. PMID: 23834666.
NCT01507896	B only	Phase 3 open label,	Bulgaria, Chile, Columbia, Czech Republic, Poland, Romania, Russia, Ukraine	Nonacog gamma (RIXUBIS™), NA, n=40	Exclude, outcomes	Windyga J, Timofeeva M, Stasyshyn O, et al. Phase 3 Clinical Trial: Perioperative Use of Nonacog Gamma, a Recombinant Factor IX, in Previously Treated Patients With Moderate/Severe Hemophilia B. Clin Appl Thromb

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		single-arm trial			from BASIS not reported	Hemost. 2020 Jan-Dec;26:1076029620946839. doi: 10.1177/1076029620946839. PMID: 32816519; PMCID: PMC7444148.
KB037, EudraCT: 2005-006186-14	B only	Phase 2 open label, single-arm trial	Italy, Romania, Turkey	Kedrion FIX concentrate (AIMAFIX®), prophylaxis, on-demand, NA, n=16	Exclude, outcomes from BASIS not reported	Castaman G, Borchiellini A, Santagostino E, et al. Non-Compartment and compartmental pharmacokinetics, efficacy, and safety of Kedrion FIX concentrate. Eur J Pharm Sci. 2020 Oct 1;153:105485. doi: 10.1016/j.ejps.2020.105485. Epub 2020 Jul 23. PMID: 32712218.
NR	B only	Open label, single-arm trial (Phase NR)	NR	Plasma-derived FIX concentrate (Haemonine), prophylaxis, on-demand, NA, n=29	Exclude, historical product not widely used	**Serban M, Skotnicki AB, Colovic M,** et al. **Clinical efficacy, safety and pharmacokinetic properties of the plasma-derived factor IX concentrate Haemonine in previously treated patients with severe haemophilia B.** Haemophilia. 2012 Mar;18(2):175-81. doi: 10.1111/j.1365-2516.2011.02624.x. Epub 2011 Aug 3. PMID: 21812863
IB1001-01, NCT00768287	B only	Phase 3 crossover RCT & open label non-RCT	France, India, Israel, Italy, Poland, UK, US	Trenonacog alfa (Ixinity®), prophylaxis, on-demand, n=76	Exclude, not relevant comparator	**Collins PW, Quon DVK, Makris M,** et al. **Pharmacokinetics, safety and efficacy of a recombinant factor IX product, trenonacog alfa in previously treated haemophilia B patients. Haemophilia, Vol24, Issue1: 104-112. doi.org/10.1111/hae.13324**

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
PROLONG-9FP (primary study), NCT01496274	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®), n=63	Exclude, not relevant comparator	Santagostino E, Martinowitz U, Lissitchkov T, et al; PROLONG-9FP Investigators Study Group. Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. Blood. 2016 Apr 7;127(14):1761-9. doi: 10.1182/blood-2015-09-669234. Epub 2016 Jan 11. PMID: 26755710; PMCID: PMC4825413.
PROLONG-9FP (extension), NCT02053792	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, n=59	Exclude, no outcome data 6-24 months	Mancuso ME, Lubetsky A, Pan-Petesch B, et al: Long-term safety and efficacy of rIX-FP prophylaxis with extended dosing intervals up to 21 days in adults/adolescents with hemophilia B. J Thromb Haemost. 2020 Mar 30;18(5):1065–1074. **doi: 10.1111/jth.14778. PMID: 32078256. PMCID: PMC7318213**
DLZ-20, NCT03995784	B only	Phase 2 open label single-arm trial	South Africa	Dalcinonacog alfa (DalcA), prophylaxis, NA, n=6	Exclude, outcomes from BASIS not reported	Mahlangu J, Levy H, Lee M, et al. Efficacy and safety of subcutaneous prophylaxis with dalcinonacog alfa in adults with haemophilia B. Haemophilia. 2021 Jul;27(4):574-580. doi: 10.1111/hae.14315. Epub 2021 May 6. PMID: 33960073; PMCID: PMC8359950.
ISU304-001/CB2679d, NCT03186677	B only	Phase 1/2a open label non-RCT	South Korea	Dalcinonacog alfa (DalcA), prophylaxis Different dosing, n=13	Exclude, outcomes from BASIS not reported	You CW, Hong SB, Kim S, et al. Safety, pharmacokinetics, and pharmacodynamics of a next-generation subcutaneously administered coagulation factor IX variant, dalcinonacog alfa, in previously treated

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
						hemophilia B patients. J Thromb Haemost. 2021 Apr;19(4):967-975. doi: 10.1111/jth.15259. Epub 2021 Mar 24. PMID: 33540485.
B-LONG, NCT01027364	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, n=123	Exclude, not a relevant comparator	Powell JS, Pasi KJ, Ragni MV, et al; B-LONG Investigators. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013 Dec 12;369(24):2313-23. doi: 10.1056/NEJMoa1305074. Epub 2013 Dec 4. PMID: 24304002.
B-YOND, NCT01425723	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, n=116	Exclude, no outcome data between 6 and 24 months	Pasi KJ, Fischer K, Ragni M, et al. Long-term safety and efficacy of extended-interval prophylaxis with recombinant factor IX Fc fusion protein (rFIXFc) in subjects with haemophilia B. Thromb Haemost. 2017 Feb 28;117(3):508-518. doi: 10.1160/TH16-05-0398. Epub 2016 Dec 22. PMID: 28004057
Paradigm 2, NCT01333111	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, n=74	Exclude, not relevant comparator	Collins PW, Young G, Knobe K, et al; paradigm 2 Investigators. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial. Blood. 2014 Dec 18;124(26):3880-6. doi: 10.1182/blood-2014-05-573055. Epub 2014 Sep 26. PMID: 25261199; PMCID: PMC4271178.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
Paradigm 4, NCT01395810	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, n=71	Exclude, no outcome data 6-24 months	Young G, Collins PW, Colberg T, et al. Nonacog beta pegol (N9-GP) in haemophilia B: A multinational phase 3 safety and efficacy extension trial (paradigm™4). Thromb Res. 2016 May:141:69-76. doi: 10.1016/j.thromres.2016.02.030. PMID: 26970716

Table 38. Manually added study of relevance included from other sources

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
NCT05145127	A and B	Phase 3 interventional, multi-centre, multi-country, open-label extension study	Australia, Canada, China, Croatia, France, Hong Kong, India, Israel, Italy, Japan, Republic of Korea, Mexico, Oman, Serbia, South Africa, Spain, Taiwan, Turkey, US	Marstacimab (PF-06741086), Factor replacement (lead-in) estimated n=245	Include	Clinicaltrial.gov, Not yet published

Table 39: Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
BASIS, NCT03938792	To demonstrate the efficacy and safety of marstacimab for routine prophylaxis	Phase 3 one-way crossover single-arm trial	Haemophilia A or B participants	Marstacimab Factor replacement (lead-in), n=128	ABR for treated bleeds at 12 months post-marstacimab initiation versus factor replacement therapy use in the observation phase	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 at 12 months HAL/pedHAL PGIC-H QoL: Haem-A-QoL/Haemo-QoL , EQ-5D-5L Safety and tolerability outcomes
HAVEN 3, NCT02847637	Evaluates two prophylactic emicizumab regimens versus no prophylaxis	Phase 3 open-label, partial RCT	Patients with severe haemophilia A ≥12	Emicizumab (HEMLIBRA®) Dose escalation, no prophylaxis, and dose maintenance, n=152	Annualized bleeding rate for treated bleeds	Annnualized bleeding rate misc. bleedings Haem-A-QoL) Questionnaire EQ-5D-5L Questionnaire Safety and tolerability outcomes

D.1.4 Quality assessment

As recommended by the National Institute for Health and Care Excellence (NICE), the quality assessment of all included studies was conducted using the Cochrane Risk of Bias Assessment Tool 2 for randomised controlled trials. In addition, non-randomised trials, including single-arm trials, were assessed using a modified version of the Downs and Black Checklist. The initial feasibility assessment consisted of the following seven points:

- Were baseline characteristics reported for the target population?
- Did the trial report at least one primary or secondary outcome from the BASIS trial?
- Did the trial include any individuals from North America, Europe, or the United Kingdom? 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? 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? If so, the most relevant data for a given comparator treatment is the phase 3 or 4 data.
- 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 39.

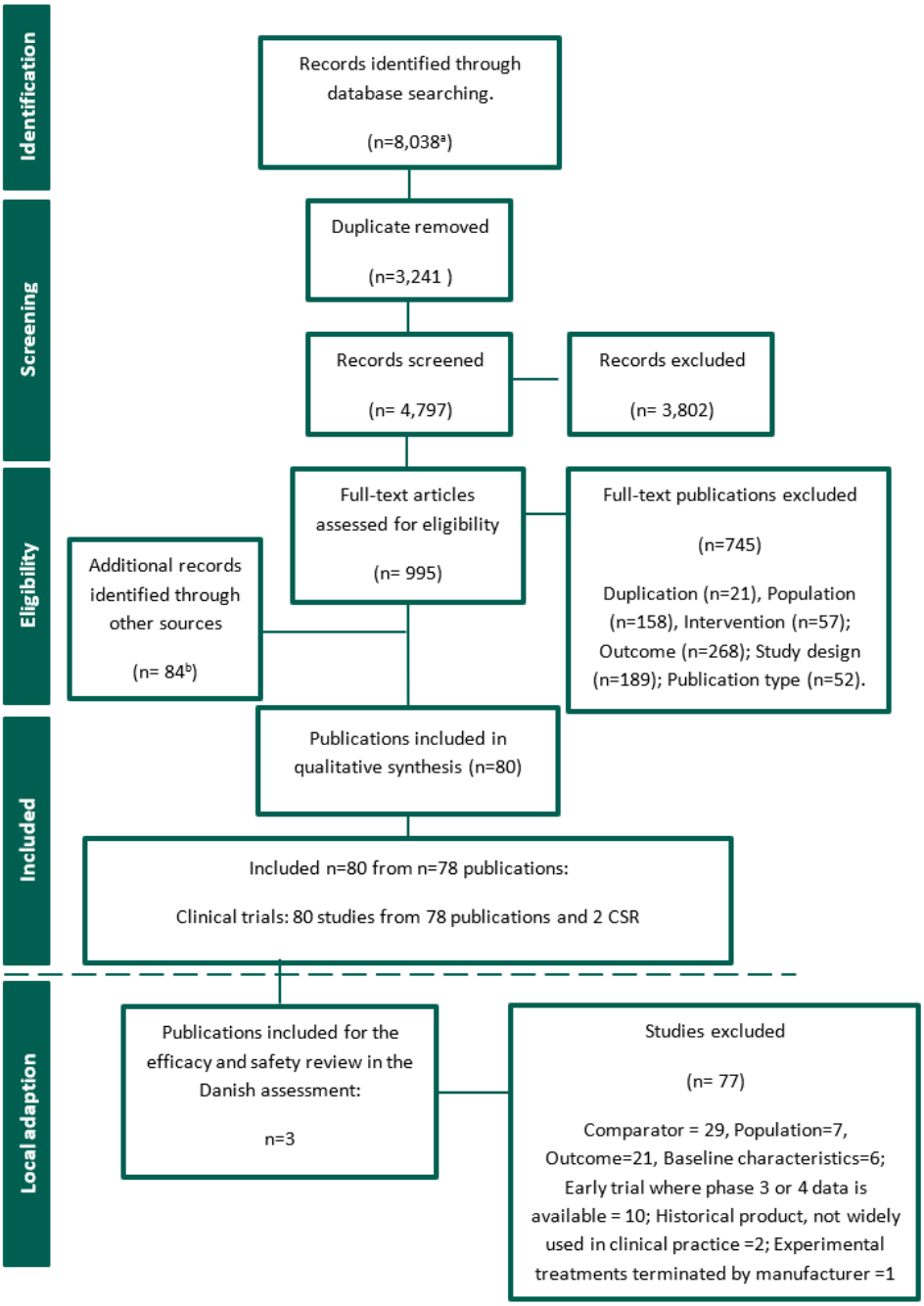
D.1.5 Unpublished data

The application contains unpublished data from two sources:

Some data from BASIS is derived from the clinical study report and is not expected to be published.

Data from the long-term extension of BASIS, the OLE-study will be published, but the study is ongoing, and the specific data included in this application is not yet peer-reviewed. As this is a long-term extension of the BASIS-study, the publication of results is not yet planned, and the timepoint published may deviate from those reported in this application.

Figure 3. PRISMA diagram



[a]Databases: MEDLINE (n=2,740), Embase (n=4,524), CENTRAL (n=437), CDSR (n=45), DARE (n=8), EconLit (n=4), NHSEED (n=26). Trial registries: Clinical trial.gov (n=107), ICTRP (n=124); EMA EPAR (n=23); [b]Conference manual search (n=73); Citation searching (n=53); Hand search (n=38); Clinical study report (n=1). These 165 records were screened, whereas 82 were excluded, and 83 continued to eligibility and one was added manually. Note that after the publication of BASIS 1, the real results are an incluion of n=80 from 79 publications and 2 CSR.

Appendix E. Safety data for marstacimab

Injection Site Reactions

Injection-site reactions occurred in [redacted] of all patients treated with marstacimab in the BASIS study (previously treated with on-demand and prophylactic treatment) (20). In the population previously treated with prophylactic treatment, injection site reactions occurred in 9 (10.8%) patients. No occurrence of injections site reactions led to a dose adjustment or discontinuation of marstacimab .

The majority of the injection-site reactions observed in the clinical studies with marstacimab were transient, all were reported as mild to moderate in severity, and no occurrences led to a dose adjustment or drug discontinuation. Injection site reactions included: injection site bruising, injection site erythema, injection site haematoma, injection site induration, injection site oedema, injection site pain, injection site pruritus, and injection site swelling

Serious Adverse Events

In Table 40 SAEs in BASIS and its long-term extension study are listed for all patients (for patients treated with prophylactic and on demand). A total of 87 of the 116 patients completing the 12-month treatment period had enrolled into the OLE study at the time of data cut-off 17th Apr 2023. The median duration of exposure was [redacted] (20).

Table 40. Summary of serious adverse events (all causalities) by system organ class and preferred term – marstacimab dataset

	BASIS (n=116) n (%)	NCT05145127 (n=[redacted]) n (%)
Number of participants with SAE (%)	7 (6.0)	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Tympanic membrane perforation	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Inflammation	[redacted]	[redacted]
Peripheral swelling	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]
Infections and infestastations	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]

Contusion	[redacted]	[redacted]
Traumatic haemorrhage	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Haemarthrosis	[redacted]	[redacted]
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]
Meningioma	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Haemorrhage	[redacted]	[redacted]
Total Number of Cases[a]	[redacted]	[redacted]

[a]Total number of events per participant per cohort, number of cases that started in the cohort; Data collection of SAE from Safety Data Warehouse or Argus. MedDRA v25.1 coding dictionary applied. Source: EPAR (44). Abbreviations: SAE= Severe Adverse Event

Safety for dose escalated patients

Eleven patients ([redacted]) were dose escalated from 150 mg marstacimab weekly to 300 mg weekly during the active treatment phase (32).

Of these, none experienced an SAE or TEAE that led to discontinuation of the study intervention (32). TEAEs while on 300 mg weekly marstacimab for patients who increased their marstacimab dose from 150 mg to 300 mg are presented in Table 41.

Table 41. Summary of TEAEs in patients who dose escalated during the BASIS study

	Dose adjusted marstacimab prophylaxis during ATP (n=11)
Number of patients, n (%)	
With any TEAE	[redacted]
Infections and Infestations	[redacted]
Laryngitis	[redacted]
Rhinitis	[redacted]
Musculoskeletal and Connective Tissue Disorders	[redacted]
Arthralgia	[redacted]
Joint range of motion decreased	[redacted]

Abbreviations: ATP: active treatment phase; mg: milligram; TEAE: Treatment Emergent Adverse Event. Source: Pfizer marstacimab Phase 3 BASIS trial CSR. 2023 (27)

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk

Application for the assessment of Hympavzi® (marstacimab) by updating the treatment guidelines for haemophilia B

Contact information

Contact information	
Name	**Sara Engstrand / Pfizer**
Title	Senior Market Access Lead
Phone number	[redacted]
E-mail	[redacted]
Name (External representation)	**N/A**
Title	
Phone number	
E-mail	

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Tables and Figures

Abbreviations

ABR	Annualised Bleeding Rate
AE	Adverse Event
AJBR	Annualised joint bleeding rate
CENTRAL	Cochrane Central Registry of Controlled Trials
CI	Confidence Interval
CL	Clearance
CSR	Clinical Study Report
DMC	Danish Medicines Council
EC	European Commission
EHL	Extended Half-Life
EMA	European Medicines Authority
EQ-5D	EuroQol 5-Dimensional Quality of Life-Questionnaire
FVIII	Factor VIII
FIX	Factor IX
FX	Factor X
HAL	Haemophilia Activities List
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
Haemo-QoL	Haemophilia-specific health-related quality of life questionnaire
HJHS	Haemophilia Joint Health Score
ICTRP	International Clinical Trials Registry Platform
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
IU	International Unit
IV	Intravenous
mITT	modified intention-to-treat (ITT)
NA	Not Applicable
NICE	National Institute for Health and Care Excellence
NIS	Non-Interventional Study
NR	Not Reported
OLE	Open Label Extension
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta
PK	Pharmacokinetic
PTP	Previous Treated Patients
RCT	Randomised Controlled Trial
rFIX	recombinant Factor IX
rFIXFc	eftrenonacog alfa
SAE	Serious Adverse Event
SD	Standard Deviation
SLR	Systematic Literature Review
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment emergent serious adverse event
TFPI	Tissue Factor Pathway Inhibitor
WHO	World Health Organization

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Hympavzi®
Generic name	Marstacimab
Therapeutic indication as defined by EMA	Marstacimab is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with: • severe haemophilia A (congenital factor VIII (FVIII) deficiency, FVIII < 1%) without factor VIII inhibitors, or • severe haemophilia B (congenital factor IX (FIX) deficiency, FIX < 1%) without factor IX inhibitors.
Marketing authorization holder in Denmark	Pfizer ApS
ATC code	B02BX11
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	18 November 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	1 pre-filled pen with 150 mg solution for subcutaneous injection

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Marstacimab is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with: • severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.
Dosage regiment and administration:	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 subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, with a pre-filled auto injectable pen.
Choice of comparator [if any]	In haemophilia B, the choose comparator is eftrenonacog alfa (Alprolix®) for haemophilia B. For long term prophylaxis against bleeding, the recommended starting regimens are either: 50 IU/kg once weekly, adjust dose based on individual response or 100 IU/kg once every 10 days, adjust interval based on individual response. Some patients who are well-controlled on a once every 10 days regimen might be treated on an interval of 14 days or longer. The highest recommended dose for prophylaxis is 100 IU/kg The DMC uses 50 IU/kg once weekly as the norm for dosing.
Most important efficacy endpoints (Difference/gain compared to comparator)	Median ABR: [redacted] Median ABR treated bleeds long term: [redacted] Inhibitor: 0 Anaphylaxis: 0 Thromboembolism: 0 Haem-A-QoL (adults): [redacted] Through above 5%: Not Relevant
Most important serious adverse events for the intervention and comparator	Marstacimab: 1 SAE considered by the investigator to be treatment related but was diagnostically confirmed to be unrelated to a bleeding or thrombotic event. Eftrenonacog alfa: 1 SAE was considered to be possibly related to treatment with rFIXFc (in the B-LONG study).

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

Haemophilia is a rare, genetic, non-progressive disease that mainly affects males. Untreated, severe disease results in repeated spontaneous bleeding episodes that leads to progressive joint damage, severe pain, impaired mobility, and an early death (1).

The severity of haemophilia is classified according to the relative plasma level of blood coagulation factor VIII (FVIII) or factor IX (FIX). This application is only concerned with patients with severe haemophilia, i.e. with patients with less than 1% of normal blood clotting activity, i.e. <1 International unit (IU)/dL (2-4).

The average life expectancy of a newborn person with severe haemophilia is approaching that of the background population in the Nordic countries, all of which practice early and continuing prophylactic treatment. Furthermore, with modern prophylactic treatment from toddler age, young adult men with severe haemophilia are expected to live a normal life (1).

Despite this, prophylactic treatment with factor replacement products alone appears to be insufficient to normalise quality of life for all patients, leaving an unaddressed unmet need (5). Some patients with haemophilia A and B without inhibitors still have bleeds (6, 7), due to a particularly severe bleeding phenotype or compliance issues, for example due to the mode of administration. The Danish treatment recommendations for haemophilia A and B are taking the burden of treatment into account, by making specific recommendations for the treatment of patients with difficult venous access, problems with compliance, and with breakthrough bleeds despite optimised prophylactic treatment (8), (9).

Even with today's prophylactic treatment, an unmet need exists for patients with severe haemophilia; a substantial psychological burden is associated with the disease; anxiety and depression are commonly reported due to the unpredictability of bleeding events, frustration with treatment, and issues with venous access (17, 16, (10). Further underlying reasons for psychological impacts of the condition are expected to include 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 infusions (11).

Furthermore, an 11-year Nordic registry study analysed longitudinal national data from 2007–2017 of people with haemophilia (n=3,246). The study showed a markedly higher

use of pain medicine, antidepressants, and anxiety medications amongst patients with haemophilia compared with those without the disorder (10).

Current treatment and comparators

Danish patients with severe haemophilia B are currently treated with prophylactic factor replacement therapy (9). Factor replacement therapy is administered through intravenous injections, and is taken at varying intervals, depending on the product and on patients bleeding profiles. Most patients are well controlled and those who are not may be so due to a particularly severe bleeding phenotype or compliance issues, for example due to the mode of administration. In the Danish treatment guidelines, such patients are recommended to be treated with eftrenonacog alfa (9). Due to subcutaneous administration, it is expected that these patients are the most likely to be treated with marstacimab. Therefore, the appropriate comparator is expected to be eftrenoncog alfa, a recombinant Factor IX (rFIX) with extended half-life for treatment of haemophilia B.

For long term prophylaxis against bleeding, the recommended starting regimens are either: 50 IU/kg once weekly, adjust dose based on individual response or 100 IU/kg once every 10 days, adjust interval based on individual response. The Danish Medicines Council (DMC) uses 50 IU/kg once weekly for comparisons between products (9). The administration of eftrenonacog alfa is intravenous injection over several minutes and the rate of administration should not exceed 10 ml/min.

For more information regarding the burden of disease and the standard of care in Denmark, please see "Medicinrådets Behandlingsvejledning (version 1.1)", "Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til hæmofili A (version 1.1)", and"Medicinrådets gennemgang af terapiområdet for hæmofili B (ver. 1.1)" (12).

Patient population

Globally, the incidence of severe haemophilia A is 9.5 out of 100,000 male births and 1.5 for severe haemophilia B (13), with haemophilia B comprising approximately 20% of these patients (14).

In Denmark, the treatment of haemophilia is handled by the two haemophilia centres in Aarhus and Copenhagen. During the summer of 2023, the centres reported approximately 150 patients 12 years or older with severe haemophilia A and 25 patients with severe haemophilia B on prophylactic treatment. Based on clinician input, approximately 12% of the patients are estimated to be aged 12-17 years (15).

Table 1. Estimated number of patients in Denmark aged ≥12 years with haemophilia B

Year	Year 1	Year 2	Year 3	Year 4	Year 5
No. of haemophilia B patients in Denmark ≥12 years	25	25	25	25	26

Source: Bassed on information received from haemophilia centres in Summer of 2023: haemophilia B: 20 adults, 5 adolescents. Assuming numbers from the summer 2023 were accurate for 2024, 2024 was used as index year. The male population 12 years and older was calculated according to table FRDK 124 (16).

Table 1 shows the expected number of patients with haemophilia in the coming 5 years, counting 2025 as "year 1". 2024 was used as index year, using the number of patients from the summer 2023. For the following years, the expected number of patients was estimated using data from Statistics Denmark (16).

Most treatments for haemophilia are dosed based on patient weight. The average weight of adult men in Denmark was 81.9 kg, according to a national Danish health examination survey in 2007-2008 (17). Subsequent surveys from the Danish Health Authority ("Den nationale sundhedsprofil"), showing BMI indicate that the average weight of Danish men is increasing, which means that patients are heavier today.

According to the growth curve for Danish boys, the average normal weight of Danish boys 12-17 years of age should be 57 kg[1] (18). However, even though the curve describes the ideal growth, it may not be indicative of actual weight. The 2024 survey for Danish school boys shows that the average weight for boys aged 13 to 16 years and 5 months is 63.97 kg (19). The higher weight compared to the growth curve may be explained by that 77.5% of boys were normal weight, while 15.5% were overweight, and 5.0% obese (19).

3.2 The intervention

Marstacimab is the first subcutaneous treatment available for both haemophilia A and B and is a human monoclonal IgG1 antibody targeting anti-tissue factor pathway inhibitor (anti-TFPI), which is the primary inhibitor of the extrinsic (external) coagulation pathway. Treatment with anti-TFPI is a novel mechanism of action.

Haemophilia A and haemophilia B are caused by a lack of clotting factor VIII and clotting factor IX, respectively, both of which are part of the intrinsic (internal) clotting pathway.

In blood clotting, anticoagulants play a crucial role in preventing blood clots from forming by inhibiting various factors in the clotting cascade. By inhibiting specific clotting factors, anticoagulants disrupt the cascade and thus reduce the likelihood of clot formation. TFPI is one of these natural anticoagulants that counteracts the extrinsic coagulation pathway by inhibiting TF-VIIa complex and activated factor X (factor Xa)(20).

The action of marstacimab to neutralise the inhibitory activity of TFPI may enhance the extrinsic coagulation pathway and compensate for deficiencies in the intrinsic coagulation pathway by increasing the available free factor Xa and thrombin formation (factor IIa) and thereby promote hemostasis (21), see Figure 1. Simply put, marstacimab is an inhibitor of the "break", TFPI, so that the extrinsic coagulation pathway is strengthened and thus also the common coagulation pathway.

As there is no difference in TFPI levels in patients with haemophilia A and haemophilia B, the mechanism of action is independent of the lack of FVIII or FIX in patients (22), (23). In

[1] The growth curve shows a mean weight for 12-year-olds of 42 kg, and 57 kg just when they turn 18. The average weight is 57 kg

other words, with this mechanism of action balance in haemostasis can be achieved for both patients with haemophilia A and B.

The marstacimab molecule has a lower binding affinity and exhibits slower clearance rates compared to factor replacement therapies, resulting in a longer steady-state half-life; therefore, marstacimab requires less frequent, fixed, once-weekly dosing (24), (25), (26). Additionally, this enables flat dosing, and no monitoring of drug concentration is needed (21). Furthermore, a flat (fixed) dosing regimen is supported by comparable pharmacodynamics, annualised bleeding rates (ABRs) across weight ranges(27).

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

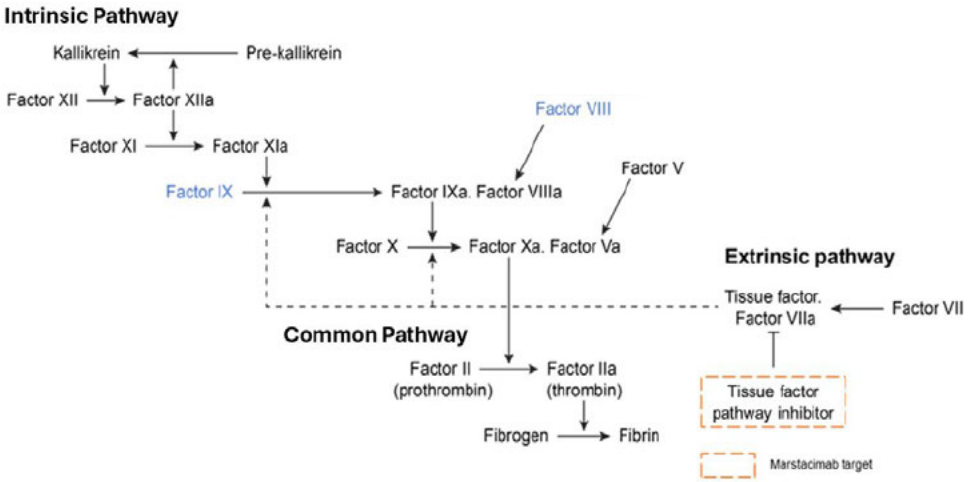


Table 2. Overview of the intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.
Method of administration	Subcutaneous administration with a pre-filled auto injecting pen
Dosing	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 subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, at any time of day. The dose is not weight based.
Should the pharmaceutical be administered with other medicines?	No. Before starting treatment, the patient should stop prophylaxis (preventive) treatment with clotting factors. Patients can initiate treatment with marstacimab at any time after discontinuing clotting factor concentrates.

Overview of intervention	
Treatment duration / criteria for end of treatment	Life-long treatment
Necessary monitoring, both during administration and during the treatment period	Not required
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	NA
Package size(s)	1 pre-filled pen with 150 mg solution

3.2.1 The intervention in relation to Danish clinical practice

In Danish clinical practice, marstacimab can be directly placed into the current treatment guidelines (12). This corresponds to a direct placement into Table 2 of the current recommendation i.e. for patients for whom there is a medical indication for prophylaxis with an extended half-life recombinant Factor IX (rFIX) product (9). Pfizer expects that marstacimab will predominantly be seen as a relevant treatment alternative for patients with difficult venous access or compliance problems where it is not possible to carry out prophylaxis treatment with weekly intravenous injections.

4. Overview of literature

Table 3. Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
BASIS, NCT03938792 CSR, data on file (28)	One way, cross-over, open-label, multi-centre, phase 3 with an observational and an active treatment period	6-month observational phase followed by a 12-month open label period	Start: 9 March 2020 Data cut-off: 17 April 2023 (including the completion of non-inhibitor treatment arms) Estimated completion: 16 June 2025	Males 12-74 years with severe haemophilia A or moderately severe to severe haemophilia B (FIX activity ≤2%) with or without inhibitors, receiving episodic or prophylactic factor replacement therapy. Only patients without inhibitors, receiving prophylactic treatment during the observational period are included in the application (n=83).	Marstacimab initial loading dose of 300 mg subcutaneously followed thereafter by 150 mg by subcutaneously once weekly	Factor replacement therapy (or bypass therapy) during a 6-month observational period	Intervention, Outcomes	Outcomes at 12 months: ABR, treated bleeds, median ABR, all bleeds, median Haem-A-QoL, total score, adult Haemo-QoL, total score, adolescent Incidence and severity of thrombotic events Incidence and severity of injection site reaction Incidence of severe hypersensitivity and anaphylactic reactions
Open Label Extension	Phase 3, interventional open-label	7 years	Start: November 2021 Cut-off: 10 March 2023	Patients from the BASIS trial	Marstacimab 150 mg, once weekly.	None, open-label extension study	Intervention, Outcomes	ABR, treated bleeds, median ABR, total bleeds, median Haem-A-QoL, total score, adult

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
NCT05145127 (BASIS OLE) CSR (29) SmPC (21)	extension study		Expected completion date: July 2030					Haemo-QoL, total score, adolescent Incidence and severity of thrombotic events Incidence and severity of injection site reaction Incidence of severe hypersensitivity and anaphylactic reactions
B-LONG (NCT01027364) Powell, J.S. et al (30), Wyrwich KW et al (31) Pasi KJ et al (32)	Phase 3, non-randomised, Interventional study	52 weeks Followed for up to 77 weeks	Study start December2009 Study completion: July 2012	Male, 12 years of age and older and weigh at least 40 kg diagnosed with severe haemophilia B Only Group 1, i.e. patients who received 50 IU/kg once weekly is included, and where possible, only patients from Group 1 receiving prophylactic treatment prior to the study are included.	50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially (Group 1)	At baseline	Comparator, Outcomes	Outcomes week 52: ABR, treated bleeds, median ABR, all bleeds, median Incidence Rate of FIX Inhibitor Development Haem-A-QoL, total score, adult Haemo-QoL, total score, adolescent

5. Clinical question 3.1

Clinical question: Are there clinically relevant differences between rFIX products for prophylactic treatment of PTP?

As marstacimab is not a rFIX, the following question will be answered: *Are there clinically relevant differences between marstacimab and the relevant comparator in relation to prophylactic treatment of PTP?*

5.1 Efficacy of marstacimab compared to eftrenonacog alfa therapy for haemophilia B patients

5.1.1 Relevant studies

BASIS and its open label extension study (OLE) (NCT05145127) represent the pivotal clinical trials demonstrating the efficacy and safety of patients receiving weekly marstacimab prophylaxis compared with factor prophylaxis. Please note that neither BASIS nor the OLE are published yet. The BASIS study was published during the DMC process, therefore, unpublished data was submitted and marked as confidential, but references and markings were updated when the data was published. The OLE study is ongoing and not expected to be published within acceptable time for this application. Therefore, only information that may be published, i.e. data that is already public through the SmPC or clinicaltrials.gov is submitted.

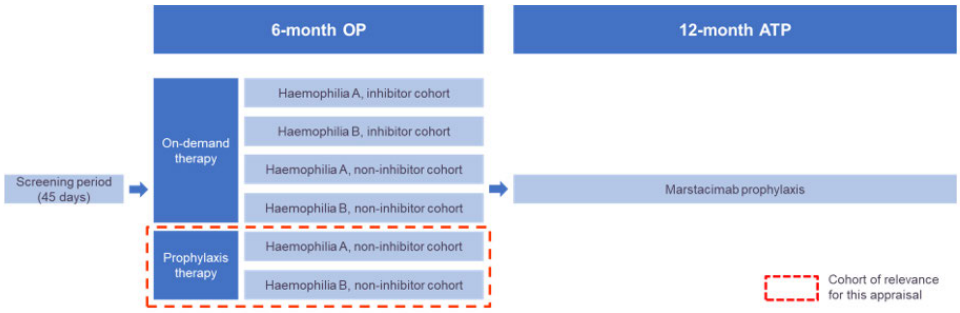
The **BASIS study** (NCT03938792) is a phase 3 study, one-way, cross-over, open-label, multi-centre, multi-country study planned in approximately 145 adolescent and adult participants aged 12 to <75 years. Included patients had severe haemophilia A or moderately severe to severe haemophilia B (defined as FVIII or FIX activity <1% or ≤2%, respectively) with and without inhibitors. The enrolment protocol included patients with moderately severe haemophilia B, but ultimately only patients with severe disease enrolled (33).

Patients who previously received on-demand or prophylactic treatment were included in separate treatment arms. The trial also has a still ongoing part, including patients with inhibitors, which in not included in this application (Figure 2) (28). As this application only concerns patients previously treated with prophylactic treatment, all data presented will be for this population only.

The study compared treatment with marstacimab in an active treatment phase to factor treatment during a 6-month observational phase. 91 patients who had previously received prophylactic treatment enrolled in the observational phase, of whom 84 (92.3%) completed and 83 of these patients progressed to the 12-month active treatment phase, during which participants received prophylactic treatment with marstacimab. Approximately 20% of participants were adolescents (34).

The mITT (modified Intention to Treat) Analysis Set consisted of participants who completed observational phase and received at least 1 dose of marstacimab in the active treatment phase. The trial outcomes were measured at the end of the 12-month active treatment phase (28). Further information about the trial can be found in Appendix A.

Figure 2. BASIS study design



Source: Adapted from Clinical Study Report 2023 (28).

The Phase 3 open label extension (**OLE**) **study** (NCT05145127) is a continuation 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 which was haemophilia A and B patients ≥ 12 years (29).

As of the interim data analysis cut-off at March 10th 2023, 88 patients had enrolled in the OLE (29). Of these, 29 patients had previously been treated with on-demand treatment, and 59 patients with prophylaxis treatment (34). One patient who received prior prophylaxis was not included in the safety analysis set, as their data was not available by the March 10th, 2023 interim data cut-off (29). A total of 87 completing the 12-month treatment period had enrolled into the OLE study at the time of data cut-off on Apr 17th, 2023. [redacted] of the patients who received prophylaxis in the BASIS trial were included in the OLE safety analysis set (29).

[redacted]

The recommended dose of marstacimab for patients 12 years of age and older, weighing at least 35 kg, is an initial loading dose of 300 mg by subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, at any time of day (21).

The BASIS study allowed patients weighing at least 50 kg to be dose escalated after 6-months on active treatment if they had experienced 2 or more spontaneous bleeds that had been treated with coagulation factor. However, if patients fulfilled the requirement, it was fully up to the physician to decide on dose escalation (28).

[redacted] with haemophilia A and [redacted] with haemophilia B met the criteria, and 11 of these [redacted] were dose escalated from

150 mg marstacimab weekly to 300 mg weekly during the active treatment phase (28). This corresponds to [redacted] of prophylaxis patients in the BASIS study.

Patients who dose escalated are almost [redacted] However, two issues should be considered: the small sample size, especially in the haemophilia B population, and that dose escalations were at the discretion of patient and physician. This meant that some treatment centres may have used the opportunity to dose escalate frequently, while others may not have used it at all.

B-LONG (NCT01027364) is a phase 3, non-randomised, open-label study of the safety, efficacy, and pharmacokinetics of eftrenonacog alfa (rFIXFc) for prophylaxis, treatment of bleeding, and perioperative hemostasis in 123 previously treated male patients. All participants were 12 years of age or older and had hemophilia B, defined as ≤2% of normal factor activity (30).

Patients were eligible for inclusion in the study if they were receiving prophylaxis or on-demand treatment and had a history of at least eight bleeding events in the year before enrollment and had been previously treated with at least 100 injections of replacement factor IX (i.e. had accrued at least 100 exposure days) (30).

The study had four treatment groups: Group 1 received weekly prophylaxis, starting with 50 IU/kg body weight, dose-adjusted as needed, Group 2 received 100 IU/kg body weight in varying intervals, but starting at every 10 days, Group 3 received on-demand treatment (20 to 100 IU/kg body weight), and Group 4 was included for perioperative treatment only (30). The dose (in Group 1) and the interval (in Group 2) were adjusted during the study to maintain a trough level of 1 to 3 IU/dL above baseline, or higher if clinically necessary (30).

After screening, patients who had been receiving a prophylactic regimen could enroll in Group 1 or 2, whereas those who had been receiving episodic treatment could enroll in any treatment arm (30).

The primary efficacy end point in the study was ABR, however, the study did not differentiate all versus treated bleeds. Safety end points included the development of inhibitors and adverse events, see Appendix A.

For this application, Group 1 is considered the most appropriate comparator, as this group included a share of patients previously treated with prophylactic treatment and is chosen by the DMC as the most relevant to the Danish clinical haemophilia B population (35).

63 patients were assigned to weekly prophylaxis in Group 1 and of these, 61 patients were included in the efficacy analysis. Two patients were excluded: one patient did not receive eftrenonacog alfa and one patient only received one dose of eftrenonacog alfa. 33 (53%) of the patients in B-LONG, Group 1 had received previous prophylactic treatment prior to the study (30).

For long term prophylaxis against bleeding with eftrenonacog alfa, the recommended regimens are either: 50 IU/kg once weekly, or 100 IU/kg once every 10 days, but the dose can be adjusted based on individual response. Especially in younger patients, shorter dosing intervals or higher doses may be necessary (36). The administration of eftrenonacog alfa is intravenous injection over several minutes and the rate of administration should not exceed 10 ml/min. The DMC uses the dose of 50 IU/kg once weekly as the starting dose (9).

5.1.2 Comparability of studies

BASIS and B-LONG are both studies investigating the efficacy and safety of therapies in patients with haemophilia but while BASIS includes patients with haemophilia A and B, B-LONG includes only patients with haemophilia B.

Both studies included patients previously treated with prophylaxis as well as with on-demand treatment. However, while patients previously treated with prophylaxis were included in a separate treatment arm in BASIS, patients previously treated with prophylactic and on-demand treatment were mixed in B-LONG. To be relevant for Danish population, only patients previously treated with prophylactic treatment should be included in the comparison. Only data for patients previously treated with prophylaxis is presented for BASIS. Only limited data is reported separately for prophylactic patients in B-LONG but these are presented separately, where possible.

In the BASIS study, an observational period where the same patients who were treated with prophylactic factor replacement therapy was compared to an active treatment period with marstacimab. In B-LONG patients in Group 1 are compared to patients treated with eftrenonacog alfa on-demand treatment (Group 3). However, limited data is also available from Group 1 vs. baseline characteristics of patients 12 months before they entered the trial, a method comparable to that in BASIS.

Patients in B-LONG, Group 1 were allowed to dose adjust during the study to maintain a trough level of 1-3% factor level, while the patients in the BASIS study were treated with a flat/fixed dose of 150 mg once weekly for the first 6 months. Thereafter, some patients were eligible for dose escalation. Despite this, marstacimab is to be considered a fixed dose regimen.

The primary endpoint in both studies was ABR. In BASIS ABR for treated bleeds was the primary endpoint, while no distinction was made between all and treated bleeds in B-LONG 3. Therefore, to be conservative, ABR for all bleeds from BASIS are used in the comparison to B-LONG. Both studies measured the primary endpoint at 12 months.

Both studies are non-randomized, interventional studies in haemophilia, measuring outcomes at 12 months. However, several important factors differ, such as how comparisons are carried out.

In line with the methods used in the treatment guideline, the comparison in this application is naïve, thus not adjusting for the differences between studies.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Baseline characteristics for patients in BASIS (non-inhibitor, prophylaxis group) and B-LONG Group 1 are provided in Table 4**.**

Both trials are described as including patients with severe hemophilia, however the inclusion of patients differ; while BASIS included patients with both haemophilia A (78%) and B (22%), B-LONG included only patients with haemophilia B. Furthermore, the definition of severe disease in the B-LONG study differed from that of ISTH and used by the DMC (<1% of normal blood clotting activity) (35) as patients with ≤2% FIX activity were included in the study (30). In fact, the BASIS study also allowed for patients with hemophilia B to have FIX activity ≤2% but the study ultimately only enrolled patients with severe disease (<1%) (33). This means that while the BASIS study includes only patients with severe haemophilia, 79% of patients in B-LONG had severe disease, while the remaining 21% of the patients had moderate disease (30).

All patients in the BASIS prophylaxis treatment group had received previous prophylactic treatment (28), while only 53% of the patients in B-LONG, Group 1 had received previous prophylactic treatment prior to the study (30).

For the purpose of comparing to the Danish haemophilia population, only patients who have previously received prophylactic replacement therapy, are relevant. Some data is available on the subgroup of patients in B-LONG who had received prior prophylaxis, but the data availability is limited.

Both trials only included patients ≥12 years, but patients in BASIS were slightly older compared to the patients in Group 1 in B-LONG and a larger proportion were adolescents (20.5% vs. 9.8%). A larger proportion of patients were Asian, and a smaller proportion were white, compared to B-LONG.

The median number of ABR for all bleeds at baseline is available for the subset of patients in Group 1, who had previously been treated with prophylactic treatment, and the ABR at baseline was higher in BASIS compared to these patients in B-LONG (3.91 versus 2.5). If all of Group 1 is taken into account however, the ABR is much higher in B-LONG (10.5) (30). A similar share of patients in both studies had ≥1 target joints ([redacted] vs. 42.9%) in all of Group 1.

One main difference between both studies and Danish patients is expected to be that patients in both studies have more target joints and higher ABR at baseline, see section 3.1.

Both studies include patients with severe haemophilia, though the definitions differ on important issues such as haemophilia type, severity, and probably most importantly for a Danish setting, the share of patients on previous prophylactic treatment. Wherever possible, data for patients previously on prophylactic treatment were presented separately, to compensate for this.

However, differences between the studies may in some respects neutralize each other; the share of patients with moderate disease (≤2% FIX activity) can be expected to have fewer bleeds at baseline than the patients in BASIS, who all had severe haemophilia. Though these patients were borderline severe, the moderate patients are also more likely to account for a major proportion of the patients previously treated with on-demand treatment in B-LONG.

On the other hand, the share of patients with previous on-demand treatment in B-LONG is larger than the share of moderate patients and would be expected to increase the ABR and number of target joints. However, ABR at baseline for the prophylactic patients in B-LONG is lower compared to in BASIS. Interestingly, the share of patients with at least one target joint, is similar across studies. The two studies are thus different, making comparisons difficult, though not impossible.

Table 4. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	Marstacimab (n=83)	Marstacimab (haemophilia B alone) (n=18)	Eftrenonacog alfa Group 1 (n=63)
Patients previously treated with prophylaxis, n (%)	83 (100)	18 (100)	33 (53.2)[a]
Age, years			
Mean (SD)	[redacted]	[redacted]	NA
Median (Min, Max)	[redacted]	[redacted]	28 (12, 71)
Sex, n (%)			
Male	83 (100)	18 (100)	63 (100)
Race, n (%)			
Asian	[redacted]	[redacted]	7 (11.1)
Black or African American	[redacted]	[redacted]	7 (11.1)
White	[redacted]	[redacted]	41 (65.1)
Not reported	[redacted]	[redacted]	NA
Other‡	[redacted]	[redacted]	8 (12.7)
Weight, kg			
Mean (SD)	[redacted]	[redacted]	NA
Median (Range)	[redacted]	[redacted]	70.2 (45.2-186.7)
Body mass index, kg/m^2			
Mean (SD)	[redacted]	[redacted]	NA
Haemophilia Type, n (%)			
Haemophilia A	[redacted]	[redacted]	0
Haemophilia B	[redacted]	[redacted]	63 (100)
Age groups, n (%)			
Adolescents (≥12 to <18 years)	17 (20.5)	4 (22.2)	6 (9.8)[b]

Adults (≥18 years)	66 (79.6)	14 (77.8)	55 (90.2)[b]
ISTH Disease Severity, n (%)			
Mild	[redacted]	[redacted]	0
Moderate	[redacted]	[redacted]	13 (21)[c]
Severe	[redacted]	[redacted]	50 (79)[c]
ABR at baseline, median, n (Q1, Q3)			
ABR, all bleeds	3.91 (0.00, 11.66)	[redacted]	10.5 /2,5[d]
ABR, treated bleeds	[redacted]	[redacted]	NR
Number of Target Joints, n (%)			
0	[redacted]	[redacted]	27 (42.9)
≥1	[redacted]	[redacted]	36 (57.1)
Definition of outcomes			
ABR, all bleeds	Any sign or symptom of a bleed, regardless of if medication/treatment is administered. Occurrences of bleeding episodes were obtained from participant diaries and medical records. No external monitoring of bleeds was necessary		No differentiation between *all* and *treated* bleeds was made.
ABR, treated bleeds	Bleeding episodes requiring treatment (intravenous coagulations factor products or bypass agents)		No differentiation between *all* and *treated* bleeds was made.

Abbreviations: mITT= modified Intention To Treat; OP: observational phase, SD = Standard Deviation. ISTH = International Society on Thrombosis and Haemostasis. ‡ Other races and ethnic groups include Native American or Alaska Native, Hispanic, and mixed races (e.g., white and Asian or white and black). [a]The pre-study regimen was unknown for one participant in group 1; percentages were calculated on the basis of participants for whom data were complete [b]61 out of 63 patients were included in efficacy analysis, and the publication mentioned only the numbers of participants in the age group Adolescents and Adults for n=61. [c] The numbers for Moderate 1-2 IU/dl and Severe <1 IU/dl are from DMC (35). [d]Data for patients previously treated with prophylactic treatment alone. Sources: BASIS: mITT analysis set (28) for redacted information and Matino (2025) (34) for unblinded data; eftrenonacog alfa: Powell et al (30).

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

BASIS, marstacimab efficacy and safety

Marstacimab was demonstrated to be an effective treatment option, providing significant reduction in mean ABR treated bleeds, the primary endpoint (34).

The median ABR for treated bleeds in patients previously treated with prophylaxis was 2.02 (0.00, 6.09 Interquartile range (IQR)) for marstacimab during the 12-month active treatment phase compared with [redacted] the 6-month observational phase(28, 34) Table 5.

The median ABR for all bleeds was 2.89 (0.00, 7.06 IQR)[2] during the active treatment phase compared with 3.91 (0.00, 11.66 IQR) during the observational phase (34).

Table 5. Results at 12 months, BASIS for patients receiving prophylactic treatment

Outcome measure	Full population (Haemophilia A & B)		Haemophilia B subgroup	
	Observational phase (n=91)	ATP (n=83)	Observational phase (n=18)	ATP (n=18)
ABR, all bleeds, median (IQR)	3.91 (0.00, 11.66)	2.89 (0.00, 7.06)[2]	[redacted]	[redacted]
ABR treated bleeds, median (IQR)	[redacted]	2.02 (0.00, 6.09)	[redacted]	[redacted]
Haem-A QoL total score, adult patients (change from baseline) Mean (95% CI)		[redacted]		NA
Haemo-QoL total score, adolescent patients (change from baseline Mean (95% CI)		[redacted]		NA
Severe venous thromboembolism	1[a]	0	[redacted]	0
SAE	2 (2.2%)	7 (8.4%)	[redacted]	[redacted]
Treatment related SAE	NA	1 (1.2%)[b]	NA	[redacted]
Permanent discontinuation due to adverse event (12 months)	0 (0%)	1 (1.2%)c	0	[redacted]

[a]SAE device occlusion reported observational phase; [b]Grade 1 peripheral calf swelling considered to be treatment related but was diagnostically confirmed to be unrelated to a bleeding or thrombotic event; [c]Adverse Event (AE)

[2] During the publication process a discrepancy was found between the SPC and the Statistical Analysis Plan (SAP) in relation to how preventative factor treatment was treated in ABR calculations. The discrepancy only affects the 100th decimal and does not affect any conclusions or significances. ABR was recalculated to fit with the SAP and the numbers have been updated. The full description of how ABR is calculated can be found in Matino et al (2025) Supplementary Materials, Section 6.

not considered treatment-related, see Appendix E; Abbreviations: ATP= Active treatment phase, ABR= Annualised Bleeding Rate, CI=Confidence interval, SAE= Severe Adverse Event, IQR=Interquartile range. Source: CSR, 2023 (28) for retracted information, and Matino (2025) (34) for unblinded information.

The *Haemophilia Quality of Life Questionnaire for Adults* (Haem-A-QoL) is a validated disease-specific tool for measuring quality of life, which assesses the physical and emotional limitations experienced by patients. The scale ranges from 0 to 100, with higher scores indicating a poorer health-related quality of life (37), (38), (39). In BASIS, the mean change from baseline to 12 months [redacted] for marstacimab prophylaxis (28). For adolescents (12 to < 17 years; [redacted]) quality of life is measured via the Haemo-QoL total score. The mean change from baseline at 12 months was [redacted] (28).

[redacted]AEs occurred in 83 marstacimab patients previously on prophylactic treatment (34). Of these, injection site reactions occurred in 9 (10.8%) patients during the active treatment phase (n=83), however reactions were generally mild and of short duration and did not cause dose adjustment or patient discontinuation.

Two Severe Adverse Events (SAEs) (2.2%) were reported during the observational phase and 7 (8.4%) during the active treatment phase, with one SAE (Grade 1 peripheral calf swelling) considered by the investigator to be treatment related. However, the swelling was diagnostically confirmed to be unrelated to a bleeding or thrombotic events (34).

One patient (1.2%) discontinued marstacimab due to meningioma. The incident was not considered related to the study intervention.

No participants reported thromboembolic events during the marstacimab active treatment phase. Furthermore, there was [redacted] deaths during the active treatment phase with marstacimab (34). For more information about safety data please see Appendix E.

BASIS long-term study (OLE) NCT05145127

In the marstacimab SPC, data is available for up to 16 months (mean 7 months) from the OLE study, i.e. additional data to the BASIS study, all in all a mean of 19 month follow up. The median ABR for all bleeds at that time was [redacted] (29).

B-LONG – eftrenonacog alfa

In B-LONG, the median ABR for patients in Group 1 was 3.12 (95% CI: 2.46, 3.95), compared to 10.5 at baseline (30) Table 6. The study did not differentiate between all and treated bleeds.

Only 33 (53,2%) of the patients in Group 1 had prior to start been in prophylactic treatment. This subset of patients with prior prophylaxis had a median ABR of 2.5 (30).

Quality of life data was separated based on patient's previous treatment. In Group 1, 20 patients had previously received prophylactic treatment and of those 18 answered the Haem-A-QoL survey. For them, the Haem-A-QoL total score mean (SD) change from baseline to week 26 was -5.5 (6.7) (31).

Table 6. Results B-LONG for patients receiving prophylactic treatment and episodic treatment

Outcome measure	Group 1 Subset of prior prophylaxis n=33	Group 1 All patients (n=61)
ABR at baseline, median (range)	2.5 (Range: 0-21)[a]	10.5 (10-70) n=63
ABR, median (IQR)	NR	3.12 (95% CI: 2.46, 3.95)
Long term ABR, median	**NR**	**2.3 (IQR 0.44-3.76)[b]**
Heam-A QoL total score, adult patients (change from baseline) Mean (SD)	**NR**	-5.5 (6.7)[c]
Severe venous thromboembolism	0	0
SAE **Treatment related**	NR	5 (7.9) 1[d]
Discontinuation due to AE (12 months)	NR	No data found

[a]ABR for all Group 1 patients was 10.5 (range: 0-70)(30) . [b] After 39.5 months median follow up time form start of B-LONG N=50 (32) [c]n=18, pre-study prophylaxis and prophylaxis treatment. Only data from 26 weeks (35). [d] n=63. One participant in the B-LONG study had a single serious adverse event that was considered to be possibly related to treatment with rFIXFc (not specified in publication in which group the patient belong) Table S4 (30)
Source: Powell et al (30) where not otherwise stated.

5 patients in Group 1 experienced at least one SAE, see Appendix B (30). Furthermore, one participant receiving eftrenonacog alfa (not specified in which treatment group) had a single SAE that was considered to be possibly related to treatment with rFIXFc (30). In this participant, who had a history of painful hematuria, an obstructive clot developed in the urinary collecting system. The clot was resolved with medical management and the participant continued with the study treatment and completed the study. There were no reports of vascular thrombotic events, serious hypersensitivity, or anaphylaxis, and there were no deaths during the study (30).

5.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

In BASIS, one SAE (Grade 1 peripheral calf swelling) considered by the investigator to be treatment related that was diagnostically confirmed to be unrelated to a bleeding or thrombotic events (28).

In B-LONG, one participant had a single serious adverse event while being treated with eftrenonacog alfa that was possibly related to treatment with rFIXFc. In this participant,

who had a history of painful hematuria, an obstructive clot developed in the urinary collecting system (30).

No severe venous thromboembolism, anaphylaxis, new development of factor IX inhibitors, or deaths were seen in either BASIS (21) or B-LONG (30). [redacted]

The definition of outcomes is discussed in section 5.1.2 and 5.1.3. As there was no distinction in B-LONG between ABR for all vs. treated bleeds, the Pfizer has conservatively assumed that ABR in B-LONG represents all bleeds, as reported by the patient, as in BASIS.

5.2.3 Method of synthesis

There is no direct comparative evidence between marstacimab and eftrenonacog alfa. In line with the protocol for developing the Danish treatment guidelines for hemophilia, we have therefore conducted a naïve comparison.

Only the subset of BASIS including patients previously treated with prophylactic treatment and without inhibitors have been included in the comparison. From B-LONG data from Group 1, treated with weekly infusions were included, however, where possible, data for the subset of patients previously treated with prophylaxis was presented. The comparability of BASIS and B-LONG 3 was discussed in sections 5.1.2 and 5.1.3.

5.2.4 Results from the comparative analysis

The DMC has defined the minimal clinically relevant outcomes for each outcome measure as:

- ABR, median (critical): 3 bleeds per year per patient
- Inhibitor (critical): 2 events per year per 100 patients
- Anaphylaxis (critical): 2 events per year per 100 patients
- Thromboembolism (important): 2 events per year per 100 patients
- Quality of Life (important): 0.5 SD within the same scale
- Through Value (important) 95% Clerance (CL) lower value for average through value should be above 5% (0.05 KIE/L) – not a difference between drugs, but the outcome is that the drug reaches a through.

For ABR, there is no clinically relevant difference between the treatments: marstacimab showed a median ABR for treated bleeds after 12 months of 2.89 for patients previously treated with prophylaxis, while 3.12 was reported for eftrenonacog alfa, please see Table 7. However, it is important to note that there was no recording of study results for patients on efrenonacog alfa, who had previously received prophylactic treatment alone. Only the ABR at baseline was available for these patients, please see section 5.1, for a

discussion of this. In spite of this, 3.12 is the ABR used by the DMC in the background document for the recommendation (35).

When considering the ABR for the subgroup of patients in BASIS with hemophilia B alone, the difference between the studies meets the threshold for minimally clinically relevant difference. However, as ABR in B-LONG is not reported for patients who previously received prophylaxis alone, the ABR for eftrenonacog alfa can be expected to be overestimated, thus making the relative differences between studies less than the threshold for minimally clinically relevant differences.

No incidences were observed of venous thromboembolism, anaphylaxis, new development of factor IX inhibitors, or deaths in either BASIS (21, 34) or B-LONG (36). There is therefore no difference between products for these outcomes, see Table 7.

Table 7. Results from the comparative analysis of marstacimab vs. eftrenonacog alfa for haemophilia

Outcome measure	Marstacimab[1] mITT n=83	Eftrenonacog alfa[2] Group 1 n=61	Result Absolut difference
ABR, All bleeds, median[3]	2.89	3.12	0.23
ABR, All bleeds, haemophilia B subgroup, median[3] (n= 18)	0.02	3.12	3.10
ABR, Long term, all bleeds, median	[redacted]	2.3[5]	[redacted]
Development of inhibitors to FIX	0	0	0
Anaphylaxis	0	0	0
Thromboembolism	0	0	0
Haem-A QoL total score, mean, adult patients (change from baseline)	[redacted]	-5.5[7] n=18	[redacted]
Haemo-QoL total score, mean, adolescent patients (change from baseline at	[redacted]	No data found	[redacted]

[1]SPC table 3 (21) for redacted information and Matino (2025) (34) for unblinded information; [2]Powel at al (30);[3]ABR at 12 months, no differentiation was made between all and treated bleeds in B-LONG; [4]All Bleeds, total median follow-up: 19 months (29); [5]Total median follow-up 39.5 months (Pasi et al (32)); [6]Data on file (28). [7]Pre-study prophylaxis and prophylaxis treatment. Only data from 26 weeks Wyrwich et al (31).

Quality of life was reported separately for patients previously treated with prophylaxis in both studies. There was an absolute difference between marstacimab and eftrenonacog

alfa of [redacted] to the advantage of eftrenonacog alfa. Please note, that this is the result only for a subset of BASIS-patients as adolescents were assessed with the Haem-A QoL, the equivalent of which was not reported in B-LONG, which makes the comparison incomplete. For B-LONG, the subset of patients included in this outcome was even smaller (18 of 61 patients (see Table 7)). All in all, this makes the comparisons of quality of life invalid.

The final critical outcome measure, included by the DMC, is an absolute through value of 5%. It is not possible to measure factor IX throughs for patients treated with marstacimab, since marstacimab does not change FIX concentrations. However, marstacimab has been shown to result in a long steady-state half-life, not resulting in peaks and throughs, which indicates that it fulfills the clinical outcome. The mechanism of action for marstacimab is explained in section 3.2.

In summary, for the critical outcomes, none of the minimal clinically relevant outcomes are met. For the other outcomes, the minimal clinically relevant differences are just reached for eftrenonacog alfa vs marstacimab for quality of life. However, several points make the results incomparable: only adult patients are considered as B-LONG does not report QoL for adolescents, and only a small subset of patients are included in the B-LONG results. It is therefore not possible to conclude on any clinically meaningful difference between products.

Relative product consumption

In contrast to marstacimab, eftrenonacog alfa is dosed based on patient weight. Therefore, the absolute weight of patients is of importance to calculate product consumption. As noted in section 3.1, the average weight of adult men in Denmark is at least 81.9 kg (17), while the average weight of Danish boys 12-17 years of age may be estimated to 63.97 kg (19).

Approximately 12% of the patients are expected to be aged 12-17, based on the Danish haemophilia population, described in section 3.1. Adjusting for the proportion of adolescents, the average weight of all patients indicated for treatment with marstacimab is expected to be 79.75 kg[3].

Thus 150 mg of marstacimab weekly is comparable to 3,987.42 IU with eftrenonacog alfa (Table 8). When taking the available package sizes into account, 150mg marstacimab corresponds to one intravenous injection of 3000 IU and one of 1000 IU of eftrenonacog alfa (36).

[3] 0.12 * 63.97 kg + 0.88 * 81.9kg = 79.75 kg

Table 8. Results from the comparative analysis of marstacimab vs. eftrenonacog alfa for a patient weighing 79.75 kg

Outcome measure	Marstacimab	Eftrenonacog alfa
Loading dose (once)	300 mg flat dose once	None (same as later)
Maintenance dose, weekly	150 mg flat dose	50 IU/kg body weight
Total weekly maintenance dose	150 mg	3,987.42 IU
Total weekly maintenance dose taking available package sizes into account	150 mg	4000 IU

Based on feedback from the dialog meeting, dose escalations will be rare in Danish clinical practice. However, in case that dose escalations would occur at the rate seen in BASIS, [redacted] of patients could be expected to be dose escalated. This corresponds to an overall [redacted] increase in consumption. If so, the average maintenance dose of marstacimab would be [redacted] after escalation.

The dose of eftrenonacog alfa should be varied to individual need. For example, 100 IU can be used every 10 days, which corresponds to 70 IU weekly, resulting in a weekly dose of 5,582.4 IU/week for dose escalated individuals, or 7974.8 IU/injection. In clinical practice this is equivalent to two injections with 3000 IU and one of 2000 IU (36).

The variability of the dosing of eftrenonacog alfa makes comparisons outside the standard dose difficult to make. As dose escalations are expected to be rare, most relevant to comparators are thus the standard dose for both products, i.e. 150 mg of marstacimab equating 4000 IU of eftrenonacog alfa.

Conclusion

In summary, our comparison shows that there are no signs of clinically meaningful differences between marstacimab and eftrenonacog alfa and that the two products have a similar safety profile. However, marstacimab is the first subcutaneous product available to patients with haemophilia B, which leads to a lower burden of treatment for patients. Furthermore, having a flat dosing regimen, not dependent on patient weight, marstacimab comes at a predictable cost.

6. References

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Appendix A. Main characteristics of studies included

Table 9. Main characteristic of studies BASIS

Trial name: BASIS	NCT number: (NCT03938792)
Objective	To demonstrate the efficacy and safety of marstacimab for routine prophylaxis in severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) participants 12 to <75 years of age with or without inhibitors.
Publications – title, author, journal, year	Matino et al. (2025) (34)
Study type and design	One-way, cross-over, open-label, multi-centre, multi-country, Phase 3 study
Sample size (n)	All patients in non-inhibitor population: 128 patients were included in the 6-month, lead-in, observational phase (OP) and 116 of these progressed to the 12-month active treatment phase (ATP). 91 patients who previously received prophylactic treatment included in the observational phase; 83 patients progressed to the active treatment phase.
Main inclusion criteria	Non-inhibitor cohort • Males, 12 years of age or older • Severe haemophilia A or moderately severe to severe haemophilia B with a minimum weight of 35 kg at screening. • Signed informed consent (or minor assent, when applicable). • No detectable or documented history of inhibitors • 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 Observational Phase. • 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 observational phase.
Main exclusion criteria	• Previous or current treatment for and/or history of coronary artery diseases, venous or arterial thrombosis or ischemic disease

Trial name: BASIS	NCT number: (NCT03938792)
	• 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 • Regular, concomitant therapy with immunomodulatory drugs • Previous exposure to PF 06741086 during participation in studies B7841002 and B7841003. • Participation in other studies involving investigational drug(s) or investigational vaccines within 30 days 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 ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results. • Individuals with hypersensitivity or an allergic reaction to hamster protein or other components of the study intervention.
Intervention	Initial loading dose of 300 mg by subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, at any time of day.
Comparator(s)	Intra-individual comparison to prior factor replacement therapy during the 6-month observation phase with either prophylactic or on-demand factor replacement therapy.
Follow-up time	12 months active treatment phase and 1 month follow-up after end of study for safety monitoring. Long term study (NCT05145127) “OLE Study” planned 7 years follow-up.

Trial name: BASIS	NCT number: (NCT03938792)

Primary, secondary and exploratory endpoints	All endpoints are measured at 12 months, unless otherwise stated.
	
	Primary
	
	ABR for treated bleeds at 12 months post-marstacimab initiation versus factor replacement therapy use in the OP
	
	Primary Safety
	
	• Incidence of AEs and SAEs
	• Incidence and severity of thrombotic events
	• Incidence and severity of injection site reaction
	• 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
	
	Secondary
	
	• ABR for joint bleeds, spontaneous bleeds, target joint bleeds and total bleeds (treated and untreated) at 12 months post-marstacimab initiation (ATP) versus factor replacement therapy use in the OP
	• Number of patients with no treated bleeds
	• Change in joints as measured by Haemophilia Joint Health Score (HJHS) at 12 months post-marstacimab initiation versus factor replacement therapy use in the OP
	• Patient reported outcomes and quality of life assessments at 12 months post-marstacimab initiation versus factor replacement therapy use in the OP:
	  • HAL/pedHAL
	  • PGIC-H
	  • Haem-A-QoL/Haemo-QoL
	  • EQ-5D-5L
	
	Exploratory
	
	• Analysis of PF-06741086 (marstacimab) concentrations (trough as well as post-dose)
	• Analysis of changes in biomarkers: TFPI (total and free), PKT, PF1+2, D-dimer, and dilute prothrombin time over duration of the study

Trial name: BASIS	NCT number: (NCT03938792)
	• Hemophilia Life Impacts Questionnaire
Method of analysis	Marstacimab was compared with prior routine prophylaxis in the same individuals for various bleeding count endpoints, using a repeated measure negative binomial regression model via generalised estimating equation (GEE) approach with identity link function. If the non-inferiority on treated ABR was established, subsequent testing for superiority was conducted. The estimated mean treated ABR 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 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. 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.
Subgroup analyses	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.
Other relevant information	NA

ATP= Active Treatment phase, OP =observational phase

Table 10. Main characteristics of NCT05145127 (OLE)

Trial name: NCT05145127 "OLE"	NCT number: (NCT05145127)
Objective	To evaluate the long-term safety, tolerability, and efficacy of marstacimab prophylaxis in severe (coagulation factor activity <1%) heamophilia A participants with or without inhibitors or moderate severe to severe haemophilia B participants (coagulation factor activity ≤2%) with or without inhibitors.
Publications – title, author, journal, year	The study is not yet published.
Study type and design	Phase 3, interventional, multi-centre, multi-country, open-label extension study
Sample size (n)	Patients from the BASIS trial (NCT03938792) and from the Phase 3 study BASIS-KIDS (NCT05611801). From the BASIS trial 88 patients continued to the long-term extension study (OLE), of these, 29 patients had previously been treated with on-demand treatment, and 59 patients with prophylaxis treatment.

Trial name: NCT05145127 "OLE"	NCT number: (NCT05145127)
Main inclusion criteria	• Minimum body weight as defined by parent studies • Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures. • Participants have successfully completed participation in parent studies, defined as did not require "Early Termination".
Main exclusion criteria	• Previous or current treatment for or history of coronary artery disease, venous or arterial thrombosis (CTCAE Grade >3), or ischemic disease (except catheter-associated thrombosis) • Abnormal renal function as defined by eGFR <30 mL.min/1.73 m^2 • Known planned surgical procedure during the planned study period • Unstable hepatic function which would make the participant inappropriate for the study • Regular, concomitant therapy with immunomodulatory drugs (eg, IVIG, and routine systemic corticosteroids, rituximab) • Ongoing or planned use of immune tolerance induction or prophylaxis with FVIII or FIX replacement during the study • Participation in other studies involving investigational drug(s) or investigational vaccines within 30 days or 5 half-lives prior to study entry and/or during study participation.
Intervention	For participants aged ≥12 years 150 mg marstacimab subcutaneously once weekly. 300 mg subcutaneously once weekly for participants who were dose escalated. For participants aged ≥6 to <12 years is marstacimab 75 mg subcutaneously once weekly. 150 mg subcutaneously once weekly for participants who were dose escalated.
Comparator(s)	NA
Follow-up time	Up to an additional 7 years of participation beyond BASIS. There is currently up to 16 months (mean 7 months) of data available in this study, i.e. all in all a mean of 19 month follow up data in BASIS and OLE combined.
Primary, secondary and exploratory endpoints	All endpoints are measured form baseline up to 7 years, unless otherwise stated. **Primary** • Number of subject reporting adverse events • Number of subjects reporting serious adverse events • Incidence and severity of thrombotic events

Trial name: NCT05145127 "OLE"	NCT number: (NCT05145127)
	• Incidence and severity of thrombotic microangiopathy • Number of subjects reporting disseminated intravascular coagulopathy/consumption coagulopathy • Incidence of clinically significant persistent NAb against marstacimab • Incidence and severity of injection site reaction • Clinically significant changes in vital signs from baseline • Incidence of clinically significant laboratory value abnormalities • Incidence of severe hypersensitivity and anaphylactic reactions **Secondary** • ABR • Total coagulation factor product consumption • Incidence of joint bleeds • Incidence of spontaneous bleeds • Incidence of target joint bleeds • Incidence of total bleeds (treated and untreated) • Change in joints measured by the HJHS • Change in joints as measured by the HJHS for participants ≥4 years of age • Change in number of target joints per subject from baseline • Changes in Health Utilities Measure questionnaire data • Changes in Haem-A-QoL questionnaire data for participants ≥17 years of age • Changes in Haemo-QoL questionnaire data: Haemo-QoL CII (Ages 8 to <12 years), Haemo-QoL (Ages 12 to <17), • Total bypass product consumption • Changes in EQ-5D questionnaire data: EQ-5D-Y Proxy (Ages ≥ 4 to ≤ 6 years), EQ-5D-Y Self (Ages ≥ 7 to ≤ 11 years), EQ-5D-5L (Ages ≥12)
Method of analysis	Based on a repeated measure negative binomial regression model via generalised estimation 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.
Subgroup analyses	NA

Trial name: NCT05145127 "OLE"	NCT number: (NCT05145127)
Other relevant information	NA

Table 11. Main characteristics of B-LONG

Trial name: B-LONG	NCT number: NCT01027364
Objective	To evaluate the long-term safety of rFIXFc in participants with haemophilia B and to evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes. The focus in this application will be the prophylaxis.
Publications – title, author, journal, year	Phase 3 Study of Recombinant Factor IX FC Fusion Protein in Hemophilia B, Powell J.S. et al, NEJM 2013 (30). Changes in health-related quality of lift with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies, Wyrwich K.W. et al, Haemophilia 2016, 22, 866-872 (31) Long-term safety and efficacy of extended-interval prophylaxis with recombinant factor IX Fc fusion protein (rFIXFc) in subjects with haemophilia B, Pasi, K. J. et al, Thrombosis and Haemostasis 3/2017 (32).
Study type and design	Phase 3, non-randomised open-label study.
Sample size (n)	Totally 123 patients enrolled. 63 were assigned to Group 1 with weekly prophylaxis 50 IU/kg
Main inclusion criteria	• Male and 12 years of age and older and weigh at least 40 kg • Diagnosed with hemophilia B (baseline Factor IX level less than or equal to 2%) • History of at least 100 exposure days to any Factor IX product • Platelet count ≥100,000 cells/µL
Main exclusion criteria	• History of Factor IX inhibitors • Kidney or liver dysfunction • Diagnosed with another coagulation defect than hemophilia B • Prior history of anaphylaxis associated with any Factor IX or intravenous (IV) immunoglobulin administration
Intervention	The study included four treatment groups: Group 1 received weekly dose-adjusted prophylaxis (50 IU of rFIXFc per kilogram of body weight to start), Group 2 received interval-adjusted prophylaxis (100 IU per kilogram every 10 days to start), Group 3 received treatment as needed for bleeding episodes (20 to 100 IU per kilogram), and Group 4 received treatment in the perioperative period.

Trial name: B-LONG	NCT number: NCT01027364
Comparator(s)	NA
Follow-up time	Up to 77 weeks
Primary, secondary and exploratory endpoints	All endpoints are measured at 52 weeks, unless otherwise stated. **Primary** • Number of Participants with Potentially Clinically Significant Laboratory Abnormalities • Number of Participants with TEAEs and Treatment-emergent Serious Adverse Events (TESAEs) • Number of Participants with Non-serious TEAEs during the Surgical / Rehabilitation Period • Number of Participants with TESAEs During the Surgical / Rehabilitation Period • Incidence Rate of FIX Inhibitor Development • Annualized Bleeding Rate • Comparison of Annualized Bleeding **Secondary** • Participant Assessment of Response to Injections to Treat a Bleeding Episode • Physicians' Global Assessments of Participants' Response to Treatment With rFIXFc • Annualized rFIXFc Consumption Per Participant • Average Weekly Dose For the Fixed Weekly Interval Prophylaxis Arm • Average Dosing Interval For the Individualized Interval Prophylaxis Arm • ABR by Type of Bleed (Spontaneous and Traumatic) • ABR by Location of Bleed (Joint, Muscle, Internal, Skin/Mucosa) • Number of Days From Last Injection to Treat a New Bleeding Episode • Number of Injections Required for Resolution of a Bleeding • Number of Injections Required for Resolution of a Bleeding Episode by Location of • Total Dose Per Injection Required for Resolution of a Bleeding Episode by Location of Bleed • Haem-A-QoL Questionnaire for Adults: Change From Baseline to Week 52 • Haemo-QoL Questionnaire: Change From Baseline to Week 26 and Week 52

Trial name: B-LONG	NCT number: NCT01027364
	• The Haemo-QoL, a quality of life (QoL) assessment instrument for children and adolescents with hemophilia, was administered to participants from 13- to 17-years-old. • Investigators'/Surgeons' Assessment of Participants' Response to rFIXFc for Major Surgery • Number of Injections Required to Maintain Hemostasis During Major Surgery • Dose Per Injection and Total Dose Required to Maintain Hemostasis During Major Surgery • Estimated Total Blood Loss During Major Surgery • Number of Transfusions Required Per Surgery • Time Frame:. Each participant was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment: o Maximum Concentration o Area Under the Curve (AUC) Per Dose o Half Life Alpha and Beta o Clearance (CL) o Mean Residence Time o Volume in Steady State o Incremental Recovery o Time to 1% and 3% FIX Activity • Number of Participants With Clinically Relevant Abnormalities or Relevant Changes From Baseline in Vital Signs [Time Frame: up to 52 weeks ± 1 week] • Time Frame: Pre-dose, 1 hour post-dose, 6 hours post-dose, and 24 hours post-dose at baseline (120 hours before Day 1, for BeneFIX), Day 1, Week 26, and Week 52 (for rFIXFc): o Coagulation Parameter: Change From Pre-dose Values in Prothrombin Split Fragments 1+ 2 (F 1+2) o Coagulation Parameter: Change From Pre-dose Values in Thrombin-antithrombin (TAT) Complex o Coagulation Parameter: Change From Pre-dose Values in D-dimer.
Method of analysis	Comparisons of prophylaxis with episodic treatment (Groups 1 and 2 vs. Group 3) were based on annualized estimates of bleeding rates calculated with the use of a negative binomial regression model. Descriptive statistics included medians and interquartile ranges for groups 1, 2, and 3. Pharmacokinetic measures of rFIXFc and recombinant factor IX were compared with the use of a repeated measures analysis-of-variance model with variables for study treatment

Trial name: B-LONG	NCT number: NCT01027364
	and participant; 95% confidence intervals were calculated for geometric means and for the intraparticipant ratio of rFIXFc to recombinant factor IX for each pharmacokinetic measure. For all tests, a two-sided alpha level of 5% was considered to indicate statistical significance.
Subgroup analyses	A subgroup of Group 1 underwent comparative sequential pharmacokinetic assessments of recombinant factor IX and rFIXFc.
Other relevant information	NA

Appendix B. Efficacy results per study

Table 12. Results of BASIS – patients previously treated with prophylactic factor replacement therapy

Results of BASIS (NCT03938792)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ABR (IQR), Median, all bleeds (12 month)	Marstacimab	83	2.89 (0.00, 7.06*)	1.02	NA	NA	NA	NA	NA	Counts, single arm versus baseline	(34)
	Routine prophylaxis	83	3.91 (0.00, 11.66)								
ABR Median, treated bleeds (12 month)	Marstacimab	83	2.02 (0.00, 6.09)	[redacted]	NA	NA	NA	NA	NA	Counts, single arm versus baseline	Table 24 (28)
	Routine prophylaxis	83	[redacted]								
Heam-A QoL total score, mean, **adult** patients (change from baseline at 12 months)	Marstacimab	63		[redacted]	[redacted]	NA	NA	NA	NA	Non-parametric analysis. 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	Data on file
	Routine prophylaxis	63									
Heamo- QoL total score, mean, **adolescent** patients (change	Marstacimab	20		[redacted]	[redacted]	NA	NA	NA	NA	Non-parametric analysis Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were	Table 34 (28)
	Routine prophylaxis	20									

Results of BASIS (NCT03938792)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
from baseline at 12 months)										imputed using multiple imputation methods based on MAR assumption	
Severe venous thromboembolism (12 months)	Marstacimab	83	0	1	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	(34)
	Routine prophylaxis	91	1								
SAE	Marstacimab	83	7 (8.4) Treatment related: 1	-5 Treatment related: -1	NA	NA	NA	NA	NA	One considered by the investigator to be treatment related that was diagnostically confirmed to be unrelated to a bleeding or thrombotic event.	(34)
	Routine prophylaxis	91	2 (2.2%)								
Discontinuation due to adverse event (12 months)	Marstacimab	83	1 (1.2%)	-1	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	(34)
	Routine prophylaxis	91	0 (0%)								

*During the publication process a discrepancy was found between the SPC and the Statistical Analysis Plan (SAP) in relation to how preventative factor treatment was treated in ABR calculations. The discrepancy only affects the 100th decimal and does not affect any conclusions or significances. ABR was recalculated to fit with the SAP and the numbers have been updated. The full description of how ABR is calculated can be found in Matino et al (2025) Supplementary Materials, Section 6.

Table 13. Results of BASIS – patients previously treated with prophylactic factor replacement therapy, for haemophilia B subgroup

Results of BASIS (NCT03938792)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ABR (IQR), Median, all bleeds (12 month)	Marstacimab	18	[redacted]	[redacted]	NA	NA	NA	NA	NA	Counts, single arm versus baseline	CSR Table 22a 5
	Routine prophylaxis	18	[redacted]								
ABR Median, treated bleeds (12 month)	Marstacimab	18	[redacted]	[redacted]	NA	NA	NA	NA	NA	Counts, single arm versus baseline	CSR Table 14.2.2.1.7 (28)
	Routine prophylaxis	18	[redacted]								
Severe venous thromboembolism (12 months)	Marstacimab	18	0	1	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	CSR
	Routine prophylaxis	18	1								
SAE	Marstacimab	18	[redacted]	[redacted]	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	CSR
	Routine prophylaxis	18	[redacted]								

Results of BASIS (NCT03938792)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Discontinuation due to adverse event (12 months)	Marstacimab	18	[redacted]	[redacted]	NA	NA	NA	NA	NA	MedDRA v25.1 coding dictionary applied.	CSR
	Routine prophylaxis		[redacted]								

Table 14. Results of (NCT 05145127) "OLE" – patients previously treated with prophylactic factor replacement therapy

Results of OLE (NCT 05145127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Long-term ABR, all bleeds	Marstacimab	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA	Counts, single arm versus baseline	(29)
	Baseline of OLE study	[redacted]	[redacted]								

Table 15. Results of B-LONG – patients previously treated with prophylactic factor replacement therapy

Results of B-LONG (NCT01027364)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ABR, Median, (12 months)	Eftrenonacog alfa, Group 1	61	3.12 (2.46-3.95)	7.38	NA	NA	NA	NA	NA	Negative binomial regression model to control for participants' time in the study	Table 2 (30)
	Routine prophylaxis	63	10.5								
ABR, Median,	Eftrenonacog alfa, Group 1	61	NR	NA	NA	NA	NA	NA	NA	NA	No data found
Long-term ABR	Eftrenonacog alfa, Group 1	61	2.3 (IQR: 0.44-3.76)	NA	NA	NA	NA	NA	NA	NA	(32)
Heam-A QoL total score, adult patients (change from baseline at 26 weeks)	Eftrenonacog alfa, Group 1	18	NR	-5.5 (SD: +/- 6.7)	NA	0.0026	NA	NA	NA	Chi-square tests were employed to compare the proportions of responders between treatment groups.	Table 4 (31) Note: data from 26 weeks.
Heam-A QoL total score, adolescent patients (change from baseline)	Eftrenonacog alfa, Group 1	NR	NA	NA	NA	NA	NA	NA	NA	NA	No data found

Results of B-LONG (NCT01027364)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Severe venous thromboembolism	Eftrenonacog, Group 1	61	0	NA	NA	NA	NA	NA	NA	NA	(30) , Note: unclear time period
SAE, Patients with ≥1 SAE[a]	Eftrenonacog, Group 1	63	5 (7.9%) Treatment related: 1*	NA	NA	NA	NA	NA	NA	1 participant had a single serious adverse event that was considered to be possibly related to treatment with rFIXFc. In this participant, who had a history of painful hematuria, an obstructive clot developed in the urinary collecting system (*not specified in publication in which group the patient belong).	(30) Table S4
Discontinuation due to adverse event (12 months)	Eftrenonacog alfa 50 IU/kg weekly, (Group 1)	NR	NA	NA	NA	NA	NA	NA	NA	NA	No data found

[a]Serious adverse events in groups 1–3 in B-LONG study included cellulitis, device-related infection, peritonsillar abscess, abdominal adhesions, inguinal hernia, intestinal obstruction, small intestinal obstruction, upper GI hemorrhage, angina pectoris, road traffic accident, arthralgia, malignant hepatic neoplasm, and obstructive uropathy. Each SAE occurred in 1 subject, with the exception of cellulitis, which was reported by 2 subjects. One patient had a single SAE assessed as related or possibly related to recombinant factor IX Fc fusion protein (rFIXFc) treatment. The patient, who had a history of painful hematuria, developed an obstructive clot in the urinary collecting system (not specified in publication in which group the patient belong). The event resolved with medical management and the patient continued rFIXFc treatment and completed the study. All other SAEs were assessed as unrelated or unlikely related to rFIXFc treatment. Table S4 (30).

Appendix C. Comparative analysis of efficacy

Table 16. Comparative analysis of studies comparing marstacimab to enonacog alfa for patients with haemophilia B

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
ABR Median, all bleeds (12 month)	BASIS B-LONG	0.23	NA	NA	NA	NA	NA	Indirect naive comparison	No
ABR Median, treated bleeds (12 month)	BASIS B-LONG	NA	NA	NA	NA	NA	NA	Indirect naive comparison	No
ABR Median, Long term	BASIS B-LONG	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Quality of Life: Heam-A QoL total score, mean **adult** patients (change from baseline at 12 months)	BASIS B-LONG	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Quality of Life: Heamo- QoL total score, adolescent patients (change from baseline at (12 months)	BASIS B-LONG	NA	NA	NA	NA	NA	NA	Indirect naive comparison	No
Severe venous thromboembolism (12 months)	BASIS	0	NA	NA	NA	NA	NA	Indirect naive comparison	No

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
	B-LONG								
SAE	BASIS B-LONG	NR[a]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Discontinuation due to adverse event (33 weeks)	BASIS B-LONG	NA	NA	NA	-1.2%	NA	NA	Indirect naive comparison	No

[a]NR as there is uncertainty if the one SAE possible related to comparator eftenonacog alfa is from the relevant arm Group 1 (30)

Table 17. Comparative analysis of studies comparing marstacimab to enonacog alfa for patients with haemophilia B subgroup

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
ABR Median, all bleeds (12 month)	BASIS B-LONG	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
ABR Median, treated bleeds (12 month)	BASIS B-LONG	NA	NA	NA	NA	NA	NA	Indirect naive comparison	No

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
ABR Median, Long term	BASIS B-LONG	[redacted]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Severe venous thromboembolism (12 months)	BASIS B-LONG	0	NA	NA	NA	NA	NA	Indirect naive comparison	No
SAE	BASIS B-LONG	NR[a]	NA	NA	NA	NA	NA	Indirect naive comparison	No
Discontinuation due to adverse event (33 weeks)	BASIS B-LONG	NA	NA	NA	-1.2%	NA	NA	Indirect naive comparison	No

[a]NR as there is uncertainty if the one SAE possible related to comparator eftenonacog alfa is from the relevant arm Group 1

Appendix D. Literature searches for the clinical assessment

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

A systematic literature review (SLR) was conducted on August 4th 2020 (original SLR) and subsequently updated on August 21st 2023 and May 17th 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 detailed in the Cochrane Handbook for Systematic Reviews of Interventions, guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the National Institute for Health and Care Excellence (NICE) (40), (41).

Table 18: Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
Medline		From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
CENTRAL	Wiley platform	From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
CDSR		From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
DARE		From 2000	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)

Abbreviations: CDSR: Cochrane Database of Systematic Reviews, DARE: Database of Abstracts of Reviews of Effects.

Table 19: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	ClinicalTrials.gov	Electronic search	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)

Source name	Location/source	Search strategy	Date of search
WHO ICTRP	www.who.int/clinical-trials-registry-platform	Electronic search	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
EMA EPARs	www.ema.europa.eu	Electronic search	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)

Table 20: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ISTH	Congress of the International Society on Thrombosis and Haemostasis	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
EAHAD	Annual Congress of the European Association for Haemophilia and Allied Disorders	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
WFH	World Congress of the World Federation of Hemophilia	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
ASH	Annual Meeting of the American Society of Hematology	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)
EHA	Annual Congress of European Hematology Association	Manual search	N/A	04.08.2020, 21.08.2023 (update), 17.05.2024 (update)

D.1.2 Search strategies

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 21-Table 34). 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.

- The searches were modified from the August 4th 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 as the database was discontinued in 2015

Table 21: Search strategy table for EMBASE in the clinical SLR updates, searches 21.08.2023 and 17.05.2024

No.	Query	Results (2023)	Results (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$).ti,ab.	35,456	44,733
#2	Randomised controlled trials as Topic/ or Randomised controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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

No.	Query	Results (2023)	Results (2024)
#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
#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	1,498
#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

Table 22: Search strategy table for EMBASE in the 2020 original clinical SLR (clinical outcomes for haemophilia A), search date 04.08.2020

No.	Query	Results (2020)[a]
#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	25,601

No.	Query	Results (2020)[a]
	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$).ti,ab.	
#2	Randomised controlled trials as Topic/ or Randomised controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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
#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

No.	Query	Results (2020)[a]
#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

Table 23: Search strategy table for EMBASE in the 2020 original clinical SLR (clinical outcomes for haemophilia B), search date 04.08.2020

No.	Query	Results (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$).ti,ab.	9,169
#2	Randomised controlled trials as Topic/ or Randomised controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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.	4,031,923
#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

No.	Query	Results (2020)
#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

Table 24: Search strategy table in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conduced 21.08.2023 and 17.05.2024 (clinical outcomes for haemophilia A and B)

No.	Query	Results (2023)	Results (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$).ti,ab.	27,971	30,440
#2	Randomised controlled trials as Topic/ or Randomised controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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

No.	Query	Results (2023)	Results (2024)
#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

Table 25: Search terms used in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conduced 04.08.2020 (clinical outcomes for haemophilia A)

No.	Query	Results (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	Randomised controlled trials as Topic/ or Randomised 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

No.	Query	Results (2020)
#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

Table 26: Search terms used in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; searches conduced 04.08.2020 (clinical outcomes for haemophilia B)

No.	Query	Results (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$).ti,ab.	5,593
#2	Randomised controlled trials as Topic/ or Randomised controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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	1,100,747

No.	Query	Results (2020)
	culture/ or cell culture.mp. or diagnostic test accuracy study/ or diagnostic test accuracy study.mp.	
#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

Table 27: Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted 21.08.2023 and 17.05.2024 (clinical outcomes for haemophilia A and B)

No.	Query	Results (2023)	Results (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.	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
#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

Table 28. Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted 04.08.2020 (clinical outcomes for haemophilia A)

No.	Query	Results (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	Randomised controlled trials as Topic/ or Randomised 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 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
#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

Table 29: Search terms used for Cochrane Central Register of Controlled Trials via Ovid; searches conducted 04.08.2020 (clinical outcomes for haemophilia B)

No.	Query	Results (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	371

No.	Query	Results (2020)
	antihaemophilic factor b or hemophilic b or haemophilic b or factor 9 deficienc$).ti,ab.	
#2	Randomised controlled trials as Topic/ or Randomised controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ 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
#10	limit 8 to english language	92

Abbreviations: SLR: systematic literature review

Table 30: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted 21.08.2023 and 17.05.2024 (clinical outcomes for haemophilia A and B)

No.	Query	Results (2023)	Results (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

Table 31: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted 04.08.2020 (clinical outcomes for haemophilia A)

No.	Query	Results (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

Table 32: Search terms used for the Cochrane Database of Systematic Reviews via Ovid; searches conducted 04.08.2020 (clinical outcomes for haemophilia B)

No.	Query	Results (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"	14

Table 33: Search terms used for the DARE; searches conduced on the 04.08.2020 (clinical outcomes for haemophilia A)

No.	Query	Results (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

No.	Query	Results (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	7

Table 34: Search terms used for the DARE; searches conduced on the 04.08.2020 (clinical outcomes for haemophilia B)

No.	Query	Results (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$).af.	3
#2	((clinic$ 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

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.1.3 Systematic selection of studies

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.

The eligibility criteria for the clinical SLR are listed in Table 35. 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.

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 35). 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 35: Eligibility criteria for the clinical SLR

Clinical effectiveness	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 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	• 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 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: octocog alfa (Advate®), moroctocog alfa (ReFacto AF®), turoctocog alfa (NovoEight®), simoctocog alfa (Nuwiq®) - Extended half-life FVIII replacement therapy: turoctocog alfa pegol (Esperoct®), efmoroctocog alfa (Eloctate®), rurioctocog alfa pegol (Adynovi®), lonoctocog alfa (Afstyla®), efanesoctocog alfa (Altuviiio®), damoctocog alfa pegol (Jivi®)	Studies on interventions not intended for the treatment of haemophilia (e.g., pre or postsurgery protocols)

	- Standard half-life FIX replacement therapy,: nonacog alfa (BeneFIX®), nonacog gamma (Rixubis®) - Extended half-life FIX replacement therapy: eftrenonacog alfa (Alprolix®), albutrepenonacog alfa (Idelvion®), nonacog beta pegol (Refixia®), dalcinonacog alfa • Emicizumab (Hemlibra®) • Rebalancing agents: Marstacimab, Fitusiran, Concizumab (Alhemo®), • Gene therapies: Valoctocogene roxaparvovec (Roctavian®), Giroctocogene fitelparvovec, Etranacogene dezaparvovec (Hemgenix®), Fidanacogene elaparvovec (Beqvez®, Durveqtix®)	
Comparators	Any of the above interventions or none (no comparison is required)	NA
Outcomes	• Total 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/publication type	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	• Animal studies • In vitro/ex vivo studies

	articles of importance that may not have been identified during search or screening	• Gene expression/protein expression studies • Narrative publications • Non-systematic reviews • Phase I studies • Case studies • Case series • Case reports • Editorials
Geographical limits	No restrictions	N/A
Language restrictions	• 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.

Figure 3 shows the PRISMA diagram for the study selection for the combined SLR data cuts. Of the 8,034 unique records identified in literature search in databases and trial registries, 4,797 were screened using title/abstract for relevance according to the eligibility criteria, and 3,802 were excluded. A total of 995 citations went through full-text screening to assess for potential relevance. A total of 79 publications met the inclusion criteria corresponding to 79 unique trials, which were extracted to undergo full-text review.

Among the 80 trials included in the SLR, two investigated marstacimab (BASIS and a phase 2 trial), of which the BASIS trial was selected as the reference for the intervention and 78 investigated comparator treatments were selected for the comparator. The justification for excluding the comparator studies is presented in Table 36.

From the 78 studies, 47 were excluded based on the following reasons: Population= 7; Outcome=8; No baseline characteristics=6; Not reported at least one primary or secondary outcome assessed in the BASIS-1 trial =14; early phase trial in which phase 3 or 4 trial data were available = 10; Historical plasma-derived product that is not widely used within clinical practice =2; experimental treatments for which the manufacturer has terminated development =1.

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 Danish evaluation of haemophilia B, where the comparator of relevance is Eftrenonacog alfa. Thus, two studies, B-LONG (NCT01027364) and B-YOND (NCT01425723) were included.

Additionally, two reference were manually included as a data source in application: the marstacimab (NCT05145127) open-label long term extension “OLE” study CSR report, and Wyrwich et al. 2016 (31), which concerns quality of life in B-LONG. See Table 37Table 38Table 38 for included studies.

Table 36: List of studies included in the clinical SLR

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
BASIS, NCT03938792	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) n=128	Include	Matino D., Palladino A., Taylor C. T., et al. Marstacimab Prophylaxis in Hemophilia A/B Without Inhibitors: Results from the Phase 3 BASIS Trial. Blood. 2025 Jul 3:blood.2024027468. doi: 10.1182/blood.2024027468. Epub ahead of print. PMID: 40608864. Clinical Study Report, 2024
NCT03363321	A and B	Phase 2 open label, non-RCT	Brazil, Chile, Croatia, Poland, South Africa, Switzerland, US	Marstacimab (PF-06741086), Different dosing, n=20	Exclude, later phase results available	Mahlangu J, Luis Lamas J, Cristobal Morales J, et al. Long-term safety and efficacy of the anti-tissue factor pathway inhibitor marstacimab in participants with severe haemophilia: Phase II study results. Br J Haematol. 2023 Jan;200(2):240-248. doi: 10.1111/bjh.18495. Epub 2022 Oct 11. PMID: 36220152; PMCID: PMC10092220.
Atlas-PPX, NCT03549871	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), n=80	Exclude, not relevant comparator	Kenet G, Nolan B, Zulfikar B, et al. Fitusiran prophylaxis in people with hemophilia A or B who switched from prior BPA/CFC prophylaxis: the ATLAS-PPX trial. Blood. 2024 May 30;143(22):2256-2269. doi: 10.1182/blood.2023021864. PMID: 38452197; PMCID: PMC11181353.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
ATLAS-A/B, NCT03417245	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, n=120	Exclude, not relevant comparator	Srivastava A, Rangarajan S, Kavakli K, et al. Fitusiran prophylaxis in people with severe haemophilia A or haemophilia B without inhibitors (ATLAS-A/B): a multicentre, open-label, randomised, phase 3 trial. Lancet Haematol. 2023 May;10(5):e322-e332. doi: 10.1016/S2352-3026(23)00037-6. Epub 2023 Mar 29. PMID: 37003278.
Explorer 8, NCT04082429	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, n=148	Exclude, baseline data not available	Chowdary P, Angchaisuksiri P, Apte S, et al. Concizumab prophylaxis in people with haemophilia A or haemophilia B without inhibitors (explorer8): a prospective, multicentre, open-label, randomised, phase 3a trial. Lancet Haematol. 2024 Dec;11(12):e891-e904. doi: 10.1016/S2352-3026(24)00307-7. Epub 2024 Nov 6. Erratum in: Lancet Haematol. 2024 Dec;11(12):e886. doi: 10.1016/S2352-3026(24)00353-3. PMID: 39521008.
NR	A and B	Crossover RCT (Phase NR)	Sweden	FVIII and FIX products, Different regimens, prophylaxis, on-demand n=13	Exclude, not relevant comparator	Lindvall K, Astermark J, Björkman S, et al. Daily dosing prophylaxis for haemophilia: a randomised crossover pilot study evaluating feasibility and efficacy. Haemophilia. 2012 Nov;18(6):855-9. doi: 10.1111/j.1365-2516.2012.02879.x. Epub 2012 Jun 11. PMID: 22681244

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
Explorer 5, NCT03196297	A only	Phase 2 open-label, single-arm trial	France, Germany, Italy, Japan, Spain, Sweden, Thailand, Turkey, UK, Ukraine, US	Concizumab (Alhemo™), NA n=36	Exclude, later phase results available	Shapiro AD, Angchaisuksiri P, Astermark J, et. Al. Subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results. Blood. 2019 Nov 28;134(22):1973-1982. doi: 10.1182/blood.2019001542. PMID: 31444162; PMCID: PMC6895373.
GENEr8-1, NCT03370913	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 n=134	Exclude, not relevant comparator	Mahlangu J, Kaczmarek R, von Drygalski A, et al. GENEr8-1 Trial Group. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. N Engl J Med. 2023 Feb 23;388(8):694-705. doi: 10.1056/NEJMoa2211075. PMID: 36812433.
GENEr8-3, NCT04323098	A only	Phase 3 open-label, single-arm trial	Australia, Brazil, Taiwan, US	Valoctocogene roxaparvovec (ROCTAVIAN™), NA n=22	Exclude, not relevant comparator	**Ozelo MC, Mason J, Dunn AL, et. Al. Safety and efficacy of valoctocogene roxaparvovec with prophylactic glucocorticoids: 1-year results from the phase 3b, single-arm, open-label GENEr8-3 study. Thromb Haemost. 2025 Jan 10:S1538-7836(25)00002-9. doi: 10.1016/j.jtha.2024.12.038. PMID: 39800255**
BMN 270-201, NCT02576795, EudraCT number, 2014-003880-38	A only	Phase 1/2 open-label, dose-	UK	Valoctocogene roxaparvovec (ROCTAVIAN™), Different dosing n=9	Exclude, later phase results available	Rangarajan S, Walsh L, Lester W, et al. AAV5-Factor VIII Gene Transfer in Severe Hemophilia A. N Engl J Med. 2017 Dec 28;377(26):2519-2530. doi: 10.1056/NEJMoa1708483. Epub 2017 Dec 9. PMID: 29224506.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		escalation, single-arm				
Alta study, NCT03061201	A only	Phase 2 open-label, dose ranging, non-RCT	US	Giroctocogene fitelparvovec (PF-07055480), Different dosing n=11	Exclude, later phase results available	Leavitt AD, Konkle BA, Stine KC, et al. Giroctocogene fitelparvovec gene therapy for severe hemophilia A: 104-week analysis of the phase 1/2 Alta study. Blood. 2024 Feb 29;143(9):796-806. doi: 10.1182/blood.2022018971. PMID: 37871576; PMCID: PMC10933705.
GO-8, NCT03001830	A only	Phase 1/2 open-label, single-arm trial	UK, US	Factor VIII variant (AAV-HLP-hFVIII-V3), NA n=12	Exclude, baseline data not available	Pratima Chowdary, Ulrike M. Reiss, et al. GO-8: Stable Expression of Factor VIII over 5 Years Following Adeno-Associated Gene Transfer in Subjects with Hemophilia a Using a Novel Human Factor VIII Variant. *Blood* 2023; 142 (Supplement 1): 3624. doi: https://doi.org/10.1182/blood-2023-180803
SPK-8011-101/ SPK-8011/ 8016-LTFU, NCT0300353/ NCT03432520	A only	Phase 1/2 open-label, non-RCT	Australia, Canada, Israel, Thailand, US	SPK-8011, Different dosing n=18	Exclude, baseline data not available	George LA, Monahan PE, Eyster ME, et al. Factor VIII Expression after AAV Gene Transfer for Hemophilia A. N Engl J Med. 2021 Nov 18;385(21):1961-1973. doi: 10.1056/NEJMoa2104205. PMID: 34788507; PMCID: PMC8672712.
NCT03588299	A only	Phase 1/2 open-label,	France, Germany, the Netherlands, Bulgaria, UK, US	Peboctocogene camaparvovec (BAY 2599023;	Exclude, baseline data not available	Pipe SW, Ferrante F, Reis M, et al. First-in-Human Gene Therapy Study of AAVhu37 Capsid Vector Technology in Severe Hemophilia A - BAY 2599023 has Broad Patient

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		single-arm trial		AAVhu37FVIII), NA, n=2		Eligibility and Stable and Sustained Long-Term Expression of FVIII 6. Blood (2020) 136 (Supplement 1): 44. http://doi.org/10.1182/blood-2020-139803
HAVEN 3, NCT02847637	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, n=152	Exclude, not relevant comparator	Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018 Aug 30;379(9):811-822. doi: 10.1056/NEJMoa1803550. PMID: 30157389.
HAVEN 4, NCT03020160	A only	Phase 3 open-label, single-arm trial	Australia, Belgium, Japan, Poland, Spain, US	Emicizumab (HEMLIBRA®), NA, n=48	Exclude, not relevant comparator	Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol. 2019 Jun;6(6):e295-e305. doi: 10.1016/S2352-3026(19)30054-7. Epub 2019 Apr 16. PMID: 31003963.
HAVEN 5, NCT03315455	A only	Phase 3 open-label, RCT	China, Malaysia, Thailand	Emicizumab (HEMLIBRA®), Different dosing n=70	Exclude, conducted outside of North America, UK, Europe	Yang R, Wang S, Wang X, et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomised study (HAVEN 5). Res Pract Thromb Haemost. 2022 Mar 7;6(2):e12670. doi: 10.1002/rth2.12670. PMID: 35284778; PMCID: PMC8902287.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
CTRI/2018/05/013790	A only	Single-arm trial (Phase NR)	India	Antihemophilic factor human (HemoRel-A®), prophylaxis, NA, n=44	Exclude, outcomes from BASIS not reported	Mewada M, Sanyal S, Rangarajan Set al. A prospective, multicenter, clinical Study to evaluate the Safety, Pharmacokinetics, and Efficacy of Bleed Outcomes, with HemoRel-A® in severe Hemophilia A Patients. J Assoc Physicians India. 2022 Jul;70(7):11-12. doi: 10.5005/japi-11001-0039. PMID: 35833399.
CTTQ-NXBYZ-02, NCT04061109	A only	Phase 3 open-label, single-arm trial	China	B-domain-deleted recombinant factor VIII (TQG202), prophylaxis, NA, n=81	Exclude, conducted outside of North America, UK, Europe	Xi Y, Jin C, Liu W, et al. Efficacy, safety and bioequivalence of the human-derived B-domain-deleted recombinant factor VIII TQG202 for prophylaxis in severe haemophilia A patients. Haemophilia. 2022 Nov;28(6):e219-e227. doi: 10.1111/hae.14652. Epub 2022 Aug 22. PMID: 35996199; PMCID: PMC9805152.
GC8AIII, NCT01568580	A only	Phase 3 open-label, single-arm trial	Korea	Beroctocog Alfa (ALPHANATE®), on-demand, NA, n=88	Exclude, conducted outside of North America, UK, Europe	Hyun SY, Park SY, Lee SY, et al. Efficacy, Safety, and Pharmacokinetics of Beroctocog Alfa in Patients Previously Treated for Hemophilia A. Yonsei Med J. 2015 Jun 5;56(4):935–943. doi: **10.3349/ymj.2015.56.4.935. PMCID: PMC4479860. PMID: 26069114**
Study 310, NR	A only	Study 1: Double blind, RCT cross-over	Italy, New Zealand, Poland, UK, US	Moroctocog alfa (Xyntha®), prophylaxis and on-demand Full-length rFVIII	Exclude, not relevant comparator	Recht M, Nemes L, Matysiak M, et al. Haemophilia. Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of haemophilia A: demonstration of safety,

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		followed by open-label Study 2: open-label single-arm (Phase NR)		concentrate (FLrFVIII, Advate, Baxter), on-demand, n=204		efficacy, and pharmacokinetic equivalence to full-length recombinant factor VIII 2009 Jul;15(4):869-80. doi: 10.1111/j.1365-2516.2009.02027.x. Epub 2009 Apr 9.
SPINART, NCT00623480	A only	Phase 3b/4 randomised, controlled, parallel-group, open-label	Argentina, Bulgaria, Romania, US	Octocog alfa (Kogenate® FS), Prophylaxis and on-demand, n=84	Exclude, not relevant comparator	Manco-Johnson MJ, Kempton CL, Reding MT, et al. Randomised, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). J Thromb Haemost. 2013 Jun;11(6):1119-27. doi: 10.1111/jth.12202. Erratum in: J Thromb Haemost. 2014 Jan;12(1):119-22. PMID: 23528101.
LIPLONG, NR	A only	Phase 2 active-controlled, double-blind	Israel, US	Octocog alfa (Kogenate® FS), prophylaxis rFVIII-FS, prohylaxis, n=143	Exclude, later phase results available	Powell J, Martinowitz U, Windyga J, et al. Efficacy and safety of prophylaxis with once-weekly BAY 79-4980 compared with thrice-weekly rFVIII-FS in haemophilia A patients. A randomised, active-controlled, double-blind study. Thromb Haemost. 2012 Nov;108(5):913-22. doi: 10.1160/TH12-03-0188. PMID: 23014711. DOI: 10.1160/TH12-03-0188

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
NR	A only	Open-label, single-arm trial (Phase NR)	Europe, US	Octocog alfa (Kogenate® FS), on-demand followed by prophylaxis Different regimen, n=20	Exclude, later phase results available	Collins P, Faradji A, Morfini M et al. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia A: results from a 13-month crossover study. Journal of Thrombosis and Haemostasis, 2010. 8 (1): 83-89, doi: 10.1111/j.1538-7836.2009.03650.x.
NR	A only	Single-arm trial (Phase NR)	France, Germany	Octocog alfa (Kogenate® FS), prophylaxis NA, n=33	Exclude, later phase results available	Rothschild C, Scharrer I, Brackmann HH, et al. European data of a clinical trial with a sucrose formulated recombinant factor VIII in previously treated haemophilia A patients. Haemophilia. 2002 Mar;8 Suppl 2:10-4. doi: 10.1046/j.1351-8216.2001.00131.x. PMID: 11966846
NR	A only	Cross-over RCT (Phase NR)	North America, Europe	Octocog alfa (Kogenate® FS), prophylaxis, Different formulation, n=71	Exclude, outcomes from BASIS not reported	Abshire TC, Brackmann HH, Scharrer I, et al. Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy--International Kogenate-FS Study Group. Thromb Haemost. 2000 Jun;83(6):811-6. PMID: 10896230
NCT00717626	A only	Phase 2 open-label,	Canada	Octocog alfa (Advate®) or Octocog alfa (Kogenate® FS) or Humate-P, Recombinate, Factor	Exclude, later phase results available	No publication: https://clinicaltrials.gov/study/NCT00717626

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		single-arm trial		VIII (Helixate FS), prophylaxis n=14		
LEOPOLD I, NCT01029340	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®) prophylaxis Octocog Alfa (Kogenate), prophylaxis Octocog alfa (Kovaltry®), n=62	Exclude, not relevant comparator	Saxena K, Lalezari S, Oldenburg J, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Haemophilia. 2016 Sep;22(5):706-12. doi: 10.1111/hae.12952. Epub 2016 Jun 24. PMID: 27339736.
LEOPOLD II, NCT01233258	A only	Phase 2/3 cross-over, open-label	Europe, North America, South America, South Africa, Asia (11 countries)	Octocog alfa (Kovaltry®), On-demand, Octocog alfa (Kovaltry®), FVIII Prophylaxis, n=97	Exclude, not relevant comparator	Kavakli K, Yang R, Rusen L, et al. LEOPOLD II Study Investigators. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomised trial (LEOPOLD II). J Thromb Haemost. 2015 Mar;13(3):360-9. doi: 10.1111/jth.12828. PMID: 25546368; PMCID: PMC4671268.
SCT800-A401, NCT03947567	A only	Phase 4 open-label,	China	Omfiloctocog alfa (Ancain®), prophylaxis	Exclude, baseline data not reported	Xue F, Zhao X, Sun J, et al. P1670: Long term safety and efficacy of recombinant human coagulation factr VIII (SCT800) in previously treated patients with severe hemophilia A, Hemasphere. 2022 Jun 23;6(Suppl):1551-

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		single-arm trial		and/or on-demand NA, n=69		1552. doi: **10.1097/01.HS9.0000849536.75261.f1** PMCID: PMC9430633
SCT800-A302, NCT03815318	A only	Phase 3 open-label, single-arm trial	China	Omfiloctocog alfa (Ancain®), prophylaxis, NA, n=73	Exclude, conducted outside of North America, UK, Europe	Xue F, Zhao X, Sun J, et al. **Pharmacokinetic, efficacy and safety evaluation of B-domain-deleted recombinant FVIII (SCT800) for prophylactic treatment in adolescent and adult patients with severe haemophilia A.** Haemophilia. 2021 Sep;27(5):814-822. doi: 10.1111/hae.14350. Epub 2021 Jun 5.PMID: 34089210
NR	A only	Open-label, single-arm trial (Phase NR)	Poland	pdFVIII (Haemoctin® SDH), prophylaxis, on-demand, NA, n=61	Exclude, historical product not widely used in clinical practice	**Wolf DM, Rokicka-Milewska R, Lopaciuk S,** et al. **Clinical efficacy, safety and pharmacokinetic properties of the factor VIII concentrate Haemoctin SDH in previously treated patients with severe haemophilia A. Haemophilia. 2004 Sep;10(5):438-48. DOI: 10.1111/j.1365-2516.2004.00947.x PMID: 15357768.**
NR	A only	Randomised, four-way cross-over, subject-blinded	Russia	PEGLip-rFVIII-FS (sucrose-formulated FVIII noncovalently bound to pegylated liposomes),	Exclude, outcomes from BASIS not reported	**Spira J, Plyushch OP, Andreeva TA,** et al. **Evaluation of liposomal dose in recombinant factor VIII reconstituted with pegylated liposomes for the treatment of patients with severe haemophilia A. Thromb Haemost. 2008 Sep;100(3):429-34. PMID: 18766258**

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		trial (Phase NR)		prophylaxis, Different dosing, n=16		
NR	A only	Controlled, cross-over, patient-blinded trial (Phase NR)	The Netherlands, Russia	PEGylated liposome–reconstituted rFVIII, prophylaxis Different dosing, n=24	Exclude, outcomes from BASIS not reported	**Spira J, Plyushch OP, Andreeva TA,** et al. **Prolonged bleeding-free period following prophylactic infusion of recombinant factor VIII reconstituted with pegylated liposomes. Blood. 2006 Dec 1;108(12):3668-73. DOI: 10.1182/blood-2006-03-008276. PMID: 16888098**
GENA-21b, NCT02256917	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, n=58	Exclude, not relevant comparator	Midori S, Masashi T, Rie S, Tadashi M, et al. Efficacy and Safety of Personalized Prophylaxis with Simoctocog Alfa in Adult Japanese Previously Treated Patients with Severe Hemophilia a. *Blood* 2022; 140 (Supplement 1): 11304–11305. doi: https://doi.org/10.1182/blood-2022-167449
GENA-21, NCT01863758	A only	Phase 3b open-label, single-arm trial	Austria, Bulgaria, France, Germany, Poland, Romania, Switzerland	Simoctocog alfa (Nuwiq®), prophylaxis, Different dosing, n=66	Exclude, not relevant comparator	**Dargaud Y, Negrier C, Rusen L,** et al. **Individual thrombin generation and spontaneous bleeding rate during personalised prophylaxis with Nuwiq (human-cl rhFVIII) in previously treated patients with severe haemophilia A. Haemophilia. 2018 Jul;24(4):619-627. doi: 10.1111/hae.13493. Epub 2018 May 31.**

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
Guardian 1, NCT00840086	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, n=150	Exclude, not relevant comparator	Lentz SR, Misgav M, Ozelo M, et al. Results from a large multinational clinical trial (guardian™1) using prophylactic treatment with turoctocog alfa in adolescent and adult patients with severe haemophilia A: safety and efficacy. Haemophilia. 2013 Sep;19(5):691-7. doi: 10.1111/hae.12159. Epub 2013 May 7. PMID: 23647704.
Guardian 2, NCT00984126	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 regimen n=158	Exclude, no outcome data 6-24 months	Lentz SR, Janic D, Kavakli K, et al. Long-term safety and efficacy of turoctocog alfa in prophylaxis and treatment of bleeding episodes in severe haemophilia A: Final results from the guardian 2 extension trial. *Haemophilia*. 2018; 24: e391–e394. https://doi.org/10.1111/hae.13617
Guardian 7, NCT02938585	A only	Phase 3 open-label, non-RCT	China	Turoctocog alfa (NovoEight®) prophylaxis, on-demand, n=26	Exclude, conducted outside of North America, UK, Europe	**Wu R, Sun J, Xu W,** et al. **Safety and Efficacy of Turoctocog Alfa in the Prevention and Treatment of Bleeding Episodes in Previously Treated Patients from China with Severe Hemophilia A: Results from the Guardian 7 Trial. Ther Clin Risk Manag. 2020 Jun 23;16:567–578. doi: 10.2147/TCRM.S243146. PMCID: PMC7320881. PMID: 32606716**
NCT04085458	A only	Phase 4 open-label,	Bulgaria, Denmark, Greece, Italy, Norway, Poland, Spain	Damoctocog alfa pegol (Jivi®),	Exclude, not relevant comparator	Holme PA, Poulsen LH, Tueckmantel C, et al. Safety and efficacy of damoctocog alfa pegol prophylaxis in patients with severe haemophilia A: Results of an interventional, post-marketing study. Haemophilia. 2024 Mar;30(2):388-

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		single-arm trial		prophylaxis, Different dosing, n=32		394. doi: 10.1111/hae.14930. Epub 2024 Jan 16. PMID: 38229269.
PROTECT VIII, NCT01580293	A only	Phase 2/3 open-label, RCT	Austria, Belgium, Canada, Colombia, Denmark, France, Germany, Israel, Italy, Japan, the Netherlands, Norway, Poland, Singapore, South Korea, Taiwan, Turkey, UK, US	Damoctocog alfa pegol (Jivi®) prophylaxis every 5 or 7 days, On-demand, n=134	Exclude, not relevant comparator	**Reding MT, Ng HJ, Poulsen LH,** et al. **Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII. Journal of Thrombosis and Haemostasis. 5: 411–419. https://doi.org/10.1111/jth.13597**
XTEND-1, NCT04161495	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 (ALTUVIIIO® or ALTUVOCT®) prophylaxis, On-demand, n=159	Exclude, not relevant comparator	von Drygalski A, Chowdary P, Kulkarni R, et al. XTEND-1 Trial Group. Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A. N Engl J Med. 2023 Jan 26;388(4):310-318. doi: 10.1056/NEJMoa2209226. PMID: 36720133.
ASPIRE, NCT01454739	A only	Open-label, non-RCT (Phase NR)	Europe (Ireland, the Netherlands, Poland, and the United Kingdom), North America (US), Australia, Hong Kong, South Africa	Efmoroctocog alfa (Eloctate®), Prophylaxis, On-demand Different dosing, n=211	Exclude, no outcome data 6-24 months	Nolan B, Mahlangu J, Perry D, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A. Haemophilia. 2016 Jan;22(1):72-80. doi: 10.1111/hae.12766. Epub 2015 Jul 27. PMID: 26218032.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
A-LONG, NCT01181128	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, n=165	Exclude, not relevant comparator	Mahlangu J, Powell JS, Ragni MV, et al. A-LONG Investigators. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014 Jan 16;123(3):317-25. doi: 10.1182/blood-2013-10-529974. Epub 2013 Nov 13. PMID: 24227821; PMCID: PMC3894491.
CSL627_1001, NCT01486927	A only	Phase 1/3 open-label, non-RCT	Europe, Japan, US	Lonoctocog alfa (Afstyla®), prophylaxis, on-demand, n=175	Exclude, not relevant comparator	Mahlangu J, Kuliczkowski K, Karim FA, et al.; AFFINITY Investigators. Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A. Blood. 2016 Aug 4;128(5):630-7. doi: 10.1182/blood-2016-01-687434. Epub 2016 Jun 21. PMID: 27330001; PMCID: PMC4974198.
CTR20201212, NCT04456387	A only	Phase 3 open-label, non-RCT	China	Recombinant Factor VIII-Fc Fusion Protein (FRSW107), prophylaxis, on-demand, n=119	Exclude, baseline data not available	Feng X, Hu Z, Yun C, et al.; Pharmacokinetics, Efficacy and Safety Evaluation of FRSW107 in Previously Treated Hemophilia a Patients: A Multicentre, Open-Label, Non-Randomized Phase III Study. *Blood* 2022; 140 (Supplement 1): 8468–8469. doi: https://doi.org/10.1182/blood-2022-158760
PROPEL, NCT02585960, EudraCT:	A only	Phase 3 open-label, RCT	Australia, Austria, Bulgaria, France, Germany, Hong Kong, Hungary, Israel, Italy, Malaysia, Norway, Poland, Romania, Singapore, Spain,	Rurioctocog alfa pegol (Adynovate®/ Adynovi®) FVIII troughs of 1% to 3% or	Exclude, not relevant comparator	Klamroth R, Windyga J, Radulescu V, et al. Rurioctocog alfa pegol PK-guided prophylaxis in hemophilia A: results from the phase 3 PROPEL study. Blood. 2021 Apr

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
2014-005477-37			Sweden, Switzerland, Taiwan, Turkey, Ukraine, UK, US	g FVIII troughs of 8% to 12%, prophylaxis n=115		1;137(13):1818-1827. doi: 10.1182/blood.2020005673. PMID: 33150384; PMCID: PMC8039905.
NCT01945593	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 n=216	Exclude, no outcome data 6-24 months	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. Haemophilia. 2020 Jul;26(4):e168-e178. doi: 10.1111/hae.14052. Epub 2020 Jun 28. PMID: 32597029.
EXTEN-A, NCT03205163	A only	Phase 1–2a open-label, sequential, non-RCT	Japan, US	Rurioctocog alfa pegol (Adynovate®/ Adynovi®) followed by Efanesoctocog alfa (Altuviiio; BIVV001), prophylaxis, Different dosing, n=16	Exclude, outcomes from BASIS not reported	Konkle BA, Shapiro AD, Quon DV, et al. BIVV001 Fusion Protein as Factor VIII Replacement Therapy for Hemophilia A. N Engl J Med. 2020 Sep 10;383(11):1018-1027. doi: 10.1056/NEJMoa2002699. PMID: 32905674.
PROLONGATE, NCT01736475	A only	Phase 2/3 open-label, parallel	Australia, Austria, Bulgaria, Czechia, Germany, Israel, Japan, Korea, Lithuania, Malaysia, the Netherlands, Poland, Romania,	Rurioctocog alfa pegol (Adynovate®/ Adynovi®) –	Exclude, not relevant comparator	Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. Blood. 2015 Aug 27;126(9):1078-85. doi: 10.1182/blood-2015-03-

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		assignment, non-RCT	Spain, Sweden, Switzerland, Taiwan, Ukraine, UK, US	prophylaxis, On-demand, n=137		630897. Epub 2015 Jul 8. PMID: 26157075; PMCID: PMC4551361.
Pathfinder 10, NCT05082116	A only	Phase 3 open-label, single-arm trial	China	Turoctocog alfa pegol (Esperoct®) prophylaxis NA, n=36	Exclude, conducted outside of North America, UK, Europe	Matsushita T, Mangles S. An overview of the pathfinder clinical trials program: Long-term efficacy and safety of N8-GP in patients with hemophilia A. J Thromb Haemost. 2020 Sep;18 Suppl 1(Suppl 1):26-33. doi: 10.1111/jth.14958. PMID: 32558236. PMCID: PMC7540506
Pathfinder 2, NCT01480180	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 n=186	Exclude, not relevant comparator	Giangrande P, Abdul Karim F, Nemes L, et al. Long-term safety and efficacy of N8-GP in previously treated adults and adolescents with hemophilia A: Final results from pathfinder2. J Thromb Haemost. 2020 Sep;18 Suppl 1(Suppl 1):5-14. doi: 10.1111/jth.14959. PMID: 32544297; PMCID: PMC7540590.
HOPE-B, NCT03569891	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), n=54	Exclude, not relevant comparator	Pipe SW, Leebeek FWG, Recht M, et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. N Engl J Med. 2023 Feb 23;388(8):706-718. doi: 10.1056/NEJMoa2211644. PMID: 36812434.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
AMT-061, NCT03489291	B only	Phase 2 open label, single-arm trial	Germany, the Netherlands, US	Etranacogene dezaparvovec (HEMGENIX®), NA, n=3	Exclude, later phase trial available	Von Drygalski A, Giermasz A, Castaman G, et al. Etranacogene dezaparvovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in hemophilia B. Blood Adv. 2019 Nov 12;3(21):3241-3247. doi: 10.1182/bloodadvances.2019000811. Erratum in: Blood Adv. 2020 Aug 11;4(15):3668. doi: 10.1182/bloodadvances.2020002987. PMID: 31698454; PMCID: PMC6855101.
AMT-060, NCT02396342	B only	Phase 1/2 open label, non-RCT	Denmark, Germany, the Netherlands	AAV5-hFIX (AMT-060), Different dosing, n=10	Exclude, manufacturer terminated product development	Miesbach W, Meijer K, Coppens M, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. Blood. 2018 Mar 1;131(9):1022-1031. doi: 10.1182/blood-2017-09-804419. Epub 2017 Dec 15. PMID: 29246900; PMCID: PMC5833265.
BENEGENE-2, NCT03861273	B only	Phase 3 open label, single-arm trial	Australia, Brazil, Canada, France, Germany, Greece, Japan, Korea, Republic of, Saudi Arabia, Sweden, Taiwan, Turkey, UK, US	Fidanacogene elaparvovec (BEQVEZ), FIX prophylaxis (lead-in phase), n=45	Exclude, not relevant comparator	Cuker A, Kavakli K, Frenzel L, et al. Gene Therapy with Fidanacogene Elaparvovec in Adults with Hemophilia B. N Engl J Med. 2024 Sep 26;391(12):1108-1118. doi: 10.1056/NEJMoa2302982. PMID: 39321362
SPK-9001-101, NCT02484092	B only	Phase 1/2a open label, single-arm trial	Australia, US	Fidanacogene elaparvovec (BEQVEZ), NA, n=15	Exclude, later phase results available	George LA, Sullivan SK, Giermasz A, et al. Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant. N Engl J Med. 2017 Dec 7;377(23):2215-2227. doi:

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
						10.1056/NEJMoa1708538. PMID: 29211678; PMCID: PMC6029626.
AskBio009-101, NCT01687608	B only	Phase 1/2 open label, non-RCT	US	BAX 335 (AskBio009), Different dosing, n=8	Exclude, outcomes from BASIS not reported	Konkle BA, Walsh CE, Escobar MA, et al. BAX 335 hemophilia B gene therapy clinical trial results: potential impact of CpG sequences on gene expression. Blood. 2021 Feb 11;137(6):763-774. doi: 10.1182/blood.2019004625. PMID: 33067633; PMCID: PMC7885820.
B-AMAZE, NCT03369444, NCT03641703 EdudraCT: 2017-000852-24, 2017-005080-40	B only	Phase 1/2 open label, non-RCT	UK	Verbrinacogene setparvovec (FLT180a), Different dosing, n=10	Exclude, later phase results available	Chowdary P, Shapiro S, Makris M, et al. Phase 1-2 Trial of AAVS3 Gene Therapy in Patients with Hemophilia B. N Engl J Med. 2022 Jul 21;387(3):237-247. doi: 10.1056/NEJMoa2119913. PMID: 35857660.
NR	B only	Open label, single-arm trial (Phase NR)	Bulgaria, Poland, Spain	Factor IX Grifols (AlphaNine® SD), prophylaxis, NA, n=25	Exclude, outcomes from BASIS not reported	**Lissitchkov T, Matysiak M, Zawilska K,** et al. **Haemophilia. 2010 Mar;16(2):240-6. An open clinical study assessing the efficacy and safety of Factor IX Grifols, a high-purity Factor IX concentrate, in patients with severe haemophilia B. doi: 10.1111/j.1365-2516.2009.02090.x. Epub 2009 Dec 14. PMID: 20015218**

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
NR	B only	Phase 3/4 open label, single-arm trial	The Netherlands, Poland	Human coagulation Factor IX (Nonafact®), prophylaxis, on-demand, n=60	Exclude, no outcome data 6-24 months	Mauser-Bunschoten EP, Budde IK, et al. An ultrapure plasma-derived monoclonal antibody-purified factor IX concentrate (Nonafact®), results of phase 3 and 4 clinical studies. Haemophilia, Vol 17, Issue 3: 439-445. https://doi.org/10.1111/j.1365-2516.2010.02453.x
B1821010, NCT01335061	B only	Phase 3 open label, non-RCT	Bulgaria, Canada, Croatia, Korea, Malaysia, Mexico, Poland, Singapore, Turkey	Nonacog alfa (BeneFIX®), prophylaxis, on-demand, n=25	Exclude, not relevant comparator	Kavakli K, Smith L, Kuliczkowski K, et al. Haemophilia. Once-weekly prophylactic treatment vs. on-demand treatment with nonacog alfa in patients with moderately severe to severe haemophilia B. Haemophilia. 2016 May;22(3):381-8. doi: 10.1111/hae.12878. Epub 2016 Jan 29.PMID:26823276
B1821059, NCT04286412	B only	Phase 4 open label, single-arm trial	India	Nonacog alfa (BeneFIX®) prophylaxis, NA, n=25	Exclude, conducted outside of North America, UK, Europe	Choraria N, Rangarajan S, John MJ, et al. Nonacog Alfa for Prophylaxis and Treatment of Bleeding Episodes in Previously Treated Patients with Moderately Severe or Severe Hemophilia B in India. Indian J Hematol Blood Transfus. 2022 Nov 27;39(4):630–634. doi: 10.1007/s12288-022-01588-0. PMCID: PMC10542435.PMID: 37790744
NR	B only	Open label, non-RCT (Phase NR)	Spain	Nonacog alfa (BeneFIX®), prophylaxis, on-demand,Different regimen. n=23	Exclude, outcomes from BASIS not reported	Korth-Bradley JM, Rendo P, Smith L, et al. Pharmacokinetics, Efficacy, and Safety of Nonacog Alfa in Previously Treated Patients with Moderately Severe to Severe Hemophilia B. Clin Ther. 2016 Apr;38(4):936-44. doi: 10.1016/j.clinthera.2016.02.015. PMID: 26969334

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
NR	B only	Double-blind crossover RCT (Phase NR)	France, Spain, UK, US	Nonacog alfa (BeneFIX®), prophylaxis, on-demand, Different regimen, n=34	Exclude, later phase results available	**Lambert T, Recht M, Valentino LA,** et al. **Reformulated BeneFix: efficacy and safety in previously treated patients with moderately severe to severe haemophilia B. Haemophilia.. 2007 May;13(3):233-43. DOI: 10.1111/j.1365-2516.2007.01458.x. PMID: 17498071.**
NCT01286779	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, n=117	Exclude, not relevant comparator	Windyga J, Stasyshyn O, Lissitchkov T, et al. Safety, Immunogenicity, and Hemostatic Efficacy of Nonacog Gamma in Patients With Severe or Moderately Severe Hemophilia B: A Continuation Study. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620950836. doi: 10.1177/1076029620950836. PMID: 32866032; PMCID: PMC7469725.
NCT01174446	B only	Phase 1/3 double-blind crossover RCT and open label single-arm	Argentina, Brazil, Bulgaria, Chile, Columbia, Czechia, Japan, Poland, Romania, Russian Federation, Spain, Sweden, Ukraine, UK	Nonacog gamma (RIXUBIS™), prophylaxis, on-demand, n=86	Exclude, not relevant comparator	Windyga J, Lissitchkov T, Stasyshyn O, et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B. Haemophilia. 2014 Jan;20(1):15-24. doi: 10.1111/hae.12228. Epub 2013 Jul 9. PMID: 23834666.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
NCT01507896	B only	Phase 3 open label, single-arm trial	Bulgaria, Chile, Columbia, Czech Republic, Poland, Romania, Russia, Ukraine	Nonacog gamma (RIXUBIS™), NA, n=40	Exclude, outcomes from BASIS not reported	Windyga J, Timofeeva M, Stasyshyn O, et al. Phase 3 Clinical Trial: Perioperative Use of Nonacog Gamma, a Recombinant Factor IX, in Previously Treated Patients With Moderate/Severe Hemophilia B. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620946839. doi: 10.1177/1076029620946839. PMID: 32816519; PMCID: PMC7444148.
KB037, EudraCT: 2005-006186-14	B only	Phase 2 open label, single-arm trial	Italy, Romania, Turkey	Kedrion FIX concentrate (AIMAFIX®), prophylaxis, on-demand, NA, n=16	Exclude, outcomes from BASIS not reported	Castaman G, Borchiellini A, Santagostino E, et al. Non-Compartment and compartmental pharmacokinetics, efficacy, and safety of Kedrion FIX concentrate. Eur J Pharm Sci. 2020 Oct 1;153:105485. doi: 10.1016/j.ejps.2020.105485. Epub 2020 Jul 23. PMID: 32712218.
NR	B only	Open label, single-arm trial (Phase NR)	NR	Plasma-derived FIX concentrate (Haemonine), prophylaxis, on-demand, NA, n=29	Exclude, historical product not widely used	**Serban M, Skotnicki AB, Colovic M,** et al. **Clinical efficacy, safety and pharmacokinetic properties of the plasma-derived factor IX concentrate Haemonine in previously treated patients with severe haemophilia B. Haemophilia. 2012 Mar;18(2):175-81. doi: 10.1111/j.1365-2516.2011.02624.x. Epub 2011 Aug 3. PMID: 21812863**
IB1001-01, NCT00768287	B only	Phase 3 crossover RCT &	France, India, Israel, Italy, Poland, UK, US	Trenonacog alfa (Ixinity®),	Exclude, not relevant comparator	**Collins PW, Quon DVK, Makris M,** et al. **Pharmacokinetics, safety and efficacy of a recombinant factor IX product, trenonacog alfa in previously treated haemophilia B**

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
		open label non-RCT		prophylaxis, on-demand, n=76		patients. Haemophilia, Vol24, Issue1: 104-112. doi.org/10.1111/hae.13324
PROLONG-9FP (primary study), NCT01496274	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®), n=63	Exclude, not relevant comparator	Santagostino E, Martinowitz U, Lissitchkov T, et al; PROLONG-9FP Investigators Study Group. Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. Blood. 2016 Apr 7;127(14):1761-9. doi: 10.1182/blood-2015-09-669234. Epub 2016 Jan 11. PMID: 26755710; PMCID: PMC4825413.
PROLONG-9FP (extension), NCT02053792	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, n=59	Exclude, no outcome data 6-24 months	Mancuso ME, Lubetsky A, Pan-Petesch B, et al: Long-term safety and efficacy of rIX-FP prophylaxis with extended dosing intervals up to 21 days in adults/adolescents with hemophilia B. J Thromb Haemost. 2020 Mar 30;18(5):1065–1074. doi: 10.1111/jth.14778. PMID: 32078256. PMCID: PMC7318213
DLZ-20, NCT03995784	B only	Phase 2 open label single-arm trial	South Africa	Dalcinonacog alfa (DalcA), prophylaxis, NA, n=6	Exclude, outcomes from BASIS not reported	Mahlangu J, Levy H, Lee M, et al. Efficacy and safety of subcutaneous prophylaxis with dalcinonacog alfa in adults with haemophilia B. Haemophilia. 2021 Jul;27(4):574-580. doi: 10.1111/hae.14315. Epub 2021 May 6. PMID: 33960073; PMCID: PMC8359950.

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
ISU304-001/CB2679d, NCT03186677	B only	Phase 1/2a open label non-RCT	South Korea	Dalcinonacog alfa (DalcA), prophylaxis Different dosing, n=13	Exclude, outcomes from BASIS not reported	You CW, Hong SB, Kim S, et al. Safety, pharmacokinetics, and pharmacodynamics of a next-generation subcutaneously administered coagulation factor IX variant, dalcinonacog alfa, in previously treated hemophilia B patients. J Thromb Haemost. 2021 Apr;19(4):967-975. doi: 10.1111/jth.15259. Epub 2021 Mar 24. PMID: 33540485.
B-LONG, NCT01027364	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, n=123	Include	Powell JS, Pasi KJ, Ragni MV, et al; B-LONG Investigators. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013 Dec 12;369(24):2313-23. doi: 10.1056/NEJMoa1305074. Epub 2013 Dec 4. PMID: 24304002.
B-YOND, NCT01425723	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, n=116	Include	Pasi KJ, Fischer K, Ragni M, et al. Long-term safety and efficacy of extended-interval prophylaxis with recombinant factor IX Fc fusion protein (rFIXFc) in subjects with haemophilia B. Thromb Haemost. 2017 Feb 28;117(3):508-518. doi: 10.1160/TH16-05-0398. Epub 2016 Dec 22. PMID: 28004057
Paradigm 2, NCT01333111	B only	Phase 3 single blind RCT	France, Germany, Italy, Japan, Macedonia, Malaysia, the Netherlands, Russian Federation,	Nonacog beta pegol (Rebinyn®)	Exclude, not relevant comparator	Collins PW, Young G, Knobe K, et al; paradigm 2 Investigators. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomised

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
			South Africa, Thailand, Turkey, UK, US	prophylaxis, on-demand, n=74		phase 3 trial. Blood. 2014 Dec 18;124(26):3880-6. doi: 10.1182/blood-2014-05-573055. Epub 2014 Sep 26. PMID: 25261199; PMCID: PMC4271178.
Paradigm 4, NCT01395810	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, n=71	Exclude, no outcome data 6-24 months	Young G, Collins PW, Colberg T, et al. Nonacog beta pegol (N9-GP) in haemophilia B: A multinational phase 3 safety and efficacy extension trial (paradigm™4). Thromb Res. 2016 May:141:69-76. doi: 10.1016/j.thromres.2016.02.030. PMID: 26970716

Table 37. Manually added study of relevance included from other sources

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
NCT05145127	A and B	Phase 3 interventional, multi-centre, multi-country, open-label extension study	Australia, Canada, China, Croatia, France, Hong Kong, India, Israel, Italy, Japan, Republic of Korea, Mexico, Oman, Serbia, South Africa, Spain, Taiwan, Turkey, US	Marstacimab (PF-06741086), Factor replacement (lead-in) estimated n=245	Include	Clinicaltrial.gov, Not yet published

Study/ID	Haemophilia type	Study design	Country	Intervention and comparator (sample size (n))	Consideration for ITC assessment	Reference
B-LONG NCT01027364	B only	Phase 3, open label, non-RCT	Patients from six continents: Africa, Asia, Australia, Europe, North and South America	50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially (Group 1) rFIX: Recombinant Factor IX 50 IU/kg BeneFIX® administered IV	Include	Powell JS, Pasi KJ, Ragni MV, Ozelo MC, Valentino LA, Mahlangu JN, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013;369(24):2313-23.

Table 38: Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
BASIS, NCT03938792	To demonstrate the efficacy and safety of marstacimab for routine prophylaxis	Phase 3 one-way crossover single-arm trial	Haemophilia A or B participants	Marstacimab Factor replacement (lead-in), n=128	ABR for treated bleeds at 12 months post-marstacimab initiation versus factor replacement therapy use in the observation phase	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 at 12 months HAL/pedHAL PGIC-H QoL: Haem-A-QoL/Haemo-QoL , EQ-5D-5L Safety and tolerability outcomes
B-LONG, NCT01027364	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, vs. on-demand Different regimen, n=123	ABR for all bleeds at 52 weeks	Number of Participants with Potentially Clinically Significant Laboratory Abnormalities Number of Participants with TEAEs and TESAEs Number of Participants with Non-serious TEAEs during the Surgical / Rehabilitation Period Number of Participants with TESAEs During the Surgical / Rehabilitation Period Incidence Rate of FIX Inhibitor Development Comparison of Annualized Bleeding

B-YOND, NCT01425723	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, n=116	Number of Participants With Any Positive Inhibitor Development, at 5 years	ABR at 5 years ABR, spontaneous joint bleeds, at 5 years Total Number of Exposure Days, at 5 years Annualized rFIXFc Consumption (International Units Per Kilogram [IU/kg]), at 5 years Physicians' Global Assessment of Participant's Response to rFIXFc Regimen Using a 4-Point Scale, at 5 years Participant's Assessment of Response (Excellent or Good Response) to rFIXFc Injections for the Treatment of Bleeding Episodes Using a 4-Point Scale, at 5 years

D.1.4 Quality assessment

As recommended by the National Institute for Health and Care Excellence (NICE), the quality assessment of all included studies was conducted using the Cochrane Risk of Bias Assessment Tool 2 (RoB 2) for randomised controlled trials. In addition, non-randomised trials, including single-arm trials, were assessed using a modified version of the Downs and Black Checklist. The initial feasibility assessment consisted of the following seven points:

- Were baseline characteristics reported for the target population?
- Did the trial report at least one primary or secondary outcome from the BASIS trial?
- Did the trial include any individuals from North America, Europe, or the United Kingdom? 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? 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? If so, the most relevant data for a given comparator treatment is the phase 3 or 4 data.
- 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 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 38.

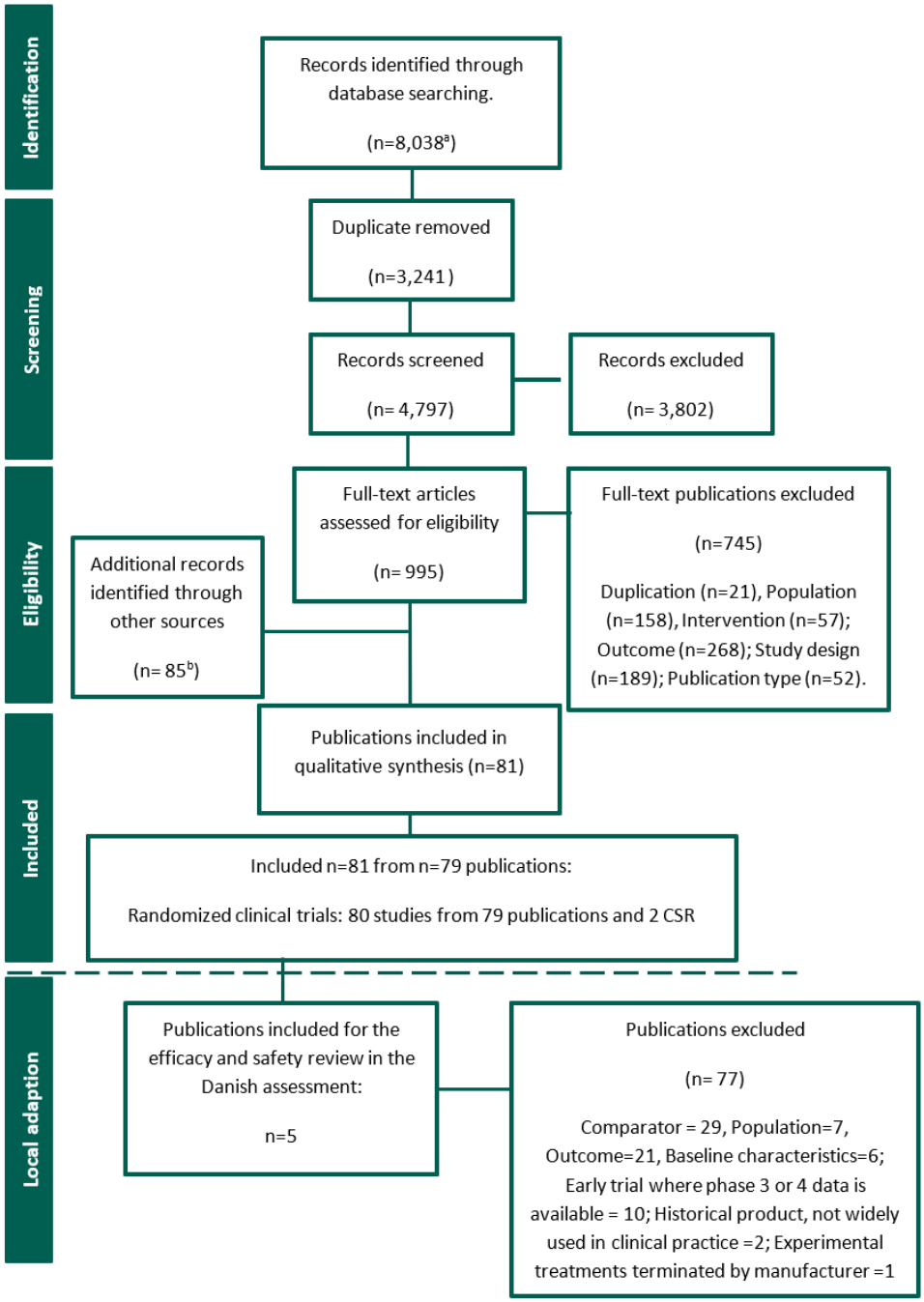
D.1.5 Unpublished data

The application contains unpublished data from two sources:

Some data from the BASIS trial is derived from the clinical study report this data is not expected to be published.

Data from the long-term extension of BASIS, the OLE-study will be published, but the study is ongoing, and the specific data included in this application is not yet peer-reviewed. As this is a long-term extension of the BASIS-study, the publication of results is not yet planned, and the timepoint published may deviate from those reported in this application.

Figure 3. PRISMA diagram



[a]Databases: MEDLINE (n=2,740), Embase (n=4,524), CENTRAL (n=437), CDSR (n=45), DARE (n=8), EconLit (n=4), NHSEED (n=26). Trial registries: Clinical trial.gov (n=107), ICTRP (n=124); EMA EPAR (n=23); [b]Conference manual search (n=73); Citation searching (n=53); Hand search (n=38); Clinical study report (n=1). These 165 records were screened, whereas 82 were excluded, and 83 continued to eligibility and 2 were added manually. Note that after the publication of BASIS 1, the real results are an inclusion of n=80 from 79 publications and 2 CSR.

Appendix E. Safety data for marstacimab

Injection Site Reactions

Injection-site reactions occurred in [redacted] of all patients treated with marstacimab in the BASIS study (previously treated with on-demand and prophylactic treatment) (21). In the population previously treated with prophylactic treatment, injection site reactions occurred in 9 (10.8%) patients. No occurrence of injections site reactions led to a dose adjustment or discontinuation of marstacimab (34).

The majority of injection-site reactions observed in the clinical studies with marstacimab were transient, all were reported as mild to moderate in severity, and no occurrences led to a dose adjustment or drug discontinuation. Injection site reactions included: injection site bruising, injection site erythema, injection site haematoma, injection site induration, injection site oedema, injection site pain, injection site pruritus, and injection site swelling (34).

Serious Adverse Events

In Table 39 SAEs in BASIS and its long-term extension study are listed in full, i.e. for patients treated with prophylactic and on demand. A total of 87 of the 116 patients completing the 12-month treatment period had enrolled into the OLE study at the time of data cut-off 17th Apr 2023. The median duration of exposure was [redacted] (21).

Table 39. Summary of serious adverse events (all causalities) by system organ class and preferred term – marstacimab dataset

	BASIS (n=116) n (%)	NCT05145127 OLE (n=[redacted]) n (%)
Number of participants with SAE (%)	7 (6.0)	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Tympanic membrane perforation	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Inflammation	[redacted]	[redacted]
Peripheral swelling	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]
Infections and infestastations	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Contusion	[redacted]	[redacted]

Traumatic haemorrhage	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Haemarthrosis	[redacted]	[redacted]
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]
Meningioma	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Haemorrhage	[redacted]	[redacted]
Total Number of Cases[a]	[redacted]	[redacted]

[a]Total number of events per participant per cohort, number of cases that started in the cohort; Data collection of SAE from Safety Data Warehouse or Argus. MedDRA v25.1 coding dictionary applied. Source: EPAR (42).

Safety for dose escalated patients

[redacted] were dose escalated from 150 mg marstacimab weekly to 300 mg weekly during the active treatment phase.

Of these, none experienced an SAE or TEAE that led to discontinuation of the study intervention (34). TEAEs while on 300 mg weekly marstacimab for patients who increased their marstacimab dose from 150 mg to 300 mg are presented in Table 40.

Table 40. Summary of TEAEs in patients who dose escalated during the BASIS study

	Dose adjusted marstacimab prophylaxis during ATP (n=11)
Number of patients, n (%)	
With any TEAE	[redacted]
Infections and Infestations	[redacted]
Laryngitis	[redacted]
Rhinitis	[redacted]
Musculoskeletal and Connective Tissue Disorders	[redacted]
Arthralgia	[redacted]
Joint range of motion decreased	[redacted]

Abbreviations: ATP: active treatment phase; mg: milligram; TEAE: Treatment Emergent Adverse Event. Source: Pfizer marstacimab Phase 3 BASIS trial CSR. 2023 (28)

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk