Medicinrådet

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

Vers. 1.0

Bilagsoversigt

1. Ansøgers bemærkninger vedr. concizumab (Alhemo)
2. Forhandlingsnotat fra Amgros vedr. concizumab (Alhemo)
3. Ansøgers endelige ansøgning vedr. concizumab (Alhemo)

Fra: CTIK (Christian Klyver Tikkanen) <ctik@novonordisk.com>
Sendt: 8. august 2025 12:33
Til: Dorte Glintborg <DGL@medicinraadet.dk>
Cc: CBHH (Christina Beathe Hartøft) <CBHH@novonordisk.com>
Emne: RE: Udkast: Direkte indplacering af concizumab: Tillæg til Medicinrådets evidensgennemgange vedrørende lægemidler til hæmofili A og B

Kære Dorte/Sekretariat,

Mange tak for tilsendte udkast til vurdering og direkte indplacering af concizumab i behandlingsvejledningen for personer med hæmofili A og B med inhibitor.

Vi deler overordnet set Medicinrådets kliniske vurdering, og har derfor kun en mindre bemærkning til et enkelt afsnit i Medicinrådets udkast, afsnit 3.4 angående "*Øvrige forhold*", hvor Medicinrådet argumenterer for, at "*de fleste patienter vil foretrække*" ugentlig fremfor daglig administration.

Vi vil her gerne lægge op til, at dette afsnit nuanceres. Omend vi anerkender at flere patienter forventelig vil foretrække ugentlig fremfor daglige injektioner, der finder vi dette teoretisk set beror på en antagelse om, at man da har at gøre med samme injektionspen (device), administration, håndtering, klargøring og volumen. Dette er som bekendt ikke tilfældet med emicizumab og conadministrationen cizumab. Vi vil derfor gerne præcisere, at daglig administration med concizumab ikke direkte kan sammenlignes med ugentlig administration af emicizumab – idet administrationen *(trods begge administreres subkutant)* er meget forskellig. Mange patienter oplever ligeledes decideret ubehag ved administration af emicizumab.[1] I tilfælde af concizumab, der anvendes en markant mindre volumen per injektion, mens klargøring af dosis er forskellig og hurtig(ere) at håndtere/klargøre for concizumab fremfor emicizumab.

Concizumab leveres i en præfyldt injektionspen, som det kendes indenfor behandling af en række områder, såsom væksthormon (*Norditropin*®)-, insulin (eks. *Tresiba*®, *Fiasp*®) samt semaglutid (*Ozempic*® & *Wegovy*®), hvorfor administration er velkendt for de fleste behandlere i dag. Det er samtidig et device, som er nemt og bekvemt for patienten at administrere – til trods for, at behandlingen skal gives dagligt.

Reference:

1. Kruis & Driessens, 2023: *Pain while injecting emicizumab predominant in children, a report of Dutch patient experiences - Kruis - 2023 - Haemophilia - Wiley Online Library*

Vi har ingen yderligere tilføjelser, og ønsker ikke at få blændet noget i vores ansøgning.

Med venlig hilsen,

Christian Klyver Tikkanen

Head of Market Access & Rare Disease

Novo Nordisk Denmark A/S

Novo Nordisk Denmark A/S | +45-30753269 (mobile) | ctik@novonordisk.com

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

10.07.25

MBA/LEJ

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	Novo Nordisk
Lægemiddel	Alhemo (concizumab)
Ansøgt indikation	Rutinemæssig profylakse af blødning hos patienter med: • Hæmofili A (medfødt faktor VIII-mangel) med FVIII-inhibitorer i alderen 12 år eller derover. • Hæmofili B (medfødt faktor IX-mangel, FIX) med FIX-inhibitorer i alderen 12 år eller derover.
Nyt lægemiddel / indikationsudvidelse	Direkte indplacering af nyt lægemiddel i behandlingsvejledningen for hhv. hæmofili A og hæmofili B

Prisinformation

Amgros har forhandlet følgende pris på Alhemo (concizumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Alhemo	150 mg. 1 stk. pen	91.200,00	[redacted]	[redacted]
Alhemo	300 mg. 1 stk. pen	182.400,00	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

For at sikre ligebehandling af leverandørerne, vil priserne i ibrugtagningsaftalen for Alhemo fremgå af Amgros' leverandør- og udbudsportal (offentliggjorte priser), da de nuværende aftalepriser på de øvrige lægemidler indenfor terapiområdet er offentliggjorte.

[redacted]

[redacted]

[redacted].

Tabel 2 viser lægemiddeludgifter i relation til andre lægemidler. Lægemiddeludgiften er opgjort pr. år for hhv. opstartsår og vedligeholdelsesår.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Alhemo*	300 mg. 1 stk.pen	Dag 1-28: 1 mg/kg dagligt Efterfølgende: 0,20 mg/kg dagligt s.c.	[redacted]	Opstartsår: [redacted] Vedligeholdelsesår: [redacted]
Hemlibra*	Tilgængelig i 12, 30, 60, 105, 105 og 300 mg hætteglas	Opstartsdosis (3 mg/kg) en gang om ugen i de første 4 uger Vedligeholdelsesdosis fra uge 5 på enten 1,5 mg/kg en gang om ugen s.c.	[redacted]	Opstartsår: [redacted] Vedligeholdelsesår: [redacted]

* [redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

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

Opsummering

[redacted].

Ansøgning om vurdering af **Alhemo®** til Hæmofili A og B med inhibitorer

Farveskema til tekstfremhævning
Fortrolige oplysninger

novo nordisk®

Alhemo®
concizumab

Contact information

Contact information/ Novo Nordisk Denmark		
Name	**Christian Klyver Tikkanen**	**Christina Hartøft**
Title	Head of Market Access & Rare Disease	Medical Manager, Rare Disease
Phone number	+45 3075 3269	+45 2069 7418
E-mail	ctik@novonordisk.com	cbhh@novonordisk.com

Table of contents

Tables and Figures

Tables

FIGURES

Abbreviations

ABR	Annualized bleeding rate
anti-TFPI	anti-tissue factor pathway inhibitor
aPCC	Activated activated prothrombin complex concentrate
CI	Confidence interval
CrI	Credible interval
DIC	Deviance information criterion
DSU	Decision support unit
EAHAD	European Association for Haemophilia and Allied Disorders
EHC	European Haemophilia Consortium
ELISA	Enzyme-linked immunosorbent assay
ETD	Estimated treatment difference
FE	Fixed effect
FIX	Factor IX
FV	Factor V
FVII	Factor VII
FVIII	Factor VIII
FX	Factor X
HA	Haemophilia A
HAwI	Haemophilia A with inhibitors
HB	Haemophilia B
HBwI	Haemophilia B with inhibitors
HRQoL	Health related quality of life
ITC	Indirect treatment comparison
ITI	Immune tolerance inhibition
IU	International units
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds ratio
PH	Physical Health
RCT	Randomised controlled trial
RE	Random effect
rFVIIa	activated recombinant factor VII
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
TF	Tissue factor
TFPI	tissue factor pathway inhibitor
TS	Total score
vWF	von Willebrand Factor
WFH	World Federation of Heamophilia

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 IX deficiency) with FIX 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	Nej
(Expected) Date of EC approval	16th december 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
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).

Overview of the pharmaceutical	
	Alhemo® 150 mg/1.5 ml solution for injection in pre-filled pen 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). Alhemo® 300 mg/3 ml solution for injection in pre-filled pen 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 in unit 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®). 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 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	• Haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors aged 12 years or older. • Haemophilia B (congenital factor IX deficiency) with FIX 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 [if any]	**Haemophilia A with inhibitor (HAwI):** **Hemlibra** (emicizumab), *Dose*: First 4 weeks: 3 mg/kg subcutaneously once weekly. Then 1.5 mg/kg once a week (maintenance dose). **Haemophilia B with inhibitor (HBwI): No immediate comparator.** The current treatment regimen is NovoSeven (rFVIIa), which is used either for bleeding "on-demand" or as a preventive treatment. Usually the dose of rFVIIa of 90 µg/kg

Summary	
	once daily as intravenous treatment, and according to the Nordic haemophilia guideline up to 270 µg/kg daily (Andersson et al. 2024) The development of inhibitory antibodies (inhibitors) is a serious complication of factor replacement therapy, which occurs in approximately 30% of patients with severe haemophilia A & 10-15% of patients with severe haemophilia B. Cf. the Nordic haemophilia guidelines, where the standard treatment for patients with inhibitors has previously been to remove the inhibitor through immunological tolerance induction (ITI) therapy. Since 2018, emicizumab has been the new standard of care for people with inhibitor haemophilia A, effectively reducing bleeding in inhibitor patients, making the use of ITI more individualized due to the need for venous access, cost, and uncertainties around maintaining tolerance/compliance.
Most important efficacy endpoints (Difference/gain compared to comparator)	Annual bleeding rate (ABR) for concizumab and emicizumab (no clinically relevant difference in indirect treatment comparison) for HAwI. Significant and clinically relevant reductions of ABR in Preventive Treatment with Concizumab vs. On-Demand Treatment for Subjects with HBwI
Most important serious adverse events for the intervention and comparator	Overall, adverse events were of a mild nature, while serious events were rare for both concizumab and emicizumab. One thromboembolic event occurred in EXPLORER 7 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. Treatment with emicizumab led to 4 thromboembolic events in patients using APCC (Feiba) for the treatment of breakthrough haemorrhages (HAVEN 1).

3. The patient population, intervention and relevant outcomes

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

Aetiology

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) (Kizilocak and Young, 2019; Dolan et al., 2018; Bannow et al., 2019). HA is estimated to account for 80–85% of all haemophilia cases. HB is less common, accounting for 15–20% of cases (Santagostino et al.,2020).

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 (World Federation of Hemophilia. eLearning Centres: Hemophilia, 2022).

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)	Severe bleeding with major trauma or surgery; Rare spontaneous bleeding;

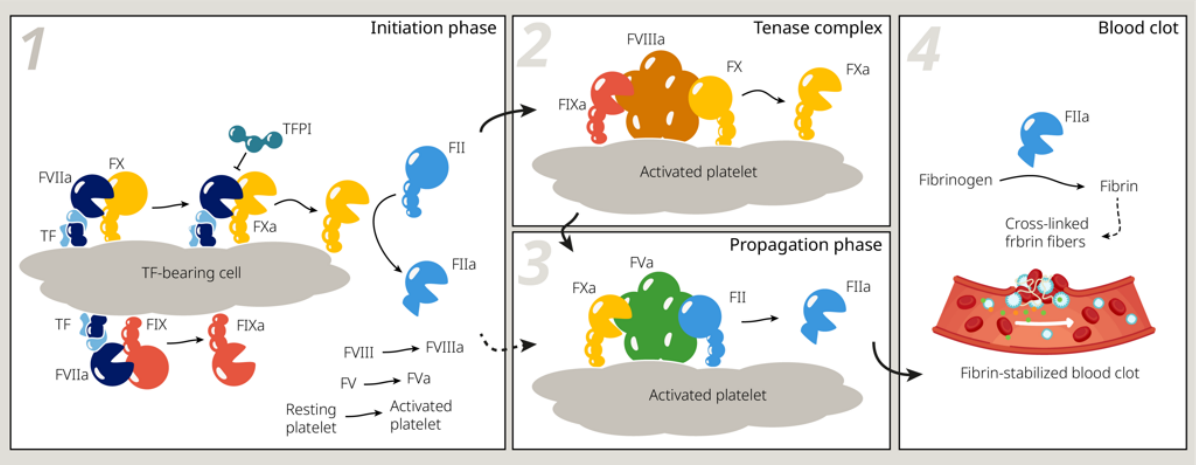
Adapted from Srivastava et al., 2020

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 (Kizilocak and Young, 2019).

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 2 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 (Ho and Pavey 2017; Hoffman and Monroe, 2001; Smith, 2009). 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 (Smith, 2009).

Figure 2: 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**.

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 (Giangrande et al., 2018; Lai et al., 2017; Lai and Lillicrap, 2017; Guelcher, 2018; Peyvandi et al., 2017). 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 (Ragni, 2017; Miller, 2018). As a result, the clinical and humanistic burden is considerably greater in people with inhibitors vs without (Oladapo et al.,2018; D'Angiolella et al.,2018; Ragni et al.,2020).

Inhibitor formation occurs when the immune system fails to recognise infused FVIII/FIX and mounts a T-cell response against the replacement factor with the production of neutralising antibodies (predominantly polyclonal immunoglobulin (Ig) G antibodies) (Miller, 2018). Early recognition and accurate diagnosis of inhibitors are essential to ensure appropriate treatment (Giangrande et al.,2018; Ragni et al., 2020). Approximately half of cases are identified by routine screening after initial exposure to factor concentrates, with the remaining cases identified in people failing to respond to replacement therapy, particularly in those who have been previously responsive (Ragni et al., 2020). The WFH and the European Haemophilia Consortium (EHC) / European Association for Haemophilia and Allied Disorders (EAHAD) recommend close monitoring and regular inhibitor screening in people with newly diagnosed haemophilia, with the first 50 days of exposure identified as the period of highest risk (Giangrande et al.,2018; Ragni et al., 2020).

Bleeding episodes

Haemophilia is characterised by spontaneous, painful bleeding episodes, and prolonged, excessive haemorrhage following trauma or surgery (Santagostino et al.,2020; Mahlangu et al., 2020; Llinás et al.,2020). 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 (Kizilocak and Young, 2019; Butterfield et al., 2020). Without adequate treatment, haemarthrosis induces a cascade of degenerative processes affecting the synovium, cartilage and bone, leading to progressive joint disease (haemophilic arthropathy) (Kizilocak and Young, 2019; Llinás et al.,2020). Arthropathy is the single largest cause of morbidity in people with haemophilia and is associated with

pain and disability (D'Angiolella et al., 2018; Hanley et al.,2017), reduced HRQoL (O'Hara et al., 2018) and long-term orthopaedic complications (Carcao et al., 2015).

The presence of inhibitors represents a major challenge in the management of bleeding and is associated with significantly increased rates of bleeding compared with haemophilia without inhibitors. In an analysis of data from the European CHESS study (Oladapo et al., 2018), the presence of inhibitors was associated with greater clinical burden compared with people without inhibitors, including more than twice the mean annual number of overall bleeds and joint bleeds (8.3 vs 3.7 and 2.2 vs 1.0; $p<0.0001$), more frequent haemophilia-related and bleed-related hospitalisations (1.8 vs 0.6 and 1.9 vs 0.8, respectively, $p<0.001$ for both), and more haemophilia-related consultations (9.3 vs 6.8, $p<0.001$) and outpatient visits (22.1 vs 11.5, $p<0.001$) (Oladapo et al., 2018).

People with haemophilia with inhibitors have increased arthropathy levels compared with people without inhibitors, due to difficulties of preventing joint bleeds in this population (Morfini et al., 2007). In a European observational study of orthopaedic status in haemophilia, greater proportions of people with inhibitors required orthopaedic procedures (66% vs 37%), had reduced mobility requiring walking aids (50% vs 29%; $p=0.048$) and had reduced mobility requiring wheelchairs (24% vs 4%; $p=0.009$), compared with the age-matched non-inhibitor cohort. People with inhibitors also had more outpatient and emergency hospital visits during the 12-month study period (mean of 11.8 vs 7.4) and significantly worse scores for joint health and joint pain (Morfini et al., 2007).

Current Treatment options

According to current national treatment guidelines for haemophilia A and B, patients, who have developed inhibitors against FVIII- or FIX, immune tolerance inhibition (ITI) will be considered until the patient again has regained tolerability towards their recombinant FVIII or FIX treatment. If ITI is not possible at the time or has not been successful, the patient may be offered prophylactic treatment with emicizumab or activated prothrombin complex concentrate (aPCC).

For HA developing inhibitors, the current recommendation from the DMC is:

Use prophylaxis with emicizumab rather than prophylaxis with aPCC in patients with inhibitor where ITI is not possible – or has not been successful.

For HB developing inhibitors, the current recommendation is not directly mentioned in the current treatment guidelines, as no available treatment options were available at the time and the Medicines Council found no significant difference btw. existing recombinant FIX therapies with regards to increased incidence of inhibitor development.

The current treatment regimen is however described in more detail in the ***Nordic haemophilia Council's treatment guidelines*** on "inhibitors", chapter 6 (Andersson et al., 2024), where DK representation is included also, and where the following treatment option is recommended:

- *The principal goal in all patients with inhibitors – both children and adults - should be to eradicate the inhibitor and to tolerize the patient.*

- *In hemophilia B, inhibitor development often occurs together with allergic reactions and after re-exposure to FIX there is possibility of development of nephrotic syndrome. FIX treatment cannot be continued in these cases.*
- *Today, aPCC is used rarely, mostly as second line treatment since it should not be combined with emicizumab and can cause allergic reactions due to containing FIX in HB.*

For treatment of bleeding episodes in Haemophilia B with inhibitors (HBwI), the guidelines specify:

- *First-line option for prophylaxis in hemophilia B is rFVIIa (90 to 270 µg/kg) once daily intravenously.*

And further, that:

- *For HB, ITI treatment may be jeopardized by the occurrence of an allergic or anaphylactoid reaction or nephrotic syndrome. The use of ITI in these patients therefore needs careful monitoring and should initially be provided in the hospital setting.*
- *The success rate in HB might be lower in patients with HB compared to HA but can be achieved even after several attempts (Kihlberg et al., 2017 red.). After successful tolerance, the dosing should be tapered to regular prophylactic treatment.*
- *In patients with hemophilia B and persistent inhibitors failing ITI protocols with and without immunosuppression or allergy to FIX, ITI may be stopped, and compassionate use of re-balancing therapies could be discussed.*

Choice of comparator(s)

HAwI (Haemophilia A with inhibitors): According to the Danish haemophilia A treatment guidelines, Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til hæmofili A (Medicinrådet, 2022), for patients with inhibitor, the comparator for concizumab will be emicizumab, as this is current standard of care (considered in >90% of cases) in Denmark, where ITI treatment hasn't been realistic to achieve; or have been deemed unsuccessful.

HBwI (Haemophilia B with inhibitors): In haemophilia B patients with inhibitor where ITI treatment isn't realistic to achieve or have been deemed unsuccessful, the Nordic Haemophilia Council guidelines (Andersson et al., 2024) recommend rFVIIa as first line option for prevention of bleeds.

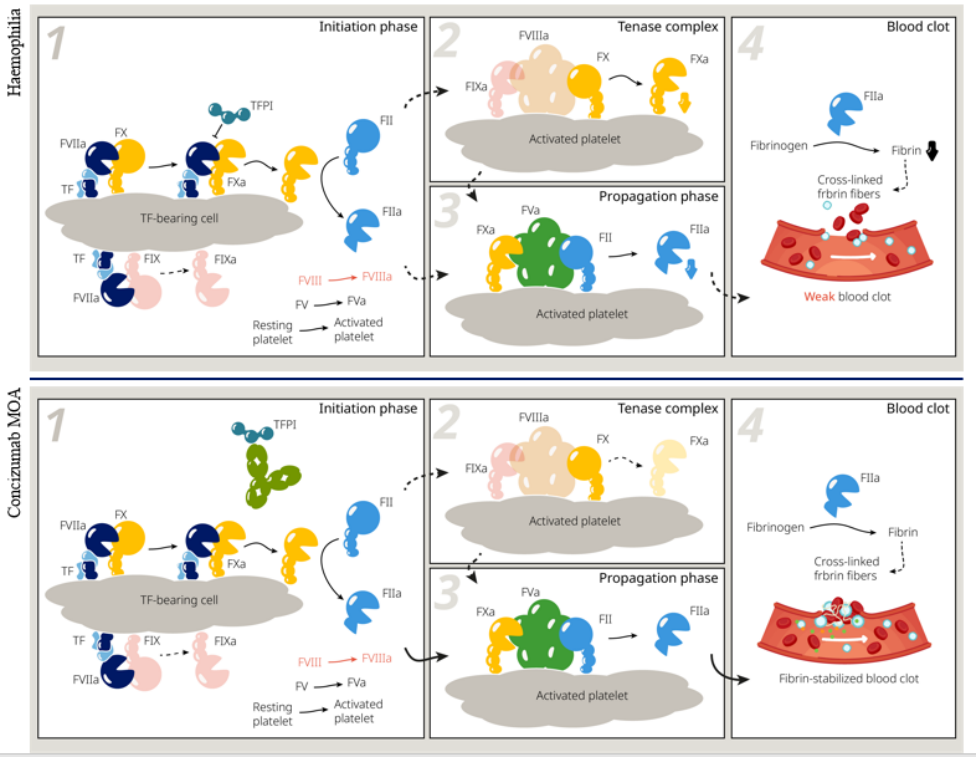
3.2 The intervention - concizumab

Concizumab is a high-affinity, monoclonal, anti-TFPI antibody (Chowdary, 2020; Hilden et al., 2012, Chowdary, 2015; Chowdary, 2018) for once-daily, subcutaneous injection for the prophylactic treatment of people with HA, HB and haemophilia with inhibitors (Shapiro, 2021; Hedner and Ezban, 2008).

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 (Hilden et al., 2012; Broze and Girard, 2012; Hansen et al., 2014). 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 (Hilden et al., 2012; Hansen et al., 2014) (Figure) (Chowdary, 2020; Hilden et al., 2012, Augustsson et al., 2023). Concizumab acts independently from FVIII and FIX, therefore is not influenced by the presence of inhibitors to FVIII or FIX.

Figure 2: Concizumab mechanism of action via inhibition of TFPI



Source: Adapted from Hilden et al, 2012 (70).
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: • haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors aged 12 years or older. • haemophilia B (congenital factor IX deficiency) with FIX inhibitors aged 12 years or older.
Method of administration	**Type 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, and 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 / N/A
Treatment duration / criteria for end of treatment	N/A
Necessary monitoring, both during administration and during the treatment period	N/A
Need for diagnostics or other tests (e.g. companion diagnostics). How	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

are these included in the model?	Alhemo® plasma concentrations is available, an individual 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 Alhemo® 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 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

Concizumab is currently indicated for treatment of haemophilia patients with inhibitors; HAwI and HBwI.

Haemophilia patients developing antibodies towards their factor medication are at serious risks of experiencing very high bleeding frequency, joint complication(s), low health-related quality of life and increased healthcare resources.

The only way to eradicate inhibitors is through immune tolerance induction (ITI), a demanding and costly treatment that requires regular (daily) infusions of rFVIII or rFIX for potentially very long periods of time, in many cases with immune-suppressive drugs before tolerance is achieved. Management of bleeding in people with HBwI is much more complex than in people without inhibitors, and treatment is complicated further by severe allergic reactions to infused FIX (Andersson et al. 2024). It is therefore currently clinical practice in Denmark to take on an individualized approach to treatment for inhibitor patients, e.g. in patients with known difficulties of adhering to a complex and

frequent treatment regimen, or where venous access issues, adverse event or poor response to prior attempts of achieving tolerance through ITI has been unsuccessful.

Despite the availability of novel treatments for haemophilia, there is still an urgent high unmet need for new haemophilia treatments that can offer effective and safe prophylaxis for people with haemophilia with inhibitor, with a minimally invasive route of administration, and a treatment that can be used concomitantly with all on-demand bypassing agents.

HAwI: Current recommended prophylactic treatment option for patients with haemophilia A with inhibitors; where ITI either hasn't been possible to initiate or prior attempts have been deemed unlikely to succeed; is emicizumab, a bispecific, monoclonal antibody and the first non-replacement therapy approved for prophylaxis in people with HAwI. Emicizumab has a very long half-life of ~4-5 weeks and can be administered via vial-and-syringe (26 gauge 9-13 mm needle) either as a weekly, bi-weekly or monthly treatment. Once emicizumab has been transferred from the vial to the syringe, the medicinal product should be used immediately as it does not contain antimicrobial preservatives (SmPC Hemlibra).

HBwI: Current prophylactic treatment options for patients with haemophilia B with inhibitors are sparse; with current available treatment option for patients not achieving successful ITI or where ITI isn't possible, only have rFVIIa (NovoSeven) available to them, a recombinant FVIIa treatment with a very short half-life requiring daily intravenous injections to maintain adequate haemostatic response. According to the Nordic Haemophilia Guidelines, compassionate use with a re-balancing agent (e.g. anti-TFPI therapy such as concizumab) could be considered in patients with a severe bleeding phenotype.

Concizumab provides individualised steady-state protection with subcutaneous once-daily dosing across haemophilia A and B with inhibitors. It can be used concomitantly with bypassing agents, reduces ABR (annualized bleeding rate) and joint bleeding vs on-demand treatment, and also further improve HRQoL.

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 (38). Further, concizumab is room temperature stable for storage up to 4 weeks after first use in up to 30°C.

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).

4. Overview of literature

A systematic literature review (SLR) was conducted to identify all relevant clinical trials that included efficacy and safety data for the prophylactic treatment of patients (≥12 years) living with HAwI and HBwI.

The SLR included the following electronic databases: Embase, MEDLINE (including MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE Daily) and Evidence Based Medicine (EBM) Reviews (including the Health Technology Assessment [HTA] database, the NHS Economic Evaluation Database (NHS EED), Cochrane Central register of Controlled trials [CENTRAL], Database of Abstracts of Reviews of Effects [DARE] and the Cochrane Database of Systematic Review) via the OVID platform. Additional searches of conference proceedings from the past four years, reference lists of included publications, HTA bodies and clinical trials registries were performed to identify relevant evidence.

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 October 2024. In total it identified 91 articles relating to 40 unique studies that met the SLR inclusion criteria. Trials that included the relevant comparators (emicizumab and rFVIIa) and same target population (HAwI & HBwI ≥12 years) were of interest for the comparative analysis.

The SLR found 2 relevant studies for emicizumab (HAVEN 1 & 5) and 2 for rFVIIa. Upon closer inspection of the studies for emicizumab, only HAVEN 1 reported data for HAwI ≥12 years, whereas HAVEN 5 in addition also included patients without inhibitors (but where data is shown separately for patients with only inhibitors). HAVEN 5 included only patients from Asia, whereas HAVEN 1 also included a majority of patients coming from the US and Europe. HAVEN 1 is therefore considered the trial that most closely mimics the HAwI population in Denmark and was also the trial the Danish Medicines Council used in 2018 when assessing emicizumab for HAwI. For the comparative analysis HAVEN 1 will therefore primarily be used when comparing the efficacy and safety of concizumab vs. emicizumab. The indirect treatment comparison is similar based on the HAVEN 1.

For rFVIIa, 2 trials were included in the SLR, but after close inspection of one of the studies this was excluded as it was a phase II study with a modified (prolonged) rFVIIa, which since then has been terminated and not marketed. The primary study therefore was by Konkle et al. 2007, which included a mix of both HAwI and HBwI patients (22 in total, of which 6 patients were <12 years (27%), and majority of them had HAwI (21) vs. HBwI (1)). Efficacy and safety data is reported for the subgroup of patients that were on a dosis of 90 $\mu g/kg^{-1}$ rFVIIa (11 patients in total), as the one patient with HBwI was included in that particular trial arm. The indirect treatment comparison was unable to include any comparator in HBwI, as there weren't sufficient data to perform the indirect treatment comparison. The analysis will therefore be done qualitatively based on EXPLORER 7 and Konkle et al. 2007.

Relevant literature included in the assessment is shown in below Table 2 and further elaborated in Appendix A.

Table 2 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
Explorer7 NCT04083781 Matsushita et al. Phase 3 Trial of Concizumab in Hemophilia with Inhibitors. N Engl J Med 2023;389:783-94.	Prospective, multicenter, open-label, phase 3a trial	24-to-32-week treatment period in the main part of the trial. 128 to 136 weeks of concizumab treatment in extension part of the trial after the 24-to-32-week treatment period in the main part of the trial	Study Start (Actual) 2019-10-21 Primary Completion (Actual) 2021-12-27	Patients with hemophilia A or B with inhibitors (of any severity) aged ≥12 years	Loading dose of 1.0 mg per kilogram, followed by an initial daily dose of 0.2 mg per kilogram, with an initial dose-adjustment period of 5 to 8 weeks, during which the dose was increased to 0.25 mg per kilogram (if the concizumab plasma concentration was less than 200 ng per milliliter), decreased to 0.15 mg per kilogram (if the concizumab plasma concentration was greater than 4000 ng per milliliter), or maintained at 0.2 mg per kilogram	No prophylaxis (On-demand treatment)	3.3 of the Danish Medicines Council's protocol for haemo-philia A	Primary outcome: comparison between treated spontaneous and traumatic bleeding episodes in group 1 and group 2 (when all the patients in group 1 (no prophylaxis) had completed at least 24 weeks of treatment or had withdrawn and when all the patients in group 2 (concizumab prophylaxis) had completed at least 32 weeks of treatment, which included the 5-to-8-week dose-adjustment period, or had withdrawn. Secondary outcome: to compare patient reported outcomes after concizumab prophylaxis with those after no prophylaxis. Key secondary end points were the change in bodily pain and physical functioning scores on the 36-Item Short-Form Health Survey, version 2 (SF-36v2), from the start of treatment to week 24.

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
HAVEN 1 NCT02622321 Oldenburg et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med 2017;377:809-18.	Phase 3, open-label, multicenter, randomized trial	≥24 weeks all randomly assigned participants had at least 24 weeks of follow-up for the primary and secondary end points. Follow-up for participants (in groups C and D) was less than 24 weeks	Study Start (Actual) 2015-11-18 Study Completion (Actual) 2020-12-01	Patients with hemophilia A with inhibitors	Subcutaneous emicizumab prophylaxis at a dose of 3.0 mg per kilogram of body weight weekly for 4 weeks, followed by 1.5 mg per kilogram weekly thereafter for patients receiving episodic treatment with bypassing agents before trial (group A). Participants who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis in group C. Patients who were unable to enroll in HAVEN 1 groups A, B, or C before they were closed to enrollement received emicizumab prophylaxis (Group D). Participants who were randomly assigned to group B could receive emicizumab prophylaxis after completing at least 24 weeks in the trial (and remained in group B).	No emicizumab prophylaxis and no subcutaneous control injections	3.3 of the Danish Medicines Council's protocol for haemo-philia A	Primary outcome: the difference in the rate of treated bleeding events (bleeding rate) over a period of at least 24 weeks between participants receiving emicizumab prophylaxis (group A) and those receiving no prophylaxis (group B) after the last randomly assigned participant had completed 24 weeks in the trial or had discontinued participation, whichever occurred first. Secondary outcomes: for the randomized comparison (group A vs. group B) secondary outocomes included additional bleeding-related end points (all bleeding events [both treated and not treated with bypassing agents] and events of spontaneous bleeding, joint bleeding, and target-joint bleeding), health-related quality of life (Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL] physical health

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
								subscale and total score at week 25), and health status (the five-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D-5L] visual-analogue scale and index utility score at week 25). Intraindividual comparisons of the bleeding rate and the rate of all bleeding events among participants in groups A and C who had participated in the noninterventional study
HAVEN 5 (NCT03315455) Yang et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN 5). Res Pract Thromb Haemost. 2022;6:e12670.	Randomized, multicenter, open-label, phase 3 clinical study	≥24 weeks Follow-up duration for evaluating prophylaxis was shorter for those who switched to emicizumab in arm C (24 weeks) than for those in arms A and B (44-46 weeks), and an	Study Start (Actual) 2018-04-26 Primary Completion (Actual) 2022-08-03 Study Completion (Estimated) 2025-06-30	Participants aged ≥12 years with a diagnosis of severe hemophilia A (intrinsic FVIII level <1%) or hemophilia A with FVIII inhibitors and required to have documented ≥5 bleeds and use	3 mg/kg emicizumab once weekly for the first 4 weeks (loading dose) followed by a maintenance dose of either 1.5 mg/kg once weekly or 6 mg/kg every 4 weeks	No emicizumab prophylaxis. After completing 24 weeks of study, participants could switch to emicizumab (3 mg/kg once weekly loading dose for 4 weeks followed by a maintenance regimen	3.3 of the Danish Medicines Council's protocol for haemo-philia A	Primary outcome: annualized bleeding rate (ABR) for treated bleeds in people with hemophilia A receiving once-weekly or every-4-weeks emicizumab prophylaxis or no prophylaxis. Secondary outcomes: ABRs for all bleeds and treated spontaneous/joint/target joint bleeds in participants receiving once-weekly or every-4-weeks emicizumab prophylaxis versus no prophylaxis. Bleeds were

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
		absence of participants <12 years of age limits the scope of the findings.		of episodic therapy (FVIII or BPAs) in the 24 weeks before study entry to be eligible for inclusion.		of 6 mg/kg every 4 weeks). After at least 24 weeks of emicizumab prophylaxis, participants could continue taking maintenance therapy (1.5 mg/kg once weekly or 6 mg/kg every 4 weeks) or, if they had suboptimal control of bleeding, change to an increased dose of 3 mg/kg once weekly.		counted as one bleed if they were of the same type and occurred at the same anatomic location within 72 hours after stopping treatment for the first bleed (the "72-hour rule"); bleeds due to procedure/surgery were excluded. As per ISTH definition, target joints were defined as major joints in which ≥3 bleeding events occurred over a 24-week period. Change from baseline in HRQoL and health status after 24 weeks of emicizumab prophylaxis versus no prophylaxis was also evaluated
NCT00108758 NOVOSEVEN (Konkle et al. Randomized, prospective	Exploratory, Multi-centre, Randomised, Double-blind,	9 months: 3-month pre-prophylaxis observation period to	Study Start 2004-03 Study Completion (Actual)	Males with severe congenital hemophilia A or B with a high	Daily rFVIIa prophylaxis with either 90 or 270 ug/kg for 3 months	Each patient served as his own control. In the 3-month preprophylaxis	N/A	Primary outcome: number of bleeds per month during the prophylaxis period as compared to the preprophylaxis period. A bleed was defined as rebleeding

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
clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. J Thromb Haemost 2007; 5: 1904–13.)	Uncontrolled Trial	determine baseline bleeding rate and exclude non-frequent bleeding patients. All patients who experienced at least two bleeds per month, and a total of ≥ 12 bleeds requiring hemostatic drug-based treatment during the observation period, entered the 3-month prophylaxis period, if not scheduled for surgery in the subsequent 3 months. The 3-	2005-11	historical inhibitor titer (with an inhibitor titer > 2 BU mL^–1 in the preceding 12 months), a requirement for current treatment of bleeds with bypassing agents, and at least four bleeds requiring hemostatic drug treatment (except dental bleeds and bruises) within the previous month		period and 3-month postprophylaxis period only conventional on-demand hemostatic therapy was administered		if it occurred at the same site within 6 h of treatment, whereas episodes beginning 6 h after treatment or occurring in another site were defined as a new episode. Secondary outcomes: the number of bleeds per month occurring in the postprophylaxis period as compared to those observed in the observation and prophylaxis period, at specific bleeding sites (target joint, joint, muscle, soft-tissue bleeds), and cause of bleed (traumatic, spontaneous and other) over the entire trial period. Target joints were defined as those joints into which bleeding had occurred ‡ 3 times in the last 6 months.

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
		month prophylaxis period was followed by a 3-month post-prophylaxis period.						

* If there are several publications connected to a trial, include all publications used.

5. Prophylactic treatment of HAwI

5.1 Efficacy of concizumab compared to emicizumab for HAwI

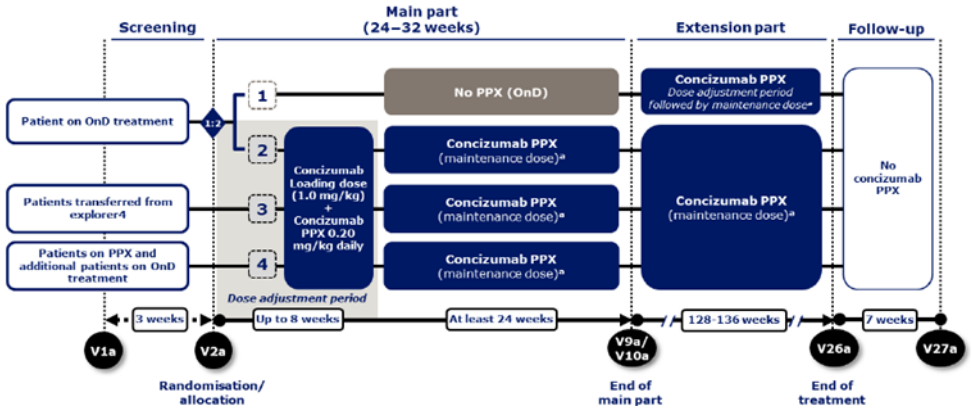
5.1.1 Relevant studies

5.1.1.1 EXPLORER 7

Explorer 7 (Matsushita et al., 2023) was a Phase 3, open-label RCT investigating the efficacy and safety of daily treatment with concizumab prophylaxis compared with no prophylaxis in adult and adolescent patients with haemophilia with inhibitors. The trial enrolled male patients aged ≥12 years with HA or HB of any severity, with documented history of inhibitor development (≥0.6 BU). An overview of the trial design is provided in Figure 3.

Patients are randomised to concizumab prophylaxis (arm 1) or no prophylaxis treatment (arm 2) if patients are receiving on-demand treatment only at screening; randomisation is stratified by haemophilia type and bleeding frequency during the 24 weeks prior to screening. In addition, patients are assigned into the non-randomised treatment arms if transferred to concizumab treatment from Explorer 4 (arm 3) or if on prophylaxis treatment with bypassing agents and any on-demand treatment (arm 4). The main part of the randomised trial consists of at least 24 weeks treatment in arm 1, or at least 32 weeks of treatment in arms 2, 3, and 4. Following completion of the main part of the trial, all patients are offered entry to the extension phase to continue concizumab for an additional 128 weeks (arms 2–4) or 136 weeks (arm 1). Following completion of the extension phase, the safety follow-up continues for a further 7 weeks.

Figure 3: Overview of Explorer 7 trial design



Abbreviations: OnD, on-demand; PPX, prophylaxis; V, visit.

aThe individual maintenance dose will be either 0.15, 0.20, or 0.25 mg/kg concizumab.

Patients randomised or allocated to concizumab prophylaxis receive 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 can 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 7:

- 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).

5.1.1.2 HAVEN 1

HAVEN 1 (Oldenburg et al., 2017) was a Phase 3, open-label RCT conducted internationally in 14 countries that investigated the efficacy and safety of daily treatment with emicizumab prophylaxis compared with no prophylaxis in adult and adolescent patients with HAwI. The trial enrolled male patients aged ≥12 years with severe congenital HA with current factor VIII inhibitors (≥5 Bethesda units/mL) receiving episodic or prophylactic factor VIII infusions.

Patients receiving prior episodic treatment were randomised to emicizumab prophylaxis (Group A) or no prophylaxis (Group B). Patients who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis (Group C), and those who were unable to enroll in the treatment groups comprised a final treatment group of emicizumab prophylaxis (prior episodic or prophylaxis treatment, Group D). Patients received emicizumab at a dose of 3 mg/kg once weekly (QW) for 4 weeks followed by 1.5 mg/kg thereafter. All patients could receive episodic treatment with bypassing agents for breakthrough bleeding, as needed. After 24 weeks of emicizumab prophylaxis, participants could continue to take maintenance therapy with 1.5 mg/kg QW. Patients in the randomly assigned no prophylaxis arm could receive emicizumab prophylaxis after completing at least 24 weeks of the trial.

The primary end point was the difference in the rate of treated bleeding events over a period of at least 24 weeks between participants receiving emicizumab prophylaxis (group A) and those receiving no prophylaxis (group B) after the last randomly assigned participant had completed 24 weeks in the trial or had discontinued participation, whichever occurred first. Secondary end points for the randomized comparison (group A vs. group B) included additional bleeding-related end points (all bleeding events [both treated and not treated with bypassing agents] and events of spontaneous bleeding,

joint bleeding, and target joint bleeding), health-related quality of life (Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL] physical health subscale and total score at week 25), and health status (the five-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D-5L] visual-analogue scale and index utility score at week 25).

5.1.1.3 HAVEN 5

Haven 5 (Yang et al., 2022) was a Phase 3, open-label RCT conducted across China, Malaysia and Thailand to compare emicizumab prophylaxis with no prophylaxis in patients with HA or HAwI. The trial enrolled patients who were at least 12 years old with severe HA with or without inhibitors and who had experienced five or more bleeds which required the use of episodic therapy in the 24 weeks prior to study entry.

Methods: Patients were randomised 2:2:1 using an interactive voice/web response system to arms A, B, or C. Arms A and B received a loading dose of emicizumab 3 mg/kg once weekly for the first four weeks. Participants in Arm A then received a maintenance dose of emicizumab 1.5 mg/kg once weekly and participants in arm B received emicizumab 6 mg/kg every four weeks. Arm C did not receive prophylaxis but after 24 weeks of study could switch to emicizumab 3 mg/kg once weekly loading dose followed by 6 mg/kg every 4 weeks maintenance dose. After 24 weeks of emicizumab prophylaxis, participants could continue the maintenance dose of 1.5 mg/kg once weekly or 6 mg/kg every four weeks, or could switch to an increased dose of 3 mg/kg once weekly if they had suboptimal bleeding control. Suboptimal bleeding control was defined as at least two spontaneous and clinically significant bleeding events during the 24 weeks of emicizumab prophylaxis, and both events had to occur at the end of the loading dose period.

The primary efficacy end point was annualized bleeding rate (ABR) for treated bleeds in people with hemophilia A receiving once-weekly or every-4-weeks emicizumab prophylaxis or no prophylaxis. Secondary efficacy endpoints were ABRs for all bleeds and treated spontaneous/joint/target joint bleeds in participants receiving once-weekly or every-4-weeks emicizumab prophylaxis versus no prophylaxis. Bleeds were counted as one bleed if they were of the same type and occurred at the same anatomic location within 72 hours after stopping treatment for the first bleed; bleeds due to procedure/surgery were excluded. Target joints were defined as major joints in which $\geq$3 bleeding events occurred over a 24-week period.

5.2 Efficacy of concizumab compared to rFVIIa for HBwI

5.2.1 Relevant studies

5.2.1.1 NovoSeven-PPX (Konkle et al. 2007)

A randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in haemophilia patients with inhibitors was conducted *(hereafter referred to as NovoSeven-PPX).* The trial was a multicenter, randomized, double-blind, parallel-group trial investigating the efficacy and safety of secondary rFVIIa prophylaxis in

patients with congenital hemophilia A or B with inhibitors and high requirements for on-demand therapy.

The trial consisted of a pre-prophylaxis period, a prophylaxis (treatment) period, and a post-prophylaxis period, each of 3 months duration. This trial was conducted in 20 sites in 11 countries: Argentina (one site), Brazil (two sites), Bulgaria (one site), the Philippines (one site), Poland (two sites), Romania (four sites), Russia (one site), South Africa (one site), Spain (three sites), Turkey (one site), and the USA (three sites).

Males with severe congenital haemophilia A or B with a high historical inhibitor titer (with an inhibitor titer > 2 BU mL–1 in the preceding 12 months), a requirement for current treatment of bleeds with bypassing agents, and at least four bleeds requiring haemostatic drug treatment (except dental bleeds and bruises) within the previous month were eligible for inclusion. Key exclusion criteria prior to trial entry included: prophylaxis with any hemostatic drug within the last 3 months, immune tolerance induction (ITI) within the last month, known pseudotumors, platelet count < 50 000 lL–1, advanced atherosclerotic disease, and congenital or acquired coagulation disorders other than haemophilia A or B.

Following screening, 38 eligible patients underwent a 3-month pre-prophylaxis observation period to determine baseline bleeding rate and exclude non-frequent bleeding patients. All patients who experienced at least two bleeds per month, and a total of ‡ 12 bleeds requiring haemostatic drug-based treatment during the observation period, entered the 3-month prophylaxis period, provided that they were not scheduled for surgery in the subsequent 3 months.

A centralized, computer-generated randomization list was used to randomly allocate patients to receive either 90 or 270 μg kg^{-1} rFVIIa once daily for 3 months. Each rFVIIa dose was to be self-administered before 11 AM in a home setting as a slow bolus i.v. injection over a period of 2 min. Blinding was maintained by providing an equal volume of trial drug to be injected in both treatment groups. Concomitant administration of other haemostatic drugs was permitted during the entire trial period, except from 1 h prior to and until 2 h after rFVIIa administration during the prophylaxis period. The 3-month prophylaxis period was followed by a 3-month post-prophylaxis period.

The primary efficacy endpoint was number of bleeds per month during the prophylaxis period as compared to the pre-prophylaxis period. A bleed was defined as rebleeding if it occurred at the same site within 6 h of treatment, whereas episodes beginning 6 h after treatment or occurring in another site were defined as a new episode.
Secondary efficacy endpoints included the number of bleeds per month occurring in the post-prophylaxis period as compared to those observed in the observation and prophylaxis period, at specific bleeding sites (target joint, joint, muscle, soft-tissue bleeds), and cause of bleed (traumatic, spontaneous and other) over the entire trial period. Target joints were defined as those joints into which bleeding had occurred ‡ 3 times in the last 6 months. Safety was evaluated by the number and type of adverse events reported during the 9-month trial period and was graded by severity and seriousness as well as probable relation to the trial product.

5.2.2 Comparability of studies

The main studies included in the comparison against concizumab for HAwI and HBwI are shown in below Table 3 and 4 below. The respective studies all have the same in common that the enrolled patient numbers were limited and lacked a direct comparator-arm (compared vs. background of on-demand use). Further both HAVEN 5 (1.5mg/kg/weekly or 6.0mg/kg/28 days) and the NovoSeven-PPX trial (90 µg/kg or 270 µg/kg rFVIIa) had different treatment arms; EXPLORER 7 and NovoSeven-PPX trial included a mixed cohort of HAwI and HBwI; while HAVEN 5 included a combination of HA and HAwI patients in the study. Furthermore, approximately ¼ of patients in NovoSeven-PPX were aged <12 years upon entry into the trial.

Overall, this underlines the complexity of assessing whether enrolled trial populations were comparable (homogenous) as patient characteristics very often were reported sparsely and not shown across separate subgroups. More information was provided when analyzing the clinical efficacy and safety data across relevant subgroups (across EXPLORER 7, HAVEN 1 and HAVEN 5, whereas no attempt was made in the NovoSeven-PPX trial to separate data btw. HAwI and HBwI, as only 1 patient with HBwI was enrolled.

The following sections of the comparative analysis and attempt of making an indirect treatment comparison btw. concizumab and emicizumab (based on EXPLORER 7 and HAVEN 1) must therefore be interpreted with caution based on amongst other the following limitations:

- The network contained only 2 studies with few enrolled participants, and therefore, due to the sparsity of the outcome-specific networks, it was not judged feasible to explore the potential impact of heterogeneity on the results.
- Further, there was limited reporting of outcomes data and definitions, and whilst efforts were made to align outcomes for each analysis, it is likely that inter-study heterogeneity remained.
- The analysis assumed that relative treatment effects within the trials would remain the same regardless of specific treatments used in the on-demand comparator arms. In EXPLORER 7, ABRs were lower in the on-demand arm compared with the on-demand arms in HAVEN 1, which could have led to a poorer relative risk reduction for concizumab versus emicizumab.

5.3 Comparative analyses of efficacy and safety

5.3.1 Efficacy and safety – results per study

Relevant primary and secondary outcomes for each of the following included clinical trial studies; EXPLORER 7, HAVEN 1, 5 and NovoSeven-PPX are provided in Appendix B.

EXPLORER 7

Both for people with HAwI and HBwI on concizumab prophylaxis (arms 1-4) the median ABR for treated spontaneous and traumatic bleeding episodes was 0.0. Although the EXPLORER 7 trial was not powered to detect statistically significant differences within the separate haemophilia subtypes, for people with HAwI there was a significant difference

between participants on concizumab prophylaxis (arm 2) and no prophylaxis (arm 1) in the number of treated spontaneous and traumatic bleeding episodes (p<0.001).

Overall, the number of serious adverse events were low and equally distributed across multiple system organ classes and preferred terms with no apparent clustering. No adverse events were reported in ≥ 5% participants across the concizumab prophylaxis arms. In total, 14 (11.0%) participants treated with concizumab prophylaxis reported 18 serious adverse events. Three (15.8%) participants on no prophylaxis reported five serious adverse events, corresponding to an event rate comparable with that for concizumab prophylaxis arms 2−4 (0.4 and 0.2 serious adverse events per patient-year, respectively). Most serious adverse events were judged as unlikely related to concizumab and reported as recovered, and there were no treatment differences in event rates with respect to outcome.

The most serious adverse reactions in clinical studies with concizumab were thromboembolic events (0.9%) and hypersensitivity (0.3%).

Injection site reactions were reported across multiple dose clinical studies. The most frequently reported symptoms were injection site erythema (5.9%), injection site bruising (4.4%), and injection site hematoma (4.1%). Most were reported as mild.

Of the 127 participants exposed to concizumab prophylaxis across arms 1−4 before, during and/or after the treatment pause, 33 participants (26%) were anti-drug-antibody-positive at one or more visits after first exposure to concizumab. All of these participants had low antibody titers except one participant who had a medium titer. Anti-drug-antibodies had no apparent impact on bleeding pattern, adverse events, PK or PD data.

Impact of prophylactic concizumab treatment was evaluated in the Haem-A-QoL questionnaire, in which lower scores correspond to better HRQoL. Mean Haem-A-QoL scores at week 24 were generally unchanged from baseline in arm 1 and lower than baseline in arms 2, 3, and 4 (Tran et al., 2024). The estimated treatment difference ETD at week 24 between patients in arm 2 and arm 1 was −22.6 points (95% CI, −42.5; −2.7) for the Haem-A-QoL “total score” and −15.7 points (95% CI, −51.8; 20.5) for “physical health”. The ETD in the domains “feeling,” “treatment,” “view of yourself,” and “sport and leisure” directionally favored concizumab, while the ETD in other domains showed no preference (Tran et al., 2024).

When switching to concizumab, it can be expected that subcutaneous administration with a pre-filled ready-to-use pen (low volume and 32G needle) and further a potentially better bleeding control will have a positive impact on the patient's quality of life. In the explorer7 study, quality of life was assessed using the 36-Item Short-Form Health Survey, version 2 (SF-36v2) in total 8 PRO questionnaires including also Haem-A-QoL (Tran et al., 2024). According to data from the study, 93% of patients preferred concizumab compared to their previous treatment, indicating a positive experience of the treatment (Matsushita et al., 2023).

HAVEN 1

Following 24 weeks of treatment, emicizumab prophylaxis was associated with a statistically significant difference in treated ABRs compared with no prophylaxis (based

on the randomised treatment arms) (RR: 0.13; p<0.0001). Similarly across the other bleeding-related outcomes explored, emicizumab prophylaxis was associated with a statistically significant difference in ABRs; all bleeds (RR: 0.20; p<0.0001), treated spontaneous bleeds (RR: 0.08; p<0.0001), treated joint bleeds (RR: 0.11; p=0.0050) and treated target joint bleeds (RR: 0.05; p=0.0002).

Overall, 198 adverse events were reported in 103 participants receiving emicizumab prophylaxis; the most frequent events were injection-site reactions (in 15% of participants). Thrombotic microangiopathy and thrombosis were reported in 2 participants each (in the primary analysis) who had received multiple infusions of activated prothrombin complex concentrate for breakthrough bleeding. No antidrug antibodies were detected.

Among participants previously treated with episodic BPAs, the difference in adjusted mean scores between the emicizumab prophylaxis group (Arm A) and the no prophylaxis group (Arm B) at week 25 was statistically significant in favour of emicizumab for both "Total" (Δ = 14.01; 95% CI: 5.56, 22.45; P = 0.0019) and "Physical Health" domain (Δ = 21.55; 95% CI: 7.89, 35.22; P = 0.0029) scores. [Oldenburg et al., 2019)

HAVEN 5

The below outlined efficacy estimates are reported for the overall population of both HA & HAwI. Details on the efficacy outcomes for the HAwI-only subgroup are found in the supplementary manuscript of HAVEN 5, and used in Appendix B.

The median efficacy periods for arms A, B and C were 43.7, 46.1 and 24 weeks, respectively. There was a statistically significant and clinically meaningful reduction in ABR for treated bleeds of 96% was observed for both arms A and B compared with arm C; the model-based ABRs (95% CI) for treated bleeds were 1 (0.53–1.85), 1 (0.50–1.84) and 27 (13.29–54.91), respectively. The proportion of patients with zero treated bleeds in arms A, B and C were 65.5% (19/29 patients), 55.6% (15/27 patients) and 17.1% (1/14 patients), respectively. Model based ABRs (95% CI) for treated spontaneous bleeds were lower in arms A and B compared with arm C (0.4 (0.18–0.96), 0.5 (0.20–1.12) and 23.6 (9.28–60.03), respectively). This was also the case for model-based ABRs (95% CI) for treated joint bleeds (0.7 (0.36–1.46), 0.6 (0.28–1.22) and 17.7 (8.33–37.57) for arms A, B and C, respectively) and treated target joint bleeds (0.4 (0.18–1.09), 0.3 (0.12–0.85) and 8.6 (3.15–23.42) for arms A, B and C, respectively).

In terms of AEs no distinct results were reported for the HAwI subgroup of patients, hence below results are based on both HA & HAwI.

A total of 185 AEs in 44 participants were reported for arms A and B and three AEs for two participants in arm C; the majority of which were grade 1 or 2. 78.6% of patients treated with emicizumab reported at least one AE compared with 14.3% of participants not receiving prophylaxis. The most reported AE was upper respiratory tract infection; nine patients in arm A (31%), five patients in arm B (18.5%) and two patients in arm C (14.3%). Four SAEs were reported in arms A and B but there were not related to study treatment.

No distinct HRQoL results were reported for the subgroup of HAwI patients. In the full population, the results were favouring emicizumab treatment over the no prophylaxis

group. Mean (95% CI) Haem-A-QoL physical health score and total score decreased from baseline with emicizumab prophylaxis, indicating improvement in HRQoL (physical health: arm A, −20.20 [−12.02 to −28.38]; arm B, −22.14 [−14.82 to −29.47]; arm C, −5.63 [−6.08 to −17.33]; total score: arm A, −10.14 [−3.46 to −16.81]; arm B, −17.61 [−10.96 to −24.25]; arm C, −2.50 [−3.74 to −8.75]).

5.3.1.1 NovoSeven-PPX

During the prophylaxis period, treatment with 90 µg/kg^{-1} rFVIIa significantly reduced bleeds per month from 5.6 to 3.0. The effective reduction in bleeding frequency with rFVIIa prophylaxis as compared to the pre-prophylaxis period was 45% with the 90 µg/kg^{-1} dose (P < 0.0001), based on a reduction in total bleeds during the pre-prophylaxis period from 212 bleeds to 106 bleeding episodes during the prophylaxis treatment period. Although a similar reduction was observed with all types of bleeds, the effect was most pronounced for spontaneous joint bleeds.

When comparing changes in the overall bleed frequency, target joint bleeds were significantly reduced by 43% (P < 0.001) during prophylaxis in the 90 µg/kg^{-1} rFVIIa treatment group (68 target joint bleeds) as compared to the pre-prophylaxis period (126 target joint bleeds).

The number of spontaneous bleeding episodes was significantly reduced from 145 in the pre-prophylaxis period to 70 in the prophylaxis period – yielding a significant 50% reduction with the 90 µg/kg^{-1} dose (P < 0.001).

Please note as previously stated that these data are based on 11 subjects, of which 10 of them are HAwI, while 4 patients (36 pct.) are below < 12 years.

Overall, there were no apparent treatment-dependent patterns in number or types of adverse events reported during the trial period. During the pre-prophylaxis period 8 patients reported an adverse event (19 events), whereas 9 patients during the prophylaxis treatment period reported 35 events. No thromboembolic adverse events occurred. Four serious adverse events were reported during the prophylaxis period (all judged by the investigator to be unlikely to be related to administration of rFVIIa).

5.3.2 Qualitative description of safety data

In general, serious adverse events are very low across the trials reported for concizumab, emicizumab and rFVIIa.

Of specific (serious) events of interest, such as the risk of thromboembolic events, it has been established in current clinical practice and guidelines that aPCC (Feiba) are not recommended for managing breakthrough bleeds in patients currently treated with emicizumab. This following the thromtobics events reported amongst other in HAVEN 1.

Similarly for concizumab, no thromboembolic events have been reported by investigators as an adverse event of special interest in participants treated with the new concizumab dosing regimen *(prior to the treatment pause, one non-fatal event of renal infarct was reported in EXPLORER 7)*.

Immunogenicity test results may be affected by several factors, including test sensitivity and specificity, specimen handling, timing of specimen collection, concomitant medications, and underlying disease. For these reasons, (any) comparison of the incidence of antibodies between the different comparators should be interpreted with caution.

No safety outcomes were deemed feasible for the comparative analysis, and no indirect treatment comparison will therefore be provided on any safety outcome in the following sections – only efficacy will be reviewed.

5.3.3 Method of synthesis

A brief description of the methods applied in the indirect treatment comparison is provided below for HAwI:

HAwI

The main objective of the indirect treatment comparison (ITC) was to compare the clinical efficacy and safety of concizumab with relevant comparators for the prophylactic treatment of patients aged ≥12 years with haemophilia A and B, with inhibitors (HAwI and HBwI) based on the SLR that was carried out.

A connected evidence network was hereafter built for patients with HAwI, which enabled an ITC of concizumab (EXPLORER 7, Arm 2, n=18) vs. emicizumab (HAVEN 1 (arm A, n=35).

Outcome data were reported for all six bleeding outcomes of interest in the HAwI population (no safety outcomes were deemed feasible for analysis):

- Treated spontaneous and traumatic bleeding episodes
- Spontaneous bleeding events treated with bypassing agents
- All bleeding events
- Treated joint bleeding events
- Treated target joint bleeds
- Proportion of patients with zero bleeding events

The outcomes were analysed using a Bayesian ITC conducted in WinBUGs. All statistical models were fitted by adapting code written by the National Institute for Health and Care Excellence (NICE) decision support unit (DSU) for their evidence synthesis. Due to a lack of reporting of the number of bleeding events and standard errors (SEs) associated with rate ratios across the comparator trials for the bleeding (rate) outcomes, two approaches were explored for the bleeding rate outcomes where feasible:

1) **Rate model (Poisson likelihood, log link):** requires the total number of events and data to estimate the duration of exposure (i.e. number of patients and the duration of the treatment period)

2) **Rate ratio model (Normal likelihood, identity link):** requires the natural logarithm (LN) rate ratio and associated measure of uncertainty

For the single binary outcome (patients with zero bleeding events) the binomial likelihood, logit link model was used.

Random effect (RE) and fixed effect (FE) models were run for each analysis and model fit was assessed by exploring the estimate of between study standard deviation of the RE model, deviance information criterion (DIC) (differences of 3–5 points to be considered important) and total residual deviance. Due to the small evidence networks, results from the FE models were considered the base-case for all outcomes and are presented in the main body of the report; results of the RE models and model fit statistics for each analysis are presented in the appendices for completeness.

Results of the NMA are presented as rate ratios (RR) or odds rations (OR) with associated 95% credible intervals (CrIs). Where the 95% CrI of relative treatment effects does not include the null value (for all outcomes in the current ITC the null value =1), it is interpreted that there is evidence for a difference between treatments.

Note that due to the limited number of studies and limited number of patients within the studies in this disease area both direct and indirect estimates of treatment effect are likely to be associated with large levels of uncertainty.

For more information and descriptions about the methodology applied in the indirect treatment comparison please refer to Appendix C.

HBwI

Notably, no studies (of any design) were identified in the clinical SLR that exclusively included HBwI populations and thus an indirect treatment comparison was deemed not feasible to carry out for this population.

5.3.4 Results from the comparative analysis

A summary of the ITC results in the HAwI population is provided in Table 5 below.

The point estimate of the ITC results were favourable for all outcomes of interest for concizumab compared with emicizumab, except for all bleeding events and the proportion of patients with zero bleeding events; however, all comparisons were associated with wide CrIs, and none of the 95% CrIs excluded the null value-suggesting there is no evidence for a difference between treatments.

The analyses presented utilise the best available evidence in this rare disease. It is important to interpret the result of the ITC in context of the limitations of the analyses (as highlighted in section 5.2.2).

The analyses assume that the relative treatment effects within each of the trials would remain the same regardless of the specific treatments used in the on-demand common

comparator arms. Furthermore, whilst it is assumed that the studies are sufficiently homogenous to combine, variability in terms of inhibitor titre, age, target joints, and disease severity cannot be avoided in this rare disease group.

Table 5 Results from the comparative analysis of concizumab vs. emicizumab for HAwI

Outcome	Model (data input)	Relative treatment effect measure	ITC estimates: concizumab versus comparator
			Emicizumab
Treated spontaneous and traumatic bleeding episodes	Poisson likelihood, log link (number of events and person-year follow-up)	Rate ratio (95% CrI)	N/A
	Normal likelihood, identity link (LN rate ratio and SE)	Rate ratio (95% CrI)	0.75 (0.26, 2.21)
Spontaneous bleeding events treated with bypassing agents	Normal likelihood, identity link (LN rate ratio and SE)	Rate ratio (95% CrI)	0.75 (0.23, 2.42)
All bleeding events	Poisson likelihood, log link (number of events and person-year follow-up)	Rate ratio (95% CrI)	N/A
	Normal likelihood, identity link (LN rate ratio and SE)	Rate ratio (95% CrI)	1.20 (0.44, 3.33)
Treated joint bleeding events	Poisson likelihood, log link (number of events and person-year follow-up)	Rate ratio (95% CrI)	N/A
	Normal likelihood, identity link (LN rate ratio and SE)	Rate ratio (95% CrI)	0.82 (0.22, 3.13)
Treated target joint bleeds	Normal likelihood, identity link (LN rate ratio and SE)	Rate ratio (95% CrI)	0.80 (0.05, 13.67)
Proportion of patients with zero bleeding events	Binomial likelihood, logit link (Number of patients at risk and number with zero bleeding events)	Odds ratio (95% CrI)	0.27 (0.00, 139.00)

Abbreviations: CrI, credible interval; ITC, indirect treatment comparison; NA, not applicable.

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

The Expert Committee for haemophilia, under the Danish Medicines Council has previously assessed the total HAwI population for emicizumab to consist of roughly 10 patients in Denmark. Novo Nordisk is furthermore aware of 1 HAwI patient from Denmark that was enrolled in the EXPLORER 7 program via site Aarhus University Hospital. Within HBwI 1 Danish patient from site Aarhus University Hospital was enrolled in EXPLORER 7. As such, Danish participants have contributed to the overall results of EXPLORER 7, giving the current Haemophilia Expert Committee a good understanding of the efficacy and safety aspects of anti-TFPI treatment (concizumab) for prophylactic treatment of patients ≥ 12 years with HAwI or HBwI.

The Danish Medicines Council has previously placed much emphasis on the results of HAVEN 1 when deciding back in 2018 to make emicizumab current standard of care within HAwI. It is therefore our assessment that the enrolled trial participants across studies are representative of the expected treatment outcome and safety profile that could be anticipated eligible Danish patients with HAwI and HBwI.

Table 3 and 4 below provide more information on relevant patient characteristics.

Table 3 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (EXPLORER 7 and Haven)

	EXPLORER 7 (HAwI subgroup)		HAVEN 1				HAVEN 5			
	Arm 1: No prophylaxis (n=9)	Arm 2: Concizumab prophylaxis (n=18) daily dose of 0.2 mg/kg*	A: Emicizumab Prophylaxis (n = 35) 1.5 mg/kg once weekly	B: No Prophylaxis (n = 18)	C: Emicizumab Prophylaxis (n = 49) 1.5 mg/kg once weekly	D: Emicizumab Prophylaxis (n = 7) 1.5 mg/kg once weekly	A: Emicizumab Prophylaxis (n = 29) 1.5 mg/kg once weekly	B: Emicizumab Prophylaxis (n = 27) 6 mg/kg every 4 weeks	C: No Prophylaxis (n=14)	
Age, years, median (min–max)	43 (15-67)	17 (12-61)	38.0 (12–68)	35.5 (13–65)	17.0 (12–75)	26.0 (19–49)	31.0 (12-57)	28.0 (13-66)	26.5 (13-46)	
Gender	Male				Male				Male	
Age, **<18 years, n (%)** **≥18-64, n (%)** **≥65, n (%)**	N/R: Age categories not reported for HawI subgroup (only median, min-max above)		4 (11.4) 30 (85.7) 1 (2.9)	2 (11.1) 15 (83.3) 1 (5.6)	26 (53.1)	0	3 (10.3) 26 (89.7) 0 (0.0)	6 (22.2) 20 (74.1) 1 (3.7)	11 (15.7) (82.9)	58 1 (1.4)
Hemophilia severity at baseline, n (%): **Mild** **Moderate** **Severe**	9 (100%)	18 (100%)	2 (5.7) 2 (5.7) 31 (88.6)	0 0 18 (100)	1 (2.0) 1 (2.0) 47 (95.9)	0 1 (14.3) 6 (85.7)	0 (0.0) 2 (6.9) 27 (93.1)	0 (0.0) 0 (0.0) 27 (100)	0 (0.0) 13 (92.9)	1 (7.1)
Bleeding events in 24 weeks prior to study entry, n (%) **≥9**	ABR during on-demand: 18.6 (SD 16.9)	ABR during on-demand: 32.2 (SD 30.2)	24 (68.6)	13 (72.2)	26 (53.1)	3 (42.9)	22 (75.9)	21 (77.8)	11 (78.6)	

	ABR during prophylaxis: 87.4 (SD 5.5) [n=1]	ABR during prophylaxis: 26.9 (SD 5.5), n=2/17							
Target joints, n (%) **Yes** **>1**	3 (33.3) 3 (33.3)	6 (35.3) 3 (17.6)	25 (71.4) 18 (72.0)	13 (72.2) 10 (76.9)	34 (69.4) 24 (70.6)	4 (57.1) 1 (25.0)	20 (69.0) 13/20 (65.0)	20 (74.1) 14/20 (70.0)	12 (85.7) 8/12 (66.7)
Highest historical inhibitor titer (BU) **Median, min–Max** **≥5 BU, n/N (%)** **Unknown, n/N (%)**	192, n=9 6 (0.3, 108) 6 (66.7, n=9) N/A	86.4, n=16 2 (0.3, 684) (29.4), n=5/17 N/A	84.5 (5–1570; n=32) 32/35 (91.4) 3/35 (8.6)	102 (18–4500; n=16) 16/18 (88.9) 2/18 (11.1)	309.0 (11–5000; n=47) 47/49 (95.9) 2/49 (4.1)	240.0 (28–2125; n=6) 6/7 (85.7) 1/7 (14.3)	Yes: 6 (20.7) No: 23(79.3)	Yes: 7 (25.9) No: 20(74.1)	Yes: 3 (21.4) No: 11 (78.6)
Previously treated with ITI, n (%)	N/A (on-going or planned ITI treatment was part of the exclusion criteria for the trial). No historical data captured		14 (40.0)	7 (38.9)	33 (67.3)	3 (42.9)	0 (0.0)	2 (28.6)	1 (33.3)
Episodic coagulation product use in 24 weeks prior to study entry, n (%) **APCC** **rFVIIa** **FVIII** **Other**	8 (87.5)	16 (88.9)	35 (100) 27 (77.1) 22 (62.9) 1 (2.9) 1 (2.9)	18 (100) 13 (72.2) 17 (94.4) 0 0	23 (47) 15 (65.2) 15 (65.2) 1 (4.3) 0	7 (100) 5 (71.4) 5 (71.4) 2 (28.6) 1 (14.3)			

Prophylactic coagulation product use in 24 weeks prior to study entry, n (%)	1 (12.5)-prior prophylaxis]	2 (11.1)-prior prophylaxis]							
APCC			0	0	49 (100)	0	0	0	49 (100)
rFVIIa			0	0	36 (73.5)	0	0	0	36 (73.5)
FVIII			0	0	15 (30.6)	0	0	0	15 (30.6)
Other			0	0	1 (2.0)	0	0	0	1 (2.0)
			0	0	1 (2.0)	0	0	0	1 (2.0)

Table 4 with baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (EXPLORER 7 and NOVOSEVEN-PPX)

	EXPLORER 7 (both HAwI & HBwI)				NOVOSEVEN-PPX
	Arm 1: No prophylaxis (n=19)	Arm 2: Concizumab prophylaxis (n=33) daily dose of 0.2 mg/kg*	Arm 3:Concizumab prophylaxis (n=21) daily dose of 0.2 mg/kg*	Arm 4: Concizumab prophylaxis (n=60) daily dose of 0.2 mg/kg*	Prophylaxis period (n=11) 90 µg/kg rFVIIa
Age, years, median (min–max)	at least 12 years of age				13.0 (5.1–50.5)
Gender	Male				Male
Age, **<18 years, n (%)** **≥18-64, n (%)** **≥65, n (%)**	6 (31.6) 12 (63.2) 1 (5.3)	18 (54.5) 15 (45.5) 0 (0)	0 (0) 21 (100) 0 (0)	18 (30.0) 41 (68.3) 1 (1.7)	4 (36) < 12 y 5 (46) 12-18 y 2 (18) ≥ 18 y
Hemophilia severity at baseline, n (%):	HAwI and HBwB, any severity (n=80 HAwI and n=53 HBwI)				Severe HA/HB 10 (91) HA 1 (9%) HB
Target joints, n (%) **Yes, ≥ 3 times in the last 6 months**	N/R				10 (91)
Highest historical inhibitor titer (BU) Median, min–max ≥5 BU, n/N (%) Unknown, n/N (%)	Yes, with inhibitors (inhibitor development (≥0.6 BU)).				Yes, inhibitor titer > 2 BU/mL–1
Previously treated with ITI, n (%)	N/A (on-going or planned ITI treatment was part of the exclusion criteria for the trial). No historical data captured				excluded if ITI was performed within a month before study start

6. References

Alhemo Alhemo,INN-concizumab (last accessed May 2025).

Andersson NG, Långström S, Ranta S, Knudsen H, Baghaeri F, Astermark J, Hoffmann M. Nordic Hemophilia Council Hemophilia Guidelines – 6 Inhibitors (last accessed May 2025).

Augustsson C, Strandberg K, Kjalke M. In vitro assessment of clinical coagulation assays in the presence of concizumab. PB0168. Presented at the 31st Congress of the International Society on Thrombosis and Haemostasis (ISTH) 2023, 24–28 June, Montréal, Canada. 2023

Broze GJ, Jr., Girard TJ. Tissue factor pathway inhibitor: structure-function. Front Biosci (Landmark Ed). 2012;17:262-80.

Butterfield JSS, Hege KM, Herzog RW, Kaczmarek R. A Molecular Revolution in the Treatment of Hemophilia. Mol Ther. 2020;28(4):997-1015.

Carcao M, Hilliard P, Escobar MA, Solimeno L, Mahlangu J, Santagostino E. Optimising musculoskeletal care for patients with haemophilia. Eur J Haematol. 2015;95 Suppl 81:11-21.

Chowdary P, Lethagen S, Friedrich U, Brand B, Hay C, Abdul Karim F, et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. J Thromb Haemost. 2015;13(5):743-54.

Chowdary P. Anti-tissue factor pathway inhibitor (TFPI) therapy: a novel approach to the treatment of haemophilia. Int J Hematol. 2020;111(1):42-50.

Chowdary P. Inhibition of Tissue Factor Pathway Inhibitor (TFPI) as a Treatment for Haemophilia: Rationale with Focus on Concizumab. Drugs. 2018;78(9):881-90.

D'Angiolella LS, Cortesi PA, Rocino A, Coppola A, Hassan HJ, Giampaolo A, et al. The socioeconomic burden of patients affected by hemophilia with inhibitors. Eur J Haematol. 2018;101(4):435-56.

Dolan G, Benson G, Duffy A, Hermans C, Jiménez-Yuste V, Lambert T, et al. Haemophilia B: Where are we now and what does the future hold? Blood Rev. 2018;32(1):52-60.

Giangrande PLF, Hermans C, O'Mahony B, de Kleijn P, Bedford M, Batorova A, et al. European principles of inhibitor management in patients with haemophilia. Orphanet J Rare Dis. 2018;13(1):66.

Guelcher C, National Hemophilia Foundation. Inhibitor Development. Available at: https://www.hemophilia.org/sites/default/files/document/files/Nurses-Guide-Chapter-12-Inhibitor-to-Factor-VIII-and-Factor-IX.pdf (last accessed May 2025). 2018.

Hanley J, McKernan A, Creagh MD, Classey S, McLaughlin P, Goddard N, et al. Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia: A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline. Haemophilia. 2017;23(4):511-20.

Hansen L, Petersen LC, Lauritzen B, Clausen JT, Grell SN, Agersø H, et al. Target-mediated clearance and bio-distribution of a monoclonal antibody against the Kunitz–type protease inhibitor 2 domain of Tissue Factor Pathway Inhibitor. Thrombosis Research. 2014;133(3):464-71

Hedner U, Ezban M. Tissue factor and factor VIIa as therapeutic targets in disorders of hemostasis. Annu Rev Med. 2008;59:29-41.

Hemlibra SmPC Hemlibra, INN-emicizumab (last accessed May 2025).

Hilden I, Lauritzen B, Sørensen BB, Clausen JT, Jespersgaard C, Krogh BO, et al. Hemostatic effect of a monoclonal antibody mAb 2021 blocking the interaction between FXa and TFPI in a rabbit hemophilia model. Blood. 2012;119(24):5871-8.

Ho KM, Pavey W. Applying the cell-based coagulation model in the management of critical bleeding. Anaesth Intensive Care. 2017;45(2):166-76.

Hoffman M, Monroe DM, 3rd. A cell-based model of hemostasis. Thromb Haemost. 2001;85(6):958-65.

Kihlberg K, Strandberg K, Rosén S, Ljung R, Astermark J. Discrepancies between the one-stage clotting assay and the chromogenic assay in haemophilia B. *Haemophilia* 2017;**23**:620–7. doi:10.1111/hae.13219.

Kizilocak H, Young G. Diagnosis and treatment of hemophilia. Clin Adv Hematol Oncol. 2019;17(6):344-51.

Konkle et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. J Thromb Haemost 2007; 5: 1904–13.

Lai J, Hough C, Tarrant J, Lillicrap D. Biological considerations of plasma-derived and recombinant factor VIII immunogenicity. Blood. 2017;129(24):3147-54.

Lai JD, Lillicrap D. Factor VIII inhibitors: Advances in basic and translational science. Int J Lab Hematol. 2017;39 Suppl 1:6-13.

Llinás A, Poonnoose P, Goddard N, Blamey G, Al Sharif A, de Kleijn P, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Chapter 10: Musculoskeletal Complications. Haemophilia. 2020;26(Suppl. 6):125-36.

Mahlangu J, Dolan G, Dougall A, Goddard N, Preza Hernández E, Ragni M, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Chapter 7: Treatment of Specific Hemorrhages. Haemophilia. 2020;26(Suppl. 6):85-107.

Matsushita T, Shapiro A, Abraham A, Angchaisuksiri P, Castaman G,Cepo K, d'Orion R, Frei-Jones M, Goh a-s, Haaning J, Hald Jacobsen J, Mahlangu J,

Mathias M, Nogami K, Skovgaard Rasmussen J, Stasyshyn O, Tran H, Vilchevska K,Villarreal Martinez L, Windyga J, You CW, Zozulya N, Zulfikar B, Jimènez-Yuste V. Phase 3 Trial of Concizumab in Hemophilia with Inhibitors N Engl J Med 2023;389:783-94.

Miller CH. Laboratory testing for factor VIII and IX inhibitors in haemophilia: A review. Haemophilia. 2018;24(2):186-97.

Medicinrådet, Protokol for Medicinrådets behandlingsvejledning for hæmofili A version 1.0, 2018. Protokol for behandlingsvejledning for hæmofili A-vers. 1.0 (last accessed May 2025).

Medicinrådet, Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til hæmofili A, version 1.1, 2022. Medicinrådets lægemiddelrek. og beh.vejl. vedr. lægemidler til hæmofili A - version 1.1 (last accessed May 2025).

Morfini M, Haya S, Tagariello G, Pollmann H, Quintana M, Siegmund B, et al. European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia. 2007;13(5):606-12.

O'Hara J, Walsh S, Camp C, Mazza G, Carroll L, Hoxer C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. Health Qual Life Outcomes. 2018;16(1):84

Oladapo AO, Lu M, Walsh S, O'Hara J, Kauf TL. Inhibitor clinical burden of disease: a comparative analysis of the CHESS data. Orphanet J Rare Dis. 2018;13(1):198.

Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, Santagostino E, Kruse-Jarres R, Negrier C, Kessler C, Valente N, Asikanius E, Levy GG, Windyga J, Shima M. Emicizumab Prophylaxis in Hemophilia A with Inhibitors., N Engl J Med 2017;377:809-18.

Oldenburg J, Mahlangu JN, Bujan W, Trask P, Callaghan MU, Young G, Asikanius E, Peyvandi F, Santagostino E, Kruse-Jarres R, Negrier C, Kessler C, Xu J, Windyga J, Shima M, von Mackensen S. The effect of emicizumab on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study., Haemophilia. 2019 Jan;25(1):33-44. doi: 10.1111/hae.13618

Peyvandi F, Ettingshausen CE, Goudemand J, Jiménez-Yuste V, Santagostino E, Makris M. New findings on inhibitor development: from registries to clinical studies. Haemophilia. 2017;23 Suppl 1:4-13.

Ragni M, Berntorp E, Carcao M, Ettingshausen C, Nedzinskas A, Ozelo M, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Chapter 8: Inhibitors to Clotting Factor. Haemophilia. 2020;26(Suppl. 6):95-107.

Ragni MV. Novel alternate hemostatic agents for patients with inhibitors: beyond bypass therapy. Hematology Am Soc Hematol Educ Program. 2017;2017(1):605-9.

Samuelson Bannow B, Recht M, Négrier C, Hermans C, Berntorp E, Eichler H, et al. Factor VIII: Long-established role in haemophilia A and emerging evidence beyond haemostasis. Blood Rev. 2019;35:43-50.

Santagostino E, Dougall A, Jackson M, Khair K, Mohan R, Chew K, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Chapter 2: Comprehensive Care of Hemophilia Haemophilia. 2020;26(Suppl. 6):19-34.

Shapiro AD. Concizumab: a novel anti-TFPI therapeutic for hemophilia. Blood Adv. 2021;5(1):279.

Smith SA. The cell-based model of coagulation. J Vet Emerg Crit Care (San Antonio). 2009;19(1):3-10.

Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158.

World Federation of Hemophilia. eLearning Centres: Hemophilia. 2022. Available at: https://elearning.wfh.org/elearning-centres/hemophilia/ [Accessed on May 2025].

Yang R, Wang S, Wang X, Sun J, Chuansumrit A, Zhou J, Schmitt C, Hsu W, Xu J, Li L, Chang T, Zhao X. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN 5). Res Pract Thromb Haemost. 2022;6:e12670.

Appendix A. Main characteristics of studies included

Table 2 Main characteristic of studies included

Table 6.1 Main characteristic of EXPLORER 7

Trial name: EXPLORER 7	NCT number: 04083781
Objective	Efficacy and safety of daily treatment with concizumab prophylaxis compared with no prophylaxis in adult and adolescent patients with haemophilia with inhibitors.
Publications – title, author, journal, year	Matsushita et al. Phase 3 Trial of Concizumab in Hemophilia with Inhibitors N Engl J Med 2023;389:783-94. DOI: 10.1056/NEJMoa2216455 Tran et al. Concizumab prophylaxis in persons with hemophilia A or B with inhibitors: patient-reported outcome results from the phase 3 explorer7 study. Res Pract Thromb Haemost. 2024 Jun 17;8(4):102476.
Study type and design	Prospective, multicenter, open-label, phase 3a trial that compared concizumab prophylaxis with no prophylaxis. The trial included two randomization groups (groups 1 and 2) and two non-randomization groups (groups 3 and 4). *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 hemophilia type (Hemophilia A or B with inhibitors [HAwI or HBwI]) and bleeding frequency during the 24 weeks prior to randomization (<9 bleeding episodes vs ≥9 bleeding episodes).
Sample size (n)	N=133. Of 133 enrolled patients, 19 were randomly assigned to group 1 and 33 to group 2; the remaining 81 were assigned to groups 3 and 4
Main inclusion criteria	• Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial. • Male aged 12 years or older at the time of signing informed consent. • Congenital Haemophilia A or B of any severity with documented history of inhibitor (equal to or above 0.6 Bethesda Units (BU). • Patient has been prescribed, or in need of, treatment with bypassing agents in the last 24 weeks prior to screening (for patients not previously enrolled in NN7415-4310 (explorer 4)).]
Main exclusion criteria	• Known or suspected hypersensitivity to any constituent of the trial product or related products. • Known inherited or acquired coagulation disorder other than congenital haemophilia. • Ongoing or planned Immune Tolerance Induction treatment. • History of thromboembolic disease (includes arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion). Current clinical signs of, or treatment for thromboembolic disease. Patients who in the

Trial name: EXPLORER 7	NCT number: 04083781
	judgement of the investigator are considered at high risk of thromboembolic events (thromboembolic risk factors could include, but are not limited to, hypercholesterolemia, diabetes mellitus, hypertension, obesity, smoking, family history of thromboembolic events, arteriosclerosis, other conditions associated with increased risk of thromboembolic events.)
Intervention	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 profylaxis (On-demand treatment)
Follow-up time	Follow-up 7 weeks (after extension 128-126 weeks)
Primary, secondary and exploratory endpoints	Primary outcome: comparison between treated spontaneous and traumatic bleeding episodes in group 1 and group 2 (when all the patients in group 1 (no prophylaxis) had completed at least 24 weeks of treatment or had withdrawn and when all the patients in group 2 (concizumab prophylaxis) had completed at least 32 weeks of treatment, which included the 5-to-8-week dose-adjustment period, or had withdrawn. Secondary outcome: to compare patient reported outcomes after concizumab prophylaxis with those after no prophylaxis. Key secondary end points were the change in bodily pain and physical functioning scores on the 36-Item Short-Form Health Survey, version 2 (SF-36v2), from the start of treatment to week 24.
Method of analysis	The primary analysis was a negative binomial regression that included treatment and the stratification factors (type of hemophilia [hemophilia A or B with inhibitors] and bleeding frequency [<9 or ≥9 bleeding episodes during the 24 weeks before screening]), as well as the logarithm of the length of the observation period, as offset. A significant difference between groups 1 and 2 was considered to indicate superiority.
Subgroup analyses	HAwI & HBwI
Other relevant information	Study Start (Actual) 2019-10-21 Primary Completion (Actual) 2021-12-27

Table 6.2 Main characteristic of HAVEN 1

Trial name: HAVEN 1	NCT number: 02622321
Objective	Efficacy, safety, and pharmacokinetics of once weekly subcutaneous emicizumab prophylaxis in patients with hemophilia A with inhibitors versus no prophylaxis.
Publications – title, author, journal, year	Oldenburg et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med 2017;377:809-18. DOI: 10.1056/NEJMoa1703068 Oldenburg et al. The effect of emicizumab on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study., Haemophilia. 2019 Jan;25(1):33-44. doi: 10.1111/hae.13618
Study type and design	Phase 3, open-label, multicenter, randomized trial. Participants receiving episodic treatment with bypassing agents before trial entry were randomly assigned in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis at a dose of 3.0 mg/kg of body weight weekly for 4 weeks, followed by 1.5 mg/kg weekly hereafter

Trial name: HAVEN 1		NCT number: 02622321
	(group A), or to the control group (no emicizumab prophylaxis and, because the trial was open-label, no subcutaneous control injections; group B). Participants who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis in group C. Group D (also receiving emicizumab prophylaxis) comprised participants who were unable to enroll in HAVEN 1 groups A, B, or C before they were closed to enrollment.	
Sample size (n)	*N=109*	
Main inclusion criteria	• Body weight >/= 40 kilograms (kg) at the time of screening • Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (that is [i.e.], >/= 5 Bethesda Units [BU]) • Documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks • >/= 6 bleeds in the last 24 weeks prior to screening (if on an episodic bypassing agent regimen) or >/=2 bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen) • Adequate hematologic, hepatic and renal function • For women who are not postmenopausal or surgically sterile: agreement to remain abstinent or use single or combined highly effective contraceptive methods	
Main exclusion criteria	• Participants with inherited or acquired bleeding disorder other than hemophilia A • Participants with ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with Factor VIII (FVIII), with the exception of participants who have received a treatment regimen of FVIII prophylaxis with concurrent bypassing agent prophylaxis • Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or current signs of thromboembolic disease • Participants with other conditions (for example [e.g.], certain autoimmune diseases) that may increase the risk of bleeding or thrombosis • History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection • Known human immunodeficiency virus (HIV) infection with cluster of differentiation 4 (CD4) count < 200 cells per microliter (cells/mcL) within 24 weeks prior to screening • Use of systemic immunomodulators (e.g., interferon or rituximab) at enrolment or planned use during the study, with the exception of antiretroviral therapy • Participants who are at high risk for thrombotic microangiopathy (TMA; e.g., have a previous medical or family history of TMA), in the investigator's judgment • Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the participant's safe participation in and completion of the study or interpretation of the study results	

Trial name: HAVEN 1	NCT number: 02622321
	• Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study • Receipt of emicizumab in a prior investigational study; An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration; A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter; An investigational drug concurrently • Unwillingness to use highly effective contraception methods for the specified duration in the protocol (females only, unless required otherwise by the local health authority) • Clinically significant abnormality on screening evaluations or laboratory tests that, in the opinion of the investigator, may pose an additional risk in administering study drug to the participant • Pregnancy or lactation, or intent to become pregnant during the study
Intervention	Subcutaneous emicizumab prophylaxis at a dose of 3.0 mg/kg of body weight weekly for 4 weeks, followed by 1.5 mg/kg weekly thereafter for patients receiving episodic treatment with bypassing agents before trial (group A). Participants who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis in group C. Patients who were unable to enroll in HAVEN 1 groups A, B, or C before they were closed to enrollment received emicizumab prophylaxis (Group D). Participants who were randomly assigned to group B could receive emicizumab prophylaxis after completing at least 24 weeks in the trial (and remained in group B).
Comparator(s)	No prophylaxis (on-demand treatment)
Follow-up time	≥24 weeks All randomly assigned participants had at least 24 weeks of follow-up for the primary and secondary end points. Follow-up for participants (in groups C and D) was less than 24 weeks
Primary, secondary and exploratory endpoints	Primary outcome: difference in the rate of treated bleeding events (bleeding rate) over a period of at least 24 weeks between participants receiving emicizumab prophylaxis (group A) and those receiving no prophylaxis (group B) after the last randomly assigned participant had completed 24 weeks in the trial or had discontinued participation, whichever occurred first. Secondary outcomes: for the randomized comparison (group A vs. group B) included additional bleeding-related end points (all bleeding events [both treated and not treated with bypassing agents] and events of spontaneous bleeding, joint bleeding, and target-joint bleeding), health-related quality of life (Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL] physical health subscale and total score at week 25), and health status (the five-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D-5L] visual-analogue scale and index utility score at week 25). Other endpoints: Additional bleeding-related end points: Intraindividual comparisons of the bleeding rate and the rate of all bleeding events among participants in groups A and C who had participated in the noninterventional study

Trial name: HAVEN 1	NCT number: 02622321
Method of analysis	For all bleeding-related end points, comparisons of the bleeding rate in group A versus group B and the intraindividual comparisons were performed with the use of a negative binomial-regression model to determine the bleeding rate per day, which was converted to an annualized bleeding rate. End points with respect to health-related quality of life and health status were analyzed with the use of analysis of covariance.
Subgroup analyses	N/A
Other relevant information	Study Start (Actual) 2015-11-18 Study Completion (Actual) 2020-12-01

Table 6.3 Main characteristic of HAVEN 5

Trial name: HAVEN 5	NCT 03315455
Objective	Efficacy, safety, immunogenicity, and pharmacokinetic (PK) profile of 1.5 mg/kg once weekly and 6 mg/kg every 4 weeks emicizumab in people with hemophilia A in the Asia-Pacific region.
Publications – title, author, journal, year	Yang et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN 5). Res Pract Thromb Haemost. 2022;6:e12670. DOI: 10.1002/rth2.12670
Study type and design	A randomized, multicenter, open-label, phase 3 clinical study. Study participants were randomized to 3 treatment arms: emicizumab 3 mg/kg once weekly for the first 4 weeks (loading dose) followed by a maintenance dose of either 1.5 mg/kg once weekly (arm A) or 6 mg/kg every 4 weeks (arm B), or no prophylaxis (arm C). After completing 24 weeks of study, participants randomized to arm C could switch to emicizumab (3 mg/kg once weekly loading dose for 4 weeks followed by a maintenance regimen of 6 mg/kg every 4 weeks).
Sample size (n)	*N=70*
Main inclusion criteria	Inclusion Criteria for Arms A, B, and C: • Diagnosis of severe congenital hemophilia A or hemophilia A with FVIII inhibitors • Aged 12 years or older at the time of informed consent • Body weight ≥40 kilograms (kg) at the time of screening • Participants without FVIII inhibitors (<0.6 Bethesda unit per milliliter [BU/mL]) who completed successful immune tolerance induction (ITI) must have done so at least 5 years before screening and have no evidence of inhibitor recurrence (permanent or temporary) • Documentation of the details of episodic therapy (FVIII or bypassing agents) and of number of bleeding episodes for at least the last 24 weeks and ≥5 bleeds in the last 24 weeks prior to study entry • Adequate hematologic, hepatic, and renal function • For women of child bearing potential: agreement to remain abstinent or use a protocol defined contraceptive measure during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug Inclusion Criteria for Arm D: • Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥5 BU/mL) • Children <12 years old at time of informed consent • Body weight >3 kg at time of informed consent • Requires treatment with bypassing agents • Adequate hematologic, hepatic, and renal function

Trial name: HAVEN 5	NCT 03315455
	• For female participants who are of childbearing potential, follow the same contraception criteria as listed above for Arms A, B, and C
Main exclusion criteria	Exclusion Criteria for Arms A, B, and C: • Inherited or acquired bleeding disorder other than hemophilia A • At high risk for thrombotic microangiopathy, in the investigator's judgment • History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment • Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease • Other conditions that may increase risk of bleeding or thrombosis • History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection • Known human immuno-deficiency virus (HIV) infection with cluster of differentiation 4 (CD4) count <200 cells/microliter (cells/mcL) within 24 weeks prior to screening. Participants with HIV infection who have CD4 >200 cells/mcL and meet all other criteria are eligible • Use of systemic immunomodulators at enrollment or planned use during the study, with the exception of anti-retroviral therapy • Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the participant's safe participation in and completion of the study • Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study • Receipt of: Emicizumab in a prior investigational study; An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration; A non-hemophilia-related investigational drug concurrently, within last 30 days or 5 half-lives, whichever is shorter • Pregnant or lactating, or intending to become pregnant during the study Exclusion Criteria for Arm D: • Inherited or acquired bleeding disorder other than hemophilia A • Ongoing (or plan to receive during the study) ITI therapy or prophylaxis treatment with FVIII • Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease • Other diseases that may increase risk of bleeding or thrombosis

Trial name: HAVEN 5	NCT 03315455
	• History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection • Known infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) • At high risk for thrombotic microangiopathy, in the investigator's judgment • Use of systemic immunomodulators at enrollment or planned use during the study • Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study • Inability (or unwillingness by caregiver) to receive (allow receipt of) blood or blood products (or any standard-of-care treatment for a life-threatening condition) • Receipt of: Emicizumab in a prior investigational study; An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration; A non-hemophilia-related investigational drug concurrently, within last 30 days or 5 half-lives, whichever is shorter • Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the participant's safe participation in and completion of the study • Pregnant or lactating, or intending to become pregnant during the study
Intervention	3 mg/kg emicizumab once weekly for the first 4 weeks (loading dose) followed by a maintenance dose of either 1.5 mg/kg once weekly or 6 mg/kg every 4 weeks.
Comparator(s)	No emicizumab prophylaxis. After completing 24 weeks of study, participants could switch to emicizumab (3 mg/kg once weekly loading dose for 4 weeks followed by a maintenance regimen of 6 mg/kg every 4 weeks). After at least 24 weeks of emicizumab prophylaxis, participants could continue taking maintenance therapy (1.5 mg/kg once weekly or 6 mg/kg every 4 weeks) or, if they had suboptimal control of bleeding, change to an increased dose of 3 mg/kg once weekly.
Follow-up time	≥ 24 weeks. Follow-up duration for evaluating prophylaxis was shorter for those who switched to emicizumab in arm C (24 weeks) than for those in arms A and B (44-46 weeks), and an absence of participants <12 years of age limits the scope of the findings.
Primary, secondary and exploratory endpoints	Primary outcome: annualized bleeding rate (ABR) for treated bleeds in people with hemophilia A receiving once-weekly or every-4-weeks emicizumab prophylaxis or no prophylaxis. Secondary outcomes: ABRs for all bleeds and treated spontaneous/joint/target joint bleeds in participants receiving once-weekly or every-4-weeks emicizumab prophylaxis versus no prophylaxis. Bleeds were counted as one bleed if they were of the same type and occurred at the same anatomic location within 72 hours after stopping treatment for the first bleed (the “72-hour rule”); bleeds due to procedure/surgery were excluded. As per ISTH definition, target joints were defined as major joints in which ≥3 bleeding events occurred over a 24-week period. Change from baseline in HRQoL and health status after 24 weeks of emicizumab prophylaxis versus no prophylaxis was also evaluated.
Method of analysis	Participant demographics and clinical characteristics are reported using descriptive statistics including mean, standard deviation (SD), median,

Trial name: HAVEN 5	NCT 03315455
	and IQR. Primary and secondary efficacy analyses were performed in the intent-to-treat (ITT) population, which comprised people with hemophilia A with/without FVIII inhibitors. Similar PK, and relationship between PK and bleed frequency, have been previously observed in inhibitor and noninhibitor populations. Formal hypothesis testing was conducted for the randomized comparisons of arm A/B versus arm C; for primary and bleed-related secondary end points, a model-based comparison of the number of bleeds over the study period in arms A/B compared with arm C was performed using a negative-binomial regression model, which takes into account the varying follow-up time for each individual. Statistical testing at the prespecified α level was based on the Wald test. Bleed rates for emicizumab and no prophylaxis groups, and rate ratio (quantifies the risk of bleeding associated with emicizumab versus no prophylaxis) including 95% confidence intervals (CIs) are described. ABR = (number of bleeds/total number of days during the efficacy period) $\times$ 365.25 was used to calculate median (IQR) and mean (95% CI) ABRs.
Subgroup analyses	The primary endpoint was analyzed by pre-defined subgroups (age: <18, ≥18; number of bleeds in the 24 weeks prior to study entry: <9, ≥9; target joints). Estimated annualized bleed rates (ABRs) including 95% confidence intervals (CIs) were calculated for all treatment arms.
Other relevant information	Study Start (Actual) 2018-04-26 Primary Completion (Actual) 2022-08-03 Study Completion (Estimated) 2025-06-30

Table 6.4 Main characteristic of NovoSeven-PPX

Trial name: NovoSeven-PPX	NCT 00108758
Objective	Efficacy and safety of secondary rFVIIa (NovoSeven®) prophylaxis in patients with congenital hemophilia A or B with inhibitors and high requirements for on-demand therapy.
Publications – title, author, journal, year	Konkle et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. J Thromb Haemost 2007; 5: 1904–13.
Study type and design	Multicenter, randomized, double-blind, parallel-group trial investigating the efficacy and safety of secondary rFVIIa prophylaxis in patients with congenital hemophilia A or B with inhibitors and high requirements for on-demand therapy. The trial consisted of a pre-prophylaxis period, a prophylaxis (treatment) period, and a post-prophylaxis period, each of 3 months duration.
Sample size (n)	N=22
Main inclusion criteria	Diagnosis of congenital haemophilia A or B with inhibitors development against FVIII or FIX, respectively.
Main exclusion criteria	Prophylactic administration of any haemostatic drug within 3 last months prior to entering the trial.
Intervention	22 patients completed the trial and were randomized 1:1 to receive daily rFVIIa prophylaxis with either 90 (10 HAwI and 1 HBwI patients) or 270 µg/kg^{-1} (11 HAwI patients) for 3 months, followed by a 3-month post-prophylaxis period where rFVIIa was administered on-demand.
Comparator(s)	Each patient served as his own control. In the 3-month pre-prophylaxis period and 3-month post-prophylaxis period only conventional on-demand hemostatic therapy was administered.
Follow-up time	12 weeks.
Primary, secondary and exploratory endpoints	Primary outcome: number of bleeds per month during the prophylaxis period as compared to the preprophylaxis period. A bleed was defined as rebleeding if it occurred at the same site within 6 h of treatment,

Trial name: NovoSeven-PPX	NCT 00108758
	whereas episodes beginning 6 h after treatment or occurring in another site were defined as a new episode. Secondary outcomes: the number of bleeds per month occurring in the postprophylaxis period as compared to those observed in the observation and prophylaxis period, at specific bleeding sites (target joint, joint, muscle, soft-tissue bleeds), and cause of bleed (traumatic, spontaneous and other) over the entire trial period. Target joints were defined as those joints into which bleeding had occurred ≥ 3 times in the last 6 months.
Method of analysis	Statistical analyses were performed with the intention-to-treat population, defined as all patients randomized and exposed to at least one dose of trial product. A logistic regression model was used to analyze changes in number of bleeds per month. The model included the ratio of number of days in each trial period as offset. To minimize interpatient variations, each patient served as his own control. The estimated changes were tested for statistical significance using Wald's test. To compare the estimated changes between the two treatment groups, a likelihood ratio test was used. No formal analysis was applied to compare adverse events. Health economic variables were analyzed using a sign test combining treatment groups. For the overall development in the orthopedic joint score throughout the trial, a Wilcoxon signed rank test was applied. FVII:C over time was analyzed by an ANOVA including visit and patient as factors. P-values < 0.05 were considered to be significant.
Subgroup analyses	N/A
Other relevant information	*Study Start 2004-03* *Primary Completion (Actual) 2005-11*

Appendix B. Efficacy & Health-related quality of life results per study

Results per study

Table 7.1 Results per study EXPLORER 7

Results of EXPLORER 7 - NCT number: 04083781									
			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 (HAwI) no prophylaxis	9	18.3 (10.2–32.9)	16.7	Arm 1 (HAwI+HBwI) no prophylaxis, n=19: Median ABR (IQR): 9.8 (6.5–20.2)	0.09 91% reduction	(0.04–0.18)	The primary analysis was a negative binomial regression that included treatment and the stratification factors (type of hemophilia [hemophilia A or B with inhibitors] and bleeding frequency [<9 or ≥9 bleeding episodes during the 24 weeks before screening]), as well as the logarithm of the length of the observation period, as offset. A significant difference between groups 1 and 2 was considered to indicate superiority.	Matsushita et al. Phase 3 Trial of Concizumab in Hemophilia with Inhibitors N Engl J Med 2023;389:783-94. DOI: 10.1056/NEJMoa2216455
	2 (HAwI) concizumab prophylaxis	18	1.6 (0.89–2.83)						
	1 (HBwI) no prophylaxis	10	7.2 (2.6–20.1)	5.0	Arm 2 (HAwI + HBwI), concizumab prophylaxis, n=33: Median ABR (IQR): 0.0 (0.0–3.3)	0.31 69% reduction	(0.07–1.36)		
	2 (HBwI) concizumab prophylaxis	15	2.2 (0.8–6.5)						
Treated spontaneous bleeding episodes	1 (HAwI) no prophylaxis	9	13.7 (7.4–25.2)	12.9	Arm 1 (HAwI+HBwI) no prophylaxis, n=19: Median ABR (IQR): 8.4 (3.9–14.3)	0.06	(0.03–0.13)		
	2 (HAwI) concizumab prophylaxis	18	0.8 (0.4–1.6)						
	1 (HBwI) no prophylaxis	10	5.8 (2.1–16.5)	3.6	Arm 2 (HAwI + HBwI), concizumab prophylaxis, n=33: Median ABR (IQR): 0.0 (0.0–1.3)	0.39	(0.09–1.74)		
	2 (HBwI) concizumab prophylaxis	15	2.2 (0.8–6.6)						
Treated joint bleeding episodes	1 (HAwI) no prophylaxis	9	15.8 (7.3–34.1)	14.30	Arm 1 (HAwI+HBwI) no prophylaxis, n=19: Median ABR (IQR): 6.5 (3.2–13.1)	0.09	(0.04–0.23)		
	2 (HAwI) concizumab prophylaxis	18	1.5 (0.8–2.9)						
	1 (HBwI) no prophylaxis	10	5.3 (2.0–13.7)	3.70	Arm 2 (HAwI + HBwI), concizumab prophylaxis, n=33: Median ABR (IQR):	0.31	(0.07–1.30)		

Results of EXPLORER 7 - NCT number: 04083781									
			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		
	2 (HBwI) concizumab prophylaxis	15	1.6 (0.5–4.8)		0.0 (0.0–2.6)				
Treated target joint bleeding episodes	1 (HAwI) no prophylaxis	9	0.0 (0.0–I)	0.0	Arm 1 (HAwI+HBwI) no prophylaxis, n=19: Median ABR (IQR): 0.0 (0.0–2.2)	0.04	(0.00–0.56)		
	2 (HAwI) concizumab prophylaxis	18	0.0 (0.0–I)						
	1 (HBwI) no prophylaxis	10	0.9 (0.2–4.3)	0.3	Arm 2 (HAwI + HBwI), concizumab prophylaxis, n=33: Median ABR (IQR): 0.0 (0.0–0.0)	0.70	(0.08–5.79)		
	2 (HBwI) concizumab prophylaxis	15	0.6 (0.1–3.4)						
All treated and untreated bleeding episodes	1 (HAwI) no prophylaxis	9	20.0 (9.6–41.6)	15.2	Arm 1 (HAwI+HBwI) no prophylaxis, n=19: Median ABR (IQR): 10.9 (6.5–20.2)	0.24	(0.11–0.56)		
	2 (HAwI) concizumab prophylaxis	18	4.8 (2.8–8.3)						
	1 (HBwI) no prophylaxis	10	8.6 (3.8–19.6)	4.0	Arm 2 (HAwI + HBwI), concizumab prophylaxis, n=33: Median ABR (IQR): 2.6 (0.0–5.5)	0.53	(0.17–1.64)		
	2 (HBwI) concizumab prophylaxis	15	4.6 (2.1–10.0)						

HRQoL	Study arm	N	Estimated treatment difference	References
Haem-A-QOL	Arm 2 (HAwI+HBwI) concizumab prohylaxis vs. Arm 1 (HAwI+HBwI) no phrofylaxis	33 vs. 19	The ETD at week 24 between patients in arm 2 and arm 1 was −22.6 points (95% CI, −42.5; −2.7) for the Haem-A-QoL "total score" and −15.7 points (95% CI, −51.8; 20.5) for "physical health". The ETD in the domains "feeling," "treatment," "view of yourself," and "sport and leisure" directionally favored concizumab, while the ETD in other domains showed no preference.	Tran et al. 2024
SF-36v2	Arm 2 (HAwI+HBwI) concizumab prohylaxis vs. Arm 1 (HAwI+HBwI) no phrofylaxis	33 vs. 19	The results of patient-reported outcomes did not differ significantly between group 1 and group 2 with respect to bodily pain and physical functioning scores on the SF-36v2 (key secondary end points). Of the 83 patients who had responded to the Hemophilia-Patient Preference Questionnaire, 77 (93%) preferred concizumab to their previous treatment, 5 (6%) had no preference, and 1 (1%) preferred the previous treatment; 16 patients did not respond.	Matsushita et al., 2023

Table 7.2 Results per study HAVEN 1

Results of HAVEN 1 - NCT number: 02622321											
			Mean ABR (95% CI)	Estimated absolute difference in effect (ARR)			Estimated relative difference in effect (rate ratio)			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Treated bleeds (with BPAs)	Goup A: Emicizumab	35	2.9 (1.7 - 5.0)	20.4	n/a	n/a	0.13	n/a	<0.0001	For all bleeding-related end points, comparisons of the bleeding rate in group A versus group B and the intraindividual comparisons were performed with the use of a negative binomial-regression model to determine the bleeding rate per day, which was converted to an annualized bleeding rate.	Oldenburg et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med 2017;377:809-18. DOI: 10.1056/NEJMoa1703068
	Group B: No Prophylaxis	18	23.3 (12.3 - 43.9)								
	Goup C: Emicizumab	49	5.1 (2.3 - 11.2)								
All bleeds (treated/not treated with BPAs)	Goup A: Emicizumab	35	5.5 (3.6 - 8.6)	19.1	n/a	n/a	0.2	n/a	<0.0001		
	Group B: No Prophylaxis	18	28.3 (16.8 - 47.8)								
	Goup C: Emicizumab	49	6.5 (3.4 - 12.4)								
Treated spontaneous bleeds	Goup A: Emicizumab	35	1.3 (0.7 - 2.2)	15.5	n/a	n/a	0.08	n/a	<0.0001		
	Group B: No Prophylaxis	18	16.8 (9.9 - 28.3)								
	Goup C: Emicizumab	49	3.1 (1.2 - 8.0)								
Treated joint bleeds	Goup A: Emicizumab	35	0.8 (0.3 - 2.2)	5.9	N/A	N/A	0.11	N/A	<0.0050		
	Group B: No Prophylaxis	18	6.7 (2.0 - 22.4)								
	Goup C: Emicizumab	49	0.6 (0.2 - 1.5)								
Treated target joint bleeds	Goup A: Emicizumab	35	0.1 (0.0 - 0.6)	2.9	N/A	N/A	0.05	N/A	<0.0002		
	Group B: No Prophylaxis	18	3.0 (1.0 - 9.1)								
	Goup C: Emicizumab	49	0.3 (0.1 - 1.0)								

HRQoL	Study arm	N	Estimated treatment difference	References
Haem-A-QOL	For emicizumab prophylaxis as compared with no	N=25 vs. n=14	Score on the Haem-A-QoL physical health subscale, 21.6 points (95% CI, 7.9 to 35.2; P=0.003) and 10 points; total score on the Haem-A-QoL	**Oldenburg et al. 2019**

Results of HAVEN 1 - NCT number: 02622321											
			Mean ABR (95% CI)	Estimated absolute difference in effect (ARR)			Estimated relative difference in effect (rate ratio)			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	prophylaxis (group A vs. group B), the adjusted means of observed differences at week 25 and clinically meaningful differences.		14.0 points (95% CI, 5.6 to 22.4; P=0.002) and 7 points; score on the EQ-5D-5L visual-analogue scale, –9.7 points (95% CI, –17.6 to –1.8; P=0.02) and 7 points; and EQ-5D-5L index utility score, –0.16 points (95% CI, –0.25 to –0.07; P=0.001) and 0.07 points.								
SF-36v2	n/a										

Table 7.3 Results per study HAVEN 5

Results of HAVEN 5 - NCT number: NCT 03315455											
			Mean ABR (95% CI)	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**		
Treated bleeds	A: Emicizumab (1.5 mg/kg once weekly)	6	0.2 (0.02–1.45)	12.1	n/a	n/a	0.1		0.0015	Formal hypothesis testing was conducted for the randomized comparisons of arm A/B versus arm C; for primary and bleed-related secondary end points, a model-based comparison of the number of bleeds over the study period in	Yang et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN
	B: Emicizumab (6 mg/kg every 4 weeks)	7	0.3 (0.05–1.53)	12	n/a	n/a	0.2		0.0011		
	C: Emicizumab no prophylaxis	3	12.3 (2.69–56.08)	N/A	N/A	N/A	N/A				
All bleeds	A: Emicizumab (1.5 mg/kg once weekly)	6	0.6 (0.22–1.82)	44.3	N/A	N/A	0.1		< .0001		

Results of HAVEN 5 - NCT number: NCT 03315455											
			Mean ABR (95% CI)	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**		
Treated spontaneous bleeds	B: Emicizumab (6 mg/kg every 4 weeks)	7	0.4 (0.13–1.40)	44.5	N/A	N/A	0.1		< .0001	arms A/B compared with arm C was performed using a negative-binomial regression model, which takes into account the varying follow-up time for each individual.	5). Res Pract Thromb Haemost. 2022;6:e12670. DOI: 10.1002/rth2.12670
	C: Emicizumab no prophylaxis	3	44.9 (23.80–84.64)	N/A	N/A	N/A	N/A				
	A: Emicizumab (1.5 mg/kg once weekly)	6	0.2 (0.02–1.24)	6.3	N/A	N/A	0.2		0.0018		
	B: Emicizumab (6 mg/kg every 4 weeks)	7	0.1 (0.02–1.09)	6.4	N/A	N/A	0.2		0.0012		
	C: Emicizumab no prophylaxis	3	6.5 (2.17–19.52)	N/A	N/A	N/A	N/A				
Treated joint bleeds	A: Emicizumab (1.5 mg/kg once weekly)	6	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	B: Emicizumab (6 mg/kg every 4 weeks)	7	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	C: Emicizumab no prophylaxis	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
Treated target joint bleeds	A: Emicizumab (1.5 mg/kg once weekly)	6	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	B: Emicizumab (6 mg/kg every 4 weeks)	7	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	C: Emicizumab no prophylaxis	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A		

HRQoL	**Study arm**	**N**	**Estimated Treatment difference**	**References**
Haem-A-QOL	Arm A (emicizumab prophylaxis) vs. Arm C (no prohylaxis). Data not reported for HAwI only (i.e. both HA and HAwI)	N= 29 N=14	Not calculated/estimated. Mean (95% CI) Haem-A-QoL physical health score and total score decreased from baseline with emicizumab prophylaxis, indicating improvement in HRQoL (physical health: arm A, −20.20 [−12.02 to −28.38]; arm B, −22.14 [−14.82 to −29.47]; arm C, −5.63 [−6.08 to −17.33]; total score: arm A, −10.14 [−3.46 to −16.81]; arm B, −17.61 [−10.96 to −24.25]; arm C, −2.50 [−3.74 to −8.75]).	Yang et al. 2022

Table 7.4 Results per study NovoSeven-PPX

Results of - NCT number: NCT 00108758											
			Mean ABR (95% CI)	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**		
Total bleeds	90 µg/kg rFVIIa Prephylaxis period	10	5.6	2.6	N/A	N/A	0.55	N/A	P < 0.0001	A logistic regression model was used to analyze changes in number of bleeds per month. The model included the ratio of number of days in each trial period as offset. To minimize interpatient variations, each patient served as his own control.	Konkle et al. 2007. J Thromb Haemost 2007; 5: 1904–13.
	90 µg/kg rFVIIa Prophylaxis period	10	3.0								
Target joint bleeds	90 µg/kg rFVIIa Prephylaxis period	10	Not reported	Not reported	N/A	N/A	0.57	N/A	P < 0.001		
	90 µg/kg rFVIIa Prophylaxis period	10	Not reported								
Spontaneous bleeds	90 µg/kg rFVIIa Prephylaxis period	10	Not reported	Not reported	N/A	N/A	0.50	N/A	P < 0.001		
	90 µg/kg rFVIIa Prophylaxis period	10	Not reported								
HRQoL	**Study arm**	**N**	**Estimated treatment difference**								**Reference**
EQ-5D	Pooled analysis (both 90 & 270 µg/kg rFVIIa Prophylaxis period)	N=22	No difference (Two of the five domains evaluated in the EQ-5D questionnaires showed trends towards change over time, with fewer patients reporting pain and mobility problems during the prophylaxis and post-prophylaxis periods.								Konkle et al., 2007

Appendix C. Comparative analysis of efficacy

Table 8 Comparative analysis of studies comparing concizumab to emicizumab for patients with HAwI

Outcome	Model (data input)	Notes	Relative treatment effect measure	ITC estimates: concizumab versus comparator
				Emicizumab
Treated spontaneous and traumatic bleeding episodes	Poisson likelihood, log link (number of events and person-year follow-up)	Same data used for 'all bleeding events'	Rate ratio (95% CrI)	**N/A**
	Normal likelihood, identity link (LN rate ratio and SE)		Rate ratio (95% CrI)	**0.75 (0.26, 2.21)**
Spontaneous bleeding events treated with bypassing agents	Normal likelihood, identity link (LN rate ratio and SE)	SE estimated from p-value for HAVEN 1	Rate ratio (95% CrI)	**0.75 (0.23, 2.42)**
All bleeding events	Poisson likelihood, log link (number of events and person-year follow-up)		Rate ratio (95% CrI)	**N/A**
	Normal likelihood, identity link (LN rate ratio and SE)	SE estimated from p-value for HAVEN 1	Rate ratio (95% CrI)	**1.20 (0.44, 3.33)**
Treated joint bleeding events	Poisson likelihood, log link (number of events and person-year follow-up)		Rate ratio (95% CrI)	**N/A**
	Normal likelihood, identity link (LN rate ratio and SE)	SE estimated from p-value for HAVEN 1	Rate ratio (95% CrI)	**0.82 (0.22, 3.13)**
Treated target joint bleeds	Normal likelihood, identity link (LN rate ratio and SE)	SE estimated from p-value for HAVEN 1	Rate ratio (95% CrI)	**0.80 (0.05, 13.67)**
Proportion of patients with zero bleeding events	Binomial likelihood, logit link (Number of patients at risk and number with zero bleeding events)		Odds ratio (95% CrI)	**0.27 (0.00, 139.00)**

Abbreviations: CrI, credible interval; FE, fixed effect; HAwI, haemophilia A with inhibitors; ITC, indirect treatment comparison; LN, natural logarithm; NA, not applicable; SE, standard error.
Results where the 95% CrI excludes the null value of 1 are indicated in bold and italics.

The main objective of the indirect treatment comparison (ITC) was to compare the clinical efficacy and safety of concizumab with relevant comparators for the treatment of haemophilia A and B with inhibitors, which is summarized in Table 8 above.

In consideration of the with inhibitor populations (i.e. aligned with the Explorer 7 subgroup data for HAwI and HBwI populations), the meta-analysis feasibility assessment generated connected evidence on RCT data in the HAwI population to allow for the ITC of concizumab with emicizumab.

Comparator outcome data were reported by at least one of the comparator trials for all seven bleeding outcomes assessed in the feasibility assessment (no safety outcomes were deemed feasible for analysis):

- Treated spontaneous and traumatic bleeding episodes
- Spontaneous bleeding events treated with bypassing agents
- All bleeding events
- Treated joint bleeding events
- Treated target joint bleeds
- Treated spontaneous joint bleeding
- Proportion of patients with zero bleeding events

Notably, no studies (of any design) were identified in the clinical SLR that exclusively included HBwI populations. Thus, the only potential source of data for the HBwI population is from studies enrolling broader haemophilia populations that report subgroup data for HBwI patients. No subgroup data for patients with HBwI were identified across these studies. Therefore, a meta-analysis was not deemed feasible for this population.

Statistical methodology

The SLR and meta-analysis feasibility reports provides the full details of the statistical approach and methodology employed for the current analysis as part of the statistical analysis plan.

Briefly, all ITC were conducted using a Bayesian approach, which involves the formal combination of a prior probability distribution that reflects a prior belief of the possible values of the pooled relative effects, with a likelihood distribution of the pooled effect based on the observed data in the different studies to obtain a posterior distribution of the pooled relative effect. The ITCs were implemented using the software package WinBUGs. All statistical models were fitted by adapting code written by the National Institute of Health and Care Excellence (NICE) decision support unit (DSU) for their evidence synthesis series:

1) Rate model (Poisson likelihood, log link): requires the total number of events and data to estimate the duration of exposure (i.e. number of patients and the duration of the treatment period)

2) Rate ratio model (Normal likelihood, identity link): requires the natural logarithm (LN) rate ratio and associated measure of uncertainty

3) Binary model (Binomial likelihood, logit link): requires the number of patients at risk and number of patients with an event

Whilst rate ratios were routinely reported in the comparator trials an associated measure of uncertainty was not always reported in the studies of the HAwI network (i.e. standard error [SE] or 95% confidence interval [CI] from which SE could be estimated) and in some instances SEs were computed from p-values. Such instances are indicated in Table 8.

Fixed versus random effect models

The available dataset is restricted in terms of there being a small number of studies and a small number of enrolled patients across the studies (i.e. <10). A random effect (RE) model will provide a poor estimate of the distribution of intervention effects. This is because the estimate of the between-studies variance (tau2) will have poor precision and consequently, there will not be sufficient information to apply the RE model correctly.

In all networks, both, RE and fixed effect (FE) models were run for completeness, and model fit was assessed by exploring the estimate of between study standard deviation of the RE model and by comparing the following across the two models:

- Deviance information criterion (DIC) (differences of 3–5 points to be considered important)
- Total residual deviance

Note that for all bleeding event outcomes both a rate model (Poisson likelihood, log link) and rate ratio model (Normal likelihood, identity link) were conducted where it was feasible (i.e. sufficient data for each model reported) and therefore for some outcomes only a single model was feasible. The single binary outcome (proportion of patients with zero bleeding event) was analysed using the binomial likelihood logit link model only.

In all analyses conducted, the FE was the better fitting model compared with the RE model; generally the FE models reported the lowest DIC and total residual deviance closer to the number of data points in comparison with the RE models.

Inconsistency

A network meta-analysis (NMA) brings together all available evidence from clinical trials to estimate treatment effects. As this involves combining direct and indirect measures of effect, it is important to examine whether or not these two ‘sources’ of evidence are consistent with one another. Note that in cases where evidence networks contain both direct and indirect evidence (closed loops) combining the direct and indirect evidence in an NMA will produce more precise estimates of direct comparisons and broaden inferences to the population samples because it links and maximizes existing information within the network. There are no closed loops of evidence within the current evidence base and, therefore, it was not necessary to assess inconsistency for the current analysis.

Interpretation of results

The results of the ITC for the bleeding outcomes in terms of rate ratios should be interpreted as follows:

- A rate ratio of 1 indicates there is no difference in the rate of bleeding between the treatment and control arm
- A rate ratio <1 indicates a lower rate of bleeding in the treatment arm versus the control arm
- A rate ratio >1 indicates a higher rate of bleeding in the treatment arm versus the control arm
- The results of the ITC for the bleeding outcome in terms of odds ratio (OR; proportion of patients with zero bleeds) should be interpreted as follows:
- An odds ratio of 1 indicates there is no difference in the odds of zero bleeds between the treatment and control arm
- An odds ratio <1 indicates a lower odds of zero bleeds in the treatment arm versus the control arm
- An odds ratio >1 indicates a higher odds of zero bleeds in the treatment arm versus the control arm

Credible intervals

Where the 95% credible interval (CrI) of relative treatment effects does not include the null value (for all outcomes in the current ITC the null value =1), it is interpreted that there is evidence for a difference between treatments.

A number of results from the current analyses were associated with wide CrIs. In the current ITCs wide CrIs are likely to result from:

- Sparseness of data (few trials per comparison or few patients in one or more treatment arms)
- Rarity of events (zero or few events in a treatment arm for the outcome of zero bleeds)

RESULTS IN THE HAWI POPULATION

The results of the ITC can be summarised as follows:

HAwI population

- The results of the ITC were favourable for all outcomes of interest for concizumab compared with emicizumab, except for all bleeding events and the proportion of patients with zero bleeding events; all these comparisons were associated with wide CrIs, and none excluded the null value.

It is important to interpret the result of the ITC in context of the associated limitations of the analyses:

- The networks for the analyses contain few studies (i.e. two studies for the comparison between concizumab and emicizumab for HAwI). The estimate of between study heterogeneity in the RE models was large and associated with large levels of uncertainty (as there is insufficient information to estimate between study heterogeneity with certainty); thus, the results from the RE models were associated with wide 95% CrIs and the estimates from the NMA for the trial level comparisons were therefore not consistent with the data reported from the trials.

- The analyses apply the assumption that relative treatment effects within each of the trials would remain the same regardless of the specific treatments used in the on-demand common comparator arms. Notably, in the EXPLORER 7 on-demand arm (no prophylaxis), the absolute rates of bleeding outcomes were markedly lower (estimated mean ABR for all treated/untreated bleeding episodes of 20.0 (95% CI, 9.6–41.6)), compared with the on-demand arm (no prophylaxis) in HAVEN 1, where the estimated mean ABR was 28.3 (95% CI,16.8-47.8)). The low ABRs for the on-demand arm will lead to a poorer rate ratio (but still < 1) for concizumab versus on-demand (nearer 1 than expected) – this in turn will give a poorer rate ratio against the active “prophylaxis comparator”, in this case emicizumab.

- Whilst the analyses assume that the studies are sufficiently homogenous to combine, variability in the populations of the networks was highlighted in the feasibility assessment. However, due to the sparsity of the outcome specific networks, it is not feasible to fully explore the potential impact of the heterogeneity via subgroup analyses or meta-regressions.

- There was limited reporting of outcome data and their definitions and whilst efforts have been made to align the outcomes for each analysis (for example assumptions regarding treatment of bleeds where not reported) it is likely that inter-study heterogeneity remained across the outcomes analysed.

Appendix D. Literature searches for the clinical assessment

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

The main objective of the systematic literature review (SLR) was to identify clinical efficacy and safety data for the treatment of haemophilia A and B with inhibitors (HAwI and HBwI).

Eligibility criteria for the SLR included studies conducted in adult and adolescent patients (≥12 years) with HAwI and HBwI investigating prophylaxis treatments.

Taken into consideration that HAwI and HBwI are small study populations, all studies that have been conducted so far is without an active comparator. We utilized a systematic literature search (SLR) as described in appendix D, from which we have listed relevant studies in table 1 selected on the basis of an a priori selection. The SLR was based on the electronic databases Embase, MEDLINE (including MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE Daily) and Evidence Based Medicine (EBM) Reviews (including the Health Technology Assessment [HTA] database, the NHS Economic Evaluation Database (NHS EED), Cochrane Central register of Controlled trials [CENTRAL], Database of Abstracts of Reviews of Effects [DARE] and the Cochrane Database of Systematic Review) were searched on the 15th October 2024 via the OVID platform.

The main objective of the systematic literature review (SLR) was to identify clinical efficacy and safety data for the treatment of haemophilia A and B with inhibitors (HAwI and HBwI).

Table 9 Bibliographic databases included in the literature search

Database	Platform/source	**Relevant period for the search**	**Date of search completion**
Embase	Embase (Ovid)	1974 to 2024 October 14	15.10.2024
Medline	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions	1946 to October 14, 2024	15.10.2024
CENTRAL	EBM Reviews (Ovid): ACP Journal Club; Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews EBM Reviews (Ovid):	ACP Journal Club 1991 to September 2024; Cochrane Central Register of Controlled Trials September 2024; Cochrane Database of Systematic Reviews; Cochrane Clinical Answers September 2024:	15.10.2024

Abbreviations:

Table 10.1 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A			
N/A			

Abbreviations:

Table 10.2 Conference material included in the literature search

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

Abbreviations:

D.1.2 Search strategies

The principal objective of the current systematic literature review (SLR) was to identify clinical efficacy and safety data for the treatment of haemophilia A and B with inhibitors (HAwI and HBwI).

As the search strategy above included a very broad scope as shown in Table 11, 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 (Figure 4, p. 80). This involved ensuring the trials included reported relevant outcomes for comparators that 1) have marketing authorization, 2) are commercialized in Denmark and recommended treatment option for patients with haemophilia and inhibitors and 3) the trials included in the final SLR are randomized clinical trials.

Table 11.1 Embase (Ovid): 1974 to 2024 October 14: searched 15 October 2024

No.	Query	Results
1	exp hemophilia/	47624
2	h?emophilia$.ti,ab,kw.	43293
3	((ahf or anti-h?emophilli$ factor or antih?emophilli$ factor or factor 8 or factor 9 or factor VIII or factor IX) adj3 deficien$).ti,ab,kw.	2581
4	christmas disease$.ti,ab,kw.	136
5	or/1-4	52235
6	recombinant blood clotting factor 8/	5717
7	blood clotting factor 8/	32009
8	blood clotting factor 9/	9846
9	recombinant blood clotting factor 7a/	8134

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 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.	3473
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,kw.	1549
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,kw.	7218
13	concizumab/	244
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,kw.	183
15	emicizumab/	2129
16	(emicizumab or ace 910 or ace910 or hemlibra or rg 6013 or rg6013 or ro 5534262 or ro5534262).ti,ab,kw.	1798
17	fitusiran/	242
18	(fitusiran or aln at3 or aln at3sc or alnat3 or alnat3sc or sar 439774 or sar439774).ti,ab,kw.	139
19	activated prothrombin complex/	2847
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,kw.	1528
21	tissue factor pathway inhibitor/	4790
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,kw.	6276
23	or/6-22	59045
24	Clinical Trial/	1093734
25	Randomized Controlled Trial/	848644
26	controlled clinical trial/	474144

27	multicenter study/	406778
28	Phase 3 clinical trial/	78805
29	Phase 4 clinical trial/	7842
30	exp RANDOMIZATION/	100605
31	Single Blind Procedure/	56683
32	Double Blind Procedure/	224852
33	Crossover Procedure/	79994
34	PLACEBO/	419112
35	randomi?ed controlled trial$.tw.	361307
36	rct.tw.	59955
37	(random$ adj2 allocat$).tw.	59077
38	single blind$.tw.	34155
39	double blind$.tw.	256852
40	((treble or triple) adj blind$).tw.	2249
41	placebo$.tw.	387159
42	Prospective Study/	945799
43	or/24-42	3132083
44	Clinical study/	167913
45	Case control study/	225084
46	Family study/	25858
47	Longitudinal study/	223408
48	Retrospective study/	1697505
49	Prospective study/	945799
50	Cohort analysis/	1231739
51	(Cohort adj (study or studies)).mp.	541861
52	(Case control adj (study or studies)).tw.	180669
53	(follow up adj (study or studies)).tw.	77512
54	(observational adj (study or studies)).tw.	289874
55	(epidemiologic$ adj (study or studies)).tw.	127781
56	(cross sectional adj (study or studies)).tw.	392303
57	or/44-56	4408044
58	43 or 57	6306336
59	5 and 23 and 58	6274
60	limit 59 to yr="2022 -Current"	1168

Table 11.2 Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: 1946 to October 14, 2024: searched 15 October 2024

No.	Query	Results
1	hemophilia a/ or hemophilia b/	25594
2	h?emophilia$.ti,ab,kw.	26843
3	((ahf or anti-h?emophilli$ factor or antih?emophilli$ factor or factor 8 or factor 9 or factor VIII or factor IX) adj3 deficien$).ti,ab,kw.	1573

4	christmas disease$.ti,ab,kw.	333
5	or/1-4	31989
6	Factor VIII/	17870
7	Factor IX/	5479
8	exp Factor VII/	7839
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.	1327
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.	601
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,kw.	3877
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.	680
14	(fitusiran or aln at3 or aln at3sc or alnat3 or alnat3sc or sar 439774 or sar439774).ti,ab,kw.	48
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.	631
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.	4417

17	or/6-16	33722
18	Randomized Controlled Trials as Topic/	174761
19	randomized controlled trial/	623290
20	Random Allocation/	107719
21	Double Blind Method/	180792
22	Single Blind Method/	34077
23	clinical trial/	540563
24	clinical trial, phase ii.pt.	42230
25	clinical trial, phase iii.pt.	23460
26	clinical trial, phase iv.pt.	2551
27	controlled clinical trial.pt.	95619
28	randomized controlled trial.pt.	623290
29	multicenter study.pt.	356021
30	clinical trial.pt.	540563
31	exp Clinical Trials as topic/	398424
32	(clinical adj trial$).tw.	528750
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	208822
34	PLACEBOS/	36012
35	placebo$.tw.	260841
36	randomly allocated.tw.	39736
37	(allocated adj2 random$).tw.	43709
38	or/18-37	2014332
39	exp case control studies/	1544022
40	exp cohort studies/	2660987
41	Case control.tw.	165999
42	(cohort adj (study or studies)).tw.	368888
43	Cohort analy$.tw.	13735
44	(Follow up adj (study or studies)).tw.	59059
45	(observational adj (study or studies)).tw.	186951
46	Longitudinal.tw.	357105
47	Retrospective.tw.	846735
48	Cross sectional.tw.	587256
49	Cross-sectional studies/	517959
50	or/39-49	4100329
51	38 or 50	5581072
52	5 and 17 and 51	2764
53	limit 52 to yr="2022 -Current"	324

Table 11.3 EBM Reviews (Ovid): ACP Journal Club 1991 to September 2024; Cochrane Central Register of Controlled Trials September 2024; Cochrane Database of Systematic Reviews EBM Reviews (Ovid): ACP Journal Club 1991 to September 2024; Cochrane Central Register of Controlled Trials September 2024; Cochrane Database of Systematic Reviews; Cochrane Clinical Answers September 2024: searched 15 October 2024

No.	Query	Results
1	hemophilia a/ or hemophilia b/	678
2	h?emophilia$.ti,ab,kw.	1848
3	((ahf or anti-h?emophilli$ factor or antih?emophilli$ factor or factor 8 or factor 9 or factor VIII or factor IX) adj3 deficien$).ti,ab,kw.	73
4	christmas disease$.ti,ab,kw.	5
5	or/1-4	1917
6	Factor VIII/	501
7	Factor IX/	99
8	exp Factor VII/	410
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.	375
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.	123
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,kw.	485
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.	57
13	(emicizumab or ace 910 or ace910 or hemlibra or rg 6013 or rg6013 or ro 5534262 or ro5534262).ti,ab,kw.	95
14	(fitusiran or aln at3 or aln at3sc or alnat3 or alnat3sc or sar 439774 or sar439774).ti,ab,kw.	28

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.	76
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.	350
17	or/6-16	2051
18	5 and 17	1003
19	limit 18 to yr="2022 -Current"	88

D.1.3 Systematic selection of studies

Table 32 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult and adolescent (age 12 and above) patients with haemophilia A or B with inhibitors.	Adult and adolescent patients with haemophilia A or B without inhibitors Studies conducted in patients <12 years of age
Intervention	*Haemophilia A with inhibitors:* Emicizumab (prophylaxis only) Concizumab prophylaxis *Haemophilia B with inhibitors:* *rFVIIa* Concizumab prophylaxis	No pharmacological treatments investigated in the studies Studies investigating gene therapies
Comparators	No prophylaxis	
Outcomes	Outcomes of interest were aligned with the ongoing/planned trial program for concizumab, to include: *Efficacy* • 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 • 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
- % of bleeds resolved with 1 or 1–2 injections

Safety

- Development of neutralising and non-neutralising antibodies (for antibody treatments)
- Development of FVIII inhibitors
- Number and incidence of overall 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

Quality of life outcomes

- Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)
- Haemophilia-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A)
- Hemo-TEM
- H-PPQ patient preference
- PROMIS Numeric Scale Pain Intensity
- PROMIS Short Form - Upper Extremity
- PGIC and PGIS on physical functioning
- Brief Pain Inventory - Short Form
- Caregiver-Reported Adapted Inhib-QoL Questionnaire

Short form-36 version 2.0

Study design/publication type	Phase 2/3/RCTs Single arm clinical studies	Guidelines Pre-clinical studies

	Prospective, non-randomised comparative studies in a clinical setting Single-arm/comparative observational studies (retrospective/prospective)	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 Letter and commentary Case reports and case series
Language restrictions	English and Non-English language No geographic limitations	N/A

Figure 4: PRISMA flow diagram for the clinical SLR – October 2024

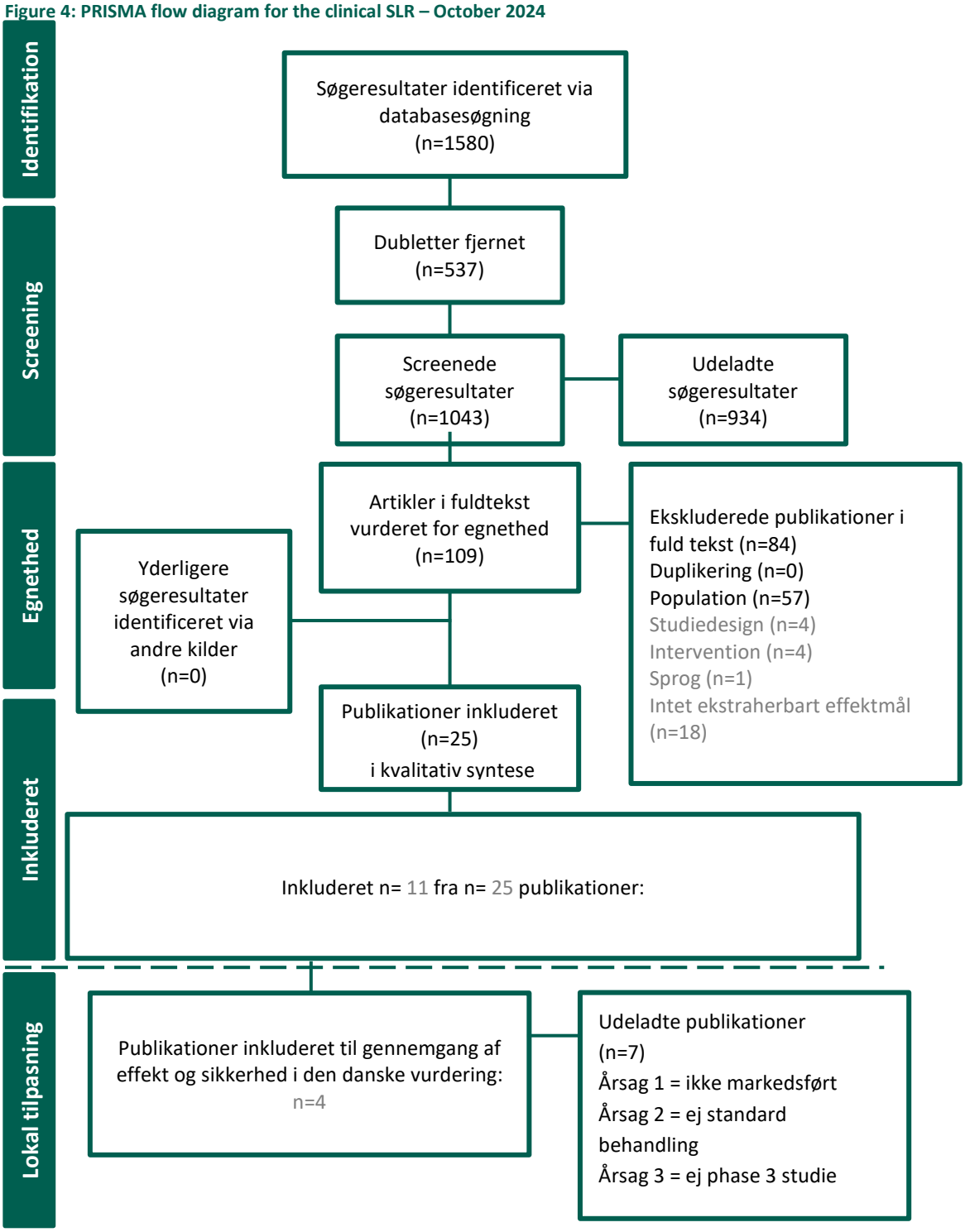


Table 13 Overview of study design for studies included in the technology assessment

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
EXPLORER 7/ NCT04083781	Efficacy and safety of daily treatment with concizumab prophylaxis compared with no prophylaxis.	Prospective, multicenter, open-label, phase 3a trial. Comparison of concizumab prophylaxis with no prophylaxis. Two randomization groups (groups 1 and 2) and two non-randomization groups (groups 3 and 4).	Adult and adolescent patients with haemophilia with inhibitors (aged 12 years or older).	Daily prophylaxis concizumab dose of 0.2 mg/kg vs. no prophylaxis (n=133)	Comparison between treated spontaneous and traumatic bleeding episodes in group 1 and group 2 (when all the patients in group 1 (no prophylaxis) had completed at least 24 weeks of treatment or had withdrawn and when all the patients in group 2 (concizumab prophylaxis) had	To compare patient reported outcomes after concizumab prophylaxis with those after no prophylaxis. Key secondary end points were the change in bodily pain and physical functioning scores on the 36-Item Short-Form Health Survey, version 2 (SF-36v2), from the start of treatment to week 24.

completed at least 32 weeks of treatment, which included the 5-to-8-week dose-adjustment period, or had withdrawn.

HAVEN 1/ NCT02622321	Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Patients With Inhibitors	Phase 3, open-label, multicenter, randomized trial.	Adult and adolescent patients (>12 years of age) with congenital hemophilia A (of any severity), had a history of a high titer of factor VIII inhibitor (≥5 Bethesda units per milliliter), and were receiving episodic or prophylactic treatment with bypassing agents.	Subcutaneous emicizumab prophylaxis dose of 3.0 mg/kg body weight weekly for 4 weeks, followed by 1.5 mg/kg weekly (n=109)	Difference in rate of treated bleeding events (bleeding rate) over a period of at least 24 weeks between participants receiving emicizumab prophylaxis (group A) and those receiving no prophylaxis (group B) after the last randomly assigned participant had completed 24 weeks in the trial or had discontinued participation, whichever occurred first.	Additional bleeding-related end points (all bleeding events [both treated and not treated with bypassing agents] and events of spontaneous bleeding, joint bleeding, and target-joint bleeding), health-related quality of life (Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL] physical health subscale and total score at week 25), and health status (the five-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D-5L] visual-analogue scale and index utility score at week 25).

HAVEN 5/ NCT03315455	Efficacy, safety, immunogenicity, and pharmacokinetic (PK) profile of 1.5 mg/kg once weekly and 6 mg/kg every 4 weeks emicizumab in people with hemophilia A (Asia-Pacific region).	A randomized, multicenter, open-label, phase 3 clinical study.	Adult and adolescent patients (>12 years of age) with severe congenital hemophilia A or hemophilia A with FVIII inhibitors	Participants randomized to 3 treatment arms: emicizumab 3 mg/kg once weekly for the first 4 weeks (loading dose) followed by maintenance dose of 1.5 mg/kg once weekly (arm A) or 6 mg/kg every 4 weeks (arm B), or no prophylaxis (arm C). (n=70)	Annualized bleeding rate (ABR) for treated bleeds in people with hemophilia A receiving once-weekly or every-4-weeks emicizumab prophylaxis or no prophylaxis.	ABRs for all bleeds and treated spontaneous/joint/target joint bleeds in participants receiving once-weekly or every-4-weeks emicizumab prophylaxis versus no prophylaxis. Change from baseline in HRQoL and health status after 24 weeks of emicizumab prophylaxis versus no prophylaxis was also evaluated

NOVOSEVEN/NTC00108758	Efficacy of secondary prophylactic treatment with NovoSeven® in haemophilia A and B patients with inhibitors.	Multicenter, randomized, double-blind, parallel-group trial. The trial consisted of a preprophylaxis period, a prophylaxis (treatment) period, and a postprophylaxis period, each of 3 months duration.	Males with severe congenital hemophilia A or B with a high historical inhibitor titer (with an inhibitor titer > 2 BU/mL in the preceding 12 months),	Twenty-two patients were randomized 1:1 to receive daily rFVIIa prophylaxis with either 90 or 270 ug/kg) for 3 months, followed by a 3-month postprophylaxis period. (n=22)	Number of bleeds/month during the prophylaxis period as compared to the preprophylaxis period. A bleed was defined as rebleeding if it occurred at the same site within 6 h of treatment, whereas episodes beginning 6 h after treatment or occurring in another site were defined as a new episode.	Number of bleeds/ per month occurring in the postprophylaxis period as compared to those observed in the observation and prophylaxis period, at specific bleeding sites target oint, joint, muscle, soft-tissue bleeds), and cause of bleed (traumatic, spontaneous and other) over the entire trial period. Target joints were defined as those joints into which leeding had occurred ≥ 3 times in the last 6 months.

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

Medicinrådet

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

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk