Medicinrådet

Bilag til direkte indplacering af concizumab (Alhemo) i Medicinrådets af evidensgennemgang vedrørende lægemidler til hæmofili B

Vers. 1.0

Bilagsoversigt

1. Ansøgers bemærkninger vedr. concizumab (Alhemo)
2. Ansøgers endelige ansøgning vedr. concizumab (Alhemo)

Til Medicinrådet

Vi takker Medicinrådet for det fremsendte udkast til tillæg til Medicinrådets evidensgennemgang vedrørende lægemidler til hæmofili B.

Novo Nordisk er enig i Medicinrådets vurdering om, at concizumab kan ligestilles med marstacimab til patienter med hæmofili B fra 12 år med vanskelig veneadgang eller complianceproblemer, og at concizumab indplaceres i behandlingsvejledningens Tabel 4-1.

Vi har et par bemærkninger til det fremsendte tillægsdokument, som vi håber, at I vil tage højde for i jeres endelige vurdering:

- Tidspunktet for Medicinrådets afgørelse står fortsat til at være d. 18. februar 2026, på trods af at vurderingen af concizumab kommer på rådsmødet d. 21. januar 2026. Vi antager, at tidspunktet for Medicinrådets afgørelse derfor skal rykkes til 21. Januar 2026.
- Der er en fejl i Medicinrådets afrapportering af antallet af patienter med reaktioner på injektionsstedet i EXPLORER 8. Det er kun 12 (19%) patienter, som har oplevet reaktioner på injektionsstedet og ikke 27, som Medicinrådet skriver.
- Vi undrer os over, at Fagudvalgets bekymring, *beskrevet i tillægget til Medicinrådets evidensgennemgang vedrørende marstacimab*, om dosisøgning af marstacimab ikke er nævnt. Fagudvalget vurderede, at de ville være forbeholdne for en dosisøgning af marstacimab til 300 mg/uge grundet det lille erfaringsgrundlag. Dette er relevant i relation til, at Medicinrådet fremhæver, at der kan være et økonomisk argument for at starte patienter med meget høj vægt op i marstacimab, da marstacimab administreres uafhængigt af vægt.
- Under 'Andre overvejelser' nævnes det, at *ifølge produktresumeerne vil et skift fra anden non-faktor-terapi formentlig kræve en udvaskningsperiode på ca. 3 måneder, hvor der kan være behov for understøttende faktorterapi*. Dette er korrekt ved et skift fra emicizumab, hvor halveringstiden er meget lang (ca. 28 dage). Halveringstiden for concizumab er til gengæld meget kort (ca. 38 timer), mens det for marstacimab er ca.16-18 dage. Der gælder derfor, at der ikke kan generaliseres indenfor non-faktor terapier, og at halveringstiden er meget kort med concizumab, hvilket er relevant at nuancere i nuværende afsnit.

Med venlig hilsen

Annie Hansen,
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Application for the assessment of Alhemo® treatment in haemophilia B without inhibitors

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Tables and Figures

Abbreviations

ABR	Annualised bleeding rate
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
CACO	Confirmatory analysis cut-off
CHO	Chinese hamster ovary
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CV	Cardiovascular
CVAD	Central venous access device
DMC	Danish Medicine Council
E	Number of events/episodes
EHL	Extended half-life
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimension
ETD	Estimated treatment difference
EU	European Union
EUR	Euros
F	Factor
FAS	Full analysis set
FDA	Food and Drug Administration
HA	Haemophilia A
Haem-A-QoL	Haemophilia A quality of life
HB	Haemophilia B
Hemo-TEM	haemophilia treatment experience measure
HIV	Human immunodeficiency virus
H-PPQ	Haemophilia Patient Preference questionnaire
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ISTH	International Society on Thrombosis and Haemostasis
ITI	Immune tolerance induction
IU	International units
IWRS	Interactive web response systems
MMRM	Mixed model for repeated measurements
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

OR	Odds ratio
OT	On-treatment
PD	Pharmacodynamic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PPX	Prophylaxis
PRO	Patient reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PYE	Patient years of exposure
QoL	Quality of life
R	Rate
RCT	Randomised controlled trial
rFVIIa	Recombinant FVIIa
RR	Rate ratio
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SF-36 v2	Short-Form-36 Dimension version 2
SLR	Systematic literature review
SPC	Summary of product characteristics
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centre Doctors' Organisation
US	United States
USD	United States dollars
WFH	World Federation of Hemophilia

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Alhemo®
Generic name	Concizumab
Therapeutic indication as defined by EMA	Concizumab is indicated for routine prophylaxis of bleeding in patients with: • Haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors aged 12 years or older • Haemophilia B (congenital factor FIX deficiency) with FIX inhibitors aged 12 years or older • Severe haemophilia A (congenital factor VIII deficiency) without FVIII inhibitors aged 12 years or older • Moderate/severe haemophilia B (congenital factor FIX deficiency) without FVIII inhibitors aged 12 years or older
Marketing authorization holder in Denmark	Novo Nordisk A/S, Novo Alle 1, DK-2880 Bagsvaerd, Danmark
ATC code	B02BX10
Combination therapy and/or co-medication	No
Date of EC approval	22 August 2025
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	No

Overview of the pharmaceutical	
Other indications that have been evaluated by the DMC (yes/no)	Yes • Haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors aged 12 years or older • Haemophilia B (congenital factor FIX deficiency) with FIX inhibitors aged 12 years or older
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Concizumab is supplied in a portable single-use, single-dose pre-filled pen consisting of a 1.5 ml or 3 ml glass cartridge sealed in a pen, made of plastic components and metal springs. The cartridge is closed at the bottom with a rubber disc and at the top with a laminate rubber disc sealed with an aluminium lid. The rubber discs are not made with natural rubber latex. The pre-filled pen is packed in a carton. Concizumab is available in the following pack sizes (pack size of 1 pre-filled pen and multipack of 5 packs of 1 pre-filled pen) and the dose button and cartridge of the pen injector are colour-coded according to strength: <u>Alhemo® 15 mg/1.5 ml solution for injection in pre-filled pen</u> One ml of solution contains 10 mg of concizumab*. Each pre-filled pen contains 15 mg of concizumab in 1.5 mL of solution (10 mg/mL). <u>Alhemo® 60 mg/1.5 ml solution for injection in pre-filled pen</u> One ml of solution contains 40 mg of concizumab*. Each pre-filled pen contains 60 mg of concizumab in 1.5 mL of solution (40 mg/mL). <u>Alhemo® 150 mg/1.5 ml solution for injection in pre-filled pen</u> One ml of solution contains 100 mg of concizumab*. Each pre-filled pen contains 150 mg of concizumab in 1.5 mL of solution (100 mg/mL). <u>Alhemo® 300 mg/3 ml solution for injection in pre-filled pen</u> One ml of solution contains 100 mg of concizumab*. Each pre-filled pen contains 300 mg of concizumab in 3 mL of solution (100 mg/mL). *Concizumab is a humanized IgG4 monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary cells (CHO). Not all pack sizes may be marketed. It is expected that concizumab in Denmark will mainly be marketed as single packs. The device for concizumab is the same device that is used in a large number of other Novo Nordisk products in e.g. diabetes (e.g. Ozempic®, Wegovy®, Tresiba®) and growth hormone treatment (Norditropin® FlexPro®). Needles are not included. Concizumab is designed for use with NovoFine Plus or NovoFine 32G needles with a length of 4 mm. If

Overview of the pharmaceutical	
	needles longer than 4 mm are used, injection techniques that minimise the risk of intramuscular injection, such as injection into a loosely held skin fold, should be used.

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Moderate/severe haemophilia B (HB) (congenital factor FIX deficiency ≤2%) without FVIII inhibitors aged 12 years or older
Dosage regiment and administration:	The recommended dosing regimen is • Day 1: Starting dose of 1 mg/kg once. • Day 2 and until individual determination of maintenance dose: once daily of 0.20 mg/kg. • 4 weeks after treatment initiation: measurement of concizumab plasma concentrations prior to administration of the next scheduled dose. The measurement must be performed using a validated in vitro diagnostic test. Once the result for concizumab plasma concentrations is available: the individual maintenance dose is determined once based on the plasma concentration of concizumab, either 0.15, 0.20 or 0.25 mg/kg once daily.
Choice of comparator	The current treatment guideline for HB recommends marstacimab (Hympavzi®) in patients with difficulty venous access and compliance issues where weekly intravenous infusions are not possible, hence marstacimab is the relevant comparator for concizumab. Marstacimab is similar to concizumab a human monoclonal antibody and an anti-tissue factor pathway inhibitor (anti-TFPI) antibody, but with a once-weekly subcutaneous injection rather than once-daily administration of concizumab. Recommended marstacimab dose: 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. During the clinical trial (BASIS) of marstacimab, 6 patients with severe HB were titrated to a weekly dose of 300mg for maintenance (equivalent to 33% of the total HB population). A dose adjustment to 300 mg subcutaneous injection weekly can be considered in patients weighing ≥ 50 kg when control of

Summary	
	bleeding events is judged to be inadequate by the healthcare professional. The maximum weekly dose of 300 mg should not be exceeded.
Most important efficacy endpoints (Difference/gain compared to comparator)	Median ABR: 1.6 (0.0–4.8) Inhibitor: 0 Anaphylaxis: 0 Thromboembolic events: 0 HRQoL: - SF-36 bodily pain: ETD 14.64 (3.37; 25.91) vs on-demand - Haem-A-QoL total score: ETD -17.55 (-28.77; -6.33) vs on-demand
Most important serious adverse events for the intervention and comparator	Overall, adverse events were of a mild nature, while serious adverse events (SAE) were rare for both concizumab and marstacimab. Two non-fatal thromboembolic events occurred in patients with HA in EXPLORER 8 for concizumab prior to study pause, while there were no events after resumption of the clinical study and new risk prevention procedures were integrated into the protocol. For marstacimab one SAE was reported. No serious thromboembolic events occurred during the 12-months intervention in the BASIS 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 chronic bleeding disorder caused by deficiency or dysfunction of the coagulation proteins Factor VIII (FVIII) in Haemophilia A (HA) or factor X (FIX) in Haemophilia B (HB) (1) (2) (3). HA is estimated to account for 80–85% of all haemophilia cases. HB is less common, accounting for 15–20% of cases (4).

Haemophilia is an X-linked recessive disorder, and therefore predominantly affects males. It usually occurs due to the inheritance of a pathogenic variant of the FVIII or FIX gene; however, in some cases haemophilia may arise following spontaneous FVIII/FIX mutations in people without previous family history (5).

Table 1: Haemophilia classification by severity

Severity	Clotting factor level	Bleeding phenotype
Severe	<1% of normal or <1 IU/dL (<0.01 IU/mL)	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable haemostatic challenge
Moderate	1–5% of normal or 1–5 IU/dL (0.01–0.05 IU/mL)	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5% to <40% of normal or 5–40 IU/dL (0.05–0.40 IU/mL)	Rare spontaneous bleeding; severe bleeding with major trauma or surgery

Source: Srivastava et al., 2020

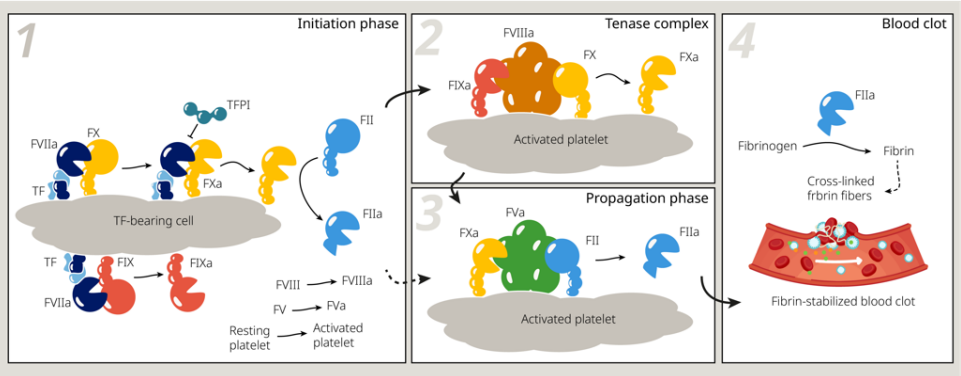
Pathophysiology

Normal haemostasis comprises a highly complex system that balances the procoagulant, anticoagulant and fibrinolytic processes. These function together to maintain blood fluidity within the vascular system while also limiting haemorrhage by initiating rapid clot formation in response to vascular damage (1).

The coagulation process is characterised by the sequential activation of three vitamin K-dependent serine proteases factor VII (FVII), factor IX (FIX) and factor X (FX) and their cofactor complexes;(tissue factor (TF), factor VIII (FVIII) and factor V (FV). The cell-based model of coagulation is summarised in Figure 1 and describes the coagulation process as it occurs *in vivo*, in three overlapping stages – initiation, amplification and propagation – that result in a burst of thrombin generation (6) (7) (8). This leads to cleavage of fibrinopeptide A from fibrinogen, resulting in the polymerisation of soluble fibrin molecules into fibrin strands, and the formation of an insoluble fibrin matrix. FVIII and FIX play essential roles in the coagulation process; in people with haemophilia FVIII/FIX

deficiency leads to haemostatic imbalance, rendering their system unable to support continued clot formation (8).

Figure 1: The cell-based model of normal coagulation



Adapted from Smith et al. 2009 and Hoffman and Monroe 2001.
The **initiation** phase occurs on TF-bearing cells generally localised outside the vasculature (e.g. fibroblasts) when injury exposes them to the flowing blood, leading to rapid binding of circulating FVIIa to exposed TF. This leads to release of a small amount of FIIa (thrombin) and activation of platelets that have leaked from the vasculature at the site of injury activated forms of FV, FVIII and FXI. The various enzymes on the activated platelet assemble on the procoagulant membrane of the activated platelet to form the intrinsic **tenase complex** (FIXa-FVIIIa), resulting in rapid FXa generation on the platelet surface. The **propagation phase** involves release of activated thrombin and a burst of thrombin generation directly on the platelet and the formation of a **blood clot**.

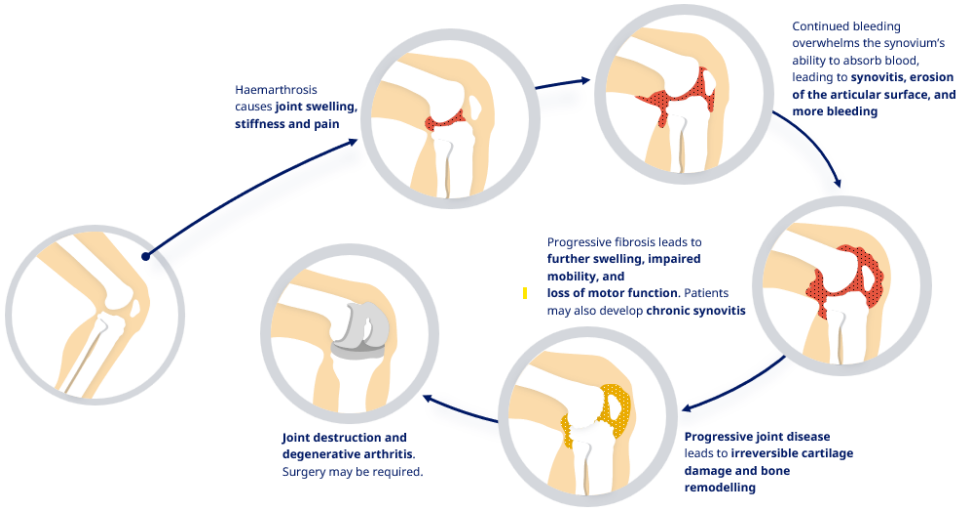
Bleeding episodes

Haemophilia is characterised by spontaneous, painful bleeding episodes, and prolonged, excessive haemorrhage following trauma or surgery (4) (9) (10). The frequency and severity of bleeding episodes generally correlate with the degree of FVIII/FIX deficiency.

Bleeding into joints (haemarthrosis) can lead to crippling joint disease and disability; this is the hallmark of the severe phenotype, with joint bleeds accounting for 70%–80% of all bleeding episodes in severe haemophilia (1) (11). Without adequate treatment, haemarthrosis induces a cascade of degenerative processes affecting the synovium, cartilage and bone, leading to progressive joint disease (haemophilic arthropathy) (1) (10). Arthropathy is the single largest cause of morbidity in people with haemophilia and is associated with pain and disability (12) (13), reduced HRQoL (14)and long-term orthopaedic complications (15).

Target joints are defined as those in which three or more spontaneous bleeds have occurred within a consecutive 6-month period (3, 120); typically, these include knees, elbows, and ankles. Target joints are a major cause of arthropathy and debilitating pain (14), and are reported to occur in 59% and 54% of HA and People with HB, respectively (1) (16). In a survey of people with haemophilia in Europe with at least one target joint (N=714), 70% of target joints required surgical intervention (17). A range of procedures are used including synovectomy, arthroscopy (especially in the ankle or elbow joint), osteotomy (to correct angular deformity), prosthetic joint replacement, or arthrodesis (for painful ankle joint arthropathy) (1) (17). However, surgery is complex in people with haemophilia due to the risk of bleeds and infection (18).

Figure 2: Long-term impact on joint bleeds



Sources: Kizilocak et al. 2019 (1) and Llinás et al. 2020 (10)

Haemophilia with inhibitors

The development of neutralising anti-FVIII/FIX antibodies (inhibitors) against exogenous clotting factor replacement therapy is one of the most serious and challenging complications of haemophilia, occurring in approximately 25–30% of people with HA and 1–6% of those with HB (19) (20) (21) (22). The presence of circulating inhibitors partially or completely inactivates infused factor proteins, impairing their clinical efficacy and making the management of bleeding much more difficult than in those without inhibitors (23) (24). As a result, the clinical and humanistic burden is considerably greater in people with inhibitors vs without (25) (26) (27).

Patient prognosis with current treatments

Current standard treatments with extended half-life (EHL) factor IX products reduce the risk of bleeding during prophylactic treatment but are administered intravenously. Intravenous treatment is a significant burden on patients' daily life and quality of life, which for some results in decreased compliance and inadequate disease control. Especially for patients with difficult venous access, where an intravenous port may be needed. However, this comes with a risk of infection, mechanical problems and catheter-related blood clots, which is a significant treatment burden for patients (28) (29). A global study in haemophilia treatment has shown that difficult venous access was the most cited factor in influencing compliance. This was indicated by both patients and nurses in the study (30).

There is therefore a need for a treatment for patients with moderate/severe HB and difficult venous access with a form of administration that ensures higher compliance and reduces the treatment burden as well as the risks associated with the intravenous infusions.

Patient population

In Denmark, the disease prevalence of HB is 1 in 30,000 boys/men (31), of which 43 patients have moderate or severe HB, and 88% of these is 12+ years at the end of 2022 (National Patient Register, the Laboratory Database and the Hospital Medicine Register (2018-2022)). All haemophilia patients in Denmark are affiliated with one of the two national haemophilia centres in Aarhus and Copenhagen.

In Pfizers' submission of marstacimab to DMC, they state that during the summer of 2023, the two centres reported 25 patients with severe HB on prophylactic treatment (32).

The Danish Medicines Council's (DMC) treatment guidelines for HA recommend considering emicizumab for patients with difficult venous access where it is not possible to carry out prophylaxis with an EHL drug, or who have compliance problems, where it is not possible to carry out prophylaxis with weekly intravenous injections, or who have breakthrough bleeds despite optimized prophylaxis with an EHL drug. The Danish Medicine Counsel (DMC) estimates that 30% of the HA population may be treated with emicizumab (33).

On this basis, it is similarly assessed that there is a proportion of patients with HB with difficult venous access, compliance problems with weekly intravenous injections or repeated documented breakthrough bleeds despite attempts of either optimized prophylaxis treatment with an EHL drug or where gene therapy is not possible, and who have a clinically unmet need for a subcutaneous form of administration.

Table 2 shows the expected number of patients with HB ≥12 years in the coming 5 years, counting 2025 as "year 1". The number of patients is based on insights from Pfizers application of marstacimab to DMC earlier this year. The no. of patients with difficult venous access and compliance issues with intravenous injections is estimated applying the 30% proportion from the DMCs treatment guidelines for HA. These are the number of HB patients in Denmark which are likely to initiate concizumab.

Table 2 Estimated number of patients in Denmark aged ≥12 years with HB

Year	Year 1	Year 2	Year 3	Year 4	Year 5
No. of HB patients in Denmark ≥12 years on prophylactic treatment	25	25	25	25	26
- **No. of HB patients with difficult venous access and compliance issues with intravenous injections**	8	8	8	8	8

Abbreviations: **HB**: Haemophilia B, **Sources**: Medicinrådet, Bilag til direkte indplacering af marstacimab i Medicinrådets evidensgennemgang vedrørende lægemidler til hæmofili A og B, vers. 1.0; (33).

Current treatment options

According to the current national treatment guideline for HB, v.1.2, approved 3rd September 2025, all extended half-life rFIX products, *nonacog beta pegol* (Refixia®), *eftrenonacog alfa* (Alprolix®) and *albutrepenonacog alfa* (Idelvion®) are recommended for patients where there is a medical indication for prophylaxis with an EHL treatment, whereas patients with a medical need for a high trough level can choose btw. *Refixia®* and *Idelvion®* only (34). Recently, the weekly anti-TFPI treatment marstacimab has been granted European marketing authorization with an indication for the prophylactic treatment of people with severe HA and HB without inhibitors aged 12 years and above.

Earlier this year, marstacimab was assessed by the DMC, which concluded that albeit the prophylactic effect on managing bleeding episodes with marstacimab was comparable to that of other recombinant extended half-life products, the Expert Committee commented on the following limitations with marstacimab:

- lack of knowledge about safety and handling of acute illness and major surgery
- Risk of thromboembolism in patients with risk factors
- Limited safety data compared to existing treatments

The above arguments – were also raised by the DMC and the Expert Committee for haemophilia in the recent decision, where concizumab was approved for treatment of HAwI & HBwI. Therefore, until further evidence has been provided, we do not see it likely that concizumab will be viewed as standard of care together with rFIX EHL products for treatment of HB patients aged 12 years and above. Hence also, why we've applied for having concizumab approved as a new treatment option for the same subgroup of patients that marstacimab recently was approved for in the DMC's national treatment

guideline for HB – i.e. in patients *with difficult venous access or compliance issues to current EHL treatment.*

Within HB there are furthermore another treatment alternative available, gene therapy, with etranacogene dezaparvovec (Hemgenix®), which has also been marketed in Denmark and recommended by the DMC as a potential standard treatment for selected subgroups of HB patients.

Choice of comparator

Concizumab is expected based on the minimal clinical relevant differences put forward by the Expert Committee members and the DMC to be considered clinically equivalent to marstacimab with similar limitations as stated above. Due to the subcutaneous form of injection, concizumab will, like marstacimab, be a potential preferable treatment alternative for HB patients with difficult venous access and compliance issues to current weekly- or bi-weekly intravenous infusions (35), or where there are repeated documented break-through bleeds despite attempts at either optimized prophylaxis with an EHL drug or where gene therapy is not deemed feasible.

Hence, the relevant comparator for concizumab will be marstacimab.

In the DMC's treatment guidelines for HA, emicizumab (subcutaneous injection) is recommended for patients with difficult venous access, and for whom prophylaxis treatment with an EHL product is not possible, or for patients who have compliance issues where prophylaxis treatment with weekly intravenous infusions is not possible, or for patients who have breakthrough bleeds despite optimized prophylaxis with an EHL product. The DMC states that treatment with emicizumab should be considered for up to 30% of the HA population. (28)

As concizumab is also a subcutaneous injection for patients with HB, where current treatment options are only intravenous infusions, it is expected that concizumab, in the same way as emicizumab for patients with HA, will be a relevant treatment option for patients with HB to a similar proportion of patients with difficult venous access, compliance issues with weekly intravenous infusions or repeated documented breakthrough bleeds despite optimized prophylaxis with an EHL product, or where gene-therapy is not possible.

Marstacimab is a once weekly subcutaneous injection and the pen comes with a 27G pre-attached hidden needle (36). In contrast, concizumab comes with a 32G needle which is thinner than the 27G needle (0.23 mm vs 0.4 mm in diameter). In addition, concizumab comes with an in vitro diagnostic measurement (ELISA Kit) of plasma concentrations to easy follow up of concizumab plasma concentration 4 weeks after initiation to determine individual maintenance dose (0.15, 0.20 or 0.25 mg/kg). Further measurement(s) of concizumab plasma concentration(s) may be made after 8 weeks on the same maintenance dose according to the patient's medical condition (37). For marstacimab, it is unclear how the plasma concentration is measured in patients, causing uncertainty about what maintenance dose to apply and when to increase dose to 300 mg. In the BASIS study with marstacimab it was allowed to increase dose from 150 mg to 300 mg at 6 months after initiation for patients weighing more than 50 kg and who had 2

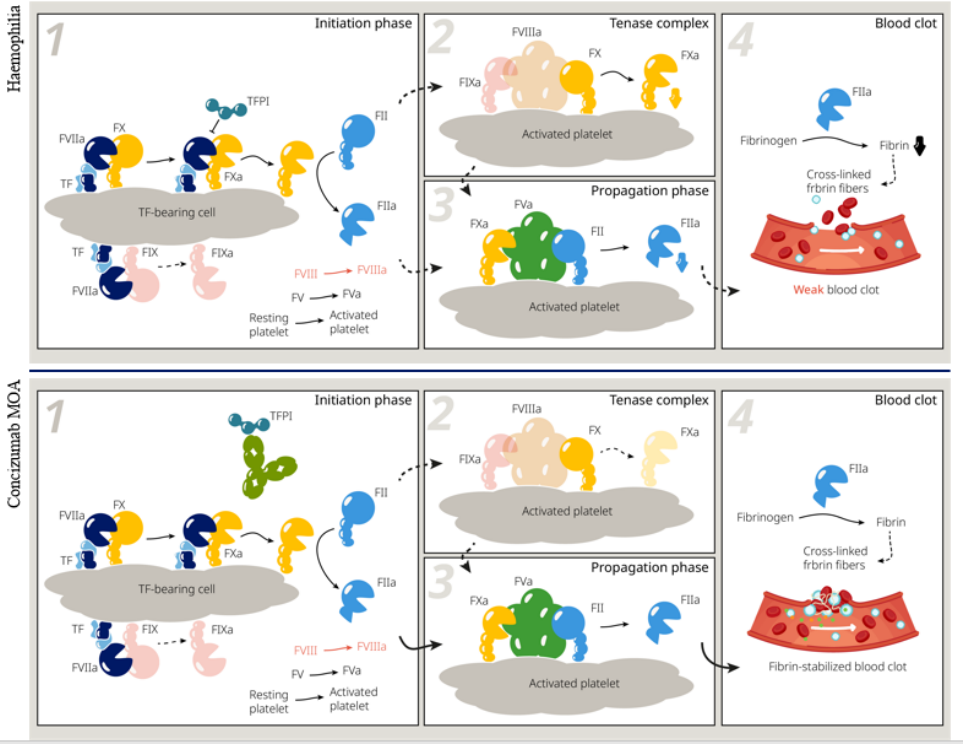
or more breakthrough bleeds. This happened to 33% of the HB population (6 patients with HB out of 18) and 7 patients with HA in the BASIS study (32). In the DMCs assessment of marstacimab, the Haemophilia Expert Committee concluded that they would be reluctant to increase the dosis of marstacimab to 300 mg due to the limited basis of experience. In combination with the lack of measurement of plasma concentration, this causes uncertainty during dose increase.

3.2 The intervention

Concizumab is a high-affinity, monoclonal, anti-TFPI antibody (38) (39) (40) (41) for once-daily, subcutaneous injection for the prophylactic treatment of people with HA, HB and haemophilia with inhibitors (42) (43).

TFPI is a glycoprotein that tightly regulates the initiation phase of the coagulation pathway, turning off early thrombin generation by inhibiting activation of FIX and FX by the TF-FVIIa-Fxa complex (39) (44) (45). Concizumab binding to TFPI prevents TFPI-mediated inhibition of FXa and prolongs the initiation phase of coagulation, allowing sufficient thrombin generation for effective haemostasis in people with haemophilia despite deficiency of FVIII or FIX, see Figure 3 (39) (45) (38) (46). Concizumab acts independently from FVIII and FIX, therefore is not influenced by the presence of inhibitors to FVIII or FIX.

Figure 3: Concizumab mechanism of action via inhibition of TFPI



Source: Adapted from Hilden et al, 2012 (39).
In people with haemophilia, lack of FVIII or FIX leads to a failure to effectively form the intrinsic tenase complex (FIXa-FVIIIa), haemostatic imbalance and insufficient thrombin generation during the propagation phase which results in the formation of weak blood clot. Concizumab binds to TFPI which boosts the initiation phase by preventing inhibition of FVIIa, Fxa and TF thus improving blood clot formation.

Overview of intervention	
Therapeutic indication relevant for the assessment	Concizumab is indicated for routine prophylaxis of bleeding in patients with: Moderate/Severe haemophilia B (congenital factor IX deficiency) without FIX inhibitors aged 12 years or older
Method of administration	Concizumab is for subcutaneous use only. Concizumab comes in a pre-filled pen that is ready for administration. Needles are not included. Concizumab should be administered daily at any time of the day, not necessarily the same time each day. Concizumab can be self-administered or administered by a caregiver after receiving appropriate training from a healthcare professional and reading the user manual. Concizumab should be administered by subcutaneous injection into the abdomen or thigh, with the injection site rotated daily. Subcutaneous injections should not be given in areas where the skin is tender, bruised, red or hard, or areas where there are moles or scars. A new needle should always be used for each injection.
Dosing	The recommended dosing regimen for concizumab is: • Day 1: a starting dose of 1 mg/kg once. • Day 2 and until individual determination of the maintenance dose (see below): once daily dosing of 0.20 mg/kg. • 4 weeks after treatment initiation: measurement of concizumab plasma concentrations prior to administration of the next scheduled dose. The measurement must be performed using a validated in vitro diagnostic test known as the ELISA test. When the result for concizumab plasma concentrations is available: the individual maintenance dose (0.15; 0.20 or 0.25mg/kg) is determined once based on the plasma concentration of concizumab. Within an initial 5–8-week dose adjustment period the dose should either increase to 0.25 mg/kg if concizumab plasma concentration was < 200 ng/mL, or decreased to 0.15 mg/kg if concizumab plasma concentration was >4.000 ng/mL or maintained at 0.2 mg/kg.
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	N/A

Overview of intervention	
Necessary monitoring, both during administration and during the treatment period	N/A
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	4 weeks after initiation of treatment, concizumab plasma concentrations are measured. The measurement must be performed using a validated in-vitro diagnostic test specifically developed for concizumab, the Randox ConcizuTraceTM ELISA kit (only validated in-vitro diagnostic test). Once the result for concizumab plasma concentrations is available, an individual maintenance dose (0.15, 0.20 or 0.25 mg/kg) is determined based on the plasma concentration of concizumab as indicated below: Plasmakoncentration af concizumab / Én daglig dosis Alhemo < 200 ng/ml / 0,25 mg/kg 200-4.000 ng/ml / 0,20 mg/kg > 4.000 ng/ml / 0,15 mg/kg The test is part of the treatment with concizumab. Further measurement(s) of concizumab plasma concentration(s) may be made after 8 weeks on the same maintenance dose according to the patient's medical condition. This should be considered, for example, if a patient experiences an increased bleeding frequency, a major change in body weight, has missed doses before setting the maintenance dose, or develops a comorbidity that may lead to an increase in overall thromboembolic risk.
Package size(s)	Concizumab is available in the following pack sizes: • 15 mg/1.5 ml (blue): Unit packs containing 1 pre-filled pen. • 60 mg/1.5 ml (brown): Unit packs containing 1 pre-filled pen. • 150 mg/1.5 ml (gold): unit packs containing 1 pre-filled pen. • 300 mg/3 ml (white/gold): unit packs containing 1 pre-filled pen. Not all pack sizes may be marketed. It is expected that concizumab in Denmark will mainly be marketed in single packs and in strengths of 150mg/1.5ml and 300mg/3ml. The device for concizumab is the same device that is used in a wide range of other Novo Nordisk products in e.g. diabetes (e.g. Ozempic®, Wegovy®). Needles are not included. Concizumab is designed for use with NovoFine Plus or NovoFine 32G needles with a length of 4 mm. If needles longer than 4 mm are used, injection

Overview of intervention	
	techniques that minimise the risk of intramuscular injection, such as injection into a loosely held skin fold, should be used.

3.2.1 The intervention in relation to Danish clinical practice

Despite the availability of novel treatments for haemophilia, there is still an unmet need for new HB treatments that can offer effective and safe prophylaxis with a minimally invasive route of administration.

Concizumab provides individualised steady-state protection with subcutaneous once-daily dosing across HB without inhibitors. It can be used concomitantly with bypassing agents, reduces ABR (annualized bleeding rate) and joint bleeding vs on-demand treatment, and further improve HRQoL. (37)

Concizumab is provided in a pre-filled pen with a thin 32G 4mm needle and a very low daily maintenance volume, which allows for immediate subcutaneous administration with minimum discomfort. Perceived treatment burden was low with concizumab; with 93% of people with inhibitors preferring concizumab compared with their previous on-demand treatment (47). Further, concizumab is room temperature stable for storage up to 4 weeks after first use in up to 30°C (37).

In vitro diagnostic measurement of concizumab plasma concentrations is part of the treatment. Concizumab therefore comes with a companion diagnostic for measuring anti-TFPI plasma concentrations. Physicians are advised to measure concizumab concentrations 4 weeks after initiation. The measurement must be performed using a validated in-vitro diagnostic test specifically developed for concizumab, the Randox ConcizuTraceTM ELISA kit (only validated in-vitro diagnostic test) (37).

In Danish clinical practice, concizumab can be directly placed into the current treatment guidelines. This corresponds to a direct placement into table 3 of the current recommendation by the DMC i.e. for patients on prophylaxis with difficult venous access and compliance issues where weekly intravenous infusions are not possible.

4. Overview of literature

A systematic literature review (SLR) was conducted to identify clinical efficacy, safety and health-related quality of life (HRQoL) evidence for treatment of patients living with HA and HB, with and without inhibitors. For this application, a further localization was done to include only studies with concizumab and marstacimab and the same target population of patients with HB without inhibitors ≥12 years of age.

Searches of electronic databases (MEDLINE, Embase and Evidence-Based Medicine Reviews [EBMR]) were performed and supplemented by searches of key congresses (that had occurred since 2022), clinical trial registries, Health Technology Assessment (HTA) bodies, and the reference lists of relevant SLRs or (network) meta-analyses ([N]MAs) captured in the review. All records were dual reviewed at title/abstract and full text stages, with conflicts arbitrated by a third reviewer if necessary. Data were extracted into a pre-specified extraction grid by one reviewer and checked for accuracy by a second reviewer. The quality of included randomized clinical trials (RCTs) was assessed using the the Risk of Bias (RoB) 1.0 tool.

The search strategy (including in- & exclusion criteria) is presented in Appendix D. The SLR was done initially in November 2021 and updated again in September 2022 and most recently in April 2025. In total, it identified 26 unique RCTs and 8 unique non-RCTs that met the SLR inclusion criteria after applying the de-prioritisation criteria. Only trials that included the relevant comparator marstacimab and same target population as concizumab (HB ≥12 years) were of interest for the comparative analysis.

The SLR found 3 clinical trials in 34 publications with concizumab and 4 relevant clinical trials in 19 publications with marstacimab. Only 9 of the publications were full publications. Upon closer inspection of the publications, 3 of the clinical trials (4 full publications) were excluded as they were not phase 3 studies. Two of the remaining 5 publications were excluded as they did not include patients with HB without inhibitors.

This left us with 3 relevant publications based on 2 clinical trials (EXPLORER 8 and BASIS) for the comparative analysis.

For the comparative analysis, BASIS will therefore be used when comparing the efficacy and safety of concizumab vs. marstacimab. The naïve indirect comparison is similarly based on the BASIS study, however the BASIS study only presents outcomes of both patients with HA and HB, as the trial was not powered to demonstrate efficacy for HB alone.

Relevant literature included in the clinical assessment of concizumab in patients with HB is shown in below Table 3 and further elaborated in Appendix D.

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
EXPLORER 8 NCT04082429 Pratima Chowdery 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; 11: e891–904. (48) Angchaisuksiri P et al. Concizumab	Phase 3, prospective, multicentre, open label clinical trial, with 4 treatment arms (2 randomized arms)	Dose setting phase (0 - ≤8 weeks) Main treatment period (24–32 weeks) Extension part (up to 265 weeks treatment period)	Start: 13/11/19 Completion: 12/07/22 Data cut-off 12/07/22 Code break date 11/08/22	Male aged ≥12 years with severe HA (FVIII <1%) or moderate/severe HB (FIX ≤2%), both without inhibitors Documented treatment with coagulation factor containing product in the last 24 weeks	Concizumab prophylaxis, once daily subcutaneous injection Loading dose of 1.0 mg/kg then 0.2 mg/kg daily in dose setting phase Maintenance dose of 0.15, 0.20 or 0.25 mg/kg	No prophylaxis (on-demand treatment with factor-containing products)	Intervention /outcomes	Outcomes at 24/32 weeks: ABR, treated bleeds, median ABR, all bleeds, median ABR, joint bleeds, median ABR, target joint bleeds, median Change in SF-36 v2 bodily pain Change in Haem-A-QoL, total score Outcomes measured up to week 56 in extension part: Incidence and severity of thromboembolic event Incidence and severity of injection site reaction

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
prophylaxis in people with hemophilia A or B without inhibitors: patient-reported outcome results from the phase 3 explorer8 study. Res Pract Thromb Haemost. 2025;9:e102705. (49)								Incidence of severe hypersensitivity and anaphylactic reactions
BASIS NCT03938792 Davide Matino et al., Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the	One way, cross-over, open-label, multi-centre, phase 3 with an observational and an active	6-month observational phase followed by a 12-month open label period	Start: 09/03/20 Data cut-off: 17/04/23 Completion: 29/04/25	Males 12-74 years with severe HA or moderately severe to severe HB (FIX activity ≤2%) with or without inhibitors, receiving episodic or prophylactic	Marstacimab initial loading dose of 300 mg subcutaneously followed thereafter by 150 mg	Factor replacement therapy (or bypass therapy) during a 6 month observational period	Intervention /outcomes	<u>Outcomes at 12-months:</u> ABR, treated bleeds, median ABR, all 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
phase 3 BASIS trial, Blood (2025) 146 (14): 1654–1663. (50)	treatment period			factor replacement therapy. Only patients without inhibitors, receiving prophylactic treatment during the observational period are included in this application (n=83)	subcutaneously once a week			Incidence and severity of thromboembolic event Incidence and severity of injection site reaction Incidence of severe hypersensitivity and anaphylactic reactions

Abbreviations: **HA:** Haemophilia A, **HB**: Haemophilia B, **ABR:** Annualized bleeding rate

5. Prophylactic treatment of HB with concizumab in patients with difficult venous access and compliance issues where weekly infusions are not possible

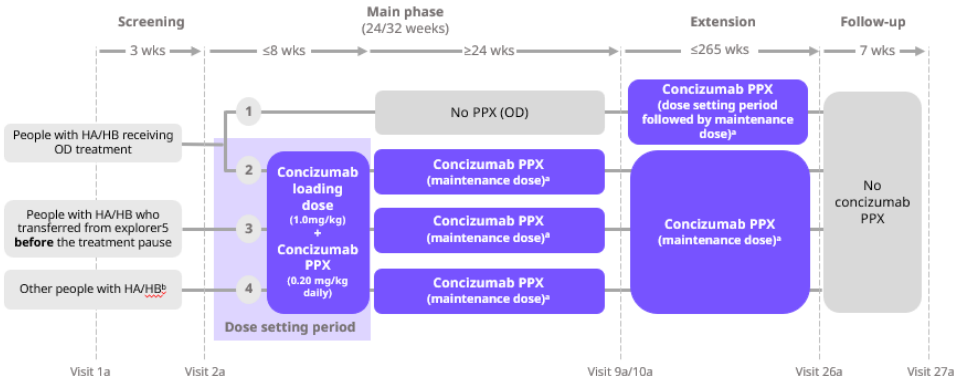
5.1 Efficacy of concizumab compared to marstacimab for HB

5.1.1 Relevant studies

EXPLORER 8

Explorer 8 was a prospective, multicentre, open label clinical trial with four treatment arms (two randomized and two non-randomized arms) designed to evaluate the efficacy and safety of daily concizumab prophylaxis administered subcutaneously in people with HA and HB, without inhibitors Figure 4 and Table 4.

Figure 4: EXPLORER 8 trial design



Abbreviations: HA, haemophilia A; HB, haemophilia B; OD, on-demand; PPX, prophylaxis.
a. Individual maintenance dose was either 0.15, 0.20 or 0.25 mg/kg concizumab.

Initially, participants were randomized to concizumab prophylaxis (arm 2) or on-demand (arm 1) or assigned to the non-randomized treatment arms (arms 3 or 4), based on their treatment regimen before entering the trial. After the treatment pause, participants who were randomized to arms 1 or 2 before the pause were to enter arm 4. Participants who were allocated to arms 3 and 4 before the treatment pause were to re-enter the arm they were initially allocated to. The randomisation into arms 1 or 2 was restarted with new participants. Below description of the trial design reflects the updated trial design

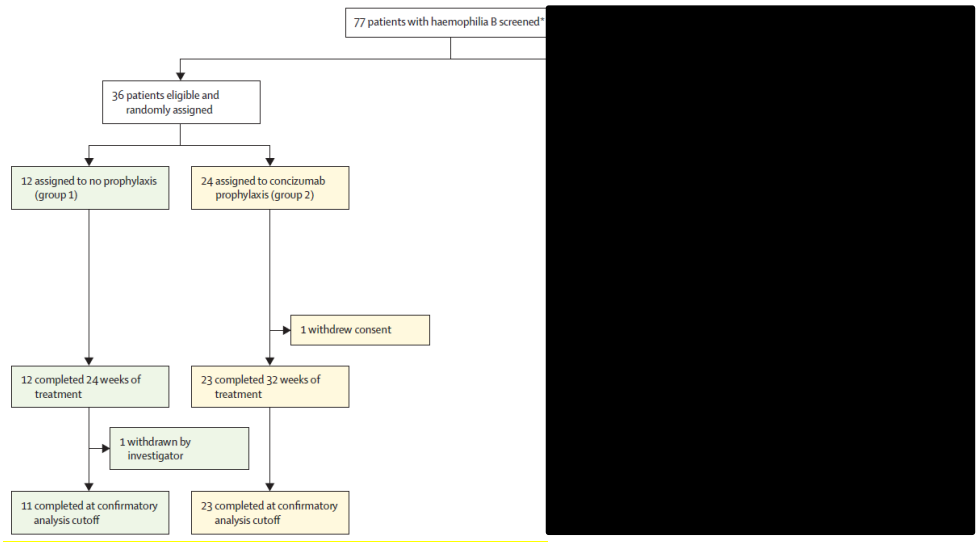
after the concizumab treatment pause and treatment restart. The four arms of the trial are briefly outlined below:

Arms 1 and 2 consisted of participants previously treated on demand who were randomized to:

- Arm 1: No prophylaxis (on-demand treatment)
- Arm 2: concizumab prophylaxis
- Arms 3 and 4 had participants allocated to receive concizumab prophylaxis treatment and consisted of:
- Arm 3: Participants who were transferred from the phase 2 trial EXPLORER 5 prior to the treatment pause
- Arm 4:
    - Participants who had been on stable prophylaxis for at least 24 weeks in the non-interventional study (EXPLORER 6)
    - Participants who were randomised to concizumab prophylaxis or no prophylaxis (on-demand treatment) prior to the treatment pause
    - Participants who were in EXPLORER 5 at the time of the treatment pause and had subsequently completed EXPLORER 5 when concizumab treatment was restarted
    - Additional on-demand participants included after arms 1 and 2 were closed

Below flowchart in Figure 5 depicts the number of patients with HB either randomized to arm 1 or 2 or assigned to arm 4 based on above outline of EXPLORER 8 treatment arms.

Figure 5: EXPLORER 8 flowchart of patients with HB



Of the 77 screened patients with HB, 12 of them were randomly assigned to no prophylaxis in arm 1 and 24 to receive concizumab prophylaxis in arm 2, whereas 30 of the screened patients with HB were assigned to concizumab prophylaxis in arm 4.

XX of the patients with HB in arm 4 had been on stable prophylaxis for at least 24 weeks in EXPLORER 6 thus were eligible for the intrapatient analysis set, whereas the remaining XX patients in arm 4 were not as they had not been on stable prophylaxis for at least 24 weeks in EXPLORER 6.

This application includes outcomes from the confirmatory analysis cut-off (CACO) at 32 weeks for arm 2 and 4 providing a comparison of concizumab to on-demand and previous prophylaxis, in addition to data regarding the efficacy and safety of concizumab up to Week 56.

Patients randomised or allocated to concizumab prophylaxis received a loading dose of 1.0 mg/kg concizumab at visit 2a (arms 2, 3 and 4) or visit 9a (arm 1) followed by an initial daily dose of 0.20 mg/kg concizumab from treatment Day 2. The concizumab dose could be adjusted from 0.20 mg/kg to 0.25 mg/kg or 0.15 mg/kg during an initial 5−8-week dose adjustment period. Notably findings from the investigations of the thromboembolic events and all available results during the treatment pause in March 2020 led to the following mitigations in EXPLORER 8 (48):

- A new guidance for treatment of mild and moderate breakthrough bleeds
- That patients must contact the study site prior to treating a suspected bleed.
- A new concizumab dosing regimen
- Elective major surgery is no longer allowed.
- Trial stopping rule requiring urgent evaluation by the Novo Nordisk Safety Committee and consultation with the DMC in case of one (instead of two) significant thromboembolic event, DIC, TMA or death of trial patient which may be related to the trial product.

The primary endpoint was the number of treated spontaneous and traumatic bleeding episodes following at the primary analysis cut-off (changed from up until week 34 prior to the treatment pause), which is defined as when all patients in arm 1 have completed visit 9/9a (or withdrawn) and all patients in arm 2 have completed visit 10a (or withdrawn).

The BASIS study

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. Patients in the trial had severe HA or moderate to severe HB with and without inhibitors. The enrolment protocol included patients with moderately severe HB, but ultimately only patients with severe disease enrolled (32).

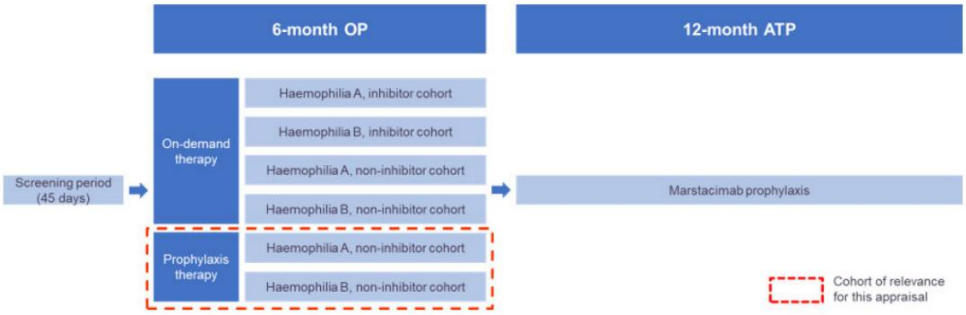
Patients who previously received on-demand or prophylactic treatment were included in separate treatment arms and data presented in this application is only for patients

without inhibitors who previously received prophylactic treatment for this population only.

The BASIS study compared treatment with marstacimab in an active treatment phase to factor treatment during a 6-month observational phase, see Figure 6. 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 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 (32).

Figure 6: BASIS trial design



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 (51).

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 (32).

Details on the proportion of patients in the BASIS study who were dose escalated is not visible for Novo Nordisk but has been included in Pfizers application to DMC.

Table 4 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
EXPLORER 8 NCT04082429 Chowdary et al., 2024 (48) Angchaisuksiri P et al., 2025 (49)	Phase 3, prospective, multicentre, open label clinical trial, with 4 treatment arms (2 randomized arms)	Dose setting phase (0 - ≤8 weeks) Main treatment period (24–32 weeks) Extension part (up to 265 weeks treatment period)	Male aged ≥12 years with severe HA (FVIII <1%) or moderate/severe HB (FIX ≤2%), both without inhibitors Documented treatment with coagulation factor containing product in the last 24 weeks	Concizumab prophylaxis, once daily subcutaneous injection Loading dose of 1.0 mg/kg then 0.2 mg/kg daily in dose setting phase Maintenance dose of 0.15, 0.20 or 0.25 mg/kg	No prophylaxis (on-demand treatment with factor-containing products)	Outcomes at 24/32 weeks: ABR, treated bleeds, median ABR, all bleeds, median ABR, joint bleeds, median ABR, target joint bleeds, median Change in SF-36 v2 bodily pain Change in Haem-A-QoL, total score Outcomes measured up to week 56 in extension part: Incidence and severity of thromboembolic event Incidence and severity of injection site reaction Incidence of severe hypersensitivity and anaphylactic reactions
BASIS NTC03938792	One way, cross-over, open-label, multi-centre, phase 3	6-month observational phase followed by a 12-month	Males 12-74 years with severe HA or moderately	Marstacimab initial loading dose of 300 mg subcutaneously	Factor replacement therapy (or bypass therapy)	<u>Outcomes at 12-months:</u> ABR, treated bleeds, median

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
Matino et al., 2025 (50)	with an observational and an active treatment period	open label period	severe to severe HB (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 this application (n=83)	followed thereafter by 150 mg subcutaneously once a week	during a 6 month observational period	ABR, all bleeds, median Haem-A-QoL, total score, adult Haemo-QoL, total score, adolescent Incidence and severity of thromboembolic event Incidence and severity of injection site reaction Incidence of severe hypersensitivity and anaphylactic reactions

Abbreviations: **HA:** Haemophilia A, **HB**: Haemophilia B, **ABR:** Annualized bleeding rate

5.1.2 Comparability of studies

The main studies included in the comparison are shown in Table 5 below. The respective studies both have the same in common that the enrolled patient numbers were limited and lacked a direct comparator-arm. Marstacimab was compared to the previous prophylactic treatments (one-way comparison), and concizumab arm 2 was compared to arm 1 with randomized patients receiving on-demand treatment and arm 4 present outcomes in patients with HB on concizumab who were previously treated with prophylaxis. EXPLORER 8 included 4 treatment arms in the main phase, two were randomized and two were non-randomized, of which this application only includes outcomes from the randomized treatment arm with concizumab in (arm 2) and the non-randomized treatment arm with concizumab (arm 4). The BASIS study was a non-randomized study only including one treatment arm in the main phase (active treatment phase), which was then compared to the treatment in the observational phase. In Pfizers application to the DMC and in this application, it is the outcomes of patients with HA and HB who has previously received prophylaxis that is used.

EXPLORER 8 and BASIS are both studies investigating efficacy and safety in patients with HA and HB. EXPLORER 8 has reported outcomes in patients with HB separately, but the BASIS study was not powered to show efficacy and safety in this subgroup of patients. Hence the outcomes in patients with HB in the BASIS study are not published. Pfizer has reported results for the HB subgroup in the application to DMC, but these have been blinded to the public. It is therefore difficult for Novo Nordisk to assess if there are any differences in the results of the patients with HB in the two studies. The outcomes of the BASIS study for patients with HA and HB are publicly available and is included in Table 6 with naïve comparison between concizumab and marstacimab. Hence the results presented in section 5.2.5 are based on two different populations

The primary endpoint in both studies was treated ABR. EXPLORER 8 measured the primary endpoint at 24/32 weeks, whereas BASIS measured the primary endpoint at 12 months.

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

Baseline characteristics for patients in the EXPLORER 8 and BASIS studies are included in below Table 5.

Since the amount of published data on baseline characteristics from the BASIS study is very limited, it is hard to identify differences. For EXPLORER 8 data is presented for two arms, arm 2 with HB patients previously treated on demand and arm 4 with HB patients previously treated with prophylaxis, whereas the data presented in below from the BASIS study, is based solely on patients previously treated with prophylaxis.

Another difference that can be identified in the baseline characteristics is the patients' factor-level in the two studies. Both studies allowed patients with either severe or moderate HB, but in the BASIS study only patients with severe HB ended up being

enrolled. In the EXPLORE 8 study, 87.5% of the patients in arm 2 and 93.3% of patients in arm 4 had severe HB. The remaining patients had moderate HB.

Table 5 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	Concizumab (HB) Arm 2 (n=24)	Concizumab (HB) Arm 4 (n=30)[a]	Marstacimab (HB) (n=18)	Marstacimab (HA + HB) (n=83)
Age group				
12-17 years, n (%)	6 (25%)	6 (20%)	4 (22.2%)	17 (20.5%)
≥ 18 years, n (%)	18 (75%)	24 (80%)	14 (77.8%)	66 (79.6%)
Average age (SD)	28.0 (12.0)	31.6 (13.3)	Not reported	Not reported
Gender				
Male, n (%)	24 (100%)	30 (100%)	18 (100%)	83 (100%)
Ethnicity				
Hispanic or Latino, n (%)	1 (4.2%)	3 (10%)	Not reported	Not reported
Not hispanic or latino, n (%)	23 (95.8%)	27 (90%)	Not reported	Not reported
Not reported, n (%)	0	0	Not reported	Not reported
Race				
American Indian or Alaska Native	0	1 (3%)	Not reported	Not reported
Asian	10 (41.7)	1 (3%)	Not reported	Not reported
Black or African American	1 (4.2%)	1 (3%)	Not reported	Not reported

	Concizumab (HB) Arm 2 (n=24)	Concizumab (HB) Arm 4 (n=30)[a]	Marstacimab (HB) (n=18)	Marstacimab (HA + HB) (n=83)
Native Hawaiian or Other Pacific Islander	0	0	Not reported	Not reported
White	12 (50.0%)	27 (90%)	Not reported	Not reported
Not reported	0	0	Not reported	Not reported
Other	1 (4.2%)	0	Not reported	Not reported
Factor IX level at diagnosis				
< 1%	21 (87.5%)	28 (93.3%)	18 (100%)	N/A
1-2%	3 (12.5%)	2 (6.7%)	0	N/A
Previous treatment				
On-demand	XXXXXXXXXX[b]	XXXXXXXXXX[b]	0	0
Prophylaxis	XXXXXXXXXX[b]	XXXXXXXXXX[b]	18 (100%)	83 (100%)
Body Weight (kg)				
Mean (SD)	67.4 (18.7)	84.2 (20.2)	Not reported	Not reported
BMI (kg/m2)				
Mean (SD)	22.9 (5.4)	27.4 (6.3)	Not reported	Not reported
ABR on previous treatment[c]				
Median (IQR)	XXXXXXXXXX[d]	XXXXXXXXXX[e]	Not reported	Not reported
Mean (SD)	XXXXXXX[d]	XXXXXXX[e]	Not reported	Not reported
No. of target joints, n (%)				

	Concizumab (HB) Arm 2 (n=24)	Concizumab (HB) Arm 4 (n=30)[a]	Marstacimab (HB) (n=18)	Marstacimab (HA + HB) (n=83)
0	3 (13.5%)	19 (64.3%)	Not reported	Not reported
≥ 1	21 (87.5%)	11 (36.7%)	Not reported	Not reported
Concizumab maintenance dose level				
0.15 mg/kg (%)	1 (4.3%)	4 (14.8%)	Not relevant	Not relevant
0.20 mg/kg (%)	13 (56.5%)	14 (51.9%)	Not relevant	Not relevant
0.25 mg/kg (%)	9 (39.1%)	9 (33.3%)	Not relevant	Not relevant

[a]XX of the 30 patients were previously treated with prophylaxis, hence the outcomes of concizumab HB arm 4 presented in Table 6 are based on XX patients [b] Patients can report both on-demand and prophylaxis prior to screening so therefore the number of patients does not necessarily add up [c]Previous treatment in concizumab arm 2 was on demand treatment and in concizumab arm 4 it was prophylaxis [d]Based on 24 patients with HB previously treated with on demand (see flowchart in Figure 5) [e]Based on XX patients with HB in the intrapatient analysis previously treated with stable prophylaxis in 24 weeks in EXPLORER 6 (see flowchart in Figure 5).
Sources: Chowdery et al. 2024 (48), Matino et al. 2025 (32), Novo Nordisk. Clinical trial report. Trial ID: NN7415-4307 (data on file) (47)

In EXPLORER 8, 2 patients with HA from Denmark was enrolled via site Rigshospitalet in Copenhagen as well as 1 patient with HAwI and 1 patient with HBwI via site Aarhus University Hospital was enrolled in EXPLORER 7. As such, Danish participants have contributed to the overall results of the clinical trials, giving the current Haemophilia Expert Committee under DMC a good understanding of the efficacy and safety aspects of anti-TFPI treatment (concizumab) for prophylactic treatment of patients ≥ 12 years.

One main difference between EXPLORER 8 and BASIS and Danish patients is that patients in both studies have more target joints at baseline (47) (50). Notably, a large proportion of patients with HB in EXPLORER 8 have ≥ 1 at baseline as the majority of patients were treated on-demand until enrolment in the study.

EXPLORER 8 included patients both with moderate or severe HB, whereas BASIS only included patients with severe HB. In Danish clinical practice it will primarily be patients with severe HB and previously treated with another prophylaxis that will be the relevant population. In section 3.1 this is estimated to be 25 patients, however only around 30% is expected to have difficult venous access and compliance issues with intravenous injections and be eligible for treatment with concizumab.

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy with concizumab in the EXPLORER 8 study

In patients with HB, concizumab was superior to on-demand, and was associated with a 79% reduction in ABR compared with on-demand. The median ABR was 1.6 (0.0–4.8) while on concizumab and 14.9 (3.3–22.1) while on on-demand in arm 2. In arm 4, median ABR was [redacted] after treatment with concizumab.

Ten (42%) patients with HB on concizumab had zero bleeds compared with 1 (8%) patient on on-demand in arm 2. [redacted] had zero bleeds on concizumab in arm 4.

47 treated joint bleeds occurred in 14 (58%) patients with HB on concizumab, and 28 treated target joint bleeds in 9 (38%) patients on on-demand in arm 2. 100 treated joint bleeds occurred in 19 (63.3%) patients with HB on concizumab in arm 4.

Ten serious adverse events were reported in seven patients with HB treated with concizumab (0.2 SAEs per PYE) (48). The majority of these SAEs were judged as unlikely related to concizumab and were reported as recovered. Seven SAEs were reported in two people with HB on on-demand (arm 1; 1.2 SAEs per PYE).

Two AEs (0.0 AEs per PYE) in 2 (4.0%) people with HB on concizumab led to permanent discontinuation of trial product during the on-treatment period (48) (47).

No thromboembolic events were reported for patients with HB in the trial, however two patients with HA had non-fatal thromboembolic events before the trial pause.

No hypersensitivity-type reactions were reported until the confirmatory analysis cutoff.

27 injection-site reactions occurred in 12 (19%) of 64 patients with HB treated with concizumab. All injection site reactions were mild except for one event of injection-site pain (moderate), which led to the withdrawal of concizumab.

Low-titre (range 50−6400) anti-concizumab antibodies were detected in six (9%) of 64 patients with haemophilia B, with no apparent effect on bleeding episodes, adverse events, or pharmacokinetic and pharmacodynamic measures (48).

Change in SF-36 v2 bodily pain and in SF-36 v2 physical functioning were key secondary endpoints in EXPLORER 8 (47). Concizumab showed a reduction in bodily pain vs on-demand in patients with HB. The estimated treatment difference at Week 24 between concizumab (arm 2) and on-demand (arm 1) was 14.64 (95% CI; 3.37; 25.91). The change in SF-36 scores at week 24 for patients with HB favoured receiving concizumab vs on-demand for all health scales (49).

[redacted] of concizumab patients experienced a SF-36 score improvement of 6.2 points (threshold for a clinically meaningful within-patient change) for bodily pain at week 24 vs [redacted] of patients receiving on-demand treatment. For physical function, the number of responders at week 24 for patients with HB on concizumab was [redacted] (arm 2) and for on-demand it was [redacted] (arm 1) (47).

For the disease specific HRQoL questionnaire Haem-A-QoL, assessing the physical and emotional limitations experienced by patients, there was a significant improvement in the Total Score between baseline and Week 24 for people with HB on concizumab (arm

2) compared with those on on-demand. Lower values of Heam-A-QoL scores indicate a better quality of life rating. The Haem-A-QoL total scores at week 24 for patients on concizumab was [redacted] vs [redacted] on on-demand. The estimated treatment difference at Week 24 between concizumab (arm 2) and on-demand (arm 1) was −17.55 (95% CI; −28.77, −6.33) (49) (47).

The estimate of the difference in change from baseline to Week 24 was in favour of arm 2 (concizumab) over arm 1 (on-demand) for all individual domain scores (49).

In patients with HB on concizumab in arm 4, the change from baseline in SF-36 v2 was [redacted] and the Change from baseline in Haem-A-QoL total score was [redacted]

5.2.2 Efficacy with marstacimab in the BASIS study

Efficacy of marstacimab has been investigated in the BASIS study. In NICE's review of marstacimab (52), it is stated that since marstacimab was targeting treatment for both HA and HB, the BASIS study was not powered to detect differences within subgroups. Therefore, most published outcomes are presented for the entire group of patients with HA and HB together. However, Novo Nordisk have identified a small number of outcomes published for the HB subgroup in the marstacimab EPAR (51) and the NICE review (52) which are presented in Table 6.

In patients with HB treated with marstacimab the mean ABR for all bleeds was 4.71 (52) during the active treatment phase of 12 months.

The following outcomes has been sourced from Pfizer's application to DMC and is based on the entire group of patients with HA and HB together in the BASIS study after 12 months of treatment.

The median ABR for all bleeds was 2.89 (0.00; 7,06 IQR) during the active treatment phase of 12 months.

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 no deaths during the active treatment phase with marstacimab (50).

The mean change in HRQoL for marstacimab is not reported in public available sources and also not reported for HB alone. The results for the combined population of HA and HB are included in the DMC assessment of marstacimab but these are blinded to the public. Hence it is not possible for Novo Nordisk to compare these to the results of

concizumab in patients with HB. The DMC can use the results reported in the marstacimab assessment when performing an indirect comparison with concizumab.

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

In general, SAEs are very low and similar across the trials reported for concizumab and marstacimab.

In EXPLORER 8, 10 SAEs were reported in seven patients with HB treated with concizumab (0.2 SAEs per PYE) (48). The majority of these SAEs were judged as unlikely related to concizumab and were reported as recovered. In BASIS, 7 SAEs were reported for marstacimab during the active treatment phase.

Two AEs (0.0 AEs per PYE) in 2 (4.0%) people with HB on concizumab led to permanent discontinuation of trial product during the on-treatment period (48) (47), whereas this was 1 patient that discontinued marstacimab due to meningioma.

No thromboembolic events were reported for patients with HB in EXPLORER 8, however two patients with HA had non-fatal thromboembolic events before the trial pause. In the active treatment phase in BASIS, no participants reported thromboembolic events with marstacimab.

5.2.4 Method of synthesis

Both concizumab and marstacimab are new treatments for patients with haemophilia and only just recently approved by EMA, hence no direct comparative evidence between the two exists. In line with the protocol for developing the Danish treatment guidelines for haemophilia, a naïve comparison has been conducted.

From EXPLORER 8, only patients with HB in arm 2 and arm 4 have been included in this application. These are patients with HB randomized to concizumab and previously treated on-demand (arm 2) or assigned to concizumab and previously treated with prophylaxis (arm 4). From the BASIS study, it is primarily efficacy outcomes of both patients with HA and HB, which is presented in the naïve comparison, as the trial was not powered to demonstrate efficacy for HB alone, and as previously described, availability of results from the HB subgroup is very limited. Additionally, some of the efficacy outcomes from the BASIS study is only reported in ‘means’ and not in ‘median’. Hence the results of the naïve indirect comparison of EXPLORER 8 and BASIS, presented in Table 6 and in Appendix C, should be interpreted with cautious as it is outcomes of two different populations that are compared.

5.2.5 Results from the comparative analysis

In the following, results of the naïve comparison of concizumab and marstacimab is presented.

Table 6 Results from the comparative analysis of concizumab vs. marstacimab

Outcome measure		Concizumab HB arm 2 (N=24), 32 weeks	Concizumab HB arm 4 (N=30)[d], 32 weeks	Marstacimab HB (N=18), 12 months	Marstacimab HA+HB (N=83), 12 months
Treated bleeds, ABR	Median (IQR)	1.6 (0.0;4.8)	XXXXXXXXXX	NR	2.02 (0.00, 6.09)
	Mean (95% CI)	3.1 (1.91; 5.04)	XXXXXXXXXX[d, e]	NR	5.08 (3.40,6.77)
All bleeds, ABR	Median (IQR)	XXXXXXXXXX	XXXXXXXXXX	NR	2.89 (0.00, 7.06)
	Mean (95% CI)	XXXXXXXXXX	XXXXXXXXXX[d, e]	4.71	5.97 (4.13, 7.18)
Treated target joint bleeds, ABR	Median (IQR)	XXXXXXXXXX	XXXXXXXXXX	NR	NR
	Mean (95% CI)	XXXXXXXXXX	XXXXXXXXXX[d, e]	NR	2.51 (1.25; 3.76)
Treated joint bleeds, ABR	Median (IQR)	XXXXXXXXXX	XXXXXXXXXX	NR	NR
	Mean (95% CI)	XXXXXXXXXX	XXXXXXXXXX[d, e]	NR	4.13 (2.59, 5.67)
SF-36 v2 bodily pain, mean change	Mean (95% CI)	XXXXXXXXXX	XXX[d] XXXXXX	NR	NR

Outcome measure		Concizumab HB arm 2 (N=24), 32 weeks	Concizumab HB arm 4 (N=30)[d], 32 weeks	Marstacimab HB (N=18), 12 months	Marstacimab HA+HB (N=83), 12 months
from baseline to Week 24					
Change in Haem-A-QoL total score at week 24	Mean (95% CI)	XXXXXXXXXXX	XXX[d] XXXXXX	NR	NR
Thromboem-bolic events		0[a]		0	0
Inhibitor		0[a]		0	0
Anaphylaxis		0[a]		0	0
SAE		7 (10.9%)		NR	7 (8.4%)
Treatment related SAE		1 (1.6%)		NR	1 (1.2%)b
Permanent discontinua-tion due to adverse event		2 (3.1%)		NR	1 (1,2%)c

HB: Haemophilia B, **HA:** Haemophilia A, **ABR**: Annual bleeding rate, **SAE**: Serious adverse event**, NR:** Not reported, **IQR**: Interquartile range, **CI**: Confidence interval, [a]measured up to week 56 in the EXPLORER 8 extension period; [b]Grad 1 peripheral calf swelling considering to be treatment related but was diagnostically confirmed to be unrelated to a bleeding of thrombotic event; [c]Adverse Event (AE); [d]descriptive statistics only; [e] The relatively high mean ABRs is the results of one patient with HB in arm 4 in EXPLORER 8 who had many bleeds during the trial (Figure S3 in the Supplement to: 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; published online Nov 6. https://doi.org/10.1016/S2352-3026(24)00307-7. **Sources:** Chowdery et al. 2024 (48), Angchaisuksiri P et al. 2025 (49), Medicinrådets Bilag til direkte indplacering af marstacimab i Medicinrådets evidensgennemgang vedrørende lægemidler til hæmofili A og B, August 2025 (32), NICE's appraisal of marstacimab, August 2024 (52), Hympavzi SmPC (51), Novo Nordisk. Clinical trial report. Trial ID: NN7415-4307 (data on file) (47)

For evaluation of the naïve comparison, 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

• Trough Value (important) 95% Clerance (CL) lower value for average trough value should be above 5% (0.05 KIE/L) – not meaningful to estimate for anti-TFPI treatments.

For ABR, there is no clinically important difference between concizumab and marstacimab, where concizumab showed a median ABR on treated bleeds of respectively 1.6 and XXX vs. 2.02 for marstacimab which is lower difference than 3.

No incidences were observed of inhibitors, thromboembolism, anaphylaxis or deaths in either BASIS or EXPLORER 8. There is therefore no difference between products for these outcomes.

In addition to the clinically relevant outcomes defined by DMC, EXPLORER 8 also reports outcomes on median ABR for joint bleeds (XXX and XXX), target joint bleeds (XXX) as well as all bleeds (XXX and XXX) for patients with HB treated with concizumab in 32 weeks. These outcomes show the consistency of concizumab efficacy across the various types of bleeds including the more serious types of bleeds.

For HRQoL, outcomes in HB have not been reported for marstacimab and therefore it is not possible to compare concizumab and marstacimab on this. For patients with HB on concizumab in arm 2, XXX had a 6.2 points improvement in bodily pain (SF-36 v2), which is pre-specified as the threshold for a clinically meaningful within-patient change (47).

The final critical outcome measure, included by the DMC, is an absolute trough value of 5%. It is not possible to measure factor IX throughs for patients treated with concizumab and marstacimab, since these don't change FIX concentrations.

In summary, none of the minimal clinically relevant outcomes are met for the critical outcomes, hence the two products are clinically equivalent.

Administration of concizumab vs marstacimab

When it comes to the administration of concizumab and marstacimab several differences exist. Concizumab comes in a prefilled pen with a thinner needle than the pen with marstacimab. In addition, the concizumab pen allows for several times of dosing, whereas the marstacimab pen is a one-time only pen, meaning using a new pen every week. Concizumab allows for 15 injections (days) in one pen considering a 50 kg patient

at the average dose of 20 mg/kg in the 150 mg pen, and for 21 injections (days) in one pen considering a 70 kg patient at the average dose of 20 kg/kg in the 300 mg pen. Compared to this, the marstacimab pen only allows for one injection (once a week) and therefore there would be a waste of 1 and 2 pens respectively in the two cases above. Extrapolating this to the pen consumption in a full year, this would be 24 and 17 concizumab pens in above two examples compared to 56 marstacimab pens (37) (51).

Concizumab also comes with an in vitro diagnostic measurement of plasma concentrations, in contrast to marstacimab, which does not accommodate diagnostic measurement of plasma concentration after initiation, hence causing uncertainty about maintenance dose and increasing dose to 300 mg. Further, marstacimab is not room-temperature stable and rapid dose adjustment may be limited by its pharmacokinetics; marstacimab takes 60 days to reach a steady state concentration (51) (53)

Conclusion

The naïve comparison of concizumab and marstacimab shows that there is no clinical meaningful difference in neither clinical nor safety outcomes of EXPLORER 8 and BASIS. However, concizumab comes with an in vitro diagnostic measurement of concizumab plasma concentrations allowing for individualised maintenance dosing and steady-state protection. Furthermore, concizumab comes in a subcutaneous injection pen with a 32G needle (0.23 mm in diameter) and a very low daily maintenance volume, which allows for immediate subcutaneous administration with minimum discomfort. In contrast, marstacimab comes in a thicker 27G needle (0.4 mm in diameter). The subcutaneous administration with concizumab meets the unmet need in todays haemophilia B treatment where intravenous injections until recently have been the standard of care and is likely to improve compliance and reduce treatment burden in patients with HB and difficult venous access and compliance issues.

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Appendix A. Main characteristics of studies included

Table 7 Main characteristic of studies included – EXPLORER 8

Trial name: EXPLORER 8	**NCT number: 04082429**
Objective	To demonstrate the efficacy and safety of daily treatment with concizumab prophylaxis compared with no prophylaxis in adult and adolescent patients with haemophilia A and B without inhibitors.
Publications – title, author, journal, year	Chowdary 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; 11: e891-904. Angchaisuksiri P et al. Concizumab prophylaxis in people with hemophilia A or B without inhibitors: patient-reported outcome results from the phase 3 explorer8 study. Res Pract Thromb Haemost. 2025;9:e102705.
Study type and design	A prospective, multicentre, open label clinical trial with four treatment arms (two randomised and two non-randomised arms). Randomization, stratification and blinding For the randomized arms 1 and 2, patients meeting randomization criteria were centrally randomized using an interactive web response system and assigned to the next available treatment according to the randomization schedule. Patients were stratified by haemophilia type (haemophilia A or B) and bleeding frequency during the 24 weeks prior to randomization (<9 bleeding episodes vs ≥9 bleeding episodes). This is an open-label trial where the trial product was packed open-label; however, the specific treatment for a patient was assigned using IWRS.
Sample size (n)	N=156. Of 156 enrolled patients, 21 were randomly assigned to group 1 and 42 to group 2; the remaining 93 were assigned to groups 3 and 4
Main inclusion criteria	• Male aged ≥12 years at the time of signing informed consent • Body weight >25 kg at screening • Congenital severe HA (FVIII <1%) or moderate/severe HB (FIX ≤2%) • Documented treatment with coagulation factor containing product in the last 24 weeks (not applicable for explorer5 participants enrolled prior to the treatment pause)

Trial name: EXPLORER 8	NCT number: 04082429
Main exclusion criteria	• Previous participation in this trial. Participation is defined as signed informed consent. However, this is not applicable for participants who were screen failed at Sponsor's decision due to the treatment pause • Participation in any clinical trial of an approved or non-approved IMP within 5 half-lives or 30 days from screening, whichever is longer (not applicable for explorer5 participants enrolled prior to the treatment pause) • Known or suspected hypersensitivity to any constituent of the trial product or related products • Known inherited or acquired coagulation disorder other than congenital haemophilia • History of thromboembolic disease† • Current clinical signs of or treatment for thromboembolic disease. Participants who in the judgement of the investigator are considered at high risk of thromboembolic events‡ • Treatment with emicizumab within 180 days before screening • Presence of confirmed inhibitor ≥0.6 BU at screening • Known history of inhibitors ≥0.6 BU in the last 5 years according to the medical records
Intervention	Concicumab. Loading dose of 1.0 mg/kg, followed by an initial daily dose of 0.2 mg/kg, with an initial dose-adjustment period of 5 to 8 weeks, during which the dose was increased to 0.25 mg/kg (if concizumab plasma concentration < 200 ng/mL), decreased to 0.15 mg/kg (if concizumab plasma concentration > 4000 ng/mL), or maintained at 0.2 mg/mL
Comparator(s)	No prophylaxis (on-demand treatment)
Follow-up time	Follow-up 7 weeks (after extension ≤265 weeks)
Primary, secondary and exploratory endpoints	**Primary endpoint** • Number of treated spontaneous and traumatic bleeding episodes. **Confirmatory secondary endpoints** • Number of treated spontaneous and traumatic bleeding episodes in participants who received previous prophylaxis in explorer6 followed by concizumab prophylaxis in explorer8 (intrapatient analysis comparing previous prophylaxis with concizumab prophylaxis)

Trial name: EXPLORER 8	NCT number: 04082429
	• Number of treated spontaneous and traumatic joint bleeds, number of treated spontaneous and traumatic target joint bleeds **Supportive secondary endpoints** • Number of treated spontaneous bleeding episodes • Number of treated spontaneous and traumatic joint bleeds • Number of treated spontaneous and traumatic target joint bleeds • People with zero bleeding episodes: concizumab prophylaxis vs no prophylaxis **Exploratory endpoints:** Patient-reported outcomes: • Change in SF-36v2 bodily pain • Change in SF-36v2 physical functioning • Change in SF-36v2 health scale scores • Change in PROMIS numeric rating scale v.1.0 – pain intensity 1a • Change in PROMIS short form v2.0 -upper extremity 7av • Change in Haem-A-QoL Total Score • Change in Haem-A-QoL Physical Health domain score • Change in Haem-A-QoL Total Score • Change in Haem-A-QoL Physical Health domain score • Haem-A-QoL domain scores • PGI-S on physical functioning • PGI-C on physical functioning • Patient preference assessed by questionnaire • Change in patient's treatment burden using Hemo-TEM Total Score Physical activity • Change in time spent in moderate to vigorous physical • activity per day
Method of analysis	Main analytical approach For the primary endpoint, number of treated bleeds between arms 1 and 2 was compared based on the FAS and the 'on-treatment without ancillary therapy excl. data on initial regimen for participants exposed

Trial name: EXPLORER 8	NCT number: 04082429
	to both regimens' analysis data set using negative binomial regression with the number of bleeds analysed as a function of the randomized treatment regimen, type of haemophilia (HA or HB) and bleeding frequency (<9 or ≥ 9 bleeding episodes during the past 24 weeks prior to screening) and the logarithm of the length of the observation period included as an offset in the model. From the statistical model, an estimate of the RR of the ABR between the treatment regimens (concizumab prophylaxis and no prophylaxis) with corresponding 95% CI and a p-value for the test for superiority.
Subgroup analyses	People with HA People with HB
Other relevant information	N/A

Table 8 Main characteristics of studies included - BASIS

Trial name: BASIS	NCT number: 03938792
Objective	To demonstrate the efficacy and safety of marstacimab for routine prophylaxis in patients with severe haemophilia A or moderately to severe haemophilia B from 12 to <75 years of age with or without inhibitors.
Publications – title, author, journal, year	Davide Matino et al., Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the phase 3 BASIS trial, Blood (2025) 146 (14): 1654–1663.
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 OP; 83 patients progressed to the ATP.
Main inclusion criteria	Non-inhibitor cohort • males, 12+ years • Severe haemophilia A or moderately to severe haemophilia B with a minimum weight at screening of 35 kg

Trial name: BASIS		NCT number: 03938792
	• Signed informed consent (or minor assent when applicable) • No detectable or documented history og 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 with FVIII/FIX replacement during OP • On-demand treatment regimen with ≥6 acute bleeding episodes (spontaneous or traumatic) that required coagulation factor infusion during the 6 months period prior to enrolment and willing to continue to receive on-demand treatment during the OP	
Main exclusion criteria	• Previous or current treatment for and/or history of coronary artery diseases, venous or arterial thrombosis or ischemic disease • Known planned surgerical procedure during the planned study period • Known haemostatic defect other than haemophilia A or B • Abnormal renal or hepatic function • Current unstable lever 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, on the judgement 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 06747086 during participation in studies B7841002 and B7841003 • Participation in other studies involving investigational drug(s) or investigational vaccines within 30 days of 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	

Trial name: BASIS		NCT number: 03938792
	• 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 OP 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.	
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 thromboembolic events • Incidence and severeity 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	

Trial name: BASIS	NCT number: 03938792

	• Change in joints as measured by Haemophilia Joint Health Score (HJHS) at 12 months post marstacimab initiation (ATP) versus factor replacement therapy use in the OP
	• Patient reported outcomes in quality-of-life assessments at 12 months post marstacimab initiation (ATP) 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 (through 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 study
	• Haemophilia 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 generalized 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 was 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 formation	N/A

Appendix B. Efficacy results per study

Results per study

Table 9 Results per study - EXPLORER 8

Results of EXPLORER 8 (NCT04082429)									
			ABR			Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	Study arm	N	Mean ABR (95% CI)	Absolute difference	Median ABR (IQR)	Difference	95% CI		
Treated spontaneous and traumatic bleeding episodes	1 (HB) no prophylaxis	12	14.8 (8.1; 26.9)	11.7	14.9 (3.3-22.1)	0.21	(0.10; 0.45)	Number of bleeds between arms 1 and 2 was compared based on the FAS and the 'on-treatment without ancillary therapy excl. data on initial regimen for participants exposed to both regimens' analysis data set using negative binomial regression with the number of bleeds analysed as a function of the randomized treatment regimen, type of haemophilia (HA or HB) and bleeding frequency (<9 or ≥ 9 bleeding episodes during the past 24 weeks prior to screening) and the logarithm of	Chowdary 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
	2 (HB) concizumab prophylaxis	24	3.1 (1.9; 5.0)		1.6 (0.0–4.8)	79% reduction			
	4 (HB) concizumab prophylaxis	26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Treated spontaneous bleeding episodes	1 (HB) no prophylaxis	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	2 (HB) concizumab prophylaxis	24	[redacted]		[redacted]				

Results of EXPLORER 8 (NCT04082429)									
			ABR			Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	Study arm	N	Mean ABR (95% CI)	Absolute difference	Median ABR (IQR)	Difference	95% CI		
			XXXXXXX		XXXXXXX			the length of the observation period included as an offset in the model. From the statistical model, an estimate of the RR of the ABR between the treatment regimens (concizumab prophylaxis and no prophylaxis) with corresponding 95% CI and a p-value for the test for superiority. No comparative statistical analyses have been performed for arm 4, hence only descriptive statistics is presented.	Haematol 2024; 11: e891-904. Novo Nordisk. Clinical Trial Report. Trial ID: NN7415-4307. Efficacy and safety of concizumab prophylaxis in patients with haemophilia A or B without inhibitors [Data on file]
	4 (HB) concizumab prophylaxis	26	XXXX XXXXXXX	XX	XXXX XXXXXXX	XX	XX		
Treated joint bleeding episodes	1 (HB) no prophylaxis	12	XXXX XXXXXXX	XX	XXXX XXXXXXX	XXXX XXX XXXXXXX	XXXXXXXXX		
	2 (HB) concizumab prophylaxis	24	XXXX XXXXXXX		XXXX XXXXXXX				
	4 (HB) concizumab prophylaxis	26	XXXX XXXXXXX	XX	XXXX XXXXXXX	XX	XX		
Treated target joint	1 (HB) no prophylaxis	12	XXXX XXXXXXX	XX	XXXX XXXXXXX	XXXX XXX XXXXXXX	XXXXXXXXX		

Results of EXPLORER 8 (NCT04082429)									
			ABR			Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	Study arm	N	Mean ABR (95% CI)	Absolute difference	Median ABR (IQR)	Difference	95% CI		
bleeding episodes	2 (HB) concizumab prophylaxis	24	[redacted]		[redacted]	[redacted]			
	4 (HB) concizumab prophylaxis	26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
All treated and untreated bleeds	1 (HB) no prophylaxis	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	2 (HB) concizumab prophylaxis	24	[redacted]		[redacted]				
	4 (HB) concizumab prophylaxis	26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Results of EXPLORER 8 (NCT04082429)								
			ABR			Estimated relative difference in effect	Description of methods used for estimation	References
Outcome	Study arm	N	Mean ABR (95% CI)	Absolute difference	Median ABR (IQR)	Difference 95% CI		
Outcome	**Study arm**	**N**	**No. of patients (%)**	**No. of events**	**No. of events per patient-year of exposure**	**No. of events per 100 patient-years of exposure**	**Description of methods used for estimation**	**References**
Thromboembolism	2-4 (HB) concizumab prophylaxis	64	0	0	0	0	The safety evaluation provided is based on the SAS and focusses on the OT analysis data set, including exposure to both the initial and new concizumab dosing regimen. In total, 64 participants with HB treated with concizumab prophylaxis were included in this OT analysis data set, with a total of 47 PYE.	Chowdary 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
Inhibitor	2-4 (HB) concizumab prophylaxis	64	0	0	0	0		
Anaphylaxis	2-4 (HB) concizumab prophylaxis	64	0	0	0	0		
SAE	2-4 (HB) concizumab prophylaxis	64	7 (11%)	10	0.213	21.3		
Treatment related SAE	2-4 (HB) concizumab prophylaxis	64	1 (1.6%)	1	0.021	2.1		
Drug dis-continuation due to adverse event	2-4 (HB) concizumab prophylaxis	64	2 (3%)	2	0.043	4.3		

Results of EXPLORER 8 (NCT04082429)								
			ABR			Estimated relative difference in effect	Description of methods used for estimation	References
Outcome	Study arm	N	Mean ABR (95% CI)	Absolute difference	Median ABR (IQR)	Difference 95% CI		
								2024; 11: e891-904.

HRQoL	Study arm	N	Baseline mean (SD)	Week 24 mean (SD)	Estimated treatment difference	References
SF-36v2 Bodily Pain	1 (HB) no prophylaxis	12	38.9 (7.7)	39.7 (7.7)	There was a significant difference in the estimated mean change in Bodily Pain score from baseline to Week 24 between people with HB on concizumab (arm 2) and those on no prophylaxis (arm 1). The estimated mean change from baseline to Week 24 was [redacted] for participants on concizumab (arm 2), compared with [redacted] for those on no prophylaxis (arm 1), giving a difference estimate of 14.64 (95% CI; 3.37, 25.91) at Week 24.	Angchaisuksiri P et al. Concizumab prophylaxis in people with hemophilia A or B without inhibitors: patient-reported outcome results from the phase 3 explorer8
	2 (HB) concizumab prophylaxis	24	43.6 (9.3)	50.2 (9.3)		
	4 (HB) concizumab prophylaxis	26	47.6 (9.8)	50.9 (6.9)	NR	

Results of EXPLORER 8 (NCT04082429)									
			ABR			Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	Study arm	N	Mean ABR (95% CI)	Absolute difference	Median ABR (IQR)	Difference	95% CI		

study. Res Pract Thromb Haemost. 2025;9:e102705

HRQoL	Study arm	N	Baseline mean (SD)	Week 24 mean (SD)	Estimated treatment difference	References
Haem-A-QOL	1 (HB) no prophylaxis	12	32.2 (22.5)	36.9 (31.2)	There was a significant improvement in QoL (Haem-A-QoL Total Score) between baseline and Week 24 for people with HB on concizumab (arm 2) compared with those on no prophylaxis (estimated treatment difference at Week 24 between arm 2 and arm 1 was −17.55 (95% CI; −28.77, −6.33). The estimate of the difference in change from baseline to Week 24 was in favour of arm 2 (concizumab) over arm 1 (no prophylaxis) for all individual domain scores.	Novo Nordisk. Clinical Trial Report. Trial ID: NN7415-4307. Efficacy and safety of concizumab prophylaxis in patients with haemophilia A or B without inhibitors [Data on file]
	2 (HB) concizumab prophylaxis	24	37.0 (18.3)	28.2 (14.0)		
	4 (HB) concizumab prophylaxis	26	29.4 (19.9)	21.6 (13.5)	NR	

Abbreviations: **HA:** Haemophilia A, **HB**: Haemophilia B, **ABR:** Annualized bleeding rate

Table 10: Results per study – BASIS

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**		
All bleeds, ABR (IQR), median (12 month)	Marstacimab	83	2.89 (0.00, 7.06*)	1.02	N/A	N/A	N/A	N/A	N/A	Count, single arm versus baseline	Matino et al., Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the phase 3 BASIS trial, Blood (2025) 146 (14): 1654–1663.
	Routine prophylaxis	83	3.91 (0.00, 11.66)								
Treated bleeds, ABR (IQR) median (12 month)	Marstacimab	83	2.02 (0.00, 6.09)	Not reported	N/A	N/A	N/A	N/A	N/A	Count, single arm versus baseline	Data on File. BASIS CSR. 2023.
	Routine prophylaxis	83	Not reported								

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**		
Haem-A-QoL total score, mean, adult patients (change from baseline at 12 month	Marstacimab	63	Not reported	Not reported	Not reported	N/A	N/A	N/A	N/A	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.	Pfizer data on file
	Routine prophylaxis	63	Not reported								
Haemo-QoL total score, mean, adolescent patients (change from baseline at 12 month	Marstacimab	20	Not reported	Not reported	Not reported	N/A	N/A	N/A	N/A	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. BASIS CSR. 2023.
	Routine prophylaxis	20	Not reported								

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**		
Severe venous thromboembolism (12 months)	Marstacimab	83	0	1	N/A	N/A	N/A	N/A	N/A	MedDRA v25.1 coding dictionary applied.	Matino et al., Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the phase 3 BASIS trial, Blood (2025) 146 (14): 1654–1663.
	Routine prophylaxis	91	1								
SAE (12 months)	Marstacimab	83	7 (8.4%) Treatment related: 1	-5 Treatment related: -1	N/A	N/A	N/A	N/A	N/A	One considered by the investigator to be treatment related that was diagnostically confirmed to be unrelated to a bleeding or thrombotic event.	Matino et al., Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the phase 3 BASIS trial, Blood (2025) 146 (14): 1654–1663.
	Routine prophylaxis	91	2 (2.2%)								

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	83	1 (1.2%)	-1	N/A	N/A	N/A	N/A	N/A	MedDRA v25.1 coding dictionary applied.	Matino et al., Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the phase 3 BASIS trial, Blood (2025) 146 (14): 1654–1663.
	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 preventive 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. Abbreviations: **HA:** Haemophilia A, **HB**: Haemophilia B, **ABR:** Annualized bleeding rate

Appendix C. Comparative analysis of efficacy: naïve indirect comparison

Table 11 Naïve indirect comparison of concizumab vs marstacimab for patients with haemophilia B

Outcome	Studies included in the analysis	Median/Mean (IQR/95% CI)	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference concizumab vs marstacimab	CI	P value	Difference	CI	P value		
ABR Median, all bleeds	EXPLORER 8, arm 2 BASIS	3.2 (0.6; 5.1) 2.89 (0.00, 7.06)	0.31	N/A	N/A	N/A	N/A	N/A	Indirect naïve comparison	N/A
ABR Median, treated bleeds	EXPLORER 8, arm 2 BASIS	1.6 (0.0–4.8) 2.02 (0.00, 6.09)	-0.42	N/A	N/A	N/A	N/A	N/A	Indirect naïve comparison	N/A
ABR Mean, treated joint bleeds	EXPLORER 8, arm 2 BASIS	XXXXXXXXXXX 4.13 (2.59, 5.67)	XXXX	N/A	N/A	N/A	N/A	N/A	Indirect naïve comparison	N/A
ABR Mean, treated target joint bleeds	EXPLORER 8, arm 2 BASIS	XXXXXXXXXXX 2.51 (1.25; 3.76)	XXXX	N/A	N/A	N/A	N/A	N/A	Indirect naïve comparison	N/A
Thromboembolism	EXPLORER 8, arm 2	N/A	0	NA	NA	NA	NA	N/A	Indirect naïve comparison	N/A

Outcome	Studies included in the analysis	Median/Mean (IQR/95% CI)	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
			Difference concizumab vs marstacimab	CI	P value	Difference	CI	P value		
	BASIS									
Inhibitor	EXPLORER 8, arm 2 BASIS	N/A	0	NA	NA	NA	NA	N/A	Indirect naïve comparison	N/A
Anaphylaxis	EXPLORER 8, arm 2 BASIS	N/A	0	NA	NA	NA	NA	N/A	Indirect naïve comparison	N/A
SAE	EXPLORER 8, arm 2 BASIS	N/A	0	NA	NA	NA	NA	N/A	Indirect naïve comparison	N/A
Treatment related SAE	EXPLORER 8, arm 2 BASIS	NA	0	NA	NA	NA	NA	N/A	Indirect naïve comparison	N/A
Discontinuation due to adverse event	EXPLORER 8, arm 2 BASIS	N/A	1	NA	NA	NA	NA	N/A	Indirect naïve comparison	N/A

Abbreviations: **ABR**: annual bleeding rate, **SAE:** Severe Adverse Event, **CI:** Confidence interval

Appendix D. Literature searches for the clinical assessment

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

An SLR was conducted in November 2021, and updated in September 2022 and April 2025. The main objective was to identify clinical efficacy, safety and health-related quality of life (HRQoL) evidence for treatment options in haemophilia A and B, with and without inhibitors. For this application, a further localization was done to include only studies with concizumab and marstacimab and the same target population of patients with HB without inhibitors ≥12 years of age.

Searches of electronic databases (MEDLINE, Embase and Evidence-Based Medicine Reviews [EBMR]) were performed, and supplemented by searches of key congresses (that had occurred since 2022), clinical trial registries, Health Technology Assessment (HTA) bodies, and the reference lists of relevant SLRs or (network) meta-analyses ([N]MAs) captured in the review. All records were dual reviewed at title/abstract and full text stages, with conflicts arbitrated by a third reviewer if necessary. Data were extracted into a pre-specified extraction grid by one reviewer and checked for accuracy by a second reviewer. The quality of included randomised clinical trials (RCTs) was assessed using the the Risk of Bias (RoB) 1.0 tool.

Based on the volume of evidence, at the title/abstract review stage, observational studies were deprioritised unless they reported on recombinant coagulation factor IX (eftrenonacog alfa, nonacog beta pegol and albutrepenonacog alfa), as there was limited RCT evidence for these. After the full-text review stage, studies were prioritised for data extraction if they:

- Were RCTs with at least 12 weeks of follow-up
- Were interventional non-RCTs (e.g., single-arm trials) investigating marstacimab or eftrenonacog alfa, nonacog beta pegol and albutrepenonacog alfa (due to limited RCT evidence)
- Were observational studies investigating eftrenonacog alfa, nonacog beta pegol or albutrepenonacog alfa (due to limited trial evidence)

In total, across all updates, this SLR included 643 publications, of which 26 RCTs, five interventional non-RCTs and three observational studies were prioritised for extraction. The most commonly assessed treatments were recombinant factors (n=22), including factor VII, VIII and IX; with four studies assessing eftrenonacog alfa, nonacog beta pegol and albutrepenonacog alfa. Other treatments assessed included monoclonal antibodies, Factor VIII Inhibitor Bypassing Activity (FEIBA) and Mim8. Key baseline characteristics and demographics such as age, gender and weight, were well reported and typically representative of the broader haemophilia population. Studies were most commonly conducted in patients with HA, and those without inhibitors, although around one-

quarter included mixed populations of patients with HA or HB with and without inhibitors.

Overall, a relatively large volume of evidence was identified in this SLR, which aimed to identify studies reporting evidence on the clinical efficacy, safety and HRQoL of treatment options in HA or HB, with or without inhibitors. Of the 34 clinical trials in 106 publications prioritised for extraction, most were open-label, international RCTs. The results of the SLR highlight the well-established benefits of prophylactic over on-demand treatment strategies. Although recombinant factor therapies were commonly assessed, a move towards novel non-factor replacement treatments can be observed, given that these are effective in patients with HA or HB and do not pose the risk of treatment-induced antibodies. Prophylactic treatments were well-tolerated across included studies, however, there is a need for studies with longer-term data to confirm the safety of treatments over a prolonged period of time. Risk of bias was generally low across studies, with the unblinded nature of trials as the only potential domain of concern.

Only trials that included concizumab or the relevant comparator marstacimab in same target population (HB ≥12 years) were of interest for the comparative analysis.

The SLR found 3 clinical trials in 34 publications with concizumab and 4 relevant clinical trials in 19 publications with marstacimab. Only 9 of the publications were full publications. Upon closer inspection of the publications, 3 of the clinical trials (4 full publications) were excluded as they were not phase 3 studies. Two of the remaining 5 publications were excluded as they did not include patients with HB without inhibitors.

This left us with 3 relevant publications based on 2 clinical trials (EXPLORER 8 and BASIS) for the comparative analysis.

Table 12 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Via Ovid SP	1974 to 24th April 2025	24.04.2025
Medline	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions	1946 to 24th April 2025	24.04.2025
CENTRAL	EBM Reviews (Ovid): ACP Journal Club; Cochrane Central Register of Controlled Trials Cochrane Database of Systematic Reviews Cochrane Clinical Answers	ACP Journal Club 1991 to April 2025; Cochrane Central Register of Controlled Trials March 2025; Cochrane Database of Systematic Reviews 1st January 2022 to 23rd April 2025; Cochrane Clinical Answers April 2025.	24.04.2025

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

Abbreviations:

Table 13 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
WHO ICTRP	www.who.int/clinical-trials-registry-platform	Electronic search	06.05.2025
ClinicalTrials.gov	ClinicalTrials.gov	Electronic search	07.05.2025

Abbreviations: ICTRP: International Clinical Trial Registry Platform

Table 14 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
AMCP	https://www.amcp.org/	Manual search	Haemophilia Hemophilia	April-May 2025
ASH	http://www.hematology.org/	Manual search	Haemophilia Hemophilia	April-May 2025
EAHAD	https://www.eahad.org/	Manual search	Haemophilia Hemophilia	April-May 2025
EHA	https://ehaweb.org/	Manual search	Haemophilia Hemophilia	April-May 2025
International Conference on Haematology and Blood Disorders	https://scisynopsisconferences.com/hematology/	Manual search	Haemophilia Hemophilia	April-May 2025
ISPOR: all regions	https://www.ispor.org/	Manual search	Haemophilia Hemophilia	April-May 2025
ISTH	https://www.isth.org/	Manual search	Haemophilia Hemophilia	April-May 2025

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ISOQOL	https://www.isoqol.org/	Manual search	Haemophilia Hemophilia	April-May 2025
NBDF	https://www.bleeding.org/	Manual search	Haemophilia Hemophilia	April-May 2025
WFH	https://wfh.org/	Manual search	Haemophilia Hemophilia	April-May 2025

AMCP: Academy of Managed Care Pharmacy, ASH: American Society of Haematology, EAHAD: European Association for Haemophilia and Allied Disorders, EHA: European Haematology Association, ISPOR: International Society for Pharmacoeconomics and Outcomes Research, ISTH: International Society of Thrombosis and Haemostasis, ISOQOL: International Society of Quality of Life Research, NBDF: National Hemophilia Foundation Bleeding Disorders Conference, WFH: World Federation of Haemophilia

D.1.2 Search strategies

The SLR update was performed in accordance with a pre-specified (unregistered) protocol and in accordance with the methodological principles of conduct for SLRs as detailed in the University of York Centre for Reviews and Dissemination's (CRD's) "Guidance for Undertaking Reviews in Health Care".[14] Implementation and reporting of the SLR followed the PRISMA statement.[15] This involved searching electronic databases, hand-searching of key conference proceedings from the last four years (since September 2022), clinical trial registries, key HTA body websites, and bibliographies of any relevant systematic reviews or (network) meta-analyses ([N]MAs) identified during the review.

Electronic databases

MEDLINE, Embase and EBMR databases were searched independently via the Ovid SP platform and manually deduplicated. The strategies included search terms specific to the disease area, relevant interventions and study design filters. The randomised controlled trial (RCT) and observational study search terms were based on adapted versions of the Scottish Intercollegiate Guidelines Network (SIGN) filters.

Only four of the component EBMR databases were searched as part of the SLR update, as the other databases are no longer updated and therefore do not contain records published in 2022 or later. Specifically, DARE and NHS EED only contain records published until 31st March 2015, whilst the Cochrane Methodology Register is no longer updated as of 31st May 2012 and HTA database as of 31st March 2018.

In a protocol amendment, additional searches for efanesoctocog alfa, including brand names, were conducted. They were searched without a date limit as they were not included in the 2022 SLR update.

Clinical Trial Registries

The International Clinical Trials Registry Platform (ICTRP) was searched separately to identify trial records updated since September 2022. Additionally, ClinicalTrials.gov was searched without a date limit, as this was not searched during the previous SLR.

Manual congress searching

Conference proceedings for the last four years (2022–2025), where available, from the eight conferences listed below were hand-searched to identify any relevant abstracts for inclusion in the SLR update:

- Academy of Managed Care Pharmacy (AMCP) – https://www.amcp.org/
- American Society of Haematology (ASH) – http://www.hematology.org/
- European Association for Haemophilia and Allied Disorders (EAHAD) – https://www.eahad.org/
- European Haematology Association (EHA) – https://ehaweb.org/
- International Conference on Haematology and Blood Disorders – https://scisynopsisconferences.com/hematology/
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR): all regions – https://www.ispor.org/
- International Society of Thrombosis and Haemostasis (ISTH) – https://www.isth.org/
- International Society of Quality of Life Research (ISOQOL) – https://www.isoqol.org/
- National Hemophilia Foundation Bleeding Disorders Conference (NBDF) – https://www.bleeding.org/
- World Federation of Haemophilia (WFH) – https://wfh.org/

Search terms for each conference were aligned to the terms used in the electronic database searches and the specific format and requirements of each source. For conference abstracts identified as relevant, searches were conducted to identify any associated conference posters or presentation slides, which were used for data extraction when available.

For two further conferences, “International Conference on Haematology and Blood Disorders” and “National Hemophilia Foundation Bleeding Disorders Conference”, an abstract book or website could not be located and so these congresses were not searched.

HTA body websites

The following HTA bodies were hand-searched to identify any relevant reimbursement submissions published since 2022:

- England – National Institute for Health and Clinical Excellence (NICE)
- Scotland – Scottish Medicines Consortium (SMC)
- Wales – All Wales Medicines Strategy Group (AWMSG)

- US – Institute for Clinical and Economic Review (ICER)
- Canada – Canadian Agency for Drugs and Technologies in Health (CADTH)
- Canada – Insitut national d'excellence en santé et services sociaux (INESSS)
- Australia – Pharmaceutical Benefits Advisory Committee (PBAC)
- Sweden – Tandvårds- och Läkemedelsförmånsverket (TLV)
- Norway – Norwegian Medicines Agency (NOMA)
- Germany – Gemeinsamer Bundesausschuss (G-BA)
- Germany – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)
- France – Haute Autorité de Santé (HAS)
- The Netherlands – National Health Care Institute (Zorginstituut Nederland, ZIN)
- Belgium – Centre fédéral d'expertise des soins de santé (KCE)
- Finland – Pharmaceuticals Pricing Board (HILA)
- Ireland – National Centre for Pharmacoeconomics (NCPE)
- Portugal – National Authority of Medicines and Health Products (INFARMED)

Search terms for each HTA body were aligned to the terms used in the electronic database searches and the specific format and requirements of each source.

Table 15 of search strategy table for Embase (Ovid SP)

No.	Query	Results
#1	exp hemophilia/	48375
#2	h?emophilia$.ti,ab,kf.	43955
#3	((ahf or anti-h?emophilli$ factor or antih?emophilli$ factor or factor 8 or factor 9 or factor VIII or factor IX) adj3 deficien$).ti,ab,kf.	2724
#4	christmas disease$.ti,ab,kf.	137
#5	or/1-4	53033
#6	recombinant blood clotting factor 8/	5862
#7	blood clotting factor 8/	32326
#8	blood clotting factor 9/	10007
#9	recombinant blood clotting factor 7a/	8218
#10	(advate or "advate rahf-pfm" or adynovi or afstyla or antih?emophilic factor VIII complex or bax 855 or bax855 or bay 94 9027 or bay 94-9027 or bay w 6240 or bay w6240 or bay94 9027 or "bay94-9027" or beroctocog or bioclate or csl 627 or csl627 or damoctocog or	3546

No.	Query	Results
	efmoroctocog or eloctate or helixate or helixatenexgen or human coagulation factor VIII or human recombinant blood clotting factor 8 or iblias or kogenate or kogenatebayer or kovaltry or lonoctocog or moroctocog or novoeight or nuwiq or obizur or octocog or recombinant antih?emophilic factor or recombinant coagulation factor VIII or recombinant factor viii or recombinate or refacto or rurioctocog alfa or rurioctocog alpha or simoctocog alfa or susoctocog or turoctocog or vihuma or xyntha).ti,ab,kf.	
#11	(rFIX or IDELVION or rIX-FP or CSL654 or albutrepenonacog or beneFIX or nonacog alfa or RIXUBIS or BAX 326 or nonacog gamma or ALPROLIX or rFIXFc or "BIIB 029" or eftrenonacog alfa or Refixia or REBINYN or N9-GP or NN-7999 or NN7999 or nonacog beta pegol or Ixinity or IB1001 or trenacog alfa or recombinant factor IX or recombinant FIX or recombinant factor 9 or recombinant coagulation factor FIX or human coagulation factor IX or human recombinant blood clotting factor 9).ti,ab,kf.	1574
#12	(eptacog alfa or eptacog beta or LR769 or recombinant coagulation factor VII or FVIIa or recombinant factor VIIa or rFVIIa or human coagulation factor VII activated or recombinant blood clotting factor VIIa or marzeptacog alfa or marzeptacog alpha or Marzaa or niastase or nn 1731 or nn1731 or novo seven or novoseven or novo7 or AryoSeven or Sevenfact or oreptacog alfa or oreptacog alpha or vatreptacog alfa or vatreptacog alpha).ti,ab,kf.	7320
#13	concizumab/	263
#14	(concizumab or mab 2021 or mab2021 or nn 7415 or nn7415 or "nnc 0172 0000 2021" or "nnc 0172 2021" or nnc 172 2021 or nnc017200002021 or nnc01722021 or nnc1722021).ti,ab,kf.	188
#15	emicizumab/	2251
#16	(emicizumab or ace 910 or ace910 or hemlibra or rg 6013 or rg6013 or ro 5534262 or ro5534262).ti,ab,kf.	1863
#17	fitusiran/	266
#18	(fitusiran or aln at3 or aln at3sc or alnat3 or alnat3sc or sar 439774 or sar439774).ti,ab,kf.	150
#19	activated prothrombin complex/	2902
#20	(factor eight inhibitor bypassing activity or factor VIII inhibitor bypassing activity or activated prothrombin complex concentrate or anti inhibitor coagulant complex or "anti-inhibitor coagulant complex" or autoplex or "autoplex t" or "autoplex-t" or blood clotting factor 8 inhibitor bypassing activity or coagulation factor VIII inhibitor bypassing fraction or factor viii inhibitor bypassing activity or FEIBA).ti,ab,kf.	1549

No.	Query	Results
#21	tissue factor pathway inhibitor/	4876
#22	(Anti tissue factor pathway inhibitor or "Anti-tissue factor pathway inhibitor" or tissue factor pathway inhibitor or Antithromboplastin or extrinsic coagulation pathway inhibitor or extrinsic pathway inhibitor or LACI or lipoprotein associated coagulation inhibitor or TFPI).ti,ab,kf.	6412
#23	or/6-22	59898
#24	marstacimab/	91
#25	(marstacimab).ti,ab,kf.	58
#26	or/24-25	100
#27	Clinical Trial/	1095711
#28	Randomized Controlled Trial/	878427
#29	controlled clinical trial/	445396
#30	multicenter study/	418819
#31	Phase 3 clinical trial/	82995
#32	Phase 4 clinical trial/	9213
#33	exp RANDOMIZATION/	100996
#34	Single Blind Procedure/	59042
#35	Double Blind Procedure/	231273
#36	Crossover Procedure/	82069
#37	PLACEBO/	426419
#38	randomi?ed controlled trial$.tw.	376583
#39	rct.tw.	62599
#40	(random$ adj2 allocat$).tw.	60784
#41	single blind$.tw.	35241
#42	double blind$.tw.	261154
#43	((treble or triple) adj blind$).tw.	2413

No.	Query	Results
#44	placebo$.tw.	394193
#45	Prospective Study/	968621
#46	or/27-45	3204904
#47	Clinical study/	168302
#48	Case control study/	231631
#49	Family study/	26502
#50	Longitudinal study/	236357
#51	Retrospective study/	1791486
#52	Prospective study/	968621
#53	Cohort analysis/	1321811
#54	(Cohort adj (study or studies)).mp.	571017
#55	(Case control adj (study or studies)).tw.	185302
#56	(follow up adj (study or studies)).tw.	78731
#57	(observational adj (study or studies)).tw.	305731
#58	(epidemiologic$ adj (study or studies)).tw.	129465
#59	(cross sectional adj (study or studies)).tw.	415332
#60	or/47-59	4605445
#61	46 or 60	6541368
#62	5 and 23 and 61	6428
#63	limit 62 to yr=2022 -Current	1331
#64	5 and 26 and 61	27
#65	63 or 64	**1344**

Database(s): Embase 1974 to 2025 April 24.

Table 16 of search strategy table for MEDLINE (Ovid SP)

No.	Query	Results
#1	hemophilia a/ or hemophilia b/	25847
#2	h?emophilia$.ti,ab,kf.	27339
#3	((ahf or anti-h?emophilli$ factor or antih?emophilli$ factor or factor 8 or factor 9 or factor VIII or factor IX) adj3 deficien$).ti,ab,kf.	1660
#4	christmas disease$.ti,ab,kf.	335
#5	or/1-4	32486
#6	Factor VIII/	17995
#7	Factor IX/	5502
#8	exp Factor VII/	7874
#9	(advate or "advate rahf-pfm" or adynovi or afstyla or antih?emophilic factor VIII complex or bax 855 or bax855 or bay 94 9027 or bay 94-9027 or bay w 6240 or bay w6240 or bay94 9027 or "bay94-9027" or beroctocog or bioclate or csl 627 or csl627 or damoctocog or efmoroctocog or eloctate or helixate or helixatenexgen or human coagulation factor VIII or human recombinant blood clotting factor 8 or iblias or kogenate or kogenatebayer or kovaltry or lonoctocog or moroctocog or novoeight or nuwiq or obizur or octocog or recombinant antih?emophilic factor or recombinant coagulation factor VIII or recombinant factor viii or recombinate or refacto or rurioctocog alfa or rurioctocog alpha or simoctocog alfa or susoctocog or turoctocog or vihuma or xyntha).ti,ab,kf.	1356
#10	(rFIX or IDELVION or rIX-FP or CSL654 or albutrepenonacog or beneFIX or nonacog alfa or RIXUBIS or BAX 326 or nonacog gamma or ALPROLIX or rFIXFc or "BIIB 029" or eftrenonacog alfa or Refixia or REBINYN or N9-GP or NN-7999 or NN7999 or nonacog beta pegol or Ixinity or IB1001 or trenacog alfa or recombinant factor IX or recombinant FIX or recombinant factor 9 or recombinant coagulation factor FIX or human coagulation factor IX or human recombinant blood clotting factor 9).ti,ab,kf.	609
#11	(eptacog alfa or eptacog beta or LR769 or recombinant coagulation factor VII or FVIIa or recombinant factor VIIa or rFVIIa or human coagulation factor VII activated or recombinant blood clotting factor VIIa or marzeptacog alfa or marzeptacog alpha or Marzaa or niastase or nn 1731 or nn1731 or novo seven or novoseven or novo7 or AryoSeven or Sevenfact or oreptacog alfa or oreptacog alpha or vatreptacog alfa or vatreptacog alpha).ti,ab,kf.	3937

No.	Query	Results
#12	(concizumab or mab 2021 or mab2021 or nn 7415 or nn7415 or "nnc 0172 0000 2021" or "nnc 0172 2021" or nnc 172 2021 or nnc017200002021 or nnc01722021 or nnc1722021).ti,ab,kf.	66
#13	(emicizumab or ace 910 or ace910 or hemlibra or rg 6013 or rg6013 or ro 5534262 or ro5534262).ti,ab,kf.	737
#14	(fitusiran or aln at3 or aln at3sc or alnat3 or alnat3sc or sar 439774 or sar439774).ti,ab,kf.	54
#15	(factor eight inhibitor bypassing activity or factor VIII inhibitor bypassing activity or activated prothrombin complex concentrate or anti inhibitor coagulant complex or "anti-inhibitor coagulant complex" or autoplex or "autoplex t" or "autoplex-t" or blood clotting factor 8 inhibitor bypassing activity or coagulation factor VIII inhibitor bypassing fraction or factor viii inhibitor bypassing activity or FEIBA).ti,ab,kf.	643
#16	(Anti tissue factor pathway inhibitor or "Anti-tissue factor pathway inhibitor" or tissue factor pathway inhibitor or Antithromboplastin or extrinsic coagulation pathway inhibitor or extrinsic pathway inhibitor or LACI or lipoprotein associated coagulation inhibitor or TFPI).ti,ab,kf.	4510
#17	or/6-16	34066
#18	(marstacimab).ti,ab,kf.	32
#19	Randomized Controlled Trials as Topic/	181724
#20	randomized controlled trial/	637010
#21	Random Allocation/	108380
#22	Double Blind Method/	183896
#23	Single Blind Method/	34965
#24	clinical trial/	541375
#25	clinical trial, phase ii.pt.	43414
#26	clinical trial, phase iii.pt.	24488
#27	clinical trial, phase iv.pt.	2657
#28	controlled clinical trial.pt.	95696
#29	randomized controlled trial.pt.	637010
#30	multicenter study.pt.	369939

No.	Query	Results
#31	clinical trial.pt.	541375
#32	exp Clinical Trials as topic/	407394
#33	(clinical adj trial$).tw.	552032
#34	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	213512
#35	PLACEBOS/	36098
#36	placebo$.tw.	266392
#37	randomly allocated.tw.	41129
#38	(allocated adj2 random$).tw.	45165
#39	or/19-38	2067053
#40	exp case control studies/	1600518
#41	exp cohort studies/	2741239
#42	Case control.tw.	171229
#43	(cohort adj (study or studies)).tw.	393637
#44	Cohort analy$.tw.	14742
#45	(Follow up adj (study or studies)).tw.	60209
#46	(observational adj (study or studies)).tw.	198811
#47	Longitudinal.tw.	373522
#48	Retrospective.tw.	895937
#49	Cross sectional.tw.	622842
#50	Cross-sectional studies/	542091
#51	or/40-50	4249349
#52	39 or 51	5766126
#53	5 and 17 and 52	2824
#54	limit 53 to yr=2022 -Current	383
#55	5 and 18 and 52	11

No.	Query	Results
#56	54 or 55	**385**

Database(s): Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily April 24, 2025.

Table 17: of search strategy table for EMBR (Ovid SP)

No.	Query	Results
#1	hemophilia a/ or hemophilia b/	712
#2	h?emophilia$.ti,ab,kw.	1939
#3	((ahf or anti-h?emophilli$ factor or antih?emophilli$ factor or factor 8 or factor 9 or factor VIII or factor IX) adj3 deficien$).ti,ab,kw.	78
#4	christmas disease$.ti,ab,kw.	5
#5	or/1-4	2017
#6	Factor VIII/	518
#7	Factor IX/	101
#8	exp Factor VII/	438
#9	(advate or "advate rahf-pfm" or adynovi or afstyla or antih?emophilic factor VIII complex or bax 855 or bax855 or bay 94 9027 or bay 94-9027 or bay w 6240 or bay w6240 or bay94 9027 or "bay94-9027" or beroctocog or bioclate or csl 627 or csl627 or damoctocog or efmoroctocog or eloctate or helixate or helixatenexgen or human coagulation factor VIII or human recombinant blood clotting factor 8 or iblias or kogenate or kogenatebayer or kovaltry or lonoctocog or moroctocog or novoeight or nuwiq or obizur or octocog or recombinant antih?emophilic factor or recombinant coagulation factor VIII or recombinant factor viii or recombinate or refacto or rurioctocog alfa or rurioctocog alpha or simoctocog alfa or susoctocog or turoctocog or vihuma or xyntha).ti,ab,kw.	380
#10	(rFIX or IDELVION or rIX-FP or CSL654 or albutrepenonacog or beneFIX or nonacog alfa or RIXUBIS or BAX 326 or nonacog gamma or ALPROLIX or rFIXFc or "BIIB 029" or eftrenonacog alfa or Refixia or REBINYN or N9-GP or NN-7999 or NN7999 or nonacog beta pegol or Ixinity or IB1001 or trenacog alfa or recombinant factor IX or recombinant FIX or recombinant factor 9 or recombinant coagulation factor FIX or human coagulation factor IX or human recombinant blood clotting factor 9).ti,ab,kw.	131
#11	(eptacog alfa or eptacog beta or LR769 or recombinant coagulation factor VII or FVIIa or recombinant factor VIIa or rFVIIa or human coagulation factor VII activated or recombinant blood clotting factor VIIa or marzeptacog alfa or marzeptacog alpha or Marzaa or niastase or nn 1731	511

No.	Query	Results
	or nn1731 or novo seven or novoseven or novo7 or AryoSeven or Sevenfact or oreptacog alfa or oreptacog alpha or vatreptacog alfa or vatreptacog alpha).ti,ab,kw.	
#12	(concizumab or mab 2021 or mab2021 or nn 7415 or nn7415 or "nnc 0172 0000 2021" or "nnc 0172 2021" or nnc 172 2021 or nnc017200002021 or nnc01722021 or nnc1722021).ti,ab,kw.	58
#13	(emicizumab or ace 910 or ace910 or hemlibra or rg 6013 or rg6013 or ro 5534262 or ro5534262).ti,ab,kw.	94
#14	(fitusiran or aln at3 or aln at3sc or alnat3 or alnat3sc or sar 439774 or sar439774).ti,ab,kw.	30
#15	(factor eight inhibitor bypassing activity or factor VIII inhibitor bypassing activity or activated prothrombin complex concentrate or anti inhibitor coagulant complex or "anti-inhibitor coagulant complex" or autoplex or "autoplex t" or "autoplex-t" or blood clotting factor 8 inhibitor bypassing activity or coagulation factor VIII inhibitor bypassing fraction or factor viii inhibitor bypassing activity or FEIBA).ti,ab,kw.	79
#16	(Anti tissue factor pathway inhibitor or "Anti-tissue factor pathway inhibitor" or tissue factor pathway inhibitor or Antithromboplastin or extrinsic coagulation pathway inhibitor or extrinsic pathway inhibitor or LACI or lipoprotein associated coagulation inhibitor or TFPI).ti,ab,kw.	348
#17	or/6-16	2126
#18	(marstacimab).ti,ab,kw.	17
#19	5 and 17	1054
#20	limit 19 to yr="2022 -Current"	105
#21	5 and 18	15
#22	20 or 21	**116**

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 23, 2025, EBM Reviews - ACP Journal Club 1991 to April 2025, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Cochrane Clinical Answers April 2025, EBM Reviews - Cochrane Central Register of Controlled Trials March 2025, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016

D.1.3 Systematic selection of studies

Articles were included in the SLR update if they met the eligibility criteria presented in Table 18.

As the search strategy above included a very broad scope, 2 local reviewers assessed the final studies included in the SLR to ensure the chosen trials were relevant in a Danish

setting as shown in the PRISMA Flow Diagram. This involved ensuring the trials included reported relevant outcomes for 1) a relevant intervention in the Danish treatment setting, 2) the trials included in the final SLR were phase 3 trials and 3) the trials included in the final SLR were not extension trials.

Table 18 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult or adolescent (age ≥12 years) patients with haemophilia A or B (with or without inhibitors)	- Studies conducted in patients <12 years - Studies conducted in the surgical setting
Intervention and comparators	*Haemophilia A without inhibitors:* - Emicizumab (prophylaxis only) - All available recombinant factor VIII (rFVIII) products (used prophylactically) - Mim8 (Factor VIIIa) - All available anti-tissue factor pathway inhibitor (TFPI) products (prophylaxis) - Fitusiran (prophylaxis) *Haemophilia B without inhibitors:* - All available recombinant factor IX (FIX) products (used prophylactically) - All available anti-TFPI products (prophylaxis) - Fitusiran (prophylaxis) *Haemophilia A with inhibitors:* - Emicizumab (prophylaxis only) - All available anti-TFPI products (prophylaxis) - Fitusiran (prophylaxis) - Mim8 (Factor VIII) - Factor VIII inhibitor bypassing activity (FEIBA; prophylaxis) *Haemophilia B with inhibitors:*	- No pharmacological treatments investigated in the studies - Studies investigating gene therapies

	- FEIBA (prophylaxis) - All available anti-TFPI products (prophylaxis) Fitusiran (prophylaxis)	
Outcomes	Outcomes of interest were aligned with the ongoing/planned trial program for concizumab, to include: *Efficacy* <u>Number of bleeds</u> - Number of total bleeds - Number of treated bleeds - Number of treated spontaneous bleeds - Number of treated joint bleeds - Number of treated traumatic bleeds - Number of life-threatening bleeding events - Number of target joint bleeds - Number of patients with target joint bleedsa <u>Bleeding rates</u> - Annualised bleed rate (ABR) of total bleeds - ABR of treated spontaneous/ traumatic bleeding - ABR of treated total bleeding events - ABR of treated events of joint bleeding - ABR of target-joint bleeding events and number of joints affected/developed/resolved - Total annualised joint bleeding rate (AJBR)a - Treated AJBRa <u>Other efficacy outcomes</u>[a] - Joint arthropathy	- Any outcomes not listed for inclusion

- Pettersson score
- % of bleeds resolved with 1, or 1–2 injections, including:
  - Annualised infusion rate
  - Dose and total factor consumption

Safety

- Development of neutralising and non-neutralising antibodies (for antibody treatments)
- Development of FVIII inhibitors
- Number and incidence of overall adverse events (AEs)
- Number and incidence of most common AEs (including injection-site reaction, upper respiratory tract infection, arthralgia, headache, influenza, nasopharyngitis)
- Number and incidence of thrombotic events
- Number and incidence of thrombotic microangiopathy events
- Number and incidence of serious AEs (resulting in death, life-threatening, hospitalisation, disability/permanent damage, congenital anomaly, requiring medical or surgical intervention)
- Life-threatening/disabling AEs (including bleeds)
- Hypersensitivity reactions
- Discontinuations due to AEs
- Drug-drug interactions

HRQoL outcomes

- Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)

	- Haemophilia-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A) - Hemophilia Joint Health Score (HJHS)a - Hemophilia Treatment Experience Measure (Hemo-TEM) - Heart Patients Psychological Questionnaire (H-PPQ) patient preference - Patient-Reported Outcomes Measurement Information System (PROMIS) Numeric Scale Pain Intensity - PROMIS Short Form - Upper Extremity - Patients' Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) on physical functioning - Brief Pain Inventory - Short Form - Caregiver-Reported Adapted Inhibitor Specific Quality of Life (Inhib-QoL) Questionnaire - Short form-36 version 2.0	
Study design/publication type[b]	- Published in 2022 onwards - Phase 2/3 Randomised controlled trials (RCTs) - Single arm clinical studies - Prospective, non-randomised comparative studies in a clinical setting - Single-arm/comparative observational studies (retrospective/prospective) - Relevant published systematic reviews will be listed (not included) for Novo Nordisk's reference and for the SLR team to cross-check referenced studies	- Publication date before 2022 - Guidelines - Pre-clinical studies - Studies reporting Phase 1 data only - Prognostic studies - Pooled analyses where no new data are reported compared with original trials - Studies on animals - Methodology studies or protocols - Commentary - Case reports and case series

Language restrictions	-	Any language No geographic limitations	-	NA

Footnotes: [a] Outcomes included in the eligibility criteria for the current SLR update, but not the original SLR or first update. [b] In line with the previous SLRs, only RCTs with a follow-up of ≥12 weeks were prioritised for extraction, with the exception of if evidence was limited for interventions of interest (in line with protocol Amendment 2 and 3). **Abbreviations:** ABR, annualised bleed rate; AE, adverse event; AJBR, annualised joint bleeding rate; FEIBA, factor VIII inhibitor bypassing activity; FIX, factor IX; FVIII, factor VIII; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; Haemo-QoL-A, Haemophilia-specific Quality of Life Questionnaire for Adults; Hemo-Tem, Hemophilia Treatment Experience Measure; H-PPQ, Heart Patients Psychological Questionnaire; HJHS, Hemophilia Joint Health Score; Inhib-QoL, Inhibitor Specific Quality of Life; NA, not applicable; PGIC, Patients' Global Impression of Change; PGIS, Patient Global Impression of Severity; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; RCT, randomised controlled trial; rFVIIa, recombinant activated factor VII; rFVIII, recombinant factor VIII; TFPI, tissue factor pathway inhibitor.

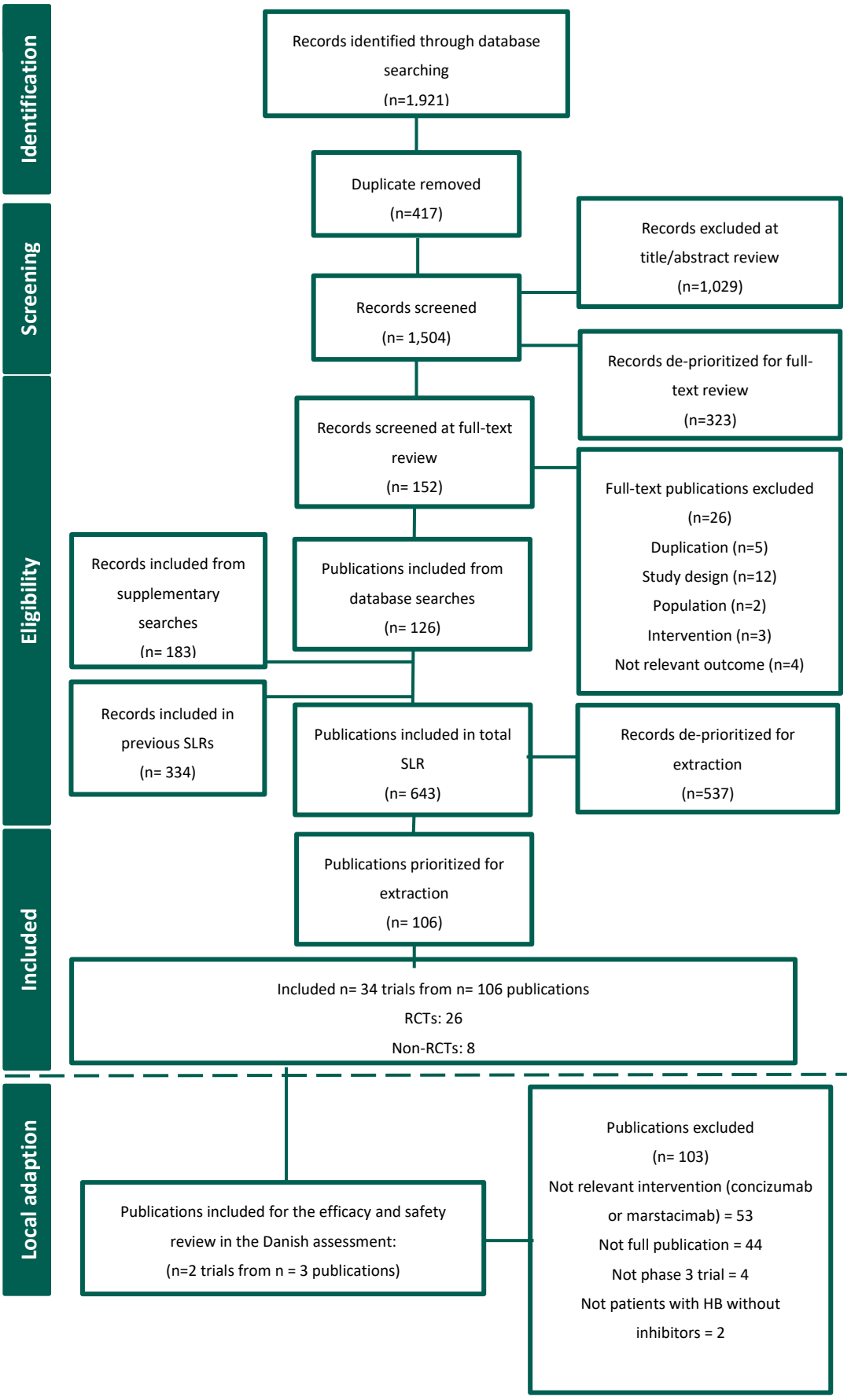
Identification
Screening
Eligibility
Included
Local adaption
Records identified through database searching (n=1,921)
Duplicate removed (n=417)
Records excluded at title/abstract review (n=1,029)
Records screened (n= 1,504)
Records de-prioritized for full-text review (n=323)
Records screened at full-text review (n= 152)
Full-text publications excluded (n=26)
Duplication (n=5)
Study design (n=12)
Population (n=2)
Intervention (n=3)
Not relevant outcome (n=4)
Records included from supplementary searches (n= 183)
Publications included from database searches (n= 126)
Records included in previous SLRs (n= 334)
Publications included in total SLR (n= 643)
Records de-prioritized for extraction (n=537)
Publications prioritized for extraction (n= 106)
Included n= 34 trials from n= 106 publications
RCTs: 26
Non-RCTs: 8
Publications included for the efficacy and safety review in the Danish assessment: (n=2 trials from n = 3 publications)
Publications excluded (n= 103)
Not relevant intervention (concizumab or marstacimab) = 53
Not full publication = 44
Not phase 3 trial = 4
Not patients with HB without inhibitors = 2

Table 19 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
EXPLORER 8 **NCT04082429** Chowdery P et al. Concizumab prophylaxis in people with haemophilia A or haemophilia B without inhibitors (explorer8): a prospective, multicentre, open-label, randomized, phase 3a trial, Lancet Haematol	Assess the efficacy and safety of concizumab in patients with haemophilia A or B without inhibitors	Phase 3a open-label RCT	- Male - Aged ≥12 years - Congenital severe haemophilia A (FVIII below 1%) or B (FIX equal to or below 2%) without inhibitors and documented treatment with clotting factor concentrate in the 24 weeks before screening - Body weight of at least 25 kg at screening	- No prophylaxis (n=21) - Concizumab prophylaxis (n=42) - Concizumab once per day (non-randomised arm, transferred from explorer5 on concizumab prophylaxis) (n=9) - Concizumab once per day (non-randomised arm, transferred from explorer6, patients already allocated to this group before treatment pause, patients who	Number of treated spontaneous and traumatic bleeding episodes (≥24 weeks for randomised on-demand arm, ≥32 weeks for randomised concizumab arm)	Number of treated spontaneous, traumatic joint, traumatic target joint bleeds, change in SF-36 v2 bodily pain and Haem-A-QoL total score as well as safety (number of thromboembolic events, number of hypersensitivity type reactions, number of injection-site reactions, and number of patients with antibodies to concizumab) (≥24 weeks for randomised on-demand arm, ≥32

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
2024; 11: e. (48) Angchaisuksiri P et al. Concizumab prophylaxis in people with hemophilia A or B without inhibitors: patient-reported outcome results from the phase 3 explorer8 study. Res Pract Thromb Haemost. 2025;9:e102705. (49)				completed explorer5 at the time of pause or after treatment restart, patients who had been initially assigned to randomised concizumab or on-demand groups before the trial pause, and new patients who had previously been receiving on-demand treatment and were recruited after randomisation had completed recruitment) (n=76)		weeks for randomised concizumab arm)

Study/ID	Aim	Study design	Patient population	Intervention and compara tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
BASIS **NCT03938792** Matino D et al. Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the phase 3 BASIS trial, Blood (2025) 146 (14): 1654–1663. (50)	To demonstrate the efficacy and safety of marstacimab for routine prophylaxis	Phase 3, open-label, non-randomised crossover study	- Male - Age ≥12 years to <75years - Severe haemophilia A (FVIII <1%) or moderately severe to severe (FIX ≤2%) HB, with or without inhibitors - Minimum weight of 35 kg at screening - Without inhibitors cohort: - No detection or history of inhibitors against FVIII or FIX - On-demand group: ≥6 acute bleeding episodes (spontaneous or traumatic) that required coagulation factor infusion before enrolment during the 6 months period prior to enrolment - Routine prophylaxis group: ≥80% compliance with FVIII/FIX	- On-demand therapy (6-month observational phase of BASIS) (n=37) - Routine prophylaxis (6-month observational phase of BASIS (n=91) - Marstacimab 150mg prophylaxis once a week (n=116) -	ABR for treated bleeds at 12 months post marstacimab initiation versus factor replacement therapy use in observation phase	ABR joint bleeds, spontaneous bleeds, target joint bleeds and total bleeds (treated and untreated) No. of patients with no treated bleeds, change in joints as measured by HHJS at 12 months HAL/pedHAL PGIC-H QoL: Haem-A-QoL/Haemo-QoL, EQ-5D-5L Safety and tolerability outcomes

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
			regimen 6 months before enrolment			

D.1.4 Quality assessment

Quality (risk of bias) assessment was conducted for the eligible studies by two independent reviewers. Disagreements were resolved by discussion and/or additional referees.

Quality assessment of eligible RCTs was conducted using the seven-criteria checklist provided in Section 2.5 of the NICE single technology appraisal user guide. This approach is based on guidance provided by the Centre for Reviews and Dissemination for assessing the quality of studies included in SLRs, and assesses the likelihood of selection, performance, attrition and detection bias.

D.1.5 Unpublished data

N/A

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