Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende emicizumab som mulig standard-behandling til hæmofili A

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om omkostningerne ved behandling med lægemidlet er rimelige i forhold til lægemidlets kliniske værdi.

Lægemidlet vurderes efter Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	19. juni 2019
Ikrafttrædelsesdato	19. juni 2019
Dokumentnummer	49450
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 19. juni 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Hemlibra
Generisk navn	Emicizumab
Firma	Roche
ATC-kode	B02BX06
Virkningsmekanisme	Monoklonalt modificeret immunglobulin G4 (IgG4).
Administration/dosis	De første 4 uger: 3 mg/kg subkutant en gang ugentlig. Herefter 1,5 mg/kg hver uge, 3 mg/kg hver 2. uge eller 6 mg/kg hver 4. uge.
EMA-indikation	Rutineprofylakse hos patienter med svær hæmofili A uden faktor VIII-aktivitet (faktor VIII < 1 %).

2 Medicinrådets anbefaling

Medicinrådet **anbefaler ikke** emicizumab som mulig standardbehandling til svær hæmofili A.

De kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

Hvad er den kliniske merværdi af emicizumab sammenlignet med standard FVIII-præparater hos patienter med svær hæmofili A?

Hvad er den kliniske merværdi af emicizumab sammenlignet med FVIII-præparater med forlænget halveringstid hos patienter med svær hæmofili A?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende emicizumab som mulig standardbehandling til patienter med svær hæmofili A er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Emicizumab kan anvendes til profylaktisk behandling hos patienter med svær hæmofili A uden faktor VIII-aktivitet (faktor VIII < 1 %).

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den endelige ansøgning den 4. april 2019. Sagsbehandlingstiden har været 10 uger og 6 dage.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at emicizumab til patienter med svær hæmofili A giver:

- Ingen klinisk merværdi sammenlignet med standard FVIII-præparatet octocog alfa og EHL-præparatet efmoroctocog alfa.

Medicinrådet finder dog, at den subkutane administrationsform og det lange dosisinterval for emicizumab er en stor fordel hos patienter med:

- Vanskelig veneadgang, hvor det ikke er muligt at gennemføre profylakse med et EHL-præparat.
- Gentagne dokumenterede gennembrudsblødninger trods optimeret profylakse med et EHL-præparat.

Evidensens kvalitet er meget lav.

6 Høring

Ansøger havde ingen indvendinger imod Medicinrådets kategorisering af den kliniske merværdi eller til vurderingsrapporten.

7 Resumé af økonomisk beslutningsgrundlag

Amgros vurderer, at der ikke er rimeligt forhold mellem meromkostningerne og den kliniske merværdi af emicizumab sammenlignet med octocog alfa og efmoroctocog alfa til patienter med svær hæmofili A. Behandling med emicizumab er forbundet med betydelige meromkostninger, som udelukkende drives af lægemiddelprisen.

8 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende blødersygdom

Forvaltningslovens § 4, stk. 2 har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
Eva Funding Overlæge	Lægevidenskabelige Selskaber og Region Hovedstaden
Medlemmer	**Udpeget af**
Har ikke en relevant specialist til fagudvalget	Region Nordjylland
Anne-Mette Hvas Professor, overlæge, ph.d.	Region Midtjylland
Lone Hvitfeldt Poulsen Overlæge	Region Midtjylland
Jesper Farup Revsholm Afdelingslæge	Region Syddanmark
Rune Larsen Overlæge	Region Sjælland
Marianne Hutchings Hoffmann Overlæge	Dansk Pædiatrisk Selskab
Peter Kampmann Overlæge, lægefaglig teamleder	Dansk Selskab for Trombose og Hæmostase
Marie Louise Schougaard Christiansen Afdelingslæge, klinisk farmakolog, ph.d.	Dansk Selskab for Klinisk Farmakologi (DSKF) *Udtrådt 30. april 2019*
Jennifer Anna Fey Andresen Farmaceut	Dansk Selskab for Sygehusapoteksledelse (DSS)
Finder det ikke længere relevant at have en kandidat i fagudvalget	Dansk Selskab for Anæstesiologi og Intensiv Medicin
Kan ikke udpege en kandidat	Dansk Selskab for Klinisk Biokemi
To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3.
2100 København Ø
+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

Sekretariatets arbejdsgruppe: Dorte Glintborg (projekt- og metodeansvarlig) Mette Hollensted (projektdeltager) Anne Sofie Gram (projektdeltager) Diana Odrabinakova (biostatistiker) Ilse Linde (fagudvalgskoordinator) Kirsten Holdt Henningsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	19. juni 2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af den kliniske merværdi af emicizumab til hæmofili A
- Ansøgers endelige ansøgning
- Protokol for vurdering af den kliniske merværdi af emicizumab til hæmofili A

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af emicizumab (Hemlibra) som mulig standardbehandling som rutineprofylakse hos patienter med svær hæmofili A (FVIII < 1 %) uden faktor VIII aktivitet. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	19-06-2019
Firma	Roche (ansøger)
Lægemiddel	Emicizumab (Hemlibra)
Indikation	Rutineprofylakse hos patienter med svær hæmofili A (FVIII < 1 %) uden faktor VIII aktivitet

Amgros' vurdering

- Amgros vurderer at der ***ikke*** er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for emicizumab (Hemlibra) som mulig standardbehandling til patienter med svær hæmofili A, sammenlignet med behandling med octocog alfa (Kovaltry)

- Amgros vurderer at der ***ikke*** er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for emicizumab (Hemlibra) som mulig standardbehandling til patienter med svær hæmofili A, sammenlignet med behandling med efmoroctocog alfa (Elocta)

Overordnet konklusion

Medicinrådet har vurderet, at emicizumab (Hemlibra) sammenlignet med henholdsvis octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta) giver **ingen klinisk merværdi.**

Behandling med emicizumab (Hemlibra) er forbundet med betydelige meromkostninger sammenlignet med octocog alfa (Kovaltry) til nævnte indikation. Amgros vurderer, at der **ikke** er rimeligt forhold mellem den

kliniske merværdi for emicizumab (Hemlibra) og meromkostningerne, sammenlignet med behandling med octocog alfa (Kovaltry).

Behandling med emicizumab (Hemlibra) er forbundet med betydelige meromkostninger sammenlignet med efmoroctocog alfa (Elocta) til nævnte indikation. Amgros vurderer, at der **ikke** er rimeligt forhold mellem den kliniske merværdi for emicizumab (Hemlibra) og meromkostninger, sammenlignet med behandling med efmoroctocog alfa (Elocta).

Meromkostninger drives udelukkende af prisen på emicizumab (Hemlibra) og komparatorer.

Andre overvejelser

Konklusionen er baseret på SAIP.

Da emicizumab (Hemlibra) har forskellig dosis alt efter vægt, vil patientens vægt have stor betydning på omkostningerne. Resultatet af Amgros' analyse baseret på dosis efter vægt resulterer i meromkostninger for emicizumab (Hemlibra) sammenlignet med begge komparatorer. Forholdet er dog ens da begge komparatorer også er vægtdoseret.

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Patienter med svær hæmofili A, som tidligere har været i profylaktisk behandling med et FVIII-præparat	Octocog alfa (Kovaltry) anvendt som profylakse	Ingen klinisk merværdi	Meget lav evidenskvalitet	Ikke rimeligt
	Efmoroctocog alfa (Elocta) anvendt som profylakse (forlænget halveringstid)	Ingen klinisk merværdi	Meget lav evidenskvalitet	Ikke rimeligt

Konklusionen er baseret på at Medicinrådet har valgt octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta) som komparator for patientpopulationerne, og vurderingen af meromkostninger og klinisk værdi beror på disse.

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med emicizumab (Hemlibra) er forbundet med meromkostninger sammenlignet med behandling med komparatorer.

I tabel 2 og 3 ses de inkrementelle omkostninger for emicizumab (Hemlibra) og henholdsvis octocog alfa (Kovaltry) og efmoroctocog (Elocta). Beregningerne tager udgangspunkt i en patientvægt på 70 kg.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for emicizumab (Hemlibra) sammenlignet med octocog alfa (Kovaltry) på ca. [redacted] DKK og sammenlignet med efmoroctocog alfa (Elocta) er de gennemsnitlige meromkostninger per patienter på ca. [redacted] DKK.

Tabel 2: Resultat af Amgros hovedanalyse for emicizumab (Hemlibra) sammenlignet med octocog alfa (Kovaltry), DKK, SAIP, per pt. per år, 70 kg pt.

Omkostningselement	Emicizumab (Hemlibra)	Octocog alfa (Kovaltry)	Inkrementelle omkostninger
Profylakse behandling	[redacted]	[redacted]	[redacted]
On-demand behandling	[redacted]	[redacted]	[redacted]
Totale gennemsnitsomkostninger per patient	[redacted]	[redacted]	[redacted]

Hvis analysen udføres på baggrund af AIP, bliver de inkrementelle omkostninger per patient for emicizumab (Hemlibra) sammenlignet med octocog alfa (Kovaltry) ca. 1.317.000 DKK. Lægemiddelomkostningerne for emicizumab (Hemlibra) er 2.750.591 DKK og for octocog alfa (Kovaltry) er lægemiddelomkostningerne 1.433.686 DKK i AIP.

Tabel 3: Resultat af Amgros hovedanalyse for emicizumab (Hemlibra) sammenlignet med efmoroctocog alfa (Elocta), DKK, SAIP, per pt. per år, 70 kg pt.

Omkostningselement	Emicizumab (Hemlibra)	Efmoroctocog alfa (Elocta)	Inkrementelle omkostninger
Profylakse behandling	[redacted]	[redacted]	[redacted]
On-demand behandling	[redacted]	[redacted]	[redacted]
Totale gennemsnitsomkostninger per patient	[redacted]	[redacted]	[redacted]

Hvis analysen udføres på baggrund af AIP, bliver de inkrementelle omkostninger per patient for emicizumab (Hemlibra) sammenlignet med efmoroctocog alfa (Elocta) ca. 525.000 DKK. Lægemiddelomkostningerne for emicizumab (Hemlibra) er 2.750.591 DKK og for efmoroctocog alfa (Elocta) er lægemiddelomkostningerne 2.225.247 DKK i AIP.

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer at anbefaling af emicizumab (Hemlibra) som mulig standardbehandling, vil resultere i budgetkonsekvenser på ca. [redacted] DKK per år i år 5. Hvis analysen udføres med AIP, vil budgetkonsekvenserne være på ca. 24 mio. DKK per år i år 5.

EMICIZUMAB (HEMLIBRA)

HÆMOFILI A UDEN INHIBITOR MOD FAKTOR VIII

AMGROS 04. juni 2019

AMGROS

OPSUMMERING

Baggrund

Emicizumab (Hemlibra) er indiceret til profylaktisk behandling mod blødninger hos patienter med hæmofili A uden faktor VIII-inhibitor. Ca. 132 patienter kandiderer til behandling af den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentationen indsendt af Roche.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med emicizumab (Hemlibra) for patienter uden inhibitor mod FVIII. I analysen sammenlignes behandling med emicizumab (Hemlibra) med octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta) for patienter med hæmofili A uden inhibitor.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af emicizumab (Hemlibra) sammenlignet med octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta). De inkrementelle omkostninger er angivet i SAIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for emicizumab (Hemlibra) ca. [redacted] DKK sammenlignet med octocog alfa (Kovaltry) og ca. [redacted] DKK sammenlignet med efmoroctocog alfa (Elocta).

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af emicizumab (Hemlibra) som standardbehandling vil være ca. [redacted] mio. DKK over 5 år.

Konklusion

Behandling med emicizumab (Hemlibra) er forbundet med betydelige meromkostninger sammenlignet med behandling med octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta). De inkrementelle omkostninger er udelukkende drevet af lægemiddelomkostningerne.

Liste over forkortelser

AIP	Apotekernes indkøbspris
SAIP	Sygehusapotekernes indkøbspris
DKK	Danske kroner
FVIII	Faktor 8
IE	International Enhed

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Roche
Handelsnavn:	Hemlibra
Generisk navn:	Emicizumab
Indikation:	Rutineprofylakse hos patienter med svær hæmofili A (FVIII < 1 %) uden faktor VIII aktivitet.
ATC-kode:	B02BX06

Proces	
Ansøgning modtaget hos Amgros:	04-04-2019
Endelig rapport færdig:	04-06-2019
Sagsbehandlingstid fra endelig ansøgning:	61 dage
Arbejdsgruppe:	**Mark Friborg** Pernille Winther Johansen Line Brøns Jensen Lianna Geertsen Louise Greve Dal

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Emicizumab (Hemlibra) er indiceret som rutineprofylakse hos patienter med svær hæmofili A (FVIII < 1 %) uden faktor VIII aktivitet. Roche (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af emicizumab (Hemlibra) og har den 04.04.2019 indsendt en ansøgning til Medicinrådet om anbefaling af emicizumab (Hemlibra) som standardbehandling på danske hospitaler af den nævnte indikation.
Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af emicizumab (Hemlibra) som standardbehandling på danske hospitaler af den nævnte indikation. I analyserne sammenlignes behandling med emicizumab (Hemlibra) med behandling med octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta).

1.2 Patientpopulation

Hæmofili A er medfødt mangel på FVIII, som er vigtigt for blodets evne til at koagulere og dermed standse blødninger. Ubehandlet vil manglen på FVIII medføre spontane led- og muskelblødninger, som på sigt medfører svære ledforandringer og invaliditet. Herudover vil blødning ved traume og kirurgi være livstruende.

I 2016 var der registreret i alt 388 patienter med hæmofili A ved de to Hæmofilicentre i hhv. Aarhus og København. Heraf var 132 af patienterne i profylaktisk behandling, mens 256 fik behandling efter behov (on-demand)(1).

1.3 Nuværende behandling

Hæmofili A behandles i dag med et rekombinant FVIII-præparat. Patienter med moderat og svær hæmofili tilbydes aktuelt profylaktisk behandling, som omfatter rutinemæssige infusioner af et FVIII-præparat. Valg af præparat sker iht. til Medicinrådets lægemiddelrekommandation fra februar 2018. Man skelner imellem såkaldte standardpræparater og præparater med forlænget halveringstid. Som udgangspunkt anvender man det billigste standard FVIII-præparat. Hvis patienten har vanskelig veneadgang eller har dokumenterede gennembrudsblødninger under behandling med et standard FVIII-præparat, kan man overveje at skifte til et FVIII-præparat med forlænget halveringstid (efmoroctocog alfa)(2). Patienten håndterer selv FVIII-præparatet derhjemme 2-4 gange om ugen afhængigt af, hvilket faktorniveau der tilstræbes hos patienten samt halveringstiden for det anvendte præparat.

1.4 Behandling med emicizumab (Hemlibra)

Indikation

Emicizumab (Hemlibra) er godkendt til rutineprofylakse hos patienter med hæmofili A uden inhibitor mod FVIII. Emicizumab (Hemlibra) kan hverken anvendes on-demand (dvs. behandling kun ved opstået blødning) eller til behandling af blødninger under profylakse med emicizumab (Hemlibra).

Virkningsmekanisme

Emicizumab er et rekombinant, humaniseret, monoklonalt modificeret immunoglobulin G4, som binder sig til faktor IXa og X, hvorved det efterligner den funktion, FVIII normalt har i koagulationskaskaden.

Dosering

Den anbefalede startdosis er 3 mg/kg givet som subkutan injektion én gang ugentligt i de første fire uger, efterfulgt af en vedligeholdelsesdosis på 1,5 mg/kg én gang ugentligt eller 3 mg/kg hver 2. uge.

Emicizumab (Hemlibra) kan som sagt ikke anvendes til at behandle en blødning, som opstår under den profylaktiske behandling med emicizumab. Her skal i stedet anvendes et FVIII-præparat on-demand.

1.4.1 Komparator

Medicinrådet har defineret octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta) som komparatorer for populationen patienter med svær hæmofili A, som tidligere har været i profylaktisk behandling med et FVIII-præparat, se tabel 1.

Tabel 1: Definerede population og komparatorer

Population	Komparator
Patienter med svær hæmofili A, som tidligere har været i profylaktisk behandling med et FVIII-præparat	Octocog alfa (Kovaltry) anvendt som profylakse
	Efmoroctocog alfa (Elocta) anvendt som profylakse (forlænget halveringstid)

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af emicizumab (Hemlibra) som mulig standardbehandling for følgende:

- Hvad er den kliniske merværdi af emicizumab (Hemlibra) sammenlignet med standard FVIII-præparater hos patienter med svær hæmofili A?
- Hvad er den kliniske merværdi af emicizumab (Hemlibra) sammenlignet med FVIII-præparater med forlænget halveringstid hos patienter med svær hæmofili A?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af inkrementelle omkostninger per patient sammenlignes behandling med emicizumab (Hemlibra) med behandling med octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta). Analysen inkluderer omkostninger til lægemidler, monitorering, administration, patienttid, transport og behandlingsrelaterede bivirkninger.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøgers analyse har til formål at estimere de inkrementelle omkostninger ved profylaktisk behandling af hæmofili A uden inhibitorer med emicizumab (Hemlibra). Modellen sammenligner emicizumab (Hemlibra) med de to specificerede komparatorer henholdsvis octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta).

Ansøgers model er en simpel omkostningsanalyse, hvor lægemiddelomkostninger til profylaktisk behandling estimeres ud fra en vægtdosering baseret på gennemsnitsvægt. Modellen inkluderer udelukkende behandlingsomkostninger tilknyttet den givne behandlingslinje og inkluderer ikke behandlingsskift. Ansøger antager at behandlingen vil være længerevarende/kronisk og modellen estimerer derfor ikke samlet behandlingstid per patient og antager at der umiddelbart ikke vil være forskel i behandlingslængder mellem de tre lægemidler. Modellen omfatter patienter som tidligere har været i profylaktisk behandling med et FVIII-præparat

Amgros' vurdering

Amgros accepterer ansøgers valg om at estimere meromkostningerne per tidsenhed, eftersom datagrundlaget til at estimere samlet behandlingslængde og eventuelle forskelle mellem de tre behandlingsarme er meget begrænset.

Amgros vurderer, at modellens struktur er acceptabel.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 10 år. Dette er valgt, da ansøger argumenterer, at den gennemsnitlige behandlingslængde med emicizumab (Hemlibra) og komparatorer ligger inden for denne tidshorisont. Omkostninger der ligger efter det første år, er diskonteret med en rate på 4 %.

Amgros' vurdering

Amgros mener at ansøgers perspektiv er i tråd med Amgros' retningslinjer og at tidshorisonten inkluderer alle relevante omkostninger.

Analysens begrænsede samfundsperspektiv og diskonteringsrate er i tråd med Amgros' retningslinjer og accepteres.

2.1.3 Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen.

Lægemiddelomkostninger

Ansøger har inkluderet omkostninger til lægemidler. De anvendte lægemiddelpriser er præsenteret i tabel 3.

Ressourceforbrug (dosering) er baseret på doseringen i Medicinrådets protokol(3).
Den anvendte dosis på octocog alfa (Kovaltry) er fra EPAR. Den er 20-50 IE/kg to gange ugentlig, tre gange ugentlig eller hver anden dag for børn mellem 0-13 år og 20-40 IE/kg to til tre gange per uge for børn og voksne over 13 år.

Den anvendte dosis på efmoroctocog alfa (Elocta) er også baseret på information fra EPAR. Den er 20-50 IE/kg to gange ugentlig, tre gange ugentlig eller hver anden dag for børn 0-13 år og 20-40 IE/kg to til tre gange ugentlig for børn og voksne over 13 år.

Gennemsnitlige ugentlige dosis for henholdsvis børn og voksne er dermed 99,7 IE/kg for børn og 75 IE/kg for voksne for octocog alfa (Kovaltry). For efmoroctocog alfa (Elocta) er den gennemsnitlige ugentlige dosis for henholdsvis børn og voksne, 113,8 IE/kg og 87,5 IE/kg.

Ansøger antager, at den gennemsnitlige vægt for patientpopulationen er 35,9 kg og 85,6 kg for hhv. >18-årige patienter og voksne patienter. Ansøger anvender på trods af de estimerede gennemsnit ikke den gennemsnitlige vægt for patientpopulationen i analysen, men estimerer i stedet gennemsnits vægten for aldersgrupperne 0-4, 5-13, 14-18, 19-44, og <45. Ansøger udregner derefter omkostningerne for hver enkelt af de nævnte patientaldersgrupper, og laver et vægtet gennemsnit af omkostningerne på baggrund af dette.

Ansøger har også inkluderet on-demand omkostninger. Ansøger har antaget at patienter der har behov for on-demand anvender det faktor VIII lægemiddel de allerede modtager. I tilfælde af emicizumab (Hemlibra) har ansøger antaget at der vil blive givet octocog alfa (Kovaltry). For at udregne frekvensen har ansøger anvendt de årlige blødningsrater fra studierne, Mahlunga et al., Kavakli et al., Mahlunga et al.(4–6). Blødningsraterne er præsenteret i tabel 2.

Tabel 2: Årlige blødningsrater for hvert lægemiddel

Lægemiddel	Årlig blødningsrate	Kilde
Emicizumab (Hemlibra)	2,55	Mahlunga et al. 2018 (6)
Octocog alfa (Kovaltry)	4,12	Kavakli et al. 2015 (5)
Efmoroctocog alfa (Elocta)	9,90	Mahlunga et al. 2014(4)

Tabel 3: Anvendte lægemiddelpriser, SAIP

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Pris per IE [DKK]	Kilde
Emicizumab (Hemlibra)	30 mg	1 stk.	[redacted]	[redacted]	Amgros
Emicizumab (Hemlibra)	60 mg	1 stk.	[redacted]	[redacted]	Amgros
Emicizumab (Hemlibra)	105 mg	1 stk.	[redacted]	[redacted]	Amgros
Emicizumab (Hemlibra)	150 mg	1 stk.	[redacted]	[redacted]	Amgros
Octocog alfa (Kovaltry)	250 IE	1 sæt	[redacted]	[redacted]	Amgros
Octocog alfa (Kovaltry)	500 IE	1 sæt	[redacted]	[redacted]	Amgros

Octocog alfa (Kovaltry)	1000 IE	1 sæt	[redacted]	[redacted]	Amgros
Octocog alfa (Kovaltry)	2000 IE	1 sæt	[redacted]	[redacted]	Amgros
Octocog alfa (Kovaltry)	3000 IE	1 sæt	[redacted]	[redacted]	Amgros
Efmoroctocog alfa (Elocta)	250 IE	1 sæt	[redacted]	[redacted]	Amgros
Efmoroctocog alfa (Elocta)	500 IE	1 sæt	[redacted]	[redacted]	Amgros
Efmoroctocog alfa (Elocta)	1000 IE	1 sæt	[redacted]	[redacted]	Amgros
Efmoroctocog alfa (Elocta)	2000 IE	1 sæt	[redacted]	[redacted]	Amgros
Efmoroctocog alfa (Elocta)	3000 IE	1 sæt	[redacted]	[redacted]	Amgros

Amgros' vurdering

Amgros er uforstående over for ansøgers valg af metode til at estimere patientvægt og således den gennemsnitlige dosis per patient. Det er en unødvendigt kompliceret tilgang, der introducerer yderligere antagelser og usikkerhed. Amgros mener, at ansøgers inddeling i hhv. børn og voksne er unødvendig, og komplicerer estimaterne. Ifølge Medicinrådets protokol er patienternes vægt afgørende for den samlede dosis af profylaksebehandlingen(3). Der er stor usikkerhed knyttet til gennemsnitsvægten for patientpopulationen i Danmark. Ligeledes må det forventes, at patientvægt for børn i patientpopulationen i gennemsnit forøges over tid, mens den for voksne holdes nogenlunde konstant. Baseret på disse faktorer, og fordi det er en meget heterogen gruppe bestående af få patienter, hvor store udsving i kropsvægt kan forekomme mellem patienter, mener Amgros det mest hensigtsmæssige er at præsentere de inkrementelle omkostninger baseret på en gennemsnitlig patientvægt på 70 kg. Amgros har fået valideret dette tal af danske kliniske eksperter og mener det er den mest hensigtsmæssige tilgang. Amgros mener at ansøgers antagelser vedrørende on-demand behandling er rimelige. Da emicizumab (Hemlibra) ikke kan gives on-demand mener Amgros også at det er en betydningsfuld del af omkostningsanalysen som Amgros vælger at inkluderer i deres lægemiddelomkostninger.

Amgros udarbejder en ny hovedanalyse, hvor gennemsnitlig vægt for hele populationen anvendes.

Hospitalsomkostninger

Ansøger har inkluderet hospitalsomkostninger i forbindelse med monitorering, hæmofili katetre (Port-a-Cath) samt omkostninger forbundet med skift af præparat. Omkostningerne forbundet med hæmofili katetre er præsenteret i tabel 4.
Omkostningen per administration afhænger af en række antagelser, som ansøger har lavet for hver behandling.

Tabel 4: Omkostninger forbundet med hæmofili katetre (Port-a-Cath) infusion, DKK

Udstyr	Antal	Pris
Gripper Braun: Surecan® Safety II	1	115
Sterile handsker	1	13,70
Spritserviet	5	2
BD Posiflush SP 10 ml	2	30
Kanyle	1	0,34
10 ml sprøjte	1	13,38
Heparin 50 IE/ml	1 hætteglas	71,29

Amgros' vurdering

Amgros vurderer, at der er stor usikkerhed knyttet til de hospitalsomkostningerne, inkluderet i analysen, eftersom de er estimeret ud fra kliniske eksperter og blandt andet evidens fra faktor IX anvendt til hæmofili B patienter. Amgros mener derfor, at estimaterne bør tolkes med stor forsigtighed. Derudover er der ikke tilstrækkeligt evidens for at antage der er forskel mellem omkostningerne forbundet med emicizumab (Hemlibra) og komparatorerne. Danske kliniske eksperter informerer dog Amgros om at omkostningerne forbundet med skift af lægemiddel ikke er ubetydeligt, men at det dog er ens for de tre lægemidler i denne analyse.

Amgros vurderer på dette grundlag, at det vil være mest retvisende udelukkende at inkludere lægemiddelomkostninger til profylakse- og on-demand behandling for de tre lægemidler i hovedanalysen.

Af gennemsigtighedshensyn præsenterer Amgros hospitalsomkostninger i resultatafsnittet for ansøgers analyse. Hospitalsomkostninger inkluderes dog ikke i Amgros' hovedanalyse.

Omkostninger til bivirkninger

Ansøger har inkluderet omkostninger til bivirkninger med en sandsynlighed på mere end 5% forekomst. Tilgangen til sammenligningen er baseret på en narrativ sammenligning af bivirkninger mellem emicizumab (Hemlibra) og komparatorer. Den eneste bivirkning som ansøger inkluderer, er hovedpine som i ansøgers analyse er 172,41 DKK for emicizumab (Hemlibra) og 0 DKK for hhv. octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta).

Amgros' vurdering

Amgros vurderer, at både relevansen og påvirkningen af omkostninger til bivirkninger i dette konkrete tilfælde er forsvindende lille. Af gennemsigtighedshensyn præsenterer Amgros omkostninger til bivirkninger i resultatafsnittet for ansøgers analyse. Omkostninger til bivirkninger inkluderes dog ikke i Amgros' hovedanalyse.

Patientomkostninger

Ansøger har valgt at inkludere omkostninger til patienttid. Dette er gjort på baggrund af lægemiddelmonitorerings besøg på hospitalet og inkluderer den effektive tid på hospitalet, ventetid og transporttid.

Amgros' vurdering

Amgros har konsulteret klinikere som mener der er minimal/ingen forskel mellem lægemidlernes patientomkostninger. Derfor mener Amgros at det er mere hensigtsmæssigt at udelukke patientomkostninger.

Amgros ekskluderer omkostninger i forbindelse med patienttid fra Amgros' hovedanalyse.

2.2 Følsomhedsanalyser

Ansøger har udarbejdet følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Ansøger har inkluderet alternativer til inputs for patientvægt og dosering.

Amgros' vurdering

Amgros vurderer at, ansøgers følsomhedsanalyser er tilstrækkelige.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 5 og tabel 6.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for emicizumab (Hemlibra) sammenlignet med octocog alfa (Kovaltry) til at være ca. [redacted] DKK og ca. [redacted] DKK sammenlignet med efmoroctocog alfa (Elocta).

Tabel 5: Resultatet af ansøgers hovedanalyse ved sammenligning med octocog alfa (Kovaltry), SAIP, DKK

	Emicizumab (Hemlibra)	Octocog alfa (Kovaltry)	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	5.350	20.620	-15.272
Patientomkostninger	2.399	12.048	-9.649
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 6: Resultatet af ansøgers hovedanalyse ved sammenligning med efmoroctocog alfa (Elocta), SAIP, DKK

	Emicizumab (Hemlibra)	Efmoroctocog alfa (Elocta)	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	5.350	39.839	-34.489
Patientomkostninger	2.443	22.805	-20.406
Totale omkostninger	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Med anvendelse af de foreskrevne doser i Medicinrådets protokol er der generelt lav usikkerhed forbundet med resultatet, eftersom den eneste variabel som udgangspunkt er patienternes vægt. Siden alle tre lægemidler er vægtdoseret, varierer de derfor i samme retning og påvirker derfor resultatet i mindre grad. Øvrige omkostninger vil med de nuværende priser for emicizumab (Hemlibra) og octocog alfa (Kovaltry) have meget lille betydning for resultatet.

Eftersom de inkrementelle omkostningerne sammenlignet med efmoroctocog alfa (Elocta) er betydeligt lavere, så vil dette resultat være mere følsomt overfor andre omkostninger end lægemidlets omkostninger. Amgros vurderer dog at hospitalsomkostninger og patientomkostninger stadig er baseret på et tilstrækkeligt usikkert grundlag som gør en udelukkelse af omkostningerne mere hensigtsmæssigt. Denne udelukkelse er baseret på danske klinikeres input, som overordnet mener at der ingen omkostningsmæssig forskel forholder sig mellem de tre lægemidler.

3.2 Amgros' hovedanalyse

Baseret på Amgros' kritiske vurdering af den tilsendte model, har Amgros udarbejdet sin egen hovedanalyse. Forudsætningerne er som i ansøgers analyse bortset fra følgende:

- Modellen omfatter udelukkende lægemiddelomkostninger for profylakse- og on-demand behandling
- Den gennemsnitlige patientvægt antages at være 70 kg
- Amgros justerer den årlige blødningsrate til henv. 3,3 for emicizumab (Hemlibra), 3,8 octocog alfa (Kovaltry) og 2,9 efmoroctocog alfa (Elocta) (6-8)

Amgros vurderer at en gennemsnitlig patientvægt på 70 kg er retvisende for den danske population og vil mindske usikkerheden forbundet med ansøgers unødig komplicerede antagelser tidligere beskrevet, omkring opdelingen af patienter i aldersgrupper og dermed vægtgrupper.

For emicizumab (Hemlibra) så er mean blødningsrate for arm D 3,3) ifølge studiet Mahlangu et al 2018(6). Da den kliniske merværdi er vurderet på arm D og denne arm er mere relevant end arm A og B i studiet så vil denne blødningsrate være mere hensigtsmæssig at anvende. For octocog alfa (Kovaltry) har ansøger anvendt LEOPOLD II studiet som ikke accepteres grundet at populationen ikke har modtaget tidligere profylaktisk behandling og derfor ikke passer på det kliniske spørgsmål. Derfor anvendes blødningsraten på 3,8 fra studiet LEOPOLD I(7). For efmoroctocog (Elocta) anvendes i stedet 2,9 som også fremgår af studiet Mahlangu et al 2014(8) og ikke ansøgers estimat som ikke fremgår af studiet.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for emicizumab (Hemlibra) sammenlignet med octocog alfa (Kovaltry) til at være ca. [redacted] DKK og ca [redacted] DKK sammenlignet med efmoroctocog alfa (Elocta).

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for emicizumab (Hemlibra) ca. 2.750.591 DKK, mens de totale inkrementelle omkostninger bliver ca. 1.317.000 DKK per patient for octocog alfa (Kovaltry). Hvis emicizumab (Hemlibra) sammenlignes med efmoroctocog alfa (Elocta), så er lægemiddelomkostningerne 2.750.591 DKK, mens de totale inkrementelle omkostninger bliver ca. 525.000 DKK per patient.

Resultaterne af Amgros' hovedanalyse vises i tabel 7 og tabel 8.

Tabel 7: Resultatet af Amgros' hovedanalyse ved sammenligning med octocog alfa (Kovaltry), DKK, SAIP, per pt. per år, 70 kg pt.

Omkostningselement	Emicizumab (Hemlibra)	Octocog alfa (Kovaltry)	Inkrementelle omkostninger
Profylakse behandling	[redacted]	[redacted]	[redacted]
On-demand behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 8: Resultatet af Amgros' hovedanalyse ved sammenligning med efmoroctocog alfa (Elocta), DKK, SAIP, per pt. per år, 70 kg pt.

Omkostningselement	Emicizumab (Hemlibra)	Efmoroctocog alfa (Elocta)	Inkrementelle omkostninger
Profylakse behandling	[redacted]	[redacted]	[redacted]
On-demand behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at emicizumab (Hemlibra) vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- Emicizumab (Hemlibra) bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- Emicizumab (Hemlibra) bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Ansøgers estimat af antal nye patienter årligt, ud fra en samlet population på 132 patienter. Ansøgers estimat af patientoptaget vises i tabel 9.

Tabel 9: Ansøgers estimat af antal nye patienter per år

	År 1	År 2	År 3	År 4	År 5
Anbefales	1	4	10	18	26
Anbefales ikke	0	0	0	0	0

Amgros' vurdering af estimeret antal patienter

Amgros vurderer at det er et acceptabelt estimat på markedsoptag af nye patienter.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen. Dog har ansøger set på markedet som helhed med andre konkurrerende lægemidler og viser derfor nogle meget større omkostninger selvom budgetkonsekvenserne er retvisende for beregningen.
Med de indlagte antagelser estimerer ansøger, at anvendelse af emicizumab (Hemlibra) vil resultere i budgetkonsekvenser på ca. [redacted] mio. DKK fra år 1 til år 5.
Samme budgetkonsekvenser vil være 1-17 mio. DKK fra år 1 til år 5 i AIP.
Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 10.

Tabel 10: Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Ansøger har inkluderet omkostninger til andre lægemidler i budgetkonsekvensanalysen. Disse budgetkonsekvenser er derfor ikke et retvisende billede, da de inkluderer omkostningerne for andre lægemidler der ikke er en del

af lægemidlerne inkluderet i protokollens kliniske spørgsmål. Disse lægemidler er Kogenate, Advate, Refacto AF og NovoEight.

Ansøgers estimater inddrager som sagt omkostninger til Kogenate, Advate, Refacto AF og NovoEight. Derfor udarbejder Amgros egen budgetkonsekvensanalyse, hvor disse omkostninger er ekskluderet. Derudover vil patientomkostninger og hospitalsomkostninger ligeledes blive ekskluderet fra Amgros budgetkonsekvensanalyse.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Kun lægemiddelomkostninger inkluderes
- Kun lægemidlerne emicizumab (Hemlibra), octocog alfa (Kovaltry) og efmoroctocog (Elocta) inkluderes
- Patientvægt er korrigeret til 70 kg for alle patienter og lægemidler

Med de indlagte antagelser estimerer Amgros, at anvendelse af emicizumab (Hemlibra) vil resultere i budgetkonsekvenser på ca. [redacted] mio. DKK per år efter år 5, ved et markedsoptag på 22-26 patienter efter 5 år, se tabel 11.

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. 1-23 mio. over 5 år. Amgros har anvendt samme antagelser om patientoptag som i ansøgers analyse.

Årsagen til den betydelige lavere budgetkonsekvens i "anbefales" og "anbefales ikke" kolonnerne er at det udelukkende er lægemidlerne emicizumab (Hemlibra), octocog alfa (Kovaltry) og efmoroctocog (Elocta) der inkluderes i Amgros' estimat af budgetkonsekvenserne.

Tabel 11: Amgros' analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 DISKUSSION

Behandling med emicizumab (Hemlibra) er forbundet med betydelige meromkostninger sammenlignet med behandling med octocog alfa (Kovaltry). Meromkostningerne er udelukkende drevet af lægemiddelomkostningerne for emicizumab (Hemlibra) og komparatorer. I ansøgers analyse udgør lægemiddelomkostninger over 95% af omkostningerne. De øvrige omkostninger udgør altså en lille andel af de samlede omkostninger. Amgros har valgt at udelade de øvrige omkostninger i vores analyse.

En begrænsning ved analysen er, at der ikke er tilstrækkelig evidens til at inkludere andre omkostninger uden betydelige usikkerheder.

6 REFERENCER

1. RADS. Baggrundsnotat for behandling af hæmofili [Internet]. 2016 [cited 2019 Apr 26]. Available from: http://rads.dk/media/4111/bgnhaemofili-m-bilag-2016-12.pdf

2. Medicinrådet. Behandlingsvejledning inklusiv laegemiddelrekommandation for behandling af haemofili [Internet]. 2018 [cited 2019 Apr 26]. Available from: https://medicinraadet.dk/media/7027/laegemiddelrekommandation-haemofili-vers-12.pdf

3. Medicinrådet. Medicinrådets protokol for vurdering af klinisk merværdi for damoctocog alfa pegol til behandling af hæmofili A. 2018;(november):1–14.

4. Mahlangu J, Powell JS, Ragni M V., Chowdary P, Josephson NC, Pabinger I, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood [Internet]. 2014 Jan 16 [cited 2019 Jun 4];123(3):317–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24227821

5. Kavakli K, Yang R, Rusen L, Beckmann H, Tseneklidou-Stoeter D, Maas Enriquez M, et al. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). J Thromb Haemost [Internet]. 2015 Mar [cited 2019 Jun 4];13(3):360–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25546368

6. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med [Internet]. 2018 Aug 30 [cited 2019 Jun 4];379(9):811–22. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1803550

7. Saxena K, Lalezari S, Oldenburg J, Tseneklidou-Stoeter D, Beckmann H, Yoon M, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Haemophilia. 2016;22(5):706–12.

8. Nolan B, Mahlangu J, Perry D, Young G, Liesner R, Konkle B, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A. Haemophilia [Internet]. 2016 Jan [cited 2019 Jun 4];22(1):72–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26218032

AMGROS

REGIONERNES
LÆGEMIDDELORGANISATION

AMGROS I/S
DAMPFÆRGEVEJ 27-29
2100 KØBENHAVN Ø

TLF: 8871 3000
WWW.AMGROS.DK

Fra: Jain, Pavika <pavika.jain@roche.com>
Sendt: 22. maj 2019 08:42
Til: Dorte Glintborg <DGL@medicinraadet.dk>
Emne: Re: Medicinrådets vurdering af den klinisk merværdi for emicizumab

Kære Dorte,

Tak for den vurderingsrapport af klinisk merværdi for emicizumab til behandling af hæmofili A.

Roche tager Medicinrådets vurdering til efterretning og har dermed ikke kommentarer til rapporten.

Bedste hilsner

Pavika

Medicinrådet

Medicinrådets vurdering af klinisk merværdi for emicizumab til behandling af hæmofili A

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om vurderingen af klinisk merværdi

Vurderingen af klinisk merværdi er Medicinrådets vurdering af, hvor effektiv og sikkert lægemidlet er i forhold til andre lægemidler til den samme gruppe patienter.

Vurderingen af klinisk merværdi indgår, når Medicinrådet skal beslutte, om lægemidlet anbefales som mulig standardbehandling.

Lægemidlet vurderes efter Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	15. maj 2019
Ikrafttrædelsesdato	15. maj 2019
Dokumentnummer	47980
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 15. maj 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Hemlibra
Generisk navn	Emicizumab
Firma	Roche
ATC-kode	B02BX06
Virkningsmekanisme	Monoklonalt modificeret immunglobulin G4 (IgG4).
Administration/dosis	De første 4 uger: 3 mg/kg subkutant en gang ugentlig. Herefter 1,5 mg/kg hver uge, 3 mg/kg hver 2. uge eller 6 mg/kg hver 4. uge.
EMA-indikation	Rutineprofylakse hos patienter med svær hæmofili A uden faktor VIII-aktivitet (faktor VIII < 1 %).

2 Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at emicizumab til patienter med svær hæmofili A giver:

- Ingen klinisk merværdi sammenlignet med standard FVIII-præparatet octocog alfa og EHL-præparatet efmoroctocog alfa.

Medicinrådet finder dog, at den subkutane administrationsform og det lange dosisinterval for emicizumab er en stor fordel hos patienter med:

- Vanskelig veneadgang, hvor det ikke er muligt at gennemføre profylakse med et EHL-præparat.
- Gentagne dokumenterede gennembrudsblødninger trods optimeret profylakse med et EHL-præparat.

Evidensens kvalitet er meget lav.

Medicinrådet kategoriserer lægemidlers kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

3 Forkortelser

ABR: *Annual Bleeding Rate*

CI: Konfidensinterval

EHL: Forlænget halveringstid (*extended half life)*

EMA: *European Medicines Agency*

EPAR: *European Public Assessment Report*

FVIII: Koagulationsfaktor VIII

GRADE: *Grading of Recommendations Assessment, Development and Evaluation*

Haem-A-QoL: *Hemophilia-Specific Quality of Life Index*

PTP: *Previously Treated Patients*

PUP: *Previously Untreated Patients*

SD: Standardafvigelse

4 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af emicizumab til patienter med svær hæmofili A er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler (komparatorer) til samme patientgruppe.

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om emicizumab anbefales som mulig standardbehandling.

5 Baggrund

Hæmofili A

Hæmofili A er medfødt mangel på faktor VIII (FVIII), som er vigtigt for blodets evne til at koagulere og dermed standse blødninger. Ubehandlet vil manglen på FVIII medføre spontane led- og muskelblødninger, som på sigt medfører svære ledforandringer og invaliditet. Herudover vil blødning ved traume og kirurgi være livstruende.

I 2016 var der registreret i alt 388 patienter med hæmofili A ved de to hæmofilicentre i hhv. Aarhus og København. Heraf var 132 af patienterne i forebyggende hjemmebehandling (profylakse), mens 256 fik behandling efter behov (on-demand) [1].

Nuværende behandling

Hæmofili A behandles i dag med et rekombinant FVIII-præparat. Patienter med moderat eller svær hæmofili tilbydes aktuelt profylaktisk behandling, som omfatter rutinemæssige infusioner af et FVIII-præparat. Valg af præparat sker iht. Medicinrådets lægemiddelrekommandation fra februar 2018 [2]. Man skelner imellem såkaldte standardpræparater og præparater med forlænget halveringstid (EHL). Som udgangspunkt anvender man det billigste standard FVIII-præparat. Hvis patienten har vanskelig veneadgang eller har dokumenterede gennembrudsblødninger under behandling med et standard FVIII-præparat, kan man overveje at skifte til et FVIII-præparat med forlænget halveringstid (efmoroctocog alfa) [2]. Patienten håndterer selv FVIII-præparatet derhjemme 2-4 gange om ugen afhængigt af, hvilket faktorniveau der tilstræbes hos patienten samt halveringstiden for det anvendte præparat.

Anvendelse af det nye lægemiddel

Medicinrådet har tidligere godkendt emicizumab som mulig standardbehandling til en snæver patientgruppe med hæmofili A, som har udviklet inhiberende antistoffer (såkaldt inhibitor) mod FVIII [3]. EMA har nu godkendt en indikationsudvidelse, så emicizumab også er godkendt til rutineprofylakse hos patienter med svær hæmofili A (FVIII < 1 %) uden FVIII-aktivitet i alle aldre.

Emicizumab er et rekombinant, humaniseret, monoklonalt modificeret immunoglobulin G4, som binder sig til faktor IXa og X, hvorved det efterligner den funktion, som FVIII normalt har i koagulationskaskaden.

Den anbefalede startdosis er 3 mg/kg givet som subkutan injektion én gang ugentligt i de første fire uger, efterfulgt af en vedligeholdelsesdosis på 1,5 mg/kg én gang ugentligt, 3 mg/kg hver 2. uge eller 6 mg/kg hver 4. uge.

Emicizumab kan ikke anvendes til at behandle en blødning, som opstår under den profylaktiske behandling med emicizumab. Her anvendes et FVIII-præparat on-demand.

Der er endnu ingen studier af eller erfaring med behandling med emicizumab hos tidligere ubehandlede patienter (PUP, previously untreated patients), dvs. patienter som aldrig tidligere har været behandlet med FVIII. On-demandbehandling af blødninger med FVIII hos denne gruppe kan medføre en risiko for udvikling af inhibitor mod FVIII. Denne risiko er ikke belyst i de kliniske studier af emicizumab. Risikoen for udvikling af inhibitor mod FVIII er lille hos patienter, som har været i profylaktisk behandling med FVIII i mere end 50 behandlingsdage (PTP, previously treated patients). Derfor forholder fagudvalget sig kun til behandling med emicizumab hos patienter, som tidligere har været i profylaktisk behandling med FVIII.

Virkningen og sikkerheden af emicizumab er ikke blevet undersøgt hos patienter, der får vedvarende immuntoleranceinduktion eller ved kirurgisk behandling [3].

6 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådets sekretariat.

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokollen, som blev godkendt i Medicinrådet den 13. februar 2019.

Ansøger har jf. protokollen foretaget en narrativ sammenligning af emicizumab og komparatorerne for patienter, som tidligere har været i profylaktisk behandling.

I mangel på sammenlignende studier har ansøger suppleret ansøgningen med en indirekte statistisk sammenligning af emicizumab og komparatorerne for en patientgruppe, som tidligere var i on-demandbehandling. Medicinrådets sekretariat har meddelt ansøger, at denne sammenligning ikke vil indgå i vurderingen, da der er fejl i beregningerne, og præmisserne for analysen ikke er acceptable ud fra et statistisk synspunkt

Herudover har ansøger indsendt upublicerede data (data-on-file) for effektmål, som ikke er præspecificerede i protokollen. Fagudvalget vil derfor ikke medtage disse data i vurderingen.

Fra evidens til kategori. Medicinrådet vurderer den kliniske merværdi af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen af klinisk merværdi vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Den kliniske merværdi kategoriseres først enkeltvis pr. effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har udført en systematisk litteratursøgning og identificeret fem publikationer fra fire kliniske studier (jf. tabel 1). Fagudvalget har derudover orienteret sig i *European public assessment report* (EPAR) og produktresuméerne for emicizumab og de to komparatorer, octocog alfa (Kovaltry) og efmoroctocog alfa (Elocta).

Tabel 1: Studier anvendt til at besvare klinisk spørgsmål 1 og 2

Reference	Studie	Intervention	Klinisk spørgsmål
Mahlangu 2018 [4]	HAVEN 3	Emicizumab (Hemlibra)	1,2
Saxena 2016 [5]	LEOPOLD I	Octocog alfa (Kovaltry)	1
Kavakli 2015 [6]	LEOPOLD II	Octocog alfa (Kovaltry)	1
Mahlangu 2014 [7]	A-LONG	Efmoroctocog alfa (Elocta)	2
Wyrwich 2016 [8]	A-LONG	Efmoroctocog alfa (Elocta)	2

8 Databehandling

Der foreligger ikke randomiserede, kontrollerede studier af patienter i tidligere profylakse. Derfor er data for vurderingen af de kliniske spørgsmål sammenstillet narrativt.

9 Klinisk merværdi

9.1 Klinisk merværdi sammenlignet med standard FVIII

RADS har vurderet, at de syv tilgængelige standard FVIII-præparater er ligestillede [1,2]. Fagudvalget finder det derfor tilstrækkeligt at sammenligne emicizumab med ét præparat, som vil være en repræsentativ komparator for gruppen af ligestillede standard FVIII-præparater, og har i protokollen foreslået octocog alfa (Kovaltry), som aktuelt er 1. valg i lægemiddelrekommandationen og har de nyeste data.

9.1.1 Konklusion klinisk spørgsmål 1

Hvad er den kliniske merværdi af emicizumab sammenlignet med standard FVIII-præparater hos patienter med svær hæmofili A?

Fagudvalget vurderer, at emicizumab til patienter med svær hæmofili A har **ingen klinisk merværdi** sammenlignet med octocog alfa (meget lav evidenskvalitet).

9.1.2 Gennemgang af studier

Karakteristika

Emicizumab:

HAVEN 3 [4] er et randomiseret, ublindet studie af patienter ≥ 12 år med svær hæmofili A, som tidligere har modtaget on-demand- eller profylaktisk behandling med et FVIII-præparat. Patienterne i tidligere on-demandbehandling blev randomiseret til et af tre behandlingsregimer: arm A: emicizumab én gang om ugen (n = 36), arm B: emicizumab to gange om ugen (n = 35) eller arm C: ingen profylakse (n = 18). Patienter, som tidligere havde været i profylakse med et FVIII-præparat, blev allokeret til behandling med emicizumab én gang om ugen (arm D) (n = 63). Studiets primære endepunkt var årlig blødningsrate (ABR) for behandlede blødninger med minimum 24 ugers opfølgning. Sekundære endepunkter i studiet var ABR for alle blødninger, livskvalitet, tromboemboliske hændelser samt behandlingsophør pga. bivirkninger. Data fra behandlingsarm D anvendes i den narrative sammenligning til at besvare både klinisk spørgsmål 1 og 2.

Octocog alfa:

Der er fundet to studier af octocog alfa (Kovaltry) hos patienter ≥ 12 år (LEOPOLD I og II) [5,6]. Da kun LEOPOLD I inkluderer patienter i tidligere profylakse, vil kun data fra dette studie indgå i den narrative sammenligning.

LEOPOLD I er er et randomiseret, ublindet fase 1/3 studie. Studiet inkluderer patienter i alderen 12 til 65 år med svær hæmofili A og minimum 150 tidligere behandlingsdage med et FVIII-præparat.

Studiet er inddelt i tre dele, hvor del A er et farmakokinetikstudie, hvor patienterne modtog octocog alfa og et rekombinant FVIII-præparat. Del B belyser effekt og sikkerhed af octocog alfa. Patienterne i del B blev randomiseret til octocog alfa (n = 63) i 12 måneder. Del C omfatter effekt og sikkerhed i forbindelse med større kirurgiske indgreb. Patienter, som ikke var randomiserede til del A eller B men havde et planlagt større kirurgisk indgreb, blev allokeret til del C. I del B var studiets primære endepunkt ABR (alle blødninger) 6 og 12 måneder efter randomisering. Sekundære endepunkter omfattede bl.a. livskvalitet. Studiets del B anvendes til at besvare klinisk spørgsmål 1.

Tabel 2: Studiekarakteristika

	Emicizumab (Helimbra)	**Octocog alfa (Kovaltry)**
Studie	HAVEN 3 (arm D)	LEOPOLD I (del B)
Design	Delvist randomiseret	Delvist randomiseret
Studielande	Australien, Costa Rica, Frankrig, Tyskland, Irland, Italien, Japan, Korea, Polen, Sydafrika, Spanien, Taiwan, England, USA.	USA, Argentina, Østrig, Kroatien, Danmark, Tyskland, Hong Kong, Indien, Indonesien, Israel, Italien, Norge, Pakistan, Polen, Serbien, Sydafrika, Spanien, Sverige, Taiwan, Thailand, Tyrkiet, England.
Opfølgningstid	6 måneder	12 måneder
Planlagt dosering Median dosis Gennemsnitsdosis	1,5 mg/kg/uge[1] Ikke angivet Ikke angivet	20-50 IE/kg 2-3 gange/uge Ikke angivet 65 IE/kg 2 gange/uge 96 IE/kg 3 gange/uge

[1]De første 4 uger: 3 mg/kg/uge

Population

Tabel 3: Patientkarakteristika

	Emicizumab (Helimbra)	**Octocog alfa (Kovaltry)**
Studie	HAVEN 3 (arm D)	LEOPOLD I (del B)
Antal patienter	63	62
Median alder, år (range)	36 (13-68)	30 (12-21)
Svær hæmofili A	100 %	100 %
Median vægt, kg (range)	Ikke angivet	77,4 (39-121)
> 1 target joint, n (%)	18 (69,2 %)	Ikke angivet
Andel patienter i tidligere FVIII-profylakse, n (%)	63 (100 %)	50 (80,6 %)
Median antal blødninger 12 mdr. forud for studiet: Tidl. profylaktisk Tidl. on-demand Patienter med > 9 blødninger 6 måneder forud for studiet	 Ikke angivet Ikke angivet 53 (84,1 %)	 4 (range 0-40) 36 (range 0-55) Ikke angivet

Forskelle mellem studierne
Fagudvalget vurderer, at patienterne i de to studier er sammenlignelige mht. demografi og opfølgningstid. Fagudvalget bemærker, at flere patienter i HAVEN 3 har været i tidligere profylaktisk behandling med et FVIII-præparat sammenlignet med LEOPOLD I. Fagudvalget vurderer, at der er færre patienter i profylakse i LEOPOLD I-studiet end man ser i dansk praksis. Det er ikke muligt at vurdere, hvorvidt patienterne er sammenlignelige mht. blødningsrisiko, da baselinedata er opgjort på to forskellige måder. Fagudvalget vurderer derfor, at der i vurderingen af de kliniske spørgsmål bør tages højde for en usikkerhed ift., om populationerne reelt er sammenlignelige, og om forskelle i patientpopulationerne er til fordel for det ene eller det andet lægemiddel.

9.1.3 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Årlig blødningsrate (ABR) (kritisk)

ABR dækker det samlede antal blødninger (spontane, led- og livstruende), som patienten rapporterer i studieperioden og omregnes til en gennemsnitlig eller median årlig blødningsrate per patient.

Tabel 4. Vurdering af klinisk merværdi: Årlig blødningsrate

Forhåndsdefineret grundlag for vurdering	Resultater	
3 blødninger per år per patient	Emicizumab [4]	Octocog alfa [5]
Absolutte forskelle	1,5 (0,0; 4,3)	1,0 (0; 5.1)
Evidensens kvalitet	Meget lav	

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Studiet af octocog alfa omfatter to studiearme, hvor patienter behandles i to perioder á 6 måneder, fordi der indgår to forskellige analysemetoder til måling af faktoraktivitet. Dette har dog ingen betydning for opgørelsen af ABR, hvorfor resultaterne for de to studiearme kan kombineres. Den mediane ABR var 1,9 i hver studiearm og 1,0, når resultaterne for begge studiearme kombineres. Den numeriske forskel i ABR (0,5) er umiddelbart til fordel for octocog alfa, men det kan, som tidligere nævnt, ikke udelukkes, at der kan være forskelle i blødningsrisiko mellem studiepopulationerne.

Behandlingsophør pga. bivirkninger (vigtig)

Da typen af bivirkninger er forskellig mellem emicizumab og FVIII-præparater, er det relevant at anvende et effektmål, som opgør den samlede byrde af klinisk relevante bivirkninger. Behandlingsophør pga. bivirkninger afspejler, hvorvidt bivirkningerne er af betydning for patienten i en sådan grad, at behandlingen ikke kan fortsætte.

I vurderingen af effektmålet er der tale om en indirekte sammenligning af studier med få patienter. Mindre forskelle (< 5 %) i graden af behandlingsophør kan derfor være helt tilfældige. Fagudvalget har derfor fastsat den mindste klinisk relevante forskel til 5 %.

Der var kun ét tilfælde af behandlingsophør pga. bivirkninger i studiet af emicizumab (< 1 %) og ingen tilfælde i studierne af octocog alfa. Da forskellen mellem studierne dermed er langt under den mindste klinisk relevante forskel, vurderer fagudvalget, at emicizumab giver ingen klinisk merværdi vedrørende behandlingsophør pga. bivirkninger.

Alvorlig venøs tromboemboli (vigtig)

Der var ingen hændelser i nogen af studierne, og emicizumab har derfor ingen klinisk merværdi vedrørende alvorlig venøs tromboemboli.

Livskvalitet (vigtig)

Livskvalitetsdata for FVIII-præparater reflekterer ofte resultatet af en bedre blødningskontrol, fordi patienterne er skiftet fra on-demandbehandling (med mange blødninger) til en profylaktisk behandling (med få blødninger). En forbedring af livskvaliteten skyldes dermed snarere et forbedret behandlingsregime end udelukkende effekten af det undersøgte FVIII-præparat.

Tabel 5. Vurdering af klinisk merværdi: Livskvalitet

Forhåndsdefineret grundlag for vurdering	Resultater	
0,5 SD eller 5 point	Emicizumab [4]	Octocog alfa [3]
Absolutte forskelle	-3,02 point	-2 point
Evidensens kvalitet	Meget lav	

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Livskvalitet er for begge lægemidler målt med *Hemophilia-Specific Quality of Life Index* (Haem-A-QoL), som er et sygdomsspecifikt redskab til vurdering af livskvalitet blandt patienter med hæmofili A. Den samlede livskvalitet scores på en skala fra 0 til 100.

Patienter i behandling med emicizumab oplevede i gennemsnit en ændring (forbedring) fra baseline på -3,02 point målt på Haem-A-QoL efter 25 ugers behandling.

Til sammenligning oplevede patienter i behandling med octocog alfa en ændring (forbedring) på -2.0 point efter 12 måneders behandling [10]. Forskellen i ændringen af livskvalitet (3,02-2 = 1,02) overstiger ikke den mindste klinisk relevante forskel, og emicizumab giver derfor ingen klinisk merværdi vedrørende livskvalitet.

9.2 Klinisk merværdi sammenlignet med FVIII med forlænget halveringstid (EHL)

EHL-præparater anvendes fortrinsvis til patienter, som har vanskelig veneadgang eller har dokumenterede gennembrudsblødninger under behandling med et standard FVIII-præparat, da man kan nedsætte antallet af infusioner. Den subkutane administration og det lange dosisinterval af emicizumab kan derfor også være et relevant tilbud til disse patienter. Der er ikke separate data for denne patientgruppe. Derfor har fagudvalget valgt at sammenligne emicizumab med et EHL-præparat for den fulde patientpopulation. Vurdering af praktiske fordele og ulemper hos subgruppen diskuteres i afsnit 10, "Andre overvejelser".

Da efmoroctocog (Elocta) aktuelt er 1. valg til både børn og voksne, har fagudvalget jf. protokollen foreslået dette præparat som komparator. Nedenfor vurderes den kliniske effekt af lægemidlerne.

9.2.1 Konklusion klinisk spørgsmål 2

Hvad er den kliniske merværdi af emicizumab sammenlignet med FVIII-præparater med forlænget halveringstid hos patienter med svær hæmofili A?

Fagudvalget vurderer, at emicizumab til patienter med svær hæmofili A har ingen **klinisk merværdi** sammenlignet med efmoroctocog alfa (meget lav evidenskvalitet).

9.2.2 Gennemgang af studier

Karakteristika

Emicizumab: Arm D fra HAVEN 3-studiet anvendes til at besvare klinisk spørgsmål 2 (jf. afsnit 9.1.1).

Efmoroctocog alfa: A-LONG var et ublindet studie, hvor patienter blev allokeret til efmoroctocog alfa som enten individuel profylakse hver 3.-5. dag (n = 118) (arm 1) eller randomiseret til fast profylakse én gang ugentlig (65 IE/kg) (n = 25) (arm 2) eller behandling ved behov (on-demand) (arm 3). De primære endepunkter var forskel i ABR ift. on-demandbehandling (arm 1 vs. arm 3), FVIII-aktivitet, udvikling af inhibitor samt uønskede hændelser. De sekundære endepunkter omfattede bl.a. livskvalitetsdata. Data for patienter, der blev allokeret til profylakse hver 3.-5.dag (arm 1), anvendes til at besvare klinisk spørgsmål 2, da den anvendte dosis er anbefalet i det godkendte produktresumé fra EMA. Desuden indgår i denne behandlingsarm patienter, som tidligere har været i profylaktisk behandling.

Tabel 6. Studiekarakteristika

	Emicizumab (Helimbra)	**Efmoroctocog alfa (Elocta)**
Studie	HAVEN 3 (arm D)	A-LONG (arm 1)
Design	Delvist randomiseret	Delvist randomiseret
Studielande	Australien, Costa Rica, Frankrig, Tyskland, Irland, Italien, Japan, Korea, Polen, Sydafrika, Spanien, Taiwan, England, USA	Australien, Belgien, Brasilien, Canada, England, Frankrig, Hong Kong, Indien, Israel, Italien, Japan, New Zealand, Schweiz, Spanien, Sydafrika, Sverige, Tyskland, USA, Østrig
Opfølgningstid	Minimum 24 uger[1]	Op til 67 uger
Planlagt dosering Median dosis Gennemsnitsdosis	1,5 mg/kg/uge[2] Ikke angivet Ikke angivet	25-65 IE/kg hver 3-5 dag[1] 78 IE/kg per uge 86 IE/kg per uge

[1] Dosis blev justeret individuelt med henblik på at opnå en dalværdi på 1-3 % eller højere. Hvis patienten oplevede 2 spontane blødninger over en 8-ugers periode, kunne dosis øges og/eller interval forkortes.

Population

Tabel 7. Patientkarakteristika

	Emicizumab (Hemlibra)	**Efmoroctocog alfa (Elocta)**
Studie	HAVEN 3 (Arm D)	A-LONG
Antal patienter, n	63	118
Median alder, år (range)	36 (13-68)	29 (12-65)
Svær hæmofili A (%)	100	100
Median vægt, kg (range)		71,6 (42-127,4)
> 1 target joint, n (%)	18 (69,2 %)	118 (100 %)
Patienter i tidligere profylakse med et FVIII-præparat, n (%)	48 (76,2 %)	87 (73,7 %)[2]
Median antal blødninger 12 mdr. forud for studiet: Tidl. profylaktisk Tidl. on-demand	53 (84,1 %)[1]	6,0 (IQR 2; 15) 27,0 (IQR 17; 41)

[1]Patienter med > 9 blødninger 6 måneder forud for studiet; [2] n = 31 (26,3 %) har været i tidligere on-demand behandling

Forskelle mellem studierne

Fagudvalget vurderer, at patienterne i de to studier er sammenlignelige mht. demografi, tidligere behandling og opfølgningstid. De fleste patienter i studierne var i profylakse forud for studierne, hvilket stemmer overens med dansk praksis. Det er vanskeligt at vurdere, om patienterne er sammenlignelige mht. blødningsrisiko, da det er opgjort på to forskellige måder. Fagudvalget bemærker, at ABR hos patienter i profylakse forud for studiet af efmoroctocog alfa er højere end ved typisk profylaktisk behandling i en dansk klinisk praksis.

Årlig blødningsrate (ABR) (kritisk)

ABR dækker det samlede antal blødninger (spontane, led- og livstruende), som patienten rapporterer i studieperioden og omregnes til en gennemsnitlig eller median årlig blødningsrate per patient.

Tabel 8. Vurdering af klinisk merværdi: Årlig blødningsrate

Forhåndsdefineret grundlag for vurdering	Resultater	
3 blødninger per år per patient	Emicizumab [4]	Efmoroctocog alfa [7]
Absolutte forskelle	1,5 (0,0; 4,3)	1,6 (0,0; 4,7)
Evidensens kvalitet	Meget lav	

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Forskellen i årlig blødningsrate mellem emicizumab og efmoroctocog alfa overstiger ikke den mindste klinisk relevante forskel på 3, og emicizumab har derfor ingen klinisk merværdi vedrørende årlig blødningsrate.

Behandlingsophør pga. bivirkninger (vigtig)

Der var kun ét tilfælde af behandlingsophør pga. bivirkninger i studiet af emicizumab (< 1 %) og ingen tilfælde i studiet af efmoroctocog alfa. Da forskellen mellem studierne dermed er under den mindste klinisk relevante forskel (5 %), vurderer fagudvalget, at emicizumab har ingen klinisk merværdi vedrørende behandlingsophør pga. bivirkninger.

Alvorlig venøs tromboemboli (vigtig)

Der var ingen hændelser i nogen af de inkluderede studier, og emicizumab har derfor ingen klinisk merværdi vedrørende alvorlig venøs tromboemboli.

Livskvalitet (vigtig)

Livskvalitetsdata for FVIII-præparater reflekterer ofte resultatet af en bedre blødningskontrol, fordi patienterne er skiftet fra on-demandbehandling (med mange blødninger) til en profylaktisk behandling (med få blødninger). En forbedring af livskvaliteten skyldes dermed snarere et forbedret behandlingsregime end udelukkende effekten af det undersøgte FVIII-præparat.

Tabel 9. Vurdering af klinisk merværdi: Livskvalitet

Forhåndsdefineret grundlag for vurdering	Resultater	
0,5 SD 5 point	Emicizumab [4]	Efmoroctocog alfa [7]
Absolutte forskelle	-3,02	-3,2
Evidensens kvalitet	Meget lav	

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Patienter i behandling med emicizumab oplevede i gennemsnit en ændring (forbedring) fra baseline på -3,02 point målt på Haem-A-QoL efter 25 ugers behandling.

Til sammenligning oplevede patienter i behandling med efmoroctocog alfa en ændring på -3,2 point efter 28 ugers behandling [8].

Forskellen i ændringen af livskvalitet overstiger ikke den mindste klinisk relevante forskel, og emicizumab har derfor ingen klinisk merværdi vedrørende livskvalitet.

9.3 Evidensens kvalitet

Evidensens kvalitet i sammenligningen af emicizumab og hhv. octocog alfa og efmoroctocog alfa er samlet set meget lav. Studierne er som udgangspunkt af lav kvalitet, og der er moderat risiko for bias i de enkelte studier, hvilket giver anledning til nedgradering fra lav til meget lav evidenskvalitet. Der foreligger ikke direkte sammenlignende studier, hvilket medfører nedgradering med minimum ét niveau for *indirectness* Samlet set vil evidenskvaliteten derfor blive meget lav, og der er derfor ikke udarbejdet GRADE-profiler.

Risiko for bias-vurderinger af de enkelte studier kan ses i bilag 1.

10 Andre overvejelser

Dosis

Effekten af emicizumab er vurderet hos patienter i tidligere profylaktisk behandling, hvor emicizumab blev givet én gang om ugen.

Effekten af de andre dosisregimer, der er anbefalet i produktresuméet er vist for patienter i tidligere on-demandbehandling i HAVEN 3 [4] og i HAVEN 4-studiet [9]. ABR ved de enkelte dosisregimer var 0,6 ved ugentlig dosering, 1,6 ved dosering hver 2. uge og 2,1 ved dosering hver 4. uge, hvilket viser en tendens til ringere effekt ved længere dosisinterval. Dog er forskellene i ABR mellem de forskellige dosisregimer af emicizumab ikke klinisk relevante. Valg af dosisregime i klinikken bør derfor foregå ud fra en individuel klinisk vurdering af patienten.

Kliniske overvejelser af fordele og ulemper

Fordele

Det er en fordel for patienterne, at emicizumab kan administreres som subkutan injektion hver uge, hver anden eller hver fjerde uge sammenlignet med standard FVIII- og EHL-præparater, der administreres som intravenøs infusion flere gange om ugen.

For patienter med høj blødningsrisiko og deraf behov for hyppige infusioner, nedsætter det lange doseringsinterval for emicizumab derfor behandlingsbyrden betydeligt, hvilket også kan have betydning for adhærens til behandlingen.

Intravenøse infusioner flere gange om ugen er en udfordring hos patienter med vanskelig veneadgang. Hos især små børn kan der være behov for en intravenøs port med deraf følgende risiko for infektion og nedsat adhærens til behandlingen. Administrationen af emicizumab (subkutan injektion) kan derfor være en fordel hos denne patientgruppe.

Ulemper

Emicizumab kan ikke anvendes til at behandle blødninger, som opstår spontant eller ved traume eller kirurgi. For patienten betyder det, at man skal have både emicizumab og et FVIII-præparat på lager (have to præparater med på rejse, holde øje med udløbsdato mv.). Der er sparsom erfaring med kirurgi under emicizumab-profylakse og herunder usikkerhed om dosering af FVIII. Hvis patienten eller forældrene ikke

selv kan administrere FVIII-præparatet, kan det resultere i forlænget indlæggelse eller ekstra ambulante besøg.

Da blødning under profylaktisk behandling for de fleste patienter forekommer relativt sjældent (1-4 gange per år), kan patienter, som tidligere har været vant til at anvende et FVIII-præparat flere gange om ugen, miste rutine i administration af FVIII-præparatet, hvilket kan betyde, at man i tilfælde af blødning er nødt til at søge skadestue.

For små børn, som ikke tidligere er behandlet med et FVIII-præparat (PUP), vil behandling med emicizumab i praksis betyde, at forældrene ikke lærer at administrere et FVIII-præparat, og forældrene vil derfor altid skulle søge skadestue i tilfælde af opstået blødning. Da der samtidig ikke er kliniske data for behandling af PUP, finder fagudvalget, at emicizumab ikke rutinemæssigt bør anvendes til denne patientgruppe.

Det er en ulempe, at behandlingen med emicizumab ikke kan monitoreres biokemisk, sådan som behandlingen med et FVIII-præparat kan. Dertil kommer, at monitorering af FVIII-behandlingen i forbindelse med f.eks. kirurgi eller behandling af større blødninger kun kan foretages med helt specifikke FVIII-assays og ikke almindelige FVIII-clot-analyser. Kombinationsbehandling med emicizumab og et FVIII-præparat kan derfor ikke monitoreres med de eksisterende analyser, og erfaringen er begrænset.

Fagudvalget finder ud fra en samlet vurdering af fordele og ulemper, at den subkutane administrationsvej og det lange dosisinterval for emicizumab er en stor fordel for patienter med:

- Vanskelig veneadgang, hvor det ikke er muligt at gennemføre profylakse med et EHL-præparat.
- Gentagne dokumenterede gennembrudsblødninger trods optimeret profylakse med et EHL-præparat.

11 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at emicizumab til patienter med svær hæmofili A giver:

- Ingen klinisk merværdi sammenlignet med standard FVIII-præparatet octocog alfa og EHL-præparatet efmoroctocog alfa.

Fagudvalget finder dog, at den subkutane administrationsform og det lange dosisinterval er en stor fordel hos patienter med:

- Vanskelig veneadgang, hvor det ikke er muligt at gennemføre profylakse med et EHL-præparat.
- Gentagne dokumenterede gennembrudsblødninger trods optimeret profylakse med et EHL-præparat.

Evidensens kvalitet er meget lav.

Fagudvalget begrunder vurderingen med, at der ikke er fundet klinisk relevante forskelle mellem emicizumab og de valgte komparatorer i nogen af de kliniske effektmål. Der er både praktiske fordele (administrationsform og langt dosisinterval) og ulemper ved behandling med emicizumab. En væsentlig ulempe er, at patienten fortsat har brug for behandling med FVIII i tilfælde af blødning, der opstår under profylakse med emicizumab. Patienten mister på sigt eller får aldrig rutinen i at selvbehandle en blødning med FVIII.

Fagudvalget vil ud fra en samlet vurdering fortsat foretrække FVIII til størstedelen af patienterne og reservere emicizumab til de patientgrupper, som ikke kan behandles tilstrækkeligt med et EHL-præparat, da fordelene her vurderes at være større end ulemperne.

12 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at emicizumab til patienter med svær hæmofili A giver:

- Ingen klinisk merværdi sammenlignet med standard FVIII-præparatet octocog alfa og EHL-præparatet efmoroctocog alfa.

Medicinrådet finder dog, at den subkutane administrationsform og det lange dosisinterval er en stor fordel hos patienter med:

- Vanskelig veneadgang, hvor det ikke er muligt at gennemføre profylakse med et EHL-præparat.
- Gentagne dokumenterede gennembrudsblødninger trods optimeret profylakse med et EHL-præparat.

Evidensens kvalitet er meget lav.

13 Relation til eksisterende behandlingsvejledning

Medicinrådet udarbejder aktuelt en behandlingsvejledning for hæmofili A, hvor emicizumab også vil indgå.

14 Referencer

1. RADS. Baggrundsnotat for behandling af hæmofili [internet]. 2016. Tilgængelig fra: http://rads.dk/media/4111/bgnhaemofili-m-bilag-2016-12.pdf
2. Medicinrådet. Behandlingsvejledning inklusiv lægemiddelrekommandation for behandling af hæmofili [internet]. 2018. Tilgængelig fra: www.medicinraadet.dk/media/7027/laegemiddelrekommandation-haemofili-vers-12.pdf
3. European Medicines Agency (EMA). Produktresumé - Emicizumab (Hemlibra). 2018; Tilgængelig fra: https://ec.europa.eu/health/documents/community-register/2017/20171003139003/anx_139003_da.pdf
4. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018;379(9):811–22.
5. Saxena K, Lalezari S, Oldenburg J, Tseneklidou-Stoeter D, Beckmann H, Yoon M, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Haemophilia. 2016;22(5):706–12.
6. Kavakli K, Yang R, Rusen L, Beckmann H, Tseneklidou-Stoeter D, Maas Enriquez M. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: Results from a randomized trial (LEOPOLD II). J Thromb Haemost. 2015;13(3):360–9.
7. Mahlangu J, Powell JS, Ragni M V., Chowdary P, Josephson NC, Pabinger I, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood [internet]. 2014;123(3):317–25. Tilgængelig fra: http://www.bloodjournal.org/cgi/doi/10.1182/blood-2013-10-529974
8. Wyrwich KW, Krishnan S, Auguste P, Poon J-L, von Maltzahn R, Yu R, et al. Changes in health-related quality of life with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. Haemophilia [internet]. 2016;22(6):866–72. Tilgængelig fra: http://doi.wiley.com/10.1111/hae.12987
9. (EMA) EMA. EPAR - emicizumab (Hemlibra). 2019.
10. (EMA) EMA. EPAR - octocog alfa (Kovaltry). 2018.

15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende blødersygdom

Forvaltningslovens § 4, stk. 2 har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
Eva Funding Overlæge	Lægevidenskabelige Selskaber og Region Hovedstaden
Medlemmer	**Udpeget af**
Har ikke en relevant specialist til fagudvalget	Region Nordjylland
Anne-Mette Hvas Professor, overlæge, ph.d.	Region Midtjylland
Lone Hvitfeldt Poulsen Overlæge	Region Midtjylland
Jesper Farup Revsholm Afdelingslæge	Region Syddanmark
Rune Larsen Overlæge	Region Sjælland
Marianne Hutchings Hoffmann Overlæge	Dansk Pædiatrisk Selskab
Peter Kampmann Overlæge, lægefaglig teamleder	Dansk Selskab for Trombose og Hæmostase
Marie Louise Schougaard Christiansen Afdelingslæge, klinisk farmakolog, ph.d.	Dansk Selskab for Klinisk Farmakologi (DSKF)
Jennifer Anna Fey Andresen. Farmaceut	Dansk Selskab for Sygehusapoteksledelse (DSS)
Finder det ikke længere relevant at have en kandidat i fagudvalget	Dansk Selskab for Anæstesiologi og Intensiv Medicin
Kan ikke udpege en kandidat	Dansk Selskab for Klinisk Biokemi
To patienter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Dorte Glintborg (projekt- og metodeansvarlig) Mette Hollensted (projektdeltager) Anne Sofie Gram (projektdeltager) Ilse Linde (koordinator) Kirsten Holdt Henningsen (teamleder)

16 Versionslog

Version	Dato	Ændring
1.0	15. maj 2019	Godkendt af Medicinrådet.

17 Bilag 1: Risk of bias profiler

Vurderet med Cochrane risk of bias for In Non-Randomized Studies of Interventions (Robins-I) assessment tool.

Emicizumab, NCT02847637 (HAVEN III)

(Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors, Mahlangu et al., 2018)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	There is no information on confounder in the single-arm (earlier prophylactic treatment) and therefore there is a potential risk of bias.
Selection of participants into the study	• Moderate	There is a moderate risk of selection bias based on assigning treatments according to the previously received ones.
Classification of interventions	• Low	The intervention is clearly defined.
Deviations from intended interventions	• Low	No concerns of bias.
Missing data	• Low	132 out of 134 patients were included in analyses, which is judged as having low risk of bias.
Measured outcomes		
ABR	• Moderate	Annual bleeding rate is according the standard practice patient-reported, which increases the potential of bias. Moreover, the study is open-label.
FVIII activity	• Low	No concern. Based on primary pharmacokinetic parameters.
Adverse events	• Low	No concern. Inhibitor is detected via clinical laboratory tests.
Selection of reported results	• Low	Even though the study protocol lists 26 different outcomes, nothing suggests that there is a risk of reporting bias.
Overall bias	• **Moderate**	Overall risk of bias judged moderate due to the moderate risk of confounding and selection bias and in measuring outcomes. Moreover, one of the issues was the open-label design of the trial.

Kovaltry, NCT01029340 (LEOPOLD I)

(Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial, Saxena et al., 2016)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	There are no confounders stated in the article, and therefore there is potential risk of bias.
Selection of participants into the study	• Low	No concerns of bias regarding the selection of participants.
Classification of interventions	• Low	The intervention is clearly defined.
Deviations from intended interventions	• Low	Nothing suggests that the intervention received deviated from the intended intervention.
Missing data	• Low	61 out of 63 patients completed both periods (Part A and Part B), which leads to low risk of bias due to missing data.
Measured outcomes		
ABR	• Moderate	The study was open-label, which poses moderate risk of bias. ABR is according the standard practice patient-reported, which might be subjective.
FVIII activity	• Low	No concern. Based on primary pharmacokinetic parameters.
Adverse events	• Low	No concerns. Inhibitor is detected via clinical laboratory tests.
Selection of reported results	• Moderate	The article mentions subgroup analyses while the study protocol does not. The reporting bias is therefore judged as moderate.
Overall bias	• **Moderate**	Overall risk of bias judged moderate due to the moderate risk of confounding, and moderate risk of bias regarding one of the measured outcomes (ABR) and regarding the reporting bias. The main issues were the open-label design of the study and the subjective nature of the efficacy endpoint measurements, as well as the subgroup analyses which were not mentioned in the original study protocol.

Efmoroctocog alfa (Elocta)

NCT01181128, A-LONG

(Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A, Mahlangu et al., 2014)

Bias	Risk of bias	Elaboration
Confounding	Moderate	It is not possible to assess confounding in a single arm study, and therefore there is a risk of bias.
Selection of participants into the study	Moderate	There is a risk of self-selection bias based on the patients' possibility to enter the prophylactic arm (arm of interest).
Classification of interventions	Low	The intervention is clearly defined.
Deviations from intended interventions	Low	Nothing suggests that the intervention received deviated essentially from the intended intervention.
Missing data	Low	117 out of 118 patients were included in analyses.
Measured outcomes		
ABR	Moderate	Annual bleeding rate is according the standard practice patient-reported, which increases the potential of bias.
FVIII activity	Low	No concern. Based on primary pharmacokinetic parameters.
Adverse events	Low	No concern. Inhibitor is detected via clinical laboratory tests.
Selection of reported results	Low	Nothing suggests bias in the selection of reported results. (Clinicaltrials.gov ID NCT01181128).
Overall bias	**Moderate**	**Concern regarding potential confounding and self-selection of patients to the treatment arm. The main outcome of interest, annual bleeding rate (ABR), is patient-reported and therefore subjective.**

Application for the assessment of clinically added value of Hemlibra® (emicizumab) as routine prophylaxis against bleedings in patients with severe hemophilia A without factor VIII inhibitors

Table of contents

1 Basic information

Table 1. **Contact information**	
Name	Henrik Sigaard Knoth
Title	Country Medical Manager
Area of responsibility	Medical Affairs
Phone	+45 42 14 29 47
E-mail	Henrik_sigaard.knoth@roche.com
Name	Pavika Jain Lyngsie
Title	Value Demonstration Manager
Area of responsibility	Market Access
Phone	+45 42 14 29 38
E-mail	Pavika.jain@roche.com

Table 2. **Overview of the pharmaceutical**	
Proprietary name	Hemlibra®
Generic name	Emicizumab
Marketing authorization holder in Denmark	Roche Registration GmbH Emil-Barrell-Strasse 1 79639 Grenzach-Wyhlen Germany
ATC code	B02BX06
Pharmacotherapeutic group	Other systemic haemostatics
Active substance(s)	Emicizumab
Pharmaceutical form(s)	Solution for subcutaneous injection.
Mechanism of action	Emicizumab bridges between activated factor IX and factor X and restores the function of the non-activation of factor VIII necessary for efficacies hemostasis. There is no structural community or sequence homology between emicizumab and factor VIII, and therefore emicizumab does not induce or potentiate the development of factor VIII inhibitor.
Dosage regimen	The recommended dose is 3 mg / kg once a week for the first 4 weeks (start-up dose) and then 1.5 mg / kg once weekly or 3 mg/kg every two weeks or 6 mg/kg every 4 weeks (maintenance dose). Hemlibra should be given as a subcutaneous injection.

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Hemlibra is indicated as routine prophylaxis against bleeding in humans with hemophilia A with factor VIII inhibitor and severe hemophilia A without factor VIII inhibitor. Hemlibra can be used by all age groups.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes (BEGR)
Combination therapy and/or co-medication	None
Packaging – types, sizes/number of units, and concentrations	Hemlibra 30 mg/ml solution for injection A 3 ml clear type-I vial with butyl rubber stopper, laminated with fluororesin film and folded with aluminum cap with tiltable plastic cap. Each box contains one vial. • Each vial of 30 mg emicizumab contains 1 ml solution for injection at a concentration of 30 mg / ml. Hemlibra 150 mg / ml solution for injection A 3 ml clear type-I vial with butyl rubber stopper, laminated with fluororesin film and folded with aluminum cap with tiltable plastic cap. Each box contains one vial. • Each vial of 60 mg emicizumab contains 0.4 ml solution for injection at a concentration of 150 mg / ml. • Each vial of 105 mg emicizumab contains 0.7 ml solution for injection at a concentration of 150 mg / ml. • Each vial of 150 mg emicizumab contains 1 ml solution for injection at a concentration of 150 mg / ml.
Orphan drug designation	No

2 Abbreviations

Table 3. **Overview of abbreviations**	
ABR	Annualized bleeding rate (ABR)
BU	Bethesda Unit
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
FVIII	Factor VIII
Haem-A-QoL	Hemophilia-Specific Quality of Life Questionnaire
Haemo-Qol-SF	Hemophilia-Specific Quality of Life - Short Form
ITC	Indirect treatment comparison
IU	International Unit
NIS	Non interventional study
PTP	Previously treated patient
PUP	Previously untreated patient
NR	Not Reported
rFVIII	Recombinant Factor VIIa
SAE	Serious adverse event
SF-36	Short Form Survey 36
SmPC	Summary of Product Characteristics
TE	thromboembolism
TMA	Thrombotic microangiopathy

3 Introduction & Summary

The Medicines Council has previously approved emicizumab (Hemlibra) as routine prophylaxis of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. EMA has now extended the approval of Hemlibra to also include routine prophylaxis of bleeding episodes in patients with severe hemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors [1].

The approval of the new indication, routine prophylaxis against bleedings in patients with severe hemophilia A without factor VIII inhibitors is based on the results of the HAVEN 3 study [2]

The purpose of this application is to answer the two asked clinical questions regarding Hemlibra in the protocol [3] in order for the Medicines Council to assess the general use of Hemlibra for the treatment of routine prophylaxis against bleedings in patients with severe hemophilia A without factor VIII inhibitors.

The final application includes relevant studies, efficacy outcomes and other considerations that the Medicines Council has requested on the basis of the preliminary application and the protocol in connection with the assessment of the clinical added value of Hemlibra.

3.1 Summary

This application provides evidence for the added clinical value of Hemlibra prophylaxis for patients previously treated with FVIII prophylaxis (standard and extended half-life) by answering the two clinical questions asked by the Medicine Council.
Data from relevant selected studies for the per protocol defined comparators, Kovaltry and Elocta is included and the added clinical value of Hemlibra prophylaxis is assessed and documented for the four following efficacy and safety outcomes defined in the protocol:

Efficacy outcomes: *Annualized bleeding rate (ABR) (Critical outcome)* and ***Quality of Life (Important outcome)***

Safety outcomes: *Discontinuation due to side effects* ***(Important outcome)*** and *Severe venous thromboembolism (Important outcome)*

As no RCTs or other studies with direct comparison exists between Hemlibra and the two defined comparators, Kovaltry and Elocta, the four outcomes have been compared in a narrative way. However, due to the inherent biases caused by narrative comparisons, an indirect trial comparison (ITC) has been undertaken for the critical outcome, ABR, as a supplement to the narrative comparison.

Clinical question 1

In conclusion the reported median ABR for Hemlibra versus Kovaltry is numerically lower for Hemlibra (1.5) than for Kovaltry (1.9). The applied ITC provides further supports that Hemlibra prophylaxis results in a lower median ABR compared to Kovaltry prophylaxis (absolute difference 4.30).

Furthermore, for Quality of Life assessment, Haem-A-QoL Total Score a small numeric improvement is found for Hemlibra versus Kovaltry.
When comparing the two defined safety outcomes, Discontinuation due to side effects and Severe venous thromboembolism, only few to none adverse effects have been reported for Hemlibra and Kovaltry and the two safety outcomes is considered to be on par.
In conclusion Hemlibra prophylaxis provides added clinical value compared to patients treated with Kovaltry, a standard FVIII product.

Clinical question 2

The reported median ABR for Hemlibra versus Elocta is numeric lower for Hemlibra (1.5) than for Elocta (1.96). The applied ITC provides further supports that Hemlibra prophylaxis results in a lower median ABR compared to Elocta prophylaxis (absolute difference 7.01).
Furthermore, for Quality of Life assessment, Haem-A-QoL Total Score a small numeric improvement is found for Hemlibra versus Elocta.
When comparing the two defined safety outcomes, Discontinuation due to side effects and Severe venous thromboembolism, only few to none adverse effects have been reported for Hemlibra and Elocta and the two safety outcomes is considered to be on par.
In conclusion Hemlibra prophylaxis provides added clinical value compared to patients treated with Elocta, an extended half-life FVIII product.

Subgroups relevant for Hemlibra in Denmark

Current treatment for Hemophilia A requires multiple IV infusions every week. This can be a burdensome treatment regime and due to this there are certain patient groups who cannot manage this, potentially due to vein access problems or adherence issues. This results in a repetitive breakthough bleeds for these patients and thus there exists a groups of Hemophilia A patients in Denmark who have a need for a more effective and convenient treatment.

Patients from HAVEN 3 arm D that had previously been on prophylaxis during the entire duration of the NIS (n=44) was analyzed. 18 patients from the group had an ABR (all bleedings) of ≥ 3. Treatment of this group of patients with Hemlibra had an impact of the median ABR reducing it from 9.42 to 0.99, with a reduction of 8.43.

Other considerations

Administration of Hemlibra:

The fact that Hemlibra is administered as a SC injection reduces the treatment load for each patient switching from FVIII products to Hemlibra. Data from HAVEN 3 shows that Hemlibra was preferred by most of the patients when asked in the EmiPref survey. The survey was completed by 95 of 134 eligible participants (71%). Of all the survey respondents, 94% (95% CI, 87 to 98) preferred Hemlibra, and 45 of 46 participants (98%; 95% CI, 88 to 100) in group D favored Hemlibra over FVIII prophylaxis.

The frequency of administration of FVIII prophylaxis is particularly challenging for pediatric and older patients due to poor venous access and tolerance to repeated venipuncture, which can lead to excessive bleeding or bruising and permanent damage to the veins.

In the recently published protocol *Protokol for Medicinrådets behandlingsvejledning for hæmofili A* the outcome 'Weekly number of doses' is defined as important. Even though it is not considered in the clinical question referring to Hemlibra, it is indeed as relevant for Hemlibra as for extended half-life FVIII products. Compared to Kovaltry, Hemlibra reduces the dosing compared to Kovaltry from 2.8 per week to 0.25 per week or 11.2 doses every 4 weeks compared to 1 dosing every 4 weeks – an absolute difference of 2.55 doses per week or 10.2 doses every 4 weeks. Compared to Elocta the dosing of Elocta is reduced from 1.8 per week to 0.25 per week or 7.2 doses every 4 weeks compared to 1 dosing every 4 weeks – an absolute difference of 1.55 doses per week or 6.2 doses every 4 weeks, indicating a clinically relevant reduction.

4 Literature search

As requested in the protocol, a systematic literature search has been carried out for relevant literature on hemophilia A without inhibitor combined with Hemlibra and its comparators; Kovaltry and Elocta.
The search was conducted in MEDLINE/Pubmed and via Cochrane Central on the 18th of February. The search contains terms that are descriptive of the area with a combination of indexed and non-indexed search terms. Pharmaceuticals were included with both generic and trade names as well as possible alternative names.

Following both searches two employees, independently of each other, screened all references on a title and abstract level using defined inclusion- and exclusion criteria in a reference management tool. Following the screening process, remaining articles would undergo full text review.
In cases of uncertainty as to whether a reference, by title and abstract level met the criteria for inclusion and exclusion, these references were selected for full text review. In the event of any disagreement, a third party (medical peer) was involved.

An overview of reviewed excluded full text articles along with justification can be found in appendix 9.2. Appendix 9.2 also contains more detailed information regarding the search such as the search string and PRISMA flow charts displaying the selection process.

4.1 Relevant studies

Based on the literature search the selected references for relevant studies including Kovaltry and Elocta are listed in Table 4.

Table 4. **Relevant studies selected for assessment**

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Mahlangu, J.; Oldenburg, J.; Paz-Priel, I. et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N. Engl J Med. 2018 [2]	HAVEN 3 (Hemlibra®)	NCT02847637	SEP 2016 - SEP 2017	1, 2
Saxena, K.; Lalezari, S.; Oldenburg, J. et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Hemophilia. 2016 [4]	LEOPOLD I (Kovaltry®)	NCT01029340	DEC 2009 – Mar 2013	1
Kavakli, K.; Yang, R.; Rusen, L. et al. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). J Thromb Haemost. 2015 [5]	LEOPOLD II (Kovaltry®)	NCT01233258	JAN 2011 – DEC 2012	1
Mahlangu, J.; Powell, J. S.; Ragni, M. V. et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014 [6]	A-LONG (Elocta®)	NCT01181128	NOV 2010 – AUG 2012	2
Wyrwich, K. W.; Krishnan, S.; Auguste, P. et al. Changes in health-related quality of life with	A-LONG (Elocta®)	NCT01181128	NOV 2010 – AUG 2012	2

treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. Hemophilia. 2016 [7]				
*when multiple clinical questions are defined in the protocol				

4.2 Main characteristics of selected studies

The application includes data from a total of four selected relevant clinical studies. Main characteristics for selected studies are tabulated in Appendix 9.1.

Studies including Hemlibra (*emicizumab*)

HAVEN 3 [2] is a phase 3, randomized, open-label, multicenter study assessing the efficacy, safety and pharmacokinetics of Hemlibra prophylaxis in patients ≥12 years who have severe hemophilia A and previously received on-demand or prophylactic FVIII infusions. Participants were randomly assigned to one of three treatment regimens based on previous episodic FVIII treatment: Hemlibra once weekly (group A) or every 2 weeks (group B) or to receive no prophylaxis (group C). Participants who had previously received adequate prophylactic FVIII, were assigned to Hemlibra once weekly (group D). Key characteristics of this study can be found in Table 16 on page 41.

Studies including Kovaltry (*octocog alfa*)

LEOPOLD I [4] is a phase 1/3, randomized, open-label, crossover, multicenter study assessing the efficacy, safety and pharmacokinetics of Kovaltry for treatment of bleedings and as prophylaxis in males aged 12 to 65 years with severe hemophilia A and ≥ 150 exposure days to any FVIII product.
Part A pharmacokinetics study: Patients received Kovaltry and rFVIII-FS separated by a washout period in a crossover design to determine the pharmacokinetic profiles.
Part B efficacy and safety study: Patients were randomized to either Kovaltry with dose determined by CS/EP or CS/ADJ for a 6-month treatment period and crossover followed by another 6-month treatment period.
Part C efficacy and safety during major surgery: Patients not participating in part A or B who were scheduled for major surgery. Key characteristics of this study can be found in Table 17 on page 44.

LEOPOLD II [5] is a phase 2/3, randomized, open-label, crossover, multicenter study investigating the superiority of prophylaxis versus on-demand therapy with Kovaltry in patients aged 12-65 years with severe hemophilia A and ≥ 150 exposure days to any FVIII product. Patients were randomized in a 3:1 ratio between prophylaxis and on-demand treatment arms. The prophylactic group was further randomized and assigned to either prophylaxis two or three times weekly. Key characteristics of this study can be found in Table 18 on page 46.

Studies including Elocta (*efmoroctocog alfa*)

A-LONG [6] is a phase 3, open-label, randomized, multicenter study evaluating the safety, efficacy and pharmacokinetics of Elocta for prophylaxis, treatment of acute bleeding, and perioperative hemostatic control in males aged ≥12 years with severe hemophilia A.
At screening, subjects entering Arm 1 were required to be on a prophylaxis regimen of ≥2 times/week with a FVIII product or on an episodic regimen with ≥12 bleeding episodes in the 12 months prior to Day 0. At screening, subjects randomized to Arms 2 and 3 were required to be on an episodic regimen with ≥12 bleeding episodes in the past 12 months prior to Day 0 Table 19 on page 49 [8].

Relevant differences and similarities in study and patient characteristics are presented in Table 6 and Table 7 in section 5.1.1 and Table 8 and Table 9 in section 5.2.1

5 Clinical questions

According to the protocol [3] the application should provide evidence for the added clinical value of Hemlibra prophylaxis for patients previously treated with FVIII prophylaxis (standard and extended half-life), i.e. PTP patients. Hence, when answering the two clinical questions, data from the selected studies for the per protocol defined comparators, Kovaltry and Elocta, will be compared in a narrative way, as no data exists that makes a direct treatment comparison between Hemlibra and Kovaltry or Elocta possible, if enrolled patients must have been in prophylactic treatment before enrollment into the study. In a narrative comparison, data will be compared merely descriptively, and therefore the analysis is associated with great bias, e.g. uncertainty regarding the included study population. Most importantly, a narrative comparison cannot differentiate the effect of the treatment from the effect of the study.

Because of these obvious weaknesses of a narrative analysis, and in order to give an opportunity for more insight into the comparison, we have decided to supplement the narrative analysis with an ITC that compares the active treatment arm with an on-demand control arm, where possible. This analysis is possible for Hemlibra vs. Kovaltry (HAVEN Arm A+B/Arm C vs. LEOPOLD II) and Hemlibra vs Elocta (HAVEN Arm A+B/Arm C vs. A-LONG weekly dosing). We acknowledge that on-demand treatment is not standard of care in Denmark and we will not use it to show whether Hemlibra is more effective than on-demand treatment. We will use this analysis to look at the effect of the treatment, by comparing the treatment effect with a common control (on-demand treatment). In this way we are approaching the real effect of the treatments, and exclude some confounding factors, e.g. differences in populations in the compared studies. The patient population in the studies are not large, and this confounding factors can have a great influence on the results in a narrative comparison. Therefore, additional information can be obtained by making an ITC with randomized data using the method described by Bucher [9][10] and Bland [11], where confounding factors do not have as much influence on the result.

In HAVEN 3 [2] the control arm is called ‘no prophylaxis’, which is defined as *Participants who received episodic treatment with FVIII prior to study entry will be randomized to continue episodic FVIII treatment*

when they start the trial (ClinicalTrials.gov). All patients entering arm A, B and C received on-demand treatment before study entry, while patients on prior prophylaxis were assigned to arm D.

Hemlibra vs. Kovaltry in ITC [2,4,5]
Median age in HAVEN 3 is a little higher than in LEOPOLD II, however, it is not considered to have any influence. The mean ABR (all bleeds) before study start in the on-demand arm was 47.6 (95% CI: 28.5–79.6) in HAVEN 3 compared to a mean ABR of 47.5 in the on-demand arm in LEOPOLD II, which is comparable. As the prophylactic effect of short-acting FVIII is comparable to extended half-life products, it is not considered to influence the comparison, which prophylactic treatment was used. From these data we conclude that baseline characteristics are comparable in the two studies.

Hemlibra vs. Elocta ITC [2,6]
Median age in HAVEN 3 is a little higher than in A-LONG, however, it is not considered to have any influence. The median ABR (all bleeds) before study start in the on-demand arm was 46.9 (26.1–73.9) in HAVEN 3 compared to a median ABR of 33,6 (Q1-Q3: 21.1-48.7 (mean data not available)) in the on-demand arm in A-LONG. Thus all patients had a lot of bleedings before entering the two studies, with the highest number of bleedings (28% higher) reported in HAVEN 3. As the prophylactic effect of short-acting FVIII is comparable to extended half-life products, it is not considered to influence the comparison, which prophylactic treatment was used. From these data we conclude that baseline characteristics are comparable in the two studies.

5.1 Clinical question 1

What is the clinical added value of emicizumab compared to standard FVIII products in patients with severe hemophilia A?

Population
Patients with severe hemophilia A (all ages) who have previously had prophylactic treatment with a FVIII product.

Intervention
Emicizumab administered subcutaneously 3 mg/kg once a week for the first 4 weeks (start-up dose) and then 1.5 mg/kg once weekly or 3 mg/kg every two weeks or 6 mg/kg every 4 weeks (maintenance dose).

Comparator
Kovaltry® (Prophylaxis)
The Medicines Council has defined Kovaltry to be used as representative comparator of the group of standard FVIII products. Hence, relevant published data for Kovaltry is used to address the clinical question within this application.

Outcomes

The outcomes defined by the Medicines Council [3] are shown in Table 5.

Table 5. **Outcomes defined by the Medicines Council**

Outcome*	**Importance**	**Category**	**Measurement**	**Minimum clinically relevant differences (absolute values)**
Annualized bleeding rate (ABR)	Critical	Severe symptoms and side efficacys	Median number of bleedings per patient in the study converted to per year	3 bleedings per year per patient
Discontinuation due to side effects	Important	Severe symptoms and side effects	Percentage of patients who stop due to side effects	5%
Severe venous thromboembolism	Important	Severe symptoms and side effects	Number of events	Difference of 2 events between each study
Quality of Life	Important	Health-related quality of life	Haem-A-QoL (adult), Haem-A-QoL-SF (young)	0.5 SD or 5 points

*For all efficacy measurements, data with the longest possible follow-up time is desired.

5.1.1 Presentation of relevant studies to answer clinical question 1

What is the clinical added value of emicizumab compared to standard FVIII products in patients with severe hemophilia A?

To answer the clinical question, the protocol states that Hemlibra should be compared to prophylaxis with Kovaltry, as a representative for the group of standard FVIII products. Information on the three selected relevant studies used to answer the clinical question is tabulated below.

Table 6 provides a compilation of study design, definition of efficacy template, etc.
Table 7 illustrates the differences and similarities in patient demographics/baseline data.

Table 6. **Studies used to answer the clinical question 1**			
	HAVEN 3	**LEOPOLD I**	**LEOPOLD II**
Reference	**Mahlangu 2018 [2]**	**Saxena 2016 [4]**	**Kavakli 2015 [5]**
Geography	Australia, Costa Rica, France, Germany, Ireland, Italy, Japan, Korea, Poland, South Africa, Spain, Taiwan, United Kingdom, United States	United States, Argentina, Austria, Croatia, Denmark, Germany, Hong Kong, India, Indonesia, Israel, Italy, Norway, Pakistan, Poland, Serbia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom	United States, Argentina, China, Colombia, Czech Republic, India, Indonesia, Japan, Mexico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Taiwan, Thailand, Turkey, Ukraine
Study period	SEP 2016 - SEP 2017	DEC 2009 – MAR 2013	JAN 2011 – DEC 2012
Intervention	**Hemlibra®** (Emicizumab): Four initial loading doses of 3.0 mg/kg per week, followed by a dose of either 1.5 mg/kg week or 3.0 mg/kg every 2 weeks (Arm B)	**Kovaltry®** (BAY 81-8973), Part B (efficacy and safety): Patients received 20–50 IU/kg administered two or three times per week for prophylaxis *Mean EMA dose is 30IU/kg Kovaltry 2,8 times a week*	**Kovaltry®** (BAY 81-8973): Prophylaxis low-dose: 20, 25 or 30 IU/kg twice per week Prophylaxis high-dose: 30, 35 or 40 IU/kg 3 times per week *Mean EMA dose is 30IU/kg Kovaltry 2,8 times a week*
Comparator	No prophylaxis (FVIII on-demand) (Arm C) Patients will continue to receive FVIII on an episodic basis for the treatment of breakthrough bleedings during the study.	Part A of the study: Kogenate FS (BAY14-2222) 50 IU/kg *(Recombinant Factor VIII)* Part B of the study: All patients received Kovaltry® according to prophylactic regimens though with potency (dose) determined by CS/EP (chromogenic substrate assay per European Pharmacopoeia) or CS/ADJ (chromogenic substrate assay /label adjusted to one-stage assay)	Kovaltry® on-demand treatment arm. The dosing for on-demand treatment was dependent on the location and severity of the bleed.
Design	Randomized (Arm A, B and C), global, multicenter, open-label, phase 3 study	Four-part, multinational, open-label, randomized, crossover, phase 1/3 study	Multicenter, open-label, randomized, crossover, phase 2/3 study
Inclusion criteria	e Additional eligibility criteria are listed in “Main characteristics”	Males aged 12–65 years with severe hemophilia A receiving on-demand or prophylactic treatment with any FVIII product, with ≥150 exposure days to any FVIII product	Males aged 12–65 years with severe hemophilia A who were receiving episodic treatment with FVIII at screening and had not received regular prophylaxis for >6 consecutive months in the previous 5 years.

Table 6. **Studies used to answer the clinical question 1**			
	HAVEN 3	**LEOPOLD I**	**LEOPOLD II**
		Additional eligibility criteria are listed in "Main characteristics"	Additional eligibility criteria are listed in "Main characteristics"
Age, median (min, max)	38.0 (13-77)	30.0 (12-61)	Prophylaxis twice/week group: 27.0 (14-54) Prophylaxis 3 times/week group: 28.0 (14-59)
Hemophilia type	Hemophilia A	Hemophilia A	Hemophilia A
Follow-up, weeks	Duration of exposure: 29.0 (0.1-50.1)	52-104	52
Time for primary outcome	24 weeks (6 months)	6 months	6 months
Definition of outcomes			
Annualized bleeding rate (ABR) Annualized bleeding rate = (number of bleeding episodes during the efficacy period / total number of days during the efficacy period)*365.25	**ABR All bleedings:** "All bleedings comprise both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded as for the primary analysis". **ABR based on treated bleedings:** "An event is considered a treated bleed if coagulation factors are administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). • Bleedings starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections are ≤ 72 hours apart, are considered the same bleed. • Any injection to treat the bleed, taken > 72 hours	**ABR in part B based on total bleedings:** defined as spontaneous and trauma-related bleedings, untreated bleedings and unspecified bleedings. Outcome is self-reported by patient.	**ABR based on total bleedings:** defined as spontaneous bleedings, trauma-related bleedings, untreated bleedings, and unspecified events for which treatment was administered. Outcome is self-reported by patient.

Table 6. **Studies used to answer the clinical question 1**			
	HAVEN 3	**LEOPOLD I**	**LEOPOLD II**
	after the preceding injection, is considered the first injection to treat a new bleed at the same location. • Any bleed at a different location is considered a separate bleed regardless of time from last injection. (From protocol)		
Severe venous thromboembolism	Percentage of participants with thromboembolic events defined as outcome	Not defined as an outcome Safety variables analyzed using summary statistics	Not defined as an outcome Safety variables analyzed using summary statistics
Discontinuation due to adverse effects	Percentage of participants with adverse events leading to withdrawal from treatment	Not defined as an outcome Safety variables analyzed using summary statistics	Not defined as an outcome Safety variables analyzed using summary statistics
Quality of life	Quality of life was investigated by the following assessments • Haem-A-QoL) (Patients aged 18 years or older) • Haemo-QoL-SF (Adolescents, 12-17 Years of Age) • Emicizumab Preference Survey	Quality of Life was investigated by the following assessments • Haemo-A-QoL questionnaire (Transformed Total Score of Haemo-QoL Questionnaire. The scoring system has 100 points. 0 is the worst possible score. 100 is the best possible score.)	Haem-A-QoL was not investigated/reported in study

Table 7. **Baseline characteristics in studies used to answer the clinical question 1**							
Study	**HAVEN 3 Arm A – Emicizumab 1 weekly (n = 36)**	**HAVEN 3 Arm B - Emicizumab every 2 weeks (n = 35)**	**HAVEN 3 Arm C – No prophylaxis (n = 18)**	**HAVEN 3 Arm D – Emicizumab 1 weekly (n = 63)**	**LEOPOLD I Total patients (n = 62)**	**LEOPOLD II Prophylaxis 2 per week (n = 28)**	**LEOPOLD II Prophylaxis 3 per week (n = 31)**
Reference	J. Mahlangu 2018 [2]	J. Mahlangu 2018 [2]	J. Mahlangu 2018 [2]	J. Mahlangu 2018 [2]	K. Saxena 2016 [4]	K. Kavakli 2014 [5]	K. Kavakli 2014 [5]
Age, (years) Median	36.5	41.0	40.0	36.0	30.0	27.0	28.0

Table 7. **Baseline characteristics in studies used to answer the clinical question 1**							
Study	**HAVEN 3 Arm A – Emicizumab 1 weekly (n = 36)**	**HAVEN 3 Arm B - Emicizumab every 2 weeks (n = 35)**	**HAVEN 3 Arm C – No prophylaxis (n = 18)**	**HAVEN 3 Arm D – Emicizumab 1 weekly (n = 63)**	**LEOPOLD I Total patients (n = 62)**	**LEOPOLD II Prophylaxis 2 per week (n = 28)**	**LEOPOLD II Prophylaxis 3 per week (n = 31)**
Range <18 yr., n (%)	19-77 0 (0)	20-65 0 (0)	16-57 1 (5.6)	13-68 7 (11.1)	12-61 10 (16.1)	14-54 4 (14.3)	14-59 4 (12.9)
Type of hemophilia, %	A: 100 %	A: 100 %	A: 100 %	A: 100 %	A: 100 %	A: 100 %	A: 100 %
Severity of hemophilia, %	Severe: 100%	Severe: 100%	Severe: 100%	Severe: 100%	Severe: 100%	Severe: 100%	Severe: 100%
Number of patients in previous prophylactic FVIII treatment, n (%)	0 (0)	0 (0)	0 (0)	48 (76.2)	50 (80.6)	0 (0) All patients were receiving episodic treat-ment with FVIII at screening	0 (0) All patients were receiving episodic treat-ment with FVIII at screening
Patients using FVIII product used before trial entry. Patients, n	36	34	18	63	NR	NR	NR
Patients using: Standard half-life, n (%)	31 (86.1)	31 (91.2)	15 (83.3)	53 (84.1)			
Extended half-life, n (%)	4 (11.1)	2 (5.9)	2 (11.1)	10 (15.9)			
Both, n (%)	1 (2.8)	1 (2.9)	1 (5.6)	0 (0)			
≥9 bleeding events in 24 weeks before trial entry, n (%)	9 (25.0)	5 (14.3)	4 (22.2)	53 (84.1)	NR	NR	NR
Number of bleedings in last 12 months before trial	NR	NR	NR	NR	Prior on-demand: 36.0	35.0	38.5

Table 7. **Baseline characteristics in studies used to answer the clinical question 1**							
Study	**HAVEN 3 Arm A – Emicizumab 1 weekly (n = 36)**	**HAVEN 3 Arm B - Emicizumab every 2 weeks (n = 35)**	**HAVEN 3 Arm C – No prophylaxis (n = 18)**	**HAVEN 3 Arm D – Emicizumab 1 weekly (n = 63)**	**LEOPOLD I Total patients (n = 62)**	**LEOPOLD II Prophylaxis 2 per week (n = 28)**	**LEOPOLD II Prophylaxis 3 per week (n = 31)**
entry, median					Prior prophylaxis: 4.0		
Target joints None, n (%) Yes, n (%) >1, n/total n (%)	2 (5.6) 34 (94.4) 20 / 34 (58.8)	8 (22.9) 27 (77.1) 22 / 27 (81.5)	3 (16.7) 15 (83.3) 14 / 15 (93.3)	37 (58.7) 26 (41.3) 18 / 26 (69.2)	18 (29.0) 44 (71.0)	3 (10.7) 25 (89.3)	3 (9.7) 28 (90.3)
Completed ≥24 weeks of trial at data cutoff, n	35	34	17	58	NR	NR	NR
Completed both 6 months periods, n (%)	NR	NR	NR	NR	61 (98.4)	28 (100.0)	31 (100.0)
NR: Not Reported							

5.1.2 Results per study

The results to answer clinical question 1 for the selected efficacy outcomes, are described quite briefly in the section below and are further indicated in the tables in Appendix 9.3 "Results per study", where the precise source of data is also listed

HAVEN 3 (Mahlangu 2018) [2]

Since the majority of Danish patients with severe hemophilia A (about 96%) are in prophylactic treatment [13], the Medicines Council has preferred only to including patients in prior prophylactic treatment as relevant to this application. Hence, the analysis of efficacy outcome, annualized bleeding rate (ABR) and quality of life will be based on data from Arm D.

For the safety outcomes; severe venous thromboembolism and discontinuation, data from all treatment arms (A, B, C and D) is included.

Annualized bleeding rate (ABR)

The median ABR for all bleedings and treated bleedings is show in table 8. Data show that patients on Hemlibra prophylaxis have a median ABR of 0.0 (treated bleeds) or 1.5 (all bleeds).

Severe venous thromboembolism

No severe venous thromboembolism was reported.

No serious adverse events (SAE) related to Hemlibra were seen, as well as no thrombotic or thromboembolic events were reported. No deaths, thrombotic microangiopathy or thrombotic events occurred.

To provide further documentation to the safety reporting of Hemlibra the latest corporate quarterly safety report for Hemlibra is included in appendix 8.6, including reported cases of TMA and other thrombotic events for the more than 1400 people with haemophilia A treated with Hemlibra in the clinical development programme and other programmes, as well as post-marketing use.

Discontinuation due to adverse effects

One participant discontinued due to reported adverse effects.

The patient was randomized to Arm B, prophylactic Hemlibra (3 mg/kg/2 weeks). Following several low-grade adverse events; lethargy, depressed mood, headache, insomnia, nightmare, pruritus and alopecia that were considered by the investigator to be related to Hemlibra the patient discontinued the study.

Quality of life

Haem-A-QoL (Patients aged 18 years or older)

In the Haem-A-QoL Total Score at Week 25, patients in Arm D had a mean change (improvement) from baseline of -3.02 points [14]

Haemo-QoL-SF (Adolescents, 12-17 Years of Age)

All 3 adolescent patients (12−17 years of age) had completed the Haemo-QoL-SF questionnaire at Week 25.

Low scores on Physical Health (denoting high levels of quality of life) were observed at baseline for each of the 3 adolescent patients who completed the Haemo-QoL-SF (18.8, 18.8, and 6.3). For the 2 patients reporting 18.8 at baseline, scores improved to 12.5 and 0.0 at Week 25, respectively. For the patient with a baseline score of 6.3, a reduction in Physical Health was observed at Week 25.

Emicizumab Preference Survey

Additional patient reported outcomes included patient preference for treatment with the Emicizumab Preference Survey (EmiPref).

The EmiPref survey was administered once during the study at Week 17.

- The EmiPref survey was completed by 95 of 134 eligible participants. 89 patients (94%) reported preferring subcutaneous Hemlibra over their previous intravenous treatment.
- 98% of patients previously on FVIII prophylaxis (Arm D) who completed the questionnaire (45 of 46 patients) favored Hemlibra.

The three reasons most frequently cited by patients for preferring HEMLIBRA prophylaxis over the former hemophilia treatment was “the frequency of treatments was lower”,” route of administration was easier”, and” worries about having a bleed were less” [14]

LEOPOLD I (Saxena 2016) [4]

Annualized bleeding rate (ABR)

The median ABR for all bleedings was 1.9 (table 8).

Severe venous thromboembolism

No serious venous thromboembolism was reported.

Discontinuation due to adverse effects

No patients withdrew due to AEs.

Quality of life

The mean Haemo-QoL-A total score (adults) at Baseline was 74.6 ± 16.7 points and remained nearly unchanged (median change: 2.0 points) up to the end of the 12-month treatment period (Ref. EPAR Kovaltry).

*LEOPOLD II (*Kavakli 2015*) [5]*

Annualized bleeding rate (ABR)

The median ABR for all bleedings was 2.0-4.0 (table 8).

Severe venous thromboembolism

Data of serious venous thromboembolism was not available.

Discontinuation due to adverse effects

No patients withdrew due to adverse effects.

Quality of life

Haem-A-QoL was not investigated/reported in the study.

5.1.3 Comparative analyses

The comparative analysis of data for Hemlibra (HAVEN 3) [2] with data for Kovaltry (LEOPOLD I and LEOPOLD II) [4,5] is performed as a narrative comparison of the four defined efficacy outcomes in alignment with the Medicines Council's recommendation. A narrative comparison is applied due to the absence of randomized studies comparing Hemlibra directly with Kovaltry. According to the clinical question the narrative comparison will include data form the selected studies for patient cohorts previously receiving FVIII prophylaxis. I.e. HAVEN 3 (arm D) and LEOPOLD I (Part B, Arm CS/EP and Arm CS/ADJ).

LEOPOLD II is not included in narrative comparison since all patients included in LEOPOLD II were previous treated with on demand FVIII (inclusion criterion).

Furthermore, to apply more insight to the critical efficacy outcome, median ABR, an indirect treatment comparison (ITC) will be applied for HAVEN 3 versus LEOPOLD II, as described previously.

Narrative analysis HAVEN 3 vs. LEOPOLD I [2,4]

Median Annual Bleeding Rate – Critical outcome

In LEOPOLD I both study arms represent individualized dosing in a cross-over design. Referring to table 8 the median ABR for Kovaltry study LEOPOLD I is 1.9 for both arms.
Median ABR for Hemlibra is 1.5 (Arm D) for all bleedings in HAVEN 3 and 0.0 (Arm D) for treated bleedings.

The study data shows a numeric reduction in median ABR of 0.4 in favor of Hemlibra. Furthermore, if compared to treated bleedings in HAVEN 3 a numeric difference of 1.9 is seen.

According to the protocol, 3 is defined as the minimum clinical relevant difference in ABR. Looking at a reported ABR for Kovaltry at 1.9 (LEOPOLD I) and 2.0 (LEOPOLD II) it is not possible to achieve a reduction in median ABR of 3. Hence, even with the most optimal prophylactic treatment (factor or non-factor) or gene therapy in the future with no reported bleedings (median ABR 0.0) this would not be sufficient to fulfill the defined minimum clinical relevant difference in ABR.

Table 8. **Narrative analysis – Hemlibra® vs. Kovaltry® prophylaxis**

Study	**HAVEN 3** **Mahlangu 2018 [2]** Arm A (weekly emicizumab, n=36) Arm B (weekly emicizumab, n=35) Arm D (weekly emicizumab, n=63) Arm D – NIS(weekly emicizumab, N=48)	**LEOPOLD I** **Saxena 2016 [4]** Part B CS/EP 6-month period arm (n=62) CS/ADJ 6-month period arm (n=61)	**LEOPOLD II** **Kavakli 2015 [5]** High dose arm(30-40 IU/kg/3xweek, n=36) Low dose arm(20-30 IU/kg/2xweek, n=28)
Median annualized bleeding rate (ABR)	<u>All bleedings</u> Arm A, ABR 0.6 (0.0-3.9) Arm B, ABR 1.6 (0.0-4.0) Arm D, ABR 1.5 (0.0-4.3) Arm D – NIS, ABR 3.3 (2.17-5.06) [2,14] <u>Treated bleedings</u> Arm A 1.5 (0.9-2.5) Arm B 1.3 (0.8-2.3) Arm D 0.0 (0.0-2.2) Arm D – NIS 0.0 (0.0-2.1)	<u>All bleedings</u> CS/EP 6-month period arm, 1.9 (0.0-4.4) CS/ADJ 6-month period arm, 1.9 (0.0-7.3)	<u>All bleedings</u> High dose arm, 2.0 (0.0-4.9) Low dose arm, 4.0 (0.0-8.0) Combined, 2.0 (0.0-7.0)
Quality of life	<u>Haem-A-QoL total score (Patients aged 18 years or older)[14]</u> Mean change from baseline: Arm D: -3.02	Haem-QoL-A total score (adults) Median change: -2.0 points (treatment end 12 months)	Not investigated

Table 8. **Narrative analysis – Hemlibra® vs. Kovaltry® prophylaxis**			
Study	**HAVEN 3** **Mahlangu 2018 [2]** Arm A (weekly emicizumab, n=36) Arm B (weekly emicizumab, n=35) Arm D (weekly emicizumab, n=63) Arm D – NIS(weekly emicizumab, N=48)	**LEOPOLD I** **Saxena 2016 [4]** Part B CS/EP 6-month period arm (n=62) CS/ADJ 6-month period arm (n=61)	**LEOPOLD II** **Kavakli 2015 [5]** High dose arm(30-40 IU/kg/3xweek, n=36) Low dose arm(20-30 IU/kg/2xweek, n=28)
	<u>Emicizumab Preference Survey</u> • 89 patients (94%) reported preferring subcutaneous Hemlibra over their previous intravenous treatment • 98% of patients previously on FVIII prophylaxis (Arm D) who completed the questionnaire (45 of 46 patients) favored Hemlibra		
Severe venous thromboembolism	None reported	None reported	Not available
Discontinuation due to side effects	One participant discontinued	None reported	None reported

ITC analysis HAVEN 3 vs. LEOPOLD II [2,5]

<u>Median Annual Bleeding Rate – Critical outcome</u>

To provide further insight to the numeric improvement in median ABR seen in the narrative comparison, an ITC for HAVEN 3 and LEOPOLD II has been performed, analyzing Arm A + Arm B pooled compared with Arm C in HAVEN 3 versus Arm 1 + Arm 2 pooled compared with Arm 3 in LEOPOLD II. Only LEOPOLD II is included in the ITC, since no on-demand treatment arm is included in LEOPOLD I making in-study comparison and calculation of on-demand versus prophylaxis not possible within the ITC.

According to the protocol and further correspondence with the Medicine Council the median ABR for all bleeds for Hemlibra should be used in the ITC. Hence, the ITC results mentioned below is based on number (n) of all bleeds calculated from median ABR for Hemlibra; 0.6 for Arm A, 1.6 for Arm B and 46.9 for Arm C, respectively [2].

From the ITC, a relative rate ratio of 0.13 (95% CI 0.12-0.15) and an absolute difference of 4.30 in ABR is found. Hereby, the result of the ITC provides further documentation to the numeric improvement seen from the narrative comparison and the absolute difference is greater than the defined clinical relevant difference in ABR of 3.

To further validate this result the ITC analysis has also been performed using annual number of all bleeds calculated from individual participant data for Hemlibra; 56 for Arm A, 58 for Arm B and 410 for arm C, respectively [14]. When using these data, a relative rate ratio of 0.41 (95% CI 0.38-0.43) and an absolute difference of 2.95 in ABR is found supporting the numeric improvement found within the ITC based on median ABR for Hemlibra.

For further information, the results of the ITC is listed in Table 30 and 31 in section 9.4. Results per PICO (clinical question).

Narrative analysis HAVEN 3 vs. LEOPOLD I & II [2,4,5]

For the narrative analysis of the two defined safety outcomes, Discontinuation due to side effects and Severe venous thromboembolism all data for patient receiving interventional treatment is included in the analysis. I.e. all data, in depended of what type FVIII treatment (on demand or prophylaxis) the patient received prior to study inclusion.

Discontinuation due to side effects – Important outcome

In HAVEN 3 one participant discontinued due to reported adverse effects. The patient was randomized to Arm B, prophylactic Hemlibra (3 mg/kg/2 weeks). Following several low-grade adverse events; lethargy, depressed mood, headache, insomnia, nightmare, pruritus and alopecia that were considered by the investigator to be related to Hemlibra the patients discontinued the study.

In LEOPOLD I and LEOPOLD II no patients discontinuing due to side effects were reported.

In comparison 1 out of 134 patients in HAVEN 3 discontinued their treatment due to side effects, which represents 0.74% and no patients (0%) discontinued in LEOPOLD I and LEOPOLD II.
According to the defined clinical minimum relevant difference of 5% the difference of 0.74% between Hemlibra and Kovaltry is not considered clinically relevant in the favor of Kovaltry.

Table 9. **Discontinuation due to side effects**

Study	**Total number of patients include**	**Number of patients discontinuing due to side effects**	**% of patients discontinuing due to side efficacy**
HAVEN 3	n = 134 (Arm A+B+D)	1	0.74
LEOPOLD I	n = 62	0	0
LEOPOLD II	n = 80	0	0

Narrative analysis HAVEN 3 vs. LEOPOLD I & II [2,4,5]

Severe venous thromboembolism – Important outcome

In HAVEN 3 no reported severe venous thromboembolism was seen. Furthermore, no serious adverse events (SAE) related to Hemlibra were reported. Furthermore, no deaths, thrombotic microangiopathy or thrombotic events occurred.

In LEOPOLD I no severe venous thromboembolism was reported and in LEOPOLD II no data of serious venous thromboembolism was available.

Comparing reported safety outcomes from HAVEN 3 with LEOPOLD I and LEOPOLD II no cases of severe venous thromboembolism were reported in neither of the studies.

Narrative analysis HAVEN 3 vs. LEOPOLD I [2,4]

Quality of Life – Important outcome

Referring to table 8 the Haemo-QoL-A total score has been reported in HAVEN 3 and LEOPOLD I. The narrative comparison is based on Haem-A-QoL data from HAVEN 3 Arm D, patients previous treated with FVIII prophylaxis prior to HAVEN 3 study entry and LEOPOLD 1 Arm 1, including a mix of patients previously treated with FVIII on-demand (20%) or prophylaxis (80%) prior to LEOPOLD I entry.

In HAVEN 3 Arm D a mean improvement of 3.02 points was reported at week 25 compared to baseline and in LEOPOLD I a median improvement of 2.0 points was reported, respectively. Hence, a small numeric absolute improvement in Haem-A-QoL Total Score is seen for Hemlibra compared to Kovaltry.

Conclusion – comparison between Hemlibra vs Kovaltry

In conclusion the reported median ABR for Hemlibra versus Kovaltry is numerically lower for Hemlibra (1.5) than for Kovaltry (1.9). The applied ITC provides further supports that Hemlibra prophylaxis results in a lower median ABR compared to Kovaltry prophylaxis (absolute difference 4.30).
Furthermore, for Quality of Life assessment, Haem-A-QoL Total Score a small numeric improvement is found for Hemlibra versus Kovaltry.
When comparing the two defined safety outcomes, Discontinuation due to side effects and Severe venous thromboembolism, only few to none adverse effects have been reported for Hemlibra and Kovaltry and the two safety outcomes is considered to be on par.
In conclusion Hemlibra prophylaxis provides added clinical value compared to patients treated with Kovaltry, a standard FVIII product.

5.2 Clinical question 2

What is the clinical added value of emicizumab compared to extended half-life FVIII products in patients with severe hemophilia A?

Population

Patients with severe hemophilia A (all ages) who have previously had prophylactic treatment with an FVIII product.

Intervention

Emicizumab administered subcutaneously 3 mg/kg once a week for the first 4 weeks (start-up dose) and then 1.5 mg/kg once weekly or 3 mg/kg every two weeks or 6 mg/kg every 4 weeks (maintenance dose).

Comparator

Elocta® (efmoroctocog alfa)

There is currently marketed two extended half-life FVIII products in Denmark. The Medicines Council has selected Elocta as comparator, since the Adynovi (Rurioctocog alfa pegol) is not approved to children below 12 years of age.

Outcome

The outcomes defined by the Medicines Council [3] are shown in Table 5.

5.2.1 Presentation of relevant studies to answer clinical question 2

To answer clinical question 2, the protocol states that Hemlibra should be compared to prophylaxis with Elocta, as a representative for the group of extended half-life FVIII products. The following studies are judged to be relevant in the comparison:

Table 10. **Studies used to answer clinical question 2**

	HAVEN 3	**A-LONG**
Reference	**Mahlangu 2018 [2]**	**Mahlangu 2014 [6]**
	Australia, Costa Rica, France, Germany, Ireland, Italy, Japan, Korea, Poland, South Africa, Spain, Taiwan, United Kingdom, United States	South Africa, United States, United Kingdom, Austria, Japan, India, Australia, Belgium, Brazil, Canada, France, Germany, Hong Kong, Israel, Italy, New Zealand, Spain, Sweden, Switzerland
Study period	SEP 2016 - SEP 2017	NOV 2010 – AUG 2012
Intervention	**Hemlibra®** (Emicizumab): Four initial loading doses of 3.0 mg/kg per week, followed by a dose of either 1.5 mg/kg per week (Arm A and D) or 3.0 mg/kg every 2 weeks (Arm B)	**Elocta®** (efmoroctocog alfa): Arm 1: (individualized dose) loading 25 IU/kg on day 1 and 4. Maintenance 25-65 IU/kg every 3-5 days Arm 2: (weekly dose) 65 IU/kg once weekly Arm 3: (episodic treatment)

Table 10. **Studies used to answer clinical question 2**		
	HAVEN 3	**A-LONG**
Comparator	No prophylaxis (FVIII on-demand) Arm C. Patients will continue to receive FVIII on an episodic basis for the treatment of breakthrough bleedings during the study.	Episodic (Elocta® on-demand) treatment arm. Patients received Elocta® 10-50IU/kg as required. *Mean EMA dose is 50IU/kg Elocta 1,8 times a week*
Design	Randomized, global, multicenter, open-label, phase 3 study	Open-label, non-randomized, multicenter, phase 3 study No randomization applied when allocating patients to treatment arms.
Inclusion criteria	Eligible male participants were 12 years of age or older with severe congenital hemophilia A without current factor VIII inhibitors who were receiving episodic or prophylactic factor VIII infusions. Additional eligibility criteria are listed in "Main characteristics"	Previously treated male patients aged ≥ 12 years with severe hemophilia A if treated prophylactically, or episodically prior to the study Additional eligibility criteria are listed in "Main characteristics"
Age, median (min, max)	38.0 (13-77)	Arm 1: 29 (12-65) Arm 2: 31.5 (18-59)
Hemophilia type	Hemophilia A	Hemophilia A
Follow-up (weeks), median (min, max)	Duration of exposure: 29.0 (0.1-50.1)	Arm1: 32.1 (9, 54) Arm2: 28.0 (<1, 38)
Time for primary outcome	24 weeks (6 months)	6 months
Definition of outcome		
Annualized bleeding rate (ABR) Annualized bleeding rate = (number of bleeding episodes during the efficacy period / total number of days during the efficacy period)*365.25	**ABR based on treated bleedings:** "An event is considered a treated **ABR All bleedings:** "All bleedings comprise both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded as for the primary analysis". **ABR based on treated bleedings:** "An event is considered a treated bleed if coagulation factors are administered to treat signs or	A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode.

Table 10. **Studies used to answer clinical question 2**		
	HAVEN 3	**A-LONG**
	symptoms of bleeding (e.g., pain, swelling, etc.). • Bleedings starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections are ≤ 72 hours apart, are considered the same bleed. • Any injection to treat the bleed, taken > 72 hours after the preceding injection, is considered the first injection to treat a new bleed at the same location. • Any bleed at a different location is considered a separate bleed regardless of time from last injection. (From protocol)	
Severe venous thromboembolism	Percentage of participants with thromboembolic events defined as outcome	Not defined as an outcome Safety variables analyzed using summary statistics
Discontinuation due to adverse efficacys	Percentage of participants with adverse effects leading to withdrawal from treatment defined as outcome	Not defined as an outcome Safety variables analyzed using summary statistics
Quality of life	Quality of life was investigated by the following assessments • Haem-A-QoL (Patients aged 18 years or older) • Haemo-QoL-SF (Adolescents, 12-17 years of Age) • Emicizumab Preference Survey	Quality of Life was investigated by • Haem-A-QoL Questionnaire

Table 11. **Baseline characteristics in studies used to answer the clinical question 2**						
Study	HAVEN 3 Arm A – Emicizumab 1 weekly (n = 36)	HAVEN 3 Arm B - Emicizumab every 2 weeks (n = 35)	HAVEN 3 Arm C – No prophylaxis (n = 18)	HAVEN 3 Arm D – Emicizumab 1 weekly (n = 63)	A-LONG Arm 1 - Individualized prophylaxis (n = 118)	A-LONG Arm 2 - Weekly prophylaxis (n = 24)
Reference	J. Mahlangu 2018 [2]	J. Mahlangu 2018 [2]	J. Mahlangu 2018 [2]	J. Mahlangu 2018 [2]	J. Mahlangu 2014 [6]	J. Mahlangu 2014 [6]
Age, (years) Median Range <18 yr, n (%)	 36.5 19-77 0 (0)	 41.0 20-65 0 (0)	 40.0 16-57 1 (5.6)	 36.0 13-68 7 (11.1)	 29.0 12-65 NR	 31.5 18-59 NR
Type of hemophilia, %	A: 100 %	A: 100 %	A: 100 %	A: 100 %	A: 100 %	A: 100 %
Severity of hemophilia, %	Severe: 100%	Severe: 100%	Severe: 100%	Severe: 100%	Severe: 100%	Severe: 100%
Number of patients in previous prophylactic FVIII treatment, n (%)	0 (0)	0 (0)	0 (0)	48 (76.2)	87 (73.7)	0 (0)
Patients using FVIII product used before trial entry. Patients, n Patients using: Standard half-life, n (%)	 36 31 (86.1)	 34 31 (91.2)	 18 15 (83.3)	 63 53 (84.1)	 NR	 NR

Table 11. **Baseline characteristics in studies used to answer the clinical question 2**						
Study	HAVEN 3 Arm A – Emicizumab 1 weekly (n = 36)	HAVEN 3 Arm B - Emicizumab every 2 weeks (n = 35)	HAVEN 3 Arm C – No prophylaxis (n = 18)	HAVEN 3 Arm D – Emicizumab 1 weekly (n = 63)	A-LONG Arm 1 - Individualized prophylaxis (n = 118)	A-LONG Arm 2 - Weekly prophylaxis (n = 24)
Extended half-life, n (%) Both, n (%)	4 (11.1) 1 (2.8)	2 (5.9) 1 (2.9)	2 (11.1) 1 (5.6)	10 (15.9) 0 (0)		
≥9 bleeding events in 24 weeks before trial entry, n (%)	9 (25.0)	5 (14.3)	4 (22.2)	53 (84.1)	NR	NR
Number of bleedings in last 12 months before trial entry, median	NR	NR	NR	NR	Prior on-demand: 27.0 Prior prophylaxis: 6.0	Prior on-demand: 29.5
Target joints None, n (%) Yes, n (%) >1, n / total n (%)	 2 (5.6) 34 (94.4) 20 / 34 (58.8)	 8 (22.9) 27 (77.1) 22 / 27 (81.5)	 3 (16.7) 15 (83.3) 14 / 15 (93.3)	 37 (58.7) 26 (41.3) 18 / 26 (69.2)	(1 or more target joints, n (%)): Prior on-demand: 26 (22.0) Prior prophylaxis: 47 (39.8)	(1 or more target joints, n (%)) Prior on-demand: 22 (91.7)
Completed ≥24 weeks of trial at data cutoff, n	35 (97.2)	34 (97.1)	17 (94.4)	58 (92.1)	NR	NR

Table 11. **Baseline characteristics in studies used to answer the clinical question 2**						
Study	HAVEN 3 Arm A – Emicizumab 1 weekly (n = 36)	HAVEN 3 Arm B - Emicizumab every 2 weeks (n = 35)	HAVEN 3 Arm C – No prophylaxis (n = 18)	HAVEN 3 Arm D – Emicizumab 1 weekly (n = 63)	A-LONG Arm 1 - Individualized prophylaxis (n = 118)	A-LONG Arm 2 - Weekly prophylaxis (n = 24)
Duration of treatment with rFVIIIFc in weeks, median (min., max)	NR	NR	NR	NR	32.1 (9-54)	28.0 (<1-38)

5.2.2 Results per study

The results, to answer clinical question 2 for the selected efficacy outcomes, are described in the section below and are further indicated in the tables in Appendix 9.3 "Results per study", where the precise source of data is also listed.

HAVEN 3 (Mahlangu 2018) [2]

See 5.1.2 for HAVEN 3 results

*A-LONG (*Mahlangu 2014) [6]

All patients on a prophylactic regimen prior to study entry were enrolled in Arm 1 (individualized prophylaxis regimen). Patients on an on-demand regimen prior to study were given the choice between either entering Arm 1 or to be randomized between Arm 2 (weekly prophylaxis regimen) or Arm 3 (on-demand).

Similar to clinical question 1 only study data representing patients on FVIII prophylaxis entering A-LONG is included in the narrative analysis of efficacy outcome, annualized bleeding rate (ABR) and quality of life, i.e. results reported in Arm 1.

Annualized bleeding rate (ABR)

Median ABR in Arm 1 is reported as 1.6

Severe venous thromboembolism

No patients experienced severe venous thromboembolism

Discontinuation due to adverse effects

Withdrawal due to adverse effect were 1 and 2 in Arm 1 (individual prophylaxis) and Arm 2 (weekly prophylaxis), respectively

Quality of life

The subgroup of patients who received pre-study prophylaxis and who were included in Arm 1 (individual prophylaxis) had an absolute mean change in Haem-A-QoL from baseline to week 28 of 2.0.

5.2.3 Comparative analyses

The comparative analysis of data for Hemlibra (HAVEN 3) [2] with data for Elocta (A-LONG) [6] is performed as a narrative comparison of the four defined efficacy outcomes.

As for clinical question 1, an ITC of the critical efficacy outcome, median ABR an indirect treatment comparison (ITC) will be applied for HAVEN 3 versus A-LONG.

Narrative analysis HAVEN 3 vs. A-LONG [2,6]

Median Annual Bleeding Rate – Critical outcome

Referring to table 12 the reported median ABR in Elocta study A-LONG is 1.6 for the individualized prophylaxis arm (Arm 1)
Median ABR for Hemlibra is 1.5 (Arm D) for all bleedings in HAVEN 3 and 0.0 (Arm D) for treated bleedings.

The study data shows a numeric reduction in median ABR of 0.1 in favor of Hemlibra. Furthermore, if compared to treated bleedings in HAVEN 3 a numeric difference improvement of 1.6 is seen.

Table 12. **Narrative analysis – Hemlibra® vs. Elocta® prophylaxis**

Study	**HAVEN 3** **Mahlangu 2018 [2]** Arm A (weekly emicizumab, n=36) Arm B (weekly emicizumab, n=35) Arm D (weekly emicizumab, n=63) Arm D – NIS(weekly emicizumab, n=48) NIS FVIII, n=48	**A-LONG** **Mahlangu 2014 [6]** Part B Arm 1 (individualized prophylaxis) (n=117) Arm 2 (weekly prophylaxis) (n=23)
Annualized bleeding rate (ABR)	All bleedings Arm A, ABR 0.6 (0.0-3.9) Arm B, ABR 1.6 (0.0-4.0) Arm D, ABR 1.5 (0.0-4.3) Arm D – NIS, ABR 3.3 (2.17-5.06) [2,14] Treated bleedings Arm A, ABR 1.5 (0.9-2.5) Arm B, ABR 1.3 (0.8-2.3) Arm D, ABR 0.0 (0.0-2.2) Arm D – NIS, ABR 0.0 (0.0-2.1)	All bleedings Arm 1, ABR 1.6 (0.0-4.7) Arm 2, ABR 3.6 (1.9-8.4)
Quality of life	Haem-A-QoL total score (Patients aged 18 years or older)[14] Mean change from baseline: Arm D: -3.02 Emicizumab Preference Survey • 89 patients (94%) reported preferring subcutaneous HEMLIBRA over their previous intravenous treatment • 98% of patients previously on FVIII prophylaxis (Arm D) who completed the questionnaire (45 of 46 patients) favored HEMLIBRA	Haem-A-QoL mean (SD) change score from baseline to week 28 Pre-study prophylaxis (Arm 1) Haem-A-QoL mean (SD) - 2.0 (8.0) P-value not significant

Table 12. **Narrative analysis – Hemlibra® vs. Elocta® prophylaxis**		
Study	**HAVEN 3** **Mahlangu 2018 [2]** Arm A (weekly emicizumab, n=36) Arm B (weekly emicizumab, n=35) Arm D (weekly emicizumab, n=63) Arm D – NIS(weekly emicizumab, n=48) NIS FVIII, n=48	**A-LONG** **Mahlangu 2014 [6]** Part B Arm 1 (individualized prophylaxis) (n=117) Arm 2 (weekly prophylaxis) (n=23)
Severe venous thromboembolism	None reported	None reported
Discontinuation due to side effects	One participant discontinued	2 patients, 1 in Arm 1 (individual prophylaxis) and 1 in Arm 2 (weekly prophylaxis)

ITC analysis HAVEN 3 vs. A-LONG [2,6]

Median Annual Bleeding Rate – Critical outcome

To provide further insight to the numeric improvement in median ABR seen from the narrative comparison an ITC is performed for HAVEN 3 and A-LONG, analyzing Arm A + Arm B pooled compared with Arm C in HAVEN 3 versus weekly prophylaxis arm compared with episodic treatment arm in A-LONG study. The individual prophylaxis arm is not randomized in A-LONG, and therefore an ITC is not possible for that arm. One could argue that this ITC is not relevant, but considering question 2 is looking at the comparison of FVIII with extended duration, and with a dosing of up to once every 4 weeks for Hemlibra, it seems reasonable to compare with the weekly dosing (65IU/kg) for Elocta from the patient's perspective, who would prefer a less frequent dosing. The minimum recommended dose in the EMA label is 50 IU/kg every 5 days, hence it should be mentioned that there is a difference in the weekly arm dosing (65IU/kg) in A-LONG and minimum recommended dose, which could affect the reported ABR result.

From the ITC, a relative rate ratio of 0.06 (95% CI 0.05-0.06) and an absolute difference of 7.01 in ABR is found. Hereby, the result of the ITC provides further documentation to the numeric improvement seen from the narrative comparison and the absolute difference is greater than the defined clinical relevant difference in ABR of 3.

To further validate this result the ITC analysis has also been performed using number of all bleeds calculated from individual participant data for Hemlibra; 56 for Arm A, 58 for Arm B and 410 for arm C, respectively [14]. When using these data, a relative rate ratio of 0.17 (95% CI 0.16-0.18) and an absolute difference of 6.17 in ABR is found supporting the numeric improvement found within the ITC based on median ABR for Hemlibra and the clinical relevant difference of 3 or more.

For further information the result of the ITC is listed in Table 30 and 31 in section 9.4. Results per PICO (clinical question).

Narrative analysis HAVEN 3 vs. A-LONG [2,6]

Discontinuation due to side effects – Important outcome

In HAVEN 3, one participant discontinued due to reported adverse effects. The patient was randomized to Arm B, prophylactic Hemlibra (3 mg/kg/2 weeks). Following several low-grade adverse events; lethargy, depressed mood, headache, insomnia, nightmare, pruritus and alopecia that were considered by the investigator to be related to Hemlibra the patients discontinued the study.

In A-LONG withdrawals due to side effects were 1 patient in Arm 1 and 2 patients in Arm 2.

In comparison one out of 134 patients in HAVEN 3 discontinued due to side effects, which represents 0.74%. Meanwhile, 2.14% discontinued in A-LONG.
According to the defined clinical minimum relevant difference of 5%, the difference between Hemlibra and Elocta is not considered clinically relevant in favor of Hemlibra.

Table 13. **Discontinuation due to side effects**

Study	**Total number of patients include**	**Number of patients discontinuing due to side effects**	**% of patients discontinuing due to side efficacy**
HAVEN 3	n = 134 (Arm A+B+D)	1	0.74
A-LONG	n = 140 (Arm 1 + 2)	3	2.14

Narrative analysis HAVEN 3 vs. A-LONG [2,6]

Severe venous thromboembolism – Important outcome

In HAVEN 3 no reported severe venous thromboembolism was seen. Furthermore, no serious adverse events (SAE) related to Hemlibra were reported as well as deaths, thrombotic microangiopathy or thrombotic events occurred.

In A-LONG no patients experienced severe venous thromboembolism.

Comparing reported safety outcomes from HAVEN 3 with A-LONG studies no cases of severe venous thromboembolism were reported in neither of the two studies.

Narrative analysis HAVEN 3 vs. A-LONG [2,6]
Quality of Life – Important outcome

Referring to table 12 the Haem-A-QoL total score has been reported in HAVEN 3 and A-LONG. The narrative comparison is based on Haem-A-QoL data from HAVEN 3 Arm D, patients previous treated with FVIII prophylaxis prior to HAVEN 3 study entry and A-LONG Arm 1, including patients previous treated with FVIII prophylaxis.

In HAVEN 3 Arm D a mean improvement of 3.02 points was reported at week 25 compared to baseline and in A-LONG a mean improvement of 2.0 points was reported. Hence, a small numeric absolute improvement in Haem-A-QoL Total Score is seen for Hemlibra compared to Elocta.

Conclusion – comparison between Hemlibra vs Elocta [2,6]

The reported median ABR for Hemlibra versus Elocta is numeric lower for Hemlibra (1.5) than for Elocta (1.96). The applied ITC provides further supports that Hemlibra prophylaxis results in a lower median ABR compared to Elocta prophylaxis (absolute difference 7.01).
Furthermore, for Quality of Life assessment, Haem-A-QoL Total Score a small numeric improvement is found for Hemlibra versus Elocta.
When comparing the two defined safety outcomes, Discontinuation due to side effects and Severe venous thromboembolism, only few to none adverse effects have been reported for Hemlibra and Elocta and the two safety outcomes is considered to be on par.
In conclusion Hemlibra prophylaxis provides added clinical value compared to patients treated with Elocta, an extended half-life FVIII product.

6 Other considerations

6.1 Administration of Hemlibra

The frequency of administration of FVIII prophylaxis is particularly challenging for pediatric and older patients due to poor venous access and tolerance to repeated venipuncture, which can lead to excessive bleeding or bruising and permanent damage to the veins. Port-a-caths, which are standard of care for children in Denmark, have been used to overcome technical difficulties and make prophylaxis feasible in the very young pediatric population. However, it should be noted that insertion of a Port-a-cath requires surgical intervention and may result in complications, including mechanical failure, dehiscence of the skin over the reservoir, infection, and thrombosis [15] In addition, as pediatric patient grows, the port-a-cath needs to be replaced.

The fact that Hemlibra is administered as a SC injection also reduces the treatment load for each patient switching from FVIII products to Hemlibra. Data from HAVEN 3 shows that Hemlibra was preferred by most of the patients when asked in the EmiPref survey. The survey was completed by 95 of 134 eligible participants (71%). Of all the survey respondents, 94% (95% CI, 87 to 98) preferred Hemlibra, and 45 of 46 participants (98%; 95% CI, 88 to 100) in group D favored Hemlibra over FVIII prophylaxis [2].

The recommended doses of subcutaneous injection of Hemlibra® is 3 mg/kg once weekly for the first 4 weeks (loading dose), followed by maintenance dose of either 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks [1]. The dosing interval of injections every four weeks was recently added to the posology, and allows for an even less frequent administration of Hemlibra.

The long half-life of Hemlibra provides a huge advantage compared to current standard and extended half-life FVIII products, which should be administered as infusions 2-4 times a week and potentially daily in patients with repeated break-through bleedings, high clearance and/or to prevent bleedings in patients with high physically activity level. Real world data from Sweden [16] indicates that a substantial proportion of patients with hemophilia A (23%) had ‘other’ as dose frequency, the majority of whom received irregular dose frequencies of ≥3 times a week. In addition, in Sweden 14% of patients received daily prophylaxis treatment [16].

In the recently published protocol *Protokol for Medicinrådets behandlingsvejledning for hæmofili A [17]* the outcome ‘Weekly number of doses’ is defined as important. Even though it is not considered in the clinical

question referring to Hemlibra, it is indeed as relevant for Hemlibra as for extended half-life FVIII products. As presented in Table 14 based on mean EMA dosing, Hemlibra reduces the dosing compared to Kovaltry from 2.8 per week to 0.25 per week or 11.2 doses every 4 weeks compared to 1 dosing every 4 weeks – an absolute difference of 2.55 doses per week or 10.2 doses every 4 weeks. Compared to Elocta the dosing of Elocta is reduced from 1.8 per week to 0.25 per week or 7.2 doses every 4 weeks compared to 1 dosing every 4 weeks – an absolute difference of 1.55 doses per week or 6.2 doses every 4 weeks, indicating a clinically relevant reduction.

Table 14. **Number of weekly doses**

Outcome	**Importance**	**Emicizumab [1]**	**Kovaltry [18]**	**Elocta [19]**	**Minimal clinical relevant difference**
Number of weekly doses	Important	0.25*	2.8#	1.8#	1 dose per week

*When dosing of emicizumab every 4 week #Calculated as mean EMA indicated dosing regime

Furthermore, the ease of subcutaneous administration versus intravenous administration provides an advantage for patients with difficult venous access, e.g. in children or elderly but also in patients with impaired motor skills in hands, arms and elbow joints due to arthropathy. As a parent or relative subcutaneous administration is also easier to handle and execute. The subcutaneous administration also reduced the time required for administration, which in addition can increase adherence to treatment.

The flexible dosing and less cumbersome subcutaneous administration of Hemlibra is an advantage in patients known to have a poor adherence or who experience repeated break-through bleeds despite being on standard and extended half-life FVIII prophylaxis.

In the protocol for evaluation of Hemlibra section 8 [3], some disadvantages of using emicizumab is mentioned:

- Introduction of emicizumab might increase the number of emergency room visits, because patients/parents will lose routine in administration of FVIII products.
    - From discussion with an expert in relation to the development of the economic analysis of Hemlibra it was identified that about 80 % of all children with break through bleedings on FVIII products already now visit the emergency room in case of a bleeding, so the additional impact seems rather small. In addition, there are very low bleeding rates associated with Hemlibra treatment [20]
- Treatment of PUPs with Hemlibra will not learn parents to administer FVIII products.
    - PUPs are not relevant in this report, as they are not in scope for treatment with Hemlibra in Denmark at this point.
- There is little experience regarding surgery during Hemlibra prophylaxis.
    - At EAHAD 2019 data was published from HAVEN 3 showing that of the 151 patients enrolled into the study, 30 patients underwent 50 surgeries. The conclusion was that major or minor surgical procedures were performed safely in these patients while receiving emicizumab

prophylaxis. Most minor procedures were performed with no or limited additional FVIII (Ref OR15 – Surgical procedures in persons with hemophilia A (PwHA) without inhibitors receiving emicizumab – experience from the HAVEN 3 study) [21].
    - In discussion with an expert in relation to the development of the economic analysis of Hemlibra it was identified that there are very few surgeries amongst hemophilia A patient in Denmark. In addition, it was anticipated that there would potentially be a reduction in hospitalizations associated with surgery for patients treated with Hemlibra [20].
- Treatment with Hemlibra can't be monitored biochemically in the same way as FVIII can.
    - At EAHAD 2019 an abstract was presented describing an assay for quantification of Hemlibra in patients (ref P027 – The effect of Hemlibra on assays of factor VIII activity in severe haemophilia A patients and artificially spiked plasma) [22].

6.2 Consideration of subpopulations

Many patients with hemophilia A treated with short or extended half-life FVIII products have very few or no bleedings and are thus well treated [23]. The advantage of switching to Hemlibra for these patients is an improvement in quality of life, as a result of a much easier administration of the drug. However, there are some patients that are not well treated on the existing FVIII treatments – patients with repeated break through bleedings, especially joint bleedings, that might cause disability in the long term. The extent of development of arthropathy is correlated with the number and extent of joint bleeding [24], therefore it is appropriate to ensure as low a bleeding rate as possible. As stated in the protocol p14: *The goal of prophylactic treatment is to avoid life-threatening bleeding and to prevent repeated joint bleeding, causing joint damage and later disability [3].* These patients with repeated bleedings should have the possibility for reduction of bleedings through treatment with Hemlibra, and a life expectancy of less disability.

There exists no common consensus regarding the acceptable level of break through bleedings in patients with hemophilia A. Therefore, we have taken a conservative approach, and looked at benefits for patients with 3 or more annual breakthrough bleedings in switching from common prophylactic treatment to Hemlibra prophylaxis. Selection of an ABR of 3 is also derived from existing protocol from the Medicines Council, which state that a reduction in a median ABR of 3 is clinically relevant [3].

For the purpose of this sub analysis we use data from HAVEN 3 arm D compared to data from the prospective non-intervention study (NIS) BH29768 [25], that evaluates real-world data on bleeding incidence, HRQoL and safety in patients with hemophilia A with and without inhibitor in standard prophylactic treatment (ie, FVIII or by-passing agents). In the NIS patients should have received more than 6 months on-demand or prophylaxis with FVIII. Data for bleeding incidents and medication were collected prospectively using identical definitions and criteria for bleedings and other parameters as used in the subsequent HAVEN 3 study. Good compliance with data reporting was achieved in both studies [2,25]. The duration of the 2 studies was similar. The NIS study was conducted with the same quality as a phase III study, including ongoing data cleaning. The robustness of the NIS study allows for a real intra-patient comparison. The validity of data from this NIS is substantiated by the prospective, highly structured design and verified by comparison of bleeding rates in a series of studies of patients in FVIII prophylaxis.

The median ABR was 1.8 for the patients in prophylactic treatment in the NIS, a median ABR which correspond to what is reported in the literature [25]. The article by Berntorp et al. [16] is a European retrospective study of real life hemophilia treatment in Belgium, France, Germany, Italy, Spain, Sweden and

England. Data for Sweden showed a median ABR of 1.0 (Q1, Q3; 0-2), which is the lowest reported median ABR in the 7 countries [16]. It is assumed that treatment of Swedish hemophilia patients is comparable or better compared to the Danish conditions. Furthermore, the AHEAD study [26] showed a median ABR of 1.7, 1.6 and 2.2 after 1, 2 and 3 years of observation, respectively.

Data are analyzed by intra-patient comparison, meaning that data from the NIS study represents the baseline for HAVEN 3. This study design is ideal to use in a conditions as hemophilia A, as the disease is not a progressive disease. Intra-patient comparison is a more robust design than a random design, as it eliminates a potential bias, that could arise, when known and unknown patient characteristics are unbalanced between the different treatment arms. Especially regarding small sample size, it is not easy to balance all patient characteristics in a randomized study. In an intra-patient comparison, patient characteristics are automatically balanced, because the treatment comparison is within one patient, this means that each patient is their own control.

The NIS enrolled 221 patients, where of 94 patients didn't develop inhibitor and 49 patients received FVIII prophylaxis. The prophylactic treatment was kept constant throughout the study period, with the exception of 4 patients who switched from on-demand treatment to prophylaxis during the study period. The median observation time was 30 weeks (12-48) and the median age of the patients in prophylactic treatment was 35 years (13-68), 6 patients were ≥12 - <18 years. For 32 of these patients, there were data on the bleeding frequency in the previous 6 months based on patient records, showing a median number of bleedings of 1.0 (range 0-13) [ref 6]. ABR during the NIS was 2.7 (0-9.4) for all bleedings. Of the 49 patients in prophylactic treatment, 41 were on short-acting FVIII with a median dose per week at 2.9 (2.1-3.1), while 9 patients received EHL FVIII treatments with a median ABR of 2.1 (1.1-2.2) doses per week. One patient in the NIS died of a myocardial infarction, why 48 patients were included in HAVEN 3 arm D [25].

Result of subgroup analysis

Patients from HAVEN 3 arm D that had previously been on prophylactics during the entire duration of the NIS (n=44) was analyzed. 18 patients from the group had an ABR (all bleedings) of ≥ 3 (Table 15). Treatment of this group of patients with a need for better prophylaxis indeed have an impact of the median ABR reducing it from 9.42 to 0.99, with a reduction of 8.43 [14].

Table 15. **Patients with <3 vs ≥ 3 annual bleedings (all bleedings) [14]**

	n	Median ABR NIS	Median ABR HAVEN 3
ABR < 3	26	0.00	0.94
ABR ≥ 3	18	9.42	0.99

Thus patients with repeated break through bleedings have a huge reduction of bleedings when switching from prophylaxis with short acting or extended half-life FVIII to Hemlibra prophylaxis.

7 References

1. Hemlibra (emicizumab). Summary of Product Characteristics. European Medicines Agency 2019.
2. Mahlangu J, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018 Aug 30;379(9):811-822.
3. Medicinrådets protokol for vurdering af klinisk merværdi for emicizumab til behandling af hæmofili A. Medicinrådet. 2019.
4. Saxena, K.; Lalezari, S.; Oldenburg, J. et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Hemophilia. 2016.
5. Kavakli, K.; Yang, R.; Rusen, L. et al. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). J Thromb Haemost. 2015.
6. Mahlangu, J.; Powell, J. S.; Ragni, M. V. et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014.
7. Wyrwich, K. W.; Krishnan, S.; Auguste, P. et al. Changes in health-related quality of life with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. Hemophilia. 2016.
8. Elocta (efmoroctocog alfa). European Public Assessment Report. European Medicines Agency. 2019.
9. Bucher HC, Guyatt GH, Cook DJ, Holbrook A, McAlister FA. Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the efficacy of an intervention on surrogate end points. Evidence-Based Medicine Working Group. Jama. 1999;282(8):771-8.
10. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-91.
11. Bland JM, Altman DG. Applying the right statistics: analyses of measurement studies. Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2003;22(1):85-93.
12. Eloctate. Full Prescribing Information. U.S. Food and Drug Administration. 2014
13. Nordic Hemophilia Guidelines version 1, valid until 31. December 2017. (www.nordhemophilia.org)
14. Data on file. Roche. 2019.
15. Epstein J, Xiong Y, Woo P, et al. Retrospective analysis of differences in annual factor VIII utilization among hemophilia A patients. Haemophilia. 2012.
16. Berntorp E, Dolan G, Hay C, et al. European retrospective study of real-life haemophilia treatment. Haemophilia. 2017 Jan;23(1):105-114
17. Protokol for Medicinrådets behandlingsvejledning for hæmofili A. Medicinrådet. 2018.
18. Kovaltry (octocog alfa). Summary of Product Characteristics. European Medicines Agency 2019.
19. Elocta (efmoroctocog alfa). Summary of Product Characteristics. European Medicines Agency 2019.
20. Expert opinion for cost analysis. Clinical expert. 2019.
21. OR15 - Surgical procedures in persons with haemophilia a (PWHA) without inhibitors receiving emicizumab – Experience from the HAVEN 3 study. Santagostino, E.; Parnes, A.; Dhalluin, C. et al. EAHAD 2019 (abstract OR15)
22. P027 - The effect of emicizumab on assays of factor VIII activity in severe haemophilia A patients and artificially spiked plasma. Bowyer, A.; Kitchen, S.; Maclean, R. et al. EAHAD 2019 (abstract P027)

23. Det gode liv: livskvalitetsundersøgelse blandt danske blødere 2012. - Kbh. : Danmarks Bløderforening, 2013.
24. Gringeri, A.; Ewenstein, B.; Reininger, A. The burden of bleeding in haemophilia: is one bleed too many? Haemophilia. 2014.
25. Kruse-Jarres, R.; Oldenburg, J.; Santagostino, E. et al. Bleeding and safety outcomes in persons with haemophilia A without inhibitors: Results from a prospective non-interventional study in a real-world setting. Haemophilia. 2019.
26. Khair K, Mazzucconi MG, Parra R et al. Pattern of bleeding in a large prospective cohort of haemophilia A patients: A three-year follow-up on the AHEAD study. Haemophilia 2018

8 Appendix

8.1 Main characteristics from selected studies

Non-intervention study as recruitment basis for HAVEN 3

Prior to initiating HAVEN 3 a non-intervention study (NIS) (BH29768/NCT02476942) was conducted. The NIS is a global, non-interventional study prospectively collecting real-world data in patients with hemophilia with and according to local routine clinical practice to characterize annualized bleeding rate (ABR), hemophilia treatment practices and adverse events (AEs) in adults/adolescents.

Eligible patients participating in the NIS could subsequently be enrolled in HAVEN 3, enabling the intra-individual comparison of reported data in NIS (FVIII prophylaxis) versus reported data in HAVEN 3 (Arm D), including intra-individual comparison of primary endpoint, Annualized bleeding rate (ABR) and secondary efficacy and safety endpoints. Hence, knowledge of both design and data from this study is important in order to have the full perspective of the results from HAVEN 3.

Since the NIS is not a randomized study, it is not included as an individual selected study in this application. Instead, it the results from intra-individual comparisons are reported as part of the results of HAVEN 3 (Table 8 on page 21.)

Main characteristics

Table 16. **Main characteristics HAVEN III (Hemlibra)**

Trial name	A Clinical Trial to Evaluate Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3)
NCT number	NCT02847637
Objective	A clinical trial to evaluate the efficacy, safety and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A participants without inhibitors
Publications – author, title, journal, year	Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018;379(9):811-22.
Study type and design	This is a randomized, global, multicenter, open-label, phase 3 clinical study in participants with severe hemophilia A without inhibitors against Factor VIII (FVIII) who are 12 years or older. Participants receiving previous episodic therapy with factor VIII were randomly assigned in a 2:2:1 ratio to receive emicizumab once weekly (group A) or every 2 weeks (group B) or to receive no prophylaxis (group C). Participants who had been receiving adequate prophylactic factor VIII, as

	determined by the investigator, were assigned to receive once weekly emicizumab (group D)
Follow-up time	Median duration of exposure in weeks, all patients (range): 29.0 (0.1-50.1) Group A: 29.3 (17.3–49.1) Group B: 30.1 (6.1–50.1) Group C: 7.1 (0.1–26.1) Group D: 33.1 (18.0–48.1)
Population (inclusion and exclusion criteria)	Inclusion criteria: • Body weight >/= 40 kilogram (kg) at the time of screening • Diagnosis of severe congenital hemophilia A • Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks • Adequate hematologic function • Adequate hepatic function • Adequate renal function • For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of less than (<) 1 percent (%) per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug Exclusion criteria: • Inherited or acquired bleeding disorder other than hemophilia A • Previous or current treatment for thromboembolic disease or signs of thromboembolic disease • Conditions that may increase risk of bleeding or thrombosis • History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection • Known human immunodeficiency virus (HIV) infection with cluster of differentiation (CD) 4 count <200 cells per microliter (cells/mcL) within 24 weeks prior to screening. Participants with HIV infection who has CD4 greater than (>) 200 and meet all other criteria are eligible • Use of systemic immunomodulators at enrollment or planned use during the study, with the exception of anti-retroviral therapy • Participants who are at high risk for thrombotic microangiopathy (TMA) (for example, have a previous medical or family history of TMA), in the investigator's judgment • Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the participant's safe participation in and completion of the study

	• Planned surgery (excluding minor procedures) during the study • Receipt of emicizumab in a prior investigational study; an investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration; a non-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
Intervention	Hemlibra® (Emicizumab): Group A: Four initial loading doses of 3.0 mg per kilogram of body weight per week, followed by a dose of 1.5 mg per kilogram per week Group B: Four initial loading doses of 3.0 mg per kilogram of body weight per week, followed by a dose 3.0 mg per kilogram every 2 weeks Group C: No prophylaxis treatment Group D: Four initial loading doses of 3.0 mg per kilogram of body weight per week, followed by a dose of 1.5 mg per kilogram per week
Baseline characteristics	See table 7: "Baseline characteristics in studies used to answer the clinical question 1"
Primary and secondary endpoints	Primary endpoint: - Annualized Bleeding Rate (ABR) for treated bleeds (from baseline to at least 24 weeks). Assessed using a negative binomial (NB) regression model, which accounts for different follow-up times. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor Secondary endpoints: - Annualized Bleeding Rate (ABR) for all bleeds, treated joint bleeds, treated spontaneous bleeds and treated target joint bleeds - Intra-participant comparison of ABR for treated bleeds and all bleeds - Quality of Life measured by Haem-A-QoL, Haemo-QoL-SF, EQ-5D-5L index utility score and VAS - Safety and tolerability All 26 secondary endpoints are described at clinicaltrials.gov
Method of analysis	For bleeding-related end points, comparisons of bleeding rate (which were calculated over the entire efficacy period) were performed with the use of a negative binomial-regression model. The model included the stratification factor (<9 or ≥9 bleeding events in the previous 24 weeks; see the Supplementary Appendix) and accounted for various follow-up times to determine the bleeding rate per day, which was converted to an annualized bleeding rate. The Haem-A-QoL scores were analyzed by means of analysis of variance (groups A vs. C and B vs. C, with baseline score and treatment by baseline interaction term included as covariates). The type I error for secondary end points was controlled with the use of a hierarchical testing framework,

	and the first two tests were the primary comparisons of group A with group C and of group B with group C (see the Supplementary Appendix). The safety of emicizumab therapy was analyzed with the use of all the data collected during exposure to emicizumab (including in group C after the switch to emicizumab). Missing data that were related to the Haem-A-QoL and EmiPref assessments were considered to be missing completely at random, and no imputation was applied to the analyses (see the statistical analysis plan in the Supplementary Appendix).
Subgroup analyses	N/A

Table 17. **Main characteristics LEOPOLD I (Kovaltry)**	
Trial name	Trial to Evaluate the Efficacy and Safety of a New Full Length Recombinant Human FVIII for Hemophilia A (Leopold I)
NCT number	NCT01029340
Objective	The overall objective of the study is to assess the pharmacokinetics, safety, tolerability and efficacy of prophylaxis treatment with BAY81-8973 (Kovaltry®) over a one-year period. Furthermore, the study will compare two different assays for measuring the amount of study drug.
Publications – author, title, journal, year	Saxena K, Lalezari S, Oldenburg J, Tseneklidou-Stoeter D, Beckmann H, Yoon M, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Haemophilia. 2016;22(5):706-12.
Study type and design	Phase 1/3, randomized, open-label, crossover, multicenter study. Part A pharmacokinetics: Patients received Kovaltry® and rFVIII-FS separated by a washout period in a crossover design. Part B efficacy and safety: Patients were randomized to either Kovaltry® with dose determined by CS/EP or CS/ADJ for period and crossover followed by another 6-month treatment period. Part C major surgery: Patients not participating in part A or B who were scheduled for major surgery.
Follow-up time	52 weeks (to 104 weeks including extension period)
Population (inclusion and exclusion criteria)	Inclusion criteria: • Male, aged 12 to 65 years • Severe hemophilia A defined as < 1% FVIII:C • >/= 150 days of previous treatment with FVIII in lifetime • Currently receiving on-demand or any type of prophylaxis treatment regimen with any FVIII product • No history of or current FVIII inhibitors Exclusion criteria:

	• Presence of another bleeding disease that is different from hemophilia A (e.g., von Willebrand disease, hemophilia B) • Low platelet count, abnormal kidney function, or liver disease • Received treatment with immune suppressing drugs within the last 3 months prior or requires treatment during the study. (Some drugs for hepatitis C, Human immunodeficiency virus (HIV), and steroids are allowed) • Receiving or has received other experimental drugs within 3 months prior to study entry • Allergy to Factor VIII or hamsters or mouse protein
Intervention	Kovaltry® (BAY 81-8973): Part A (pharmacokinetics): Patients received a single 50 IU kg_1 dose (dose determined by CS/EP) of intravenous BAY 81-8973 and rFVIII-FS separated by at least a 3-day washout period in a crossover design. Part B (efficacy and safety): Patients received 20–50 IU/kg administered two or three times per week for prophylaxis Part C (efficacy and safety during major surgery): Dosing of BAY 81-8973 was based on CS/EP potency (two patients were dosed based on CS/ADJ); patients only received BAY 81-8973 from pre-operation to discharge.
Baseline characteristics	

	Total patients (n = 62)
Age (years)	
Mean ± SD	31.5 ± 12.7 (<18 years: n = 10)
Median (range)	30.0 (12–61)
Race, n (%)	
White	55 (88.7)
Black	4 (6.5)
Hispanic or undefined	3 (4.8)
Weight (kg)	
Mean ± SD	77.0 ± 17.1
Median (range)	77.4 (39–121)
BMI (kg/m^2)	
Mean ± SD	25.3 ± 4.7
Median (range)	25.6 (16–37)
Previous treatment, n (%)	
On-demand	12 (19.4)
Prophylaxis	50 (80.6)
Target joint present, n (%)	44 (71.0)
Number of bleeds in last 12 months (previous on-demand patients)	
Mean ± SD	30.9 ± 20.8
Median (range)	36.0 (0–55)
Number of bleeds in last 12 months (previous prophylaxis patients)	
Mean ± SD	6.9 ± 8.6
Median (range)	4.0 (0–40)
Number of joint bleed in last 12 months	

	Mean ± SD Median (range)	8.0 ± 11.9 3.5 (0–55)
Primary and secondary endpoints	Primary endpoint Part A: - To demonstrate the pharmacokinetic non-inferiority of KOVALTRY as compared to Kogenate FS using bioequivalence criteria following single dose administration. Primary endpoint Part B: - Annualized number of total bleeds 12 months after randomization Secondary endpoint Part A: - To evaluate the in vivo recovery of Human factor VIII (FVIII) plasma levels 15 minutes post single injection of KOVALTRY. Secondary endpoints Part B: - Annualized number of bleeds in each 6-month potency assignment period - Quality of Life measured by Haem-A-QoL, EQ-5D index utility score Secondary endpoints Part A, B and C: - Number of Participants with Incidence of Inhibitory Antibody Formation - Number of Participants with Incidence of Antibody Formation to Heat-shock Protein (HSP-70) All 16 secondary endpoints for Part A, B and C are described at clinicaltrials.gov	
Method of analysis	Efficacy data were assessed for the intent-to-treat (ITT) population (all patients with infusion/bleeding data) Annualized bleeding rate (ABR) were measured as annualized number of total bleeding episodes, defined as spontaneous and trauma-related bleeds, untreated bleeds and unspecified bleeds in each 6-month potency period and over the whole year independent of potency. Safety was determined for the safety population (all patients who received study drug). Summary statistics (e.g. mean, SD, median) and frequencies were calculated for continuous and categorical data respectively.	
Subgroup analyses	Exploratory subgroup analyses were conducted for comparison of patients receiving twice-weekly vs. three times-weekly prophylaxes (patient characteristics; dose per infusion; ABR).	

Table 18. **Main characteristics LEOPOLD II (Kovaltry)**	
Trial name	A Trial to Compare Prophylaxis Therapy to On-demand Therapy With a New Full Length Recombinant FVIII in Patients With Severe Hemophilia A (Leopold II)
NCT number	NCT01233258
Objective	The overall objective of the study is to compare prophylaxis therapy to on-demand therapy with recombinant FVIII in patients with severe hemophilia A
Publications – author, title, journal, year	Kavakli K, Yang R, Rusen L, Beckmann H, Tseneklidou-Stoeter D, Maas Enriquez M, et al. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length

<table>
<tr><td></td><td>plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). J Thromb Haemost. 2015;13(3):360-9.</td></tr>
<tr><td>Study type and design</td><td>A Phase 2/3 randomized, open-label, crossover, multicenter study. Patients were randomized in a 3:1 ratio between prophylaxis and on-demand treatment arms. The prophylactic group were further randomized and assigned to either prophylaxis two or three times weekly.
Patients received treatment based on CS/EP or CS/ADJ for 6 months each with an intra individual crossover after 6 months. Patient assignment was performed using a centralized telephone interactive voice response system or interactive web response system.
Patients were crossed over within their respective treatment groups (prophylaxis or on-demand) to the other potency treatment regimen for another 6 months while maintaining the same nominal treatment dose</td></tr>
<tr><td>Follow-up time</td><td>52 weeks</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria:
Male, aged 12 to 65 years
Severe hemophilia A
History of more than 150 exposure days (ED) with clotting factor concentrates
Currently receiving episodic treatment with FVIII; no regular prophylaxis for more than 6 consecutive months in the past 5 years
No current Factor VIII inhibitor or history of inhibitor
Willing to use electronic patient diary
Exclusion criteria:
Presence of another bleeding disease that is different from hemophilia A
Thrombocytopenia
Abnormal renal function
Presence of active liver disease
Known hypersensitivity to FVIII
For further description of each criteria see Clinical Review of Kovaltry by FDA (March 2016)</td></tr>
<tr><td>Intervention</td><td>Kovaltry® (BAY 81-8973):
On-demand arm: The dosing for on-demand treatment and any breakthrough bleeds was dependent on the location and severity of the bleed.
Prophylaxis low-dose arm: 20, 25 or 30 IU/kg twice per week
Prophylaxis high-dose arm: 30, 35 or 40 IU/kg 3 times per week</td></tr>
<tr><td>Baseline characteristics</td><td><table>
<tr><th></th><th>On-demand (n = 21)</th><th>Prophylaxis 2 weekly (n = 28)</th><th>Prophylaxis 3 weekly (n = 31)</th></tr>
<tr><td>Age (years)</td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>31.4</td><td>28.8</td><td>29.1</td></tr>
<tr><td>Median (range)</td><td>30.0 (14–53)</td><td>27.0 (14–54)</td><td>28.0 (14–59)</td></tr>
<tr><td>< 18 years, n</td><td>2</td><td>4</td><td>4</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>6 (28.6)</td><td>16 (57.1)</td><td>14 (45.2)</td></tr>
<tr><td>Asian</td><td>9 (42.9)</td><td>9 (32.1)</td><td>14 (45.2)</td></tr>
</table></td></tr>
</table>

	Black	3 (14.3)	0 (%)	1 (3.2)
	Hispanic	3 (14.3)	3 (10.7)	2 (6.5)
	BMI (kg/m^2)			
	Mean	23.0	21.3	21.5
	Target joint yes (%)	19 (90.5)	25 (89.3)	28 (90.3)
	Number of target joints			
	Mean	3.2	3.0	2.8
	Median	3.0	3.0	2.0
	Number of bleeds in last 12 months			
	Mean	47.5	38.4	45.6
	Median	41.0	35.0	38.5
	Number of joint bleed in last 12 months			
	Mean	33.5	30.3	32.7
	Median	28.0	24.0	25.0
	Total Gilbert score			
	Mean ± SD	19.3 ± 13.3	20.9 ± 14.7	22.4 ± 14.5
Primary and secondary endpoints	Primary endpoint: - To demonstrate the superiority of prophylaxis over on-demand therapy by a clinically significant decrease in bleeding rate following 12 months of treatment with KOVALTRY. Secondary endpoints: - To demonstrate superiority of prophylaxis versus on-demand treatment (dose determined by CS/EP and CS/ADJ) as measured by bleeding rate. - To determine the non-inferiority of KOVALTRY dose determined by CS/EP vs. CS/ADJ as measured by the proportion of bleeds controlled by ≤ 2 injections in subjects treated on demand. For “other outcomes” see Clinical Review of Kovaltry by FDA (March 2016)			
Method of analysis	All patients who received study drug were assessed in the safety analysis. Patients who also had any data on injections/bleedings were included in the intent-to-treat (ITT) population, which was used for the efficacy analysis. Summary statistics such as mean, SD, median, and quartiles were calculated for continuous data; frequencies were calculated for categorical data.			
Subgroup analyses	Additional assessments were ABR during the first and second 6-month treatment periods, as well as dose per infusion and FVIII consumption for prophylaxis and bleeds. Subgroup analyses for ABR were also performed based on patient age (14–16 years vs. ≥ 18 years) and geographical region (Asia vs. non-Asia [i.e. South Africa, North America, Europe]).			

Table 19. **Main characteristics A-LONG (Elocta)**	
Trial name	A-LONG: An Open-Label, Multicenter Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia A
NCT number	NCT01181128
Objective	The overall objective of the study is to evaluate the safety, efficacy and pharmacokinetics of a recombinant FVIII Fc fusion protein (Elocta®) for prophylaxis, treatment of acute bleeding and perioperative hemostatic control in males aged ≥12 years with severe hemophilia
Publications – author, title, journal, year	1) Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014;123(3):317-25. 2) Wyrwich KW, Krishnan S, Auguste P, Poon JL, von Maltzahn R, Yu R, et al. Changes in health-related quality of life with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. Haemophilia. 2016;22(6):866-72.
Study type and design	The A-LONG clinical trial is a phase 3, open-label, randomized, multicenter study. All patients on a prophylactic regimen prior to study entry were enrolled in arm 1 (individualized prophylaxis regimen). Patients on an on-demand regimen prior to study were given the choice between either entering arm 1 or to be randomized between arm 2 (weekly prophylaxis regimen) or arm 3 (on-demand).
Follow-up time (duration of treatment with rFVIIIFc)	Arm1: median follow-up of 32.1 weeks (range 9-54) Arm2: median follow-up of 28.0 weeks (range <1-38) Arm3: median follow-up of 28.9 weeks (range 15-32)
Population (inclusion and exclusion criteria)	Inclusion criteria: • Male, ≥12 years of age with weight at least 40 kg • Diagnosed with severe hemophilia A, defined as <1 IU/dL (<1%) endogenous Factor VIII) • History of at least 150 documented prior exposure days to any Factor VIII product • Platelet count ≥100,000 cells/µL Exclusion criteria: • History of Factor VIII inhibitors • Kidney and liver dysfunction • Diagnosed with other coagulation disorder(s) in addition to hemophilia A • Prior history of hypersensitivity or anaphylaxis associated with any FVIII or IV immunoglobulin administration For the full description of criteria see the EPAR by EMA (September 2015)

<table>
<tr><td>Intervention</td><td>Arm 1 – 117 patients received rFVIIIFc:
Initial twice weekly dosing with 25 IU/kg of rFVIIIFc on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days to maintain a trough level of 1% to 3% (or higher, as clinically indicated) rFVIIIFc activity; further increases to target trough level up to 5% as required for bleeding.

Arm 2 – 24 patients received rFVIIIFc:
65 IU/kg rFVIIIFc every 7 days.

Arm 3 – 23 patients received rFVIIIFc:
Initial single dose of 50 IU/kg rFVIIIFc followed by 10 to 50 IU/kg rFVIIIFc, as required to treat a bleeding episode.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Arm 1: Individualized prophylaxis (n = 118)</th><th>Arm 2: Weely prophylaxis (n = 24)</th><th>Arm 3: Episodic treatment (n = 23)</th></tr>
<tr><td>Age (years)</td><td></td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>29 (12-65)</td><td>31.5 (18-59)</td><td>34 (13-62)</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>79 (66.9)</td><td>12 (50.0)</td><td>16 (69.6)</td></tr>
<tr><td>Asian</td><td>27 (22.9)</td><td>11 (45.8)</td><td>5 (21.7)</td></tr>
<tr><td>Black</td><td>7 (5.9)</td><td>1 (4.2)</td><td>2 (8.7)</td></tr>
<tr><td>Other</td><td>5 (4.2)</td><td>0 (0)</td><td>0 (0)</td></tr>
<tr><td>Weight (kg)</td><td></td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>71.65 (42.0, 127.4)</td><td>75.85 (50.0, 105.0)</td><td>70.00 (48.0, 110.4)</td></tr>
<tr><td>Prestudy FVIII regimen, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Prophylaxis</td><td>87 (73.7)</td><td>0 (0)</td><td>0 (0)</td></tr>
<tr><td>Episodic</td><td>31 (26.3)</td><td>24 (100)</td><td>23 (100)</td></tr>
<tr><td>1 or more target joints, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Prior prophylaxis</td><td>47 (39.8)</td><td>0 (0)</td><td>0 (0)</td></tr>
<tr><td>Prior episodic</td><td>26 (22.0)</td><td>22 (91.7)</td><td>18 (78.3)</td></tr>
<tr><td>Number of bleeds in last 12 months, median (IQR)</td><td></td><td></td><td></td></tr>
<tr><td>Prior prophylaxis</td><td>6.0 (2, 15)</td><td>0 (0)</td><td>0 (0)</td></tr>
<tr><td>Prior episodic</td><td>27.0 (17, 41)</td><td>29.5 (19, 44)</td><td>24.0 (15, 36)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoints:
- Efficacy: Annualized number of bleeding episodes (spontaneous and traumatic) Arm 1 versus Arm 3
- Pharmacokinetic parameters: Dose normalized AUC, half-life and MRT
- Safety and tolerability: Clinically notable changes from baseline in physical examinations and vital signs, incidence of AEs and development of inhibitors

Secondary endpoints:
- Comparison of Annualized Bleeding Rates: Arm 2 Versus Arm 3</td></tr>
</table>

	- Annualized number of spontaneous and joint bleeding episodes per subject - Annualized rFVIIIFc Consumption Per Participant - Participants' bleeding response to rFVIIIFc injection - Quality of Life measured by Haem-A-QoL and Haemo-QoL All 40 primary and secondary endpoints are described at clinicaltrials.gov
Method of analysis	Efficacy analyses were performed on data from all subjects who received ≥1 dose of rFVIIIFc. Safety analyses were conducted on data from subjects who received $1 dose of either rFVIII or rFVIIIFc. ABRs were calculated based on the number of bleeding episodes during the efficacy period and duration of time that subjects were evaluated for bleeding. Descriptive statistics included median and interquartile range (IQR) ABR values for each arm. Comparisons between each of arms 1 and 2 (prophylactic regimens) and arm 3 (episodic treatment) were based on ABR estimates from a negative binomial regression model. A negative binomial model was preferred over a Poisson regression model as over dispersion of the data were identified.
Subgroup analyses	N/A

8.2 Literature search

Table 20. **Overview of literature search**

Studies to include		
	Inclusion criteria	Exclusion criteria
Population	• Hemophilia A and candidates for prophylactic treatment • Includes patients over the age of 12	• Studies with other populations than hemophilia A patients • Exclusively under the age of 12
Intervention	• Emicizumab SC, 3 mg per week for 4 weeks followed by weekly dose of 1,5 mg or bi-weekly dose of 3 mg • Kovaltry • Elocta	
Comparators	• Any	
Outcomes	• Relevant for protocol	• Outcomes not included in protocol
Design	• Prospective clinical trials (I-III) • At least 1 prophylactic arm • Full text avaliable	• Retrospective • Observational • Review • Conference abstract • Follow-up longer than 1 year

Language	• English • Scandinavian	• Other language
Publication date	• Last 5 years	• Abstract only
Human/animal	• Human only	• Not human
Data sources		
Databases	• MEDLINE via PubMed • CENTRAL via Cochrane	
Other sources	• EPAR • SPC	
Process for literature selection process		
Criteria	1. Exclusion by title and abstract 2. Exclusion by full text	
Methods for literature selection	Two investigators independently screened articles for inclusion by title or abstract and full-text if necessary. Disagreements were resolved by consensus and if not possible, by discussion with a third investigator	
Time period covered		
	• Latest 5 years (2014-2019)	
Search date		
	• PubMed/MEDLINE: 18th of February 2018 • Cochrane Central: 18th of February 2018	

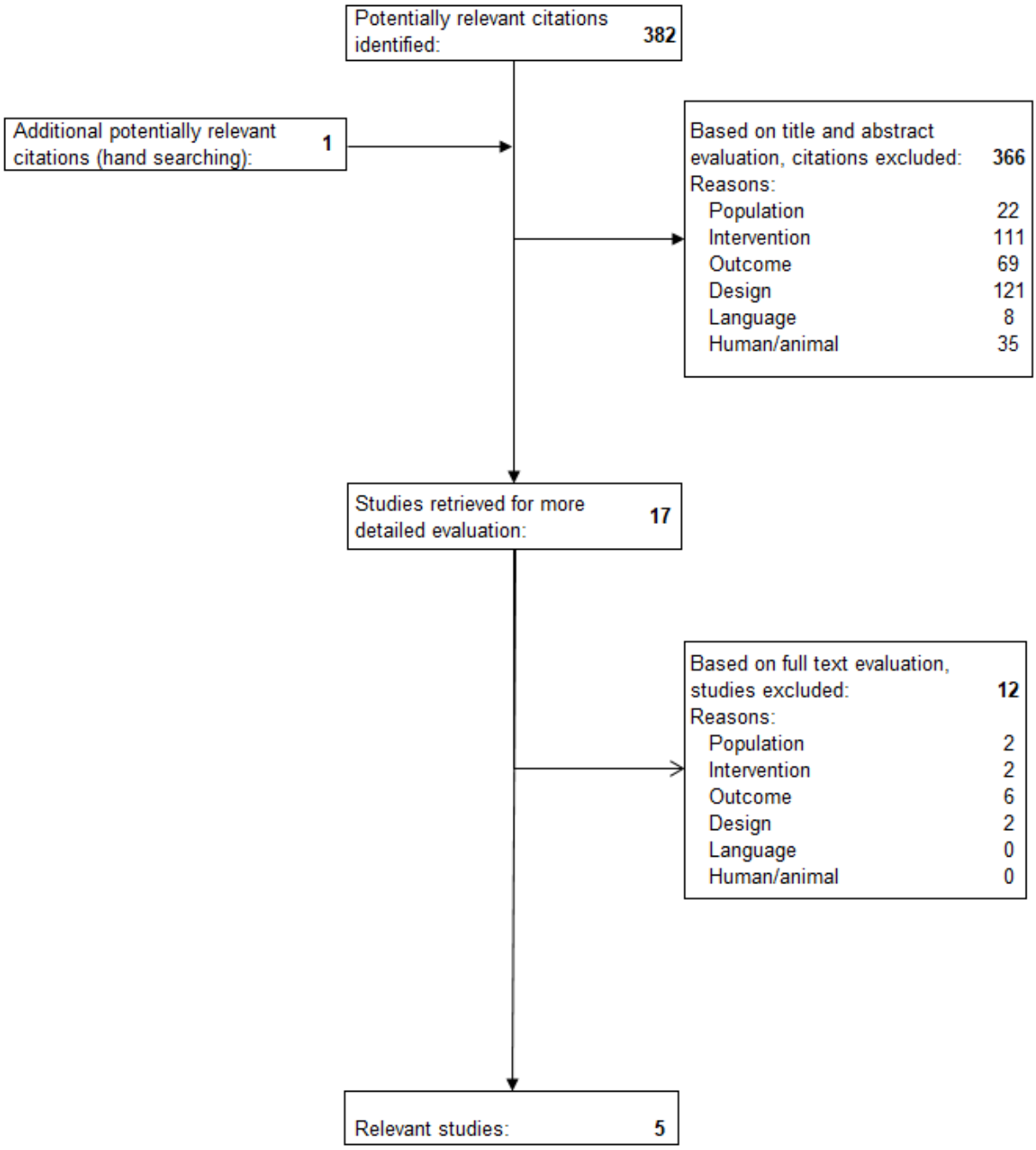
Table 21. **Pubmed/MEDLINE search strategy**	
	#3,"Search ""Hemophilia A""[Mesh]" #4,"Search ""Hemophilia A""" #5,"Search ""Hemophilia type A""" #6,"Search ""hemophilia a""" #7,"Search ""hemophilia a""" #8,"Search ""hemophilia type a""" #9,"Search (((((""Hemophilia A""[Mesh]) OR ""Hemophilia A""[Title/Abstract]) OR ""Hemophilia type A""[Title/Abstract]) OR ""hemophilia a""[Title/Abstract]) OR ""hemophilia a""[Title/Abstract]) OR ""hemophilia type a""[Title/Abstract]" #10,"Search ""factor viii""" #11,"Search ""fviii""" #14,"Search deficient" #15,"Search deficiency" #16,"Search deficiencies" #17,"Search (""factor viii""[Title/Abstract]) OR ""fviii""[Title/Abstract]" #18,"Search ((deficiencies[Title/Abstract]) OR deficiency[Title/Abstract]) OR deficient[Title/Abstract]"

	#19,"Search ((""factor viii""[Title/Abstract]) OR ""fviii""[Title/Abstract])) AND (((deficiencies[Title/Abstract]) OR deficiency[Title/Abstract]) OR deficient[Title/Abstract])" #20,"Search (((((((""Hemophilia A""[Mesh]) OR ""Hemophilia A""[Title/Abstract]) OR ""Hemophilia type A""[Title/Abstract]) OR ""hemophilia a""[Title/Abstract]) OR ""hemophilia a""[Title/Abstract]) OR ""hemophilia type a""[Title/Abstract])) OR ((((""factor viii""[Title/Abstract]) OR ""fviii""[Title/Abstract])) AND (((deficiencies[Title/Abstract]) OR deficiency[Title/Abstract]) OR deficient[Title/Abstract]))" #22,"Search ""emicizumab"" [Supplementary Concept]" #23,"Search emicizumab" #24,"Search hemlibra" #25,"Search ace910" #26,"Search ((""emicizumab"" [Supplementary Concept]) OR emicizumab[Title/Abstract]) OR hemlibra[Title/Abstract]) OR ace910[Title/Abstract]" #28,"Search ""factor VIII-Fc fusion protein"" [Supplementary Concept]" #29,"Search ""factor VIII-Fc fusion protein""" #30,"Search ""elocta*""" #31,"Search ""efraloctocog alfa""" #32,"Search ""efraloctocog alpha""" #33,"Search ""efraloctocog alpha"" Schema: all" #34,"Search ""efmoroctocog alfa""" #35,"Search ""efmoroctocog alpha""" #36,"Search ""rFVIIIFc""" #37,"Search ""rFVIII-Fc""" #38,"Search ""factor VIII-fc""" #39,"Search ""recombinant factor VIII fc""" #40,"Search ((((((((((""factor VIII-Fc fusion protein"" [Supplementary Concept]) OR ""factor VIII-Fc fusion protein""[Title/Abstract]) OR ""elocta*""[Title/Abstract]) OR ""efraloctocog alfa""[Title/Abstract]) OR ""efraloctocog alpha""[Title/Abstract]) OR ""efmoroctocog alfa""[Title/Abstract]) OR ""efmoroctocog alpha""[Title/Abstract]) OR ""rFVIIIFc""[Title/Abstract]) OR ""rFVIII-Fc""[Title/Abstract]) OR ""factor VIII-fc""[Title/Abstract]) OR ""recombinant factor VIII fc""[Title/Abstract]" #41,"Search ""BAY 81-8973""" #42,"Search ""BAY81-8973""" #43,"Search ""BAY81-8973"" Schema: all" #44,"Search rfviii" #45,"Search ""r-factor viii""" #46,"Search ""recombinant fviii""" #47,"Search ""recombinant factor viii""" #48,"Search ""recombinant factor 8""" #49,"Search ""rfactor 8"""

	#50,"Search ""octocog alfa""" #51,"Search ""octocog alpha""" #52,"Search (((((((((""BAY 81-8973""[Title/Abstract]) OR ""BAY81-8973""[Title/Abstract]) OR rfviii[Title/Abstract]) OR ""r-factor viii""[Title/Abstract]) OR ""recombinant fviii""[Title/Abstract]) OR ""recombinant factor viii""[Title/Abstract]) OR ""recombinant factor 8""[Title/Abstract]) OR ""rfactor 8""[Title/Abstract]) OR ""octocog alfa""[Title/Abstract]) OR ""octocog alpha""[Title/Abstract]" #53,"Search ((((((""emicizumab"" [Supplementary Concept]) OR emicizumab[Title/Abstract]) OR hemlibra[Title/Abstract]) OR ace910[Title/Abstract])) OR ((((((((((""factor VIII-Fc fusion protein"" [Supplementary Concept]) OR ""factor VIII-Fc fusion protein""[Title/Abstract]) OR ""elocta*""[Title/Abstract]) OR ""efraloctocog alfa""[Title/Abstract]) OR ""efraloctocog alpha""[Title/Abstract]) OR ""efmoroctocog alfa""[Title/Abstract]) OR ""efmoroctocog alpha""[Title/Abstract]) OR ""rFVIIIFc""[Title/Abstract]) OR ""rFVIII-Fc""[Title/Abstract]) OR ""factor VIII-fc""[Title/Abstract]) OR ""recombinant factor VIII fc""[Title/Abstract])) OR ((((((((((""BAY 81-8973""[Title/Abstract]) OR ""BAY81-8973""[Title/Abstract]) OR rfviii[Title/Abstract]) OR ""r-factor viii""[Title/Abstract]) OR ""recombinant fviii""[Title/Abstract]) OR ""recombinant factor viii""[Title/Abstract]) OR ""recombinant factor 8""[Title/Abstract]) OR ""rfactor 8""[Title/Abstract]) OR ""octocog alfa""[Title/Abstract]) OR ""octocog alpha""[Title/Abstract])" #54,"Search (((((((((""Hemophilia A""[Mesh]) OR ""Hemophilia A""[Title/Abstract]) OR ""Hemophilia type A""[Title/Abstract]) OR ""hemophilia a""[Title/Abstract]) OR ""hemophilia a""[Title/Abstract]) OR ""hemophilia type a""[Title/Abstract])) OR ((((""factor viii""[Title/Abstract]) OR ""fviii""[Title/Abstract])) AND (((deficiencies[Title/Abstract]) OR deficiency[Title/Abstract]) OR deficient[Title/Abstract]))))) AND (((((((""emicizumab"" [Supplementary Concept]) OR emicizumab[Title/Abstract]) OR hemlibra[Title/Abstract]) OR ace910[Title/Abstract])) OR ((((((((((""factor VIII-Fc fusion protein"" [Supplementary Concept]) OR ""factor VIII-Fc fusion protein""[Title/Abstract]) OR ""elocta*""[Title/Abstract]) OR ""efraloctocog alfa""[Title/Abstract]) OR ""efraloctocog alpha""[Title/Abstract]) OR ""efmoroctocog alfa""[Title/Abstract]) OR ""efmoroctocog alpha""[Title/Abstract]) OR ""rFVIIIFc""[Title/Abstract]) OR ""rFVIII-Fc""[Title/Abstract]) OR ""factor VIII-fc""[Title/Abstract]) OR ""recombinant factor VIII fc""[Title/Abstract])) OR ((((((((((""BAY 81-8973""[Title/Abstract]) OR ""BAY81-8973""[Title/Abstract]) OR rfviii[Title/Abstract]) OR ""r-factor viii""[Title/Abstract]) OR ""recombinant fviii""[Title/Abstract]) OR ""recombinant factor viii""[Title/Abstract]) OR ""recombinant factor 8""[Title/Abstract]) OR ""rfactor 8""[Title/Abstract]) OR ""octocog alfa""[Title/Abstract]) OR ""octocog alpha""[Title/Abstract]))" #55,"Search (((((((((""Hemophilia A""[Mesh]) OR ""Hemophilia A""[Title/Abstract]) OR ""Hemophilia type A""[Title/Abstract]) OR ""hemophilia a""[Title/Abstract]) OR ""hemophilia a""[Title/Abstract]) OR ""hemophilia type a""[Title/Abstract])) OR ((((""factor viii""[Title/Abstract]) OR ""fviii""[Title/Abstract])) AND

	(((deficiencies[Title/Abstract]) OR deficiency[Title/Abstract]) OR deficient[Title/Abstract]))) AND (((((((""emicizumab"" [Supplementary Concept]) OR emicizumab[Title/Abstract]) OR hemlibra[Title/Abstract]) OR ace910[Title/Abstract])) OR ((((((((((""factor VIII-Fc fusion protein"" [Supplementary Concept]) OR ""factor VIII-Fc fusion protein""[Title/Abstract]) OR ""elocta*""[Title/Abstract]) OR ""efraloctocog alfa""[Title/Abstract]) OR ""efraloctocog alpha""[Title/Abstract]) OR ""efmoroctocog alfa""[Title/Abstract]) OR ""efmoroctocog alpha""[Title/Abstract]) OR ""rFVIIIFc""[Title/Abstract]) OR ""rFVIII-Fc""[Title/Abstract]) OR ""factor VIII-fc""[Title/Abstract]) OR ""recombinant factor VIII fc""[Title/Abstract])) OR ((((((((((""BAY 81-8973""[Title/Abstract]) OR ""BAY81-8973""[Title/Abstract]) OR rfviii[Title/Abstract]) OR ""r-factor viii""[Title/Abstract]) OR ""recombinant fviii""[Title/Abstract]) OR ""recombinant factor viii""[Title/Abstract]) OR ""recombinant factor 8""[Title/Abstract]) OR ""rfactor 8""[Title/Abstract]) OR ""octocog alfa""[Title/Abstract]) OR ""octocog alpha""[Title/Abstract])) Filters: published in the last 5 years" **Hits: 382**
Date of search	*MEDLINE was searched the 18th of February 2018*
Methods for literature selection	*Two investigators independently screened articles for inclusion by title or abstract and full-text if necessary. Disagreements were resolved by consensus and if not possible, by disussion with a third investigator*
PRISMA flow diagram	*See figure 1*

Figure 1 PRISMA flow diagram 1 – PubMed



Cochrane Central

Table 22. **Cochrane Central search strategy**		
	#1	MeSH descriptor: [Hemophilia A] explode all trees
	#2	("hemophilia a"):ti,ab,kw (Word variations have been searched)
	#3	("hemophilia A"):ti,ab,kw (Word variations have been searched)
	#4	("hemophilia type A"):ti,ab,kw (Word variations have been searched)
	#5	("hemophilia type A"):ti,ab,kw (Word variations have been searched)
	#6	#1 OR #2 OR #3 OR #4 OR #5
	#7	("Factor VIII"):ti,ab,kw (Word variations have been searched)
	#8	(FVIII):ti,ab,kw (Word variations have been searched)
	#9	#7 OR #8
	#10	(deficient):ti,ab,kw (Word variations have been searched)
	#11	(deficiency):ti,ab,kw (Word variations have been searched)
	#12	(deficiencies):ti,ab,kw (Word variations have been searched)
	#13	#10 OR #11 OR #12
	#14	#9 AND #13
	#15	#6 OR #14
	#16	(Hemlibra):ti,ab,kw (Word variations have been searched)
	#17	(emicizumab):ti,ab,kw (Word variations have been searched)
	#18	(ACE910):ti,ab,kw (Word variations have been searched)
	#19	#16 OR #17 OR #18
	#20	(Kovaltry):ti,ab,kw (Word variations have been searched)
	#21	("BAY 81-8973"):ti,ab,kw (Word variations have been searched)
	#22	("BAY81-8973"):ti,ab,kw (Word variations have been searched)
	#23	(RFVIII):ti,ab,kw (Word variations have been searched)
	#24	("r-factor VIII"):ti,ab,kw (Word variations have been searched)
	#25	("recombinant FVIII"):ti,ab,kw (Word variations have been searched)
	#26	("recombinant factor VIII"):ti,ab,kw (Word variations have been searched)
	#27	("recombinant factor 8"):ti,ab,kw (Word variations have been searched)
	#28	("octocog alfa"):ti,ab,kw (Word variations have been searched)
	#29	("octocog alpha"):ti,ab,kw (Word variations have been searched)

	#30 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 #31 (Elocta):ti,ab,kw (Word variations have been searched) #32 ("efraloctocog alfa"):ti,ab,kw (Word variations have been searched) #33 ("efraloctocog alpha"):ti,ab,kw (Word variations have been searched) #34 ("efmoroctocog alfa"):ti,ab,kw (Word variations have been searched) #35 ("efmoroctocog alpha"):ti,ab,kw (Word variations have been searched) #36 (eloctate):ti,ab,kw (Word variations have been searched) #37 ("rFVIIIFc"):ti,ab,kw (Word variations have been searched) #38 ("fc-factor viii"):ti,ab,kw (Word variations have been searched) #39 ("factor VIII-Fc"):ti,ab,kw (Word variations have been searched) #40 ("recombinant factor VIII fc"):ti,ab,kw (Word variations have been searched) #41 ("recombinant factor viiifc"):ti,ab,kw (Word variations have been searched) #42 ("recombinant fviii fc"):ti,ab,kw (Word variations have been searched) #43 ("recombinant fviiifc"):ti,ab,kw (Word variations have been searched) #44 ("rFVIII-Fc"):ti,ab,kw (Word variations have been searched) #45 ("factor VIII-Fc fusion protein"):ti,ab,kw (Word variations have been searched) #46 #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 #47 #19 OR #30 OR #46 #48 #15 AND #47 with Publication Year from 2014 to 2019, in Trials **Hits: 157**
Date of search	*Cochrane was searched the 18th of February 2018*
Methods for literature selection	*Two investigators independently screened articles for inclusion by title or abstract and full-text if necessary. Disagreements were resolved by consensus and if not possible, by disussion with a third investigator*
PRISMA flow diagram	*See figure 2*

Figure 2 PRISMA flow diagram 2 – Cochrane

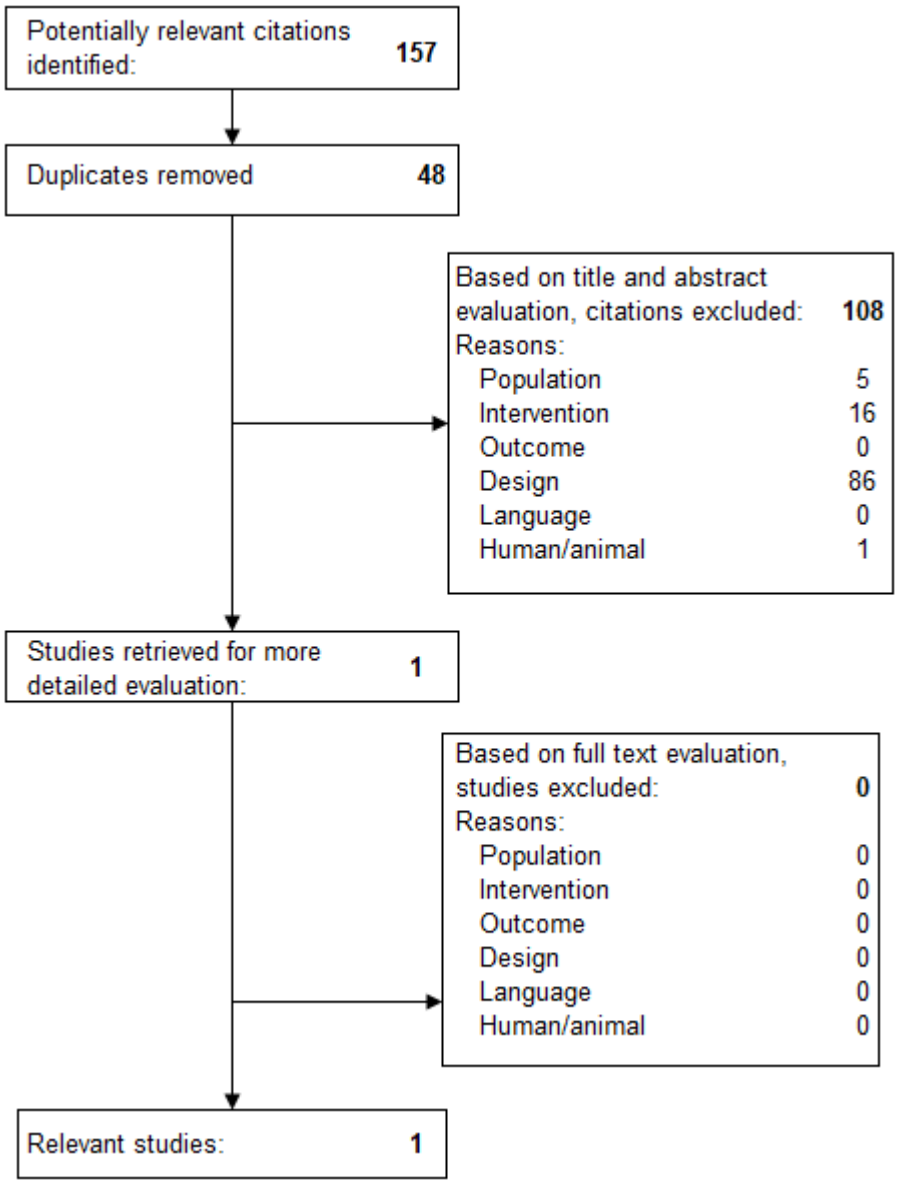


Table 23. **Studies excluded based on full text-assessment**				
Author	Title	Journal and year	Reason for not including	Search
Oldenburg, J.; Kulkarni, R.; Srivastava, A. et al	Improved joint health in subjects with severe hemophilia A treated prophylactically with recombinant factor VIII Fc fusion protein	Hemophilia 2018	Design: Follow-up longer than 12 months	PubMed/MEDLINE
Shapiro, A. D., Mahlangu, J. N., Perry, D.,	Treatment of bleeding episodes with recombinant factor VIII Fc fusion protein in A-LONG study subjects with severe hemophilia A	Hemophilia 2017	Outcome: Outcomes not relevant for protocol	PubMed/MEDLINE
Shima, M.; Hanabusa, H.; Taki, M., et al	Long-term safety and efficacy of emicizumab in a phase 1/2 study in patients with hemophilia A with or without inhibitors	Blood Adv. 2017	Intervention: Wrong dosing regimen	PubMed/MEDLINE
Fujii, T.; Hanabusa, H.; Shima, M. et al	Analysis of the Japanese subgroup in LEOPOLD II: a phase 2/3 study of BAY 81-8973, a new recombinant factor VIII product	Int J Hematol 2017	Outcome: Subgroup data. Already included in other LEOPOLD publications	PubMed/MEDLINE
Ljung, R.; Kenet, G.; Mancuso, M. E. et al	BAY 81-8973 safety and efficacy for prophylaxis and treatment of bleedings in previously treated children with severe hemophilia A: results of the LEOPOLD Kids Trial.	Hemophilia 2016	Population: Exclusively patients under the age of 12	PubMed/MEDLINE
Nolan, B.; Mahlangu, J.; Perry, D. et al.	Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with hemophilia A	Hemophilia 2016	Design: Follow-up longer than 12 months	PubMed/MEDLINE
Shima, M.; Hanabusa, H.; Taki, M. et al	Factor VIII-Mimetic Function of Humanized Bispecific Antibody in Hemophilia A	N Engl J Med 2016	Intervention: Wrong dosing regimen	PubMed/MEDLINE
Oldenburg, J.; Windyga, J.;	Safety and efficacy of BAY 81-8973 for surgery in	Hemophilia 2016	Outcome:	PubMed/MEDLINE

Hampton, K. et al	previously treated patients with hemophilia A: results of the LEOPOLD clinical trial programme		Subgroup data. Already included in other LEOPOLD publications	
Mahlangu, J. N.; Ragni, M.; Gupta, N. et al	Long-acting recombinant factor VIII Fc fusion protein (rFVIIIFc) for perioperative haemostatic management in severe hemophilia A	J Thromb Haemost 2016	Outcome: Subgroup data. Already included in other LEOPOLD publications	PubMed/MEDLINE
Young, G.; Mahlangu, J.; Kulkarni, R. et al	Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A	J Thromb Haemost 2015	Population: Exclusively patients under the age of 12	PubMed/MEDLINE
Wyrwich, K. W.; Krishnan, S.; Poon, J. L. et al	Interpreting important health-related quality of life change using the Haem-A-QoL	Hemophilia 2015	Outcome: Data already included in A-LONG study	PubMed/MEDLINE
Shapiro, A. D.; Ragni, M. V.; Kulkarni, R. et al	Recombinant factor VIII Fc fusion protein: extended-interval dosing maintains low bleeding rates and correlates with von Willebrand factor levels	J Thromb Haemost 2014	Outcome: Data already included in A-LONG study	PubMed/MEDLINE

8.3 Results per study

Table 24. **Results from HAVEN 3 study Arm A, B and C**

Trial name:	**A Clinical Trial to Evaluate Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3)** Results published in: 1) Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018;379(9):811-22. 2) ITC calculations 3) Hemlibra, International non-proprietary name: emicizumab. European Public Assesment Report (EPAR). 2019 4) Data on file. Roche. 2019 [14]
NCT number:	02847637

Annualized bleeding rate (ABR), median (1)

Outcome	Study arm	N	Result, median (IQR)	Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
				Difference	95% CI	*P* value	Rate ratio vs C: No prophylaxis	95% CI	*P* value	
Median annualized bleeding rate (ABR) Bleeding events treated with factor VIII	A: Emicizumab 1.5 mg/kg 1 weekly	36	0.0 (0.0-2.5)				0.04	(0.02-0.08)	<0.05	*Malangu et al. p 817, SmPC. A negative binomial-regression model was used to compare the number of bleeding events over time. The model accounted*
	B: 3.0 mg/kg every 2 weeks	35	0.0 (0.0-1.9)				0.03	(0.02-0.07)	<0.05	
	C: No prophylaxis (FVIII on- demand)	18	40.4 (25.3-56.7)							

						for different follow-up times, with the number of bleeding events per participant as a function of randomization and the time that each partici-pant stayed in the study included as an offset in the model. The model also included the number of bleedings (<9 or ≥9) in the 24 weeks prior to study entry.

Annualized bleeding rate (ABR), mean [2]

Outcome	Study arm	N	Result, mean			Description of methods used for estimation
Mean annualized bleeding rate (ABR) Bleeding events treated with factor VIII	A and B: Emicizumab 1.5 mg/kg 1 weekly and 3.0 mg/kg every 2 weeks arms combined	71	1.94			Calculations from excel (headquarters) ITC_10122018
	C: No prophylaxis (FVIII on- demand)	18	41			

Discontinuation due to side effects (1)

Outcome	Study arm	N	Result, n (%)	Estimated absolute difference in efficacy Difference	95% CI	*P* value	Estimated relative difference in efficacy Hazard/Odds/ Risk ratio	95% CI	*P* value	Description of methods used for estimation
Discontinuation due to side effects	A and B: Emicizumab 1.5 mg/kg 1 weekly and 3.0 mg/kg every 2 weeks arms combined	71	1 (0.014)							*Malangu et al. p 818*
	C: No prophylaxis (FVIII on- demand)	18	0 (0)							

Severe venous thromboembolism (1)

Outcome	Study arm	N	Result, n (%)	Estimated absolute difference in efficacy Difference	95% CI	*P* value	Estimated relative difference in efficacy Hazard/Odds/ Risk ratio	95% CI	*P* value	Description of methods used for estimation
Serious venous thromboembolism	A and B: Emicizumab 1.5 mg/kg 1 weekly and 3.0 mg/kg every 2 weeks arms combined	71	0 (%)							*Malangu et al. p 817.*
	C: No prophylaxis (FVIII on- demand)	18	0 (%)							

Quality of life (1)

Outcome	Study arm	N	Result	Estimated absolute difference (adjusted mean) at 25 weeks between A or B and C			Estimated relative difference in efficacy			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Haem-A-QoL Physical Health (Subscale score)	A: Emicizumab 1.5 mg/kg 1 weekly	N/A	N/A	12.5	(-2 to 27.0)	0.09				Observed difference (adjusted mean) at 25 weeks as compared with group C. The EmiPref survey was completed by 95 of 134 eligible participants (71%).
	B: Emicizumab 3.0 mg/kg every 2 weeks	N/A	N/A	16.0	(1.2 to 30.8)	Not considered significant (owing to the order of end points in the hierarchical testing framework)				
	C: No prophylaxis (FVIII on- demand)	N/A	N/A							

Quality of life (3)

Outcome	Study arm	N	Result, adjusted mean	Estimated absolute difference (adjusted mean) at 25 weeks between A or B and C			Estimated relative difference in efficacy			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Haem-A-QoL Total Score at week 25	A: Emicizumab 1.5 mg/kg 1 weekly	34	24.0	5.9		0.13				Observed difference (adjusted mean) at 25 weeks as

	B: Emicizumab 3.0 mg/kg every 2 weeks	29	21.4	8.6	0.03	compared with group C.
	C: No prophylaxis (FVIII on- demand)	13	30.0			
Quality of life [4]						
Outcome	Study arm	N	Result, mean change			Description of methods used for estimation
Haem-A-QoL total score (Patients aged 18 years or older)	Arm A: Emicizumab 1.5 mg/kg 1 weekly		-8.44 points			Mean change from baseline. Haem-A-QoL was not assessed in Arm D
	Arm B: Emicizumab 3.0 mg/kg every 2 weeks		-12.94 points			

Table 25. **Results from HAVEN 3 study Arm D**

Trial name:	**A Clinical Trial to Evaluate Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3)** Results published in: 1) Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018;379(9):811-22.
NCT number:	NCT02847637

Annualized bleeding rate (ABR)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Annual bleeding rate (ABR), median (IQR)	Emicizumab 1.5 mg/kg every week	48	0.0 (0.0-2.1)							*Malangu et al. p 817, SmPC. A negative binomial-regression model was used to compare the number of bleeding events over time. The model accounted for different follow-up times, with the number of bleeding events per participant as a function of randomization and the time that each partici-pant stayed in the study included as an offset in the model. The model also included the number of bleedings (<9 or ≥9) in the 24 weeks prior to study entry.*
	Non-inter-ventional study	48	1.8 (0.0-7.6) months							

Discontinuation due to side effects										
				Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
Outcome	Study arm	N	Result, n (%)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Withdrawal due to AEs	Emicizumab 1.5 mg/kg every week	63	0							*Malangu et al. p 818*
Severe venous thromboembolism										
				Estimated absolute difference in efficacy			Estimated absolute difference in efficacy			Estimated absolute difference in efficacy
Outcome	Study arm	N	Result, n (%)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Serious venous thromboembolism	Emicizumab 1.5 mg/kg every week	63	0							*Malangu et al. p 817.*
Quality of life										
				Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
Outcome	Study arm	N	Result, n (%)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Quality of life	Emicizumab 1.5 mg/kg every week		N/A							

Table 26. **Results from LEOPOLD I**

Trial name:	**Trial to Evaluate the Efficacy and Safety of a New Full Length Recombinant Human FVIII for Hemophilia A (Leopold I)** Results published in: 1) Saxena K, Lalezari S, Oldenburg J, Tseneklidou-Stoeter D, Beckmann H, Yoon M, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Haemophilia. 2016;22(5):706-12. 2) https://clinicaltrials.gov/ct2/show/results/NCT01029340?term=01029340&rank=1&view=results								
NCT number:	01029340								
Annualized bleeding rate (ABR) (1)									
Outcome	Study arm (Part B)	N	Result, median (IQR)	Estimated absolute difference in efficacy: Difference	95% CI	*P* value	Estimated relative difference in efficacy: Hazard/Odds/ Risk ratio	95% CI	*P* value	Description of methods used for estimation
Median annualized bleeding rate (ABR), overall Total bleeds per year	CS/EP 6-month period arm	62	1.9 (0-4.4)							
	CS/ADJ 6-month period arm	61	1.9 (0-7.3)							
Discontinuation due to side effects (1)										
Outcome	Study arm	N	Result, n (%)	Estimated absolute difference in efficacy: Difference	95% CI	*P* value	Estimated relative difference in efficacy: Hazard/Odds/ Risk ratio	95% CI	*P* value	Description of methods used for estimation
Number of patients who withdrew due to adverse effects	CS/EP 6-month period arm	62	0 (0)							
	CS/ADJ 6-month period arm	61	0 (0)							

Severe venous thromboembolism [1]										
Outcome	Study arm	N	Result, n (%)	Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Number of serious vascular thrombotic events	CS/EP 6-month period arm	62	0 (0)							
	CS/ADJ 6-month period arm	61	0 (0)							
Quality of life [2]										
Outcome	Study arm	N	Result, mean (range)	Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Haem-A-QoL	Both CS/EP and CS/ADJ 6-month period arms	51	2.02 (-22.9 to 26.5))							Measured by Transformed Total Score of Haemo-QoL Questionnaire. The scoring system has 100 points. 0 is the worst possible score. 100 is the best possible score. Positive changes from baseline indicate an improvement in quality of life Absolute changes in Haem-A-QoL scores from baseline to 12 months. ITT: Only 51 of the 62 participants had data available for the 12-month QoL analysis.

Table 27. **Results from LEOPOLD II**

Trial name:	**A Trial to Compare Prophylaxis Therapy to On-demand Therapy With a New Full Length Recombinant FVIII in Patients With Severe Hemophilia A (LEOPOLD II)** Results published in: 1) Kavakli K, Yang R, Rusen L, Beckmann H, Tseneklidou-Stoeter D, Maas Enriquez M, et al. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). J Thromb Haemost. 2015;13(3):360-9. 2) Kovaltry. European Public Assesment report (EPAR). EMA. 17 December 2015. https://www.ema.europa.eu/documents/assessment-report/kovaltry-epar-public-assessment-report_en.pdf
NCT number:	01233258

Annualized bleeding rate (ABR)

Outcome	Study arm	n	Result, median (IQR)	Estimated absolute difference in efficacy: Difference	95% CI	*P* value	Estimated relative difference in efficacy: Hazard/Odds/ Risk ratio	95% CI	*P* value	Description of methods used for estimation
Annual bleeding rate (ABR), median All bleedings per year	1 and 2: high and low dose BAY 81-8973 prophylaxis arms combined	59	2.0 (0-7.0)							*Kavali et all. P364; SmPC; Summary statistics*
Outcome	Study arm	n	Result, mean (SD)							
Annual bleeding rate (ABR), mean All bleedings per year	1 and 2: high and low dose BAY 81-8973 prophylaxis arms combined	59	4.9 (6.8)							*ABR in the intent-to-treat (ITT) population*

Discontinuation due to side effects										
				Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
Outcome	Study arm	N	Result, n (%)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Withdrawal due to AEs (%)	1, 2 and 3: high and low dose prophylaxis and on-demand BAY 81-8973 arms combined	80	0 (0%)							*EPAR p60; Der er kun data for alle 80 patienter i studiet – skal vi skrive det eller skal vi skrive NA? Eller N=59 og 0 cases?*
Severe venous thromboembolism										
				Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
Outcome	Study arm	N	Result, n (%)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Serious venous thromboembolia	1, 2 and 3: high and low dose prophylaxis and on-demand BAY 81-8973 arms combined	80	N/A							*Searched for in article and EPAR*
Quality of life										
				Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
Outcome	Study arm	N	Result, n (%)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	

Haem-A-QoL (Quality of life)	N/A N/A N/A			*Searched for in article, at clinicaltrials.gov and in EPAR*

Table 28. **Results from A-LONG**

Trial name:	**Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Previously Treated Subjects With Severe Hemophilia A** Results published in: 1) Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014;123(3):317-25. 2) Wyrwich KW, Krishnan S, Auguste P, Poon JL, von Maltzahn R, Yu R, et al. Changes in health-related quality of life with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. Hemophilia. 2016;22(6):866-72.
NCT number:	01181128

Annualized bleeding rate (ABR) (1)

Outcome	Study arm	N	Result, median (IQR)	Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Median annualized bleeding rate (ABR), overall All bleedings per year	Arm 1: individualized prophylaxis, (25-65 IU/kg every 3-5 days), **prior prophylaxis or episodic treatment**	117	1.6 (0.0, 4.7)							*The number of bleeding episodes was annualized for each subject using the following formula: Annualized bleeding rate =Number of bleeding episodes during the efficacy period /Total number of days during the eff*

	Arm 2: weekly Prophylaxis, (65 IU/kg) **prior episodic treatment**	23	3.6 (1.9, 8.4)			*icacy period × 365.25* ***(EPAR)***

Discontinuation due to side effects (1)

Outcome	Study arm	N	Result, n (%)	Estimated absolute difference in efficacy			Estimated relative difference in efficacy			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Number of patients who withdrew due to adverse effects	Arm 1: individualized prophylaxis, (25-65 IU/kg every 3-5 days)	117	Death 1 (0.8%) AE 0 (0%)							Of the 164 subjects in the 3 arms combined, 4 subjects (2.4%) experienced AEs that led to discontinuation of rFVIIIFc treatment and/or withdrawal from the study: rash in 1 subject (assessed as related to rFVIIIFc treatment), femur fracture in 1 subject (assessed as unrelated to rFVIIIFc treatment), death in 1 subject (fatal outcome of polysubstance over-dose and completed suicide, assessed as unrelated to rFVIIIFc treatment), and arthralgia in 1 subject (assessed as related to rFVIIIFc treatment, but subject was recorded to have
	Arm 2: weekly prophylaxis**,** (25-65 IU/kg)	23	2 (8.3%)							

						discontinued the study due to with-drawal of consent).
Severe venous thromboembolism [1]						
Outcome	Study arm	N	Result, n (%)	Estimated absolute difference in efficacy: Difference / 95% CI / *P* value	Estimated relative difference in efficacy: Hazard/Odds/ Risk ratio / 95% CI / *P* value	Description of methods used for estimation
Number of serious vascular thrombotic events	Arm 1: individualized prophylaxis, (25-65 IU/kg every 3-5 days)	117	0, (0)			
	Arm 2: weekly prophylaxis, (25-65 IU/kg)	23	0, (0)			
Quality of life [2]						
Outcome	Study arm	N	Result, mean change (SD)	Estimated absolute difference in efficacy: Difference / 95% CI / *P* value	Estimated relative difference in efficacy: Hazard/Odds/ Risk ratio / 95% CI / *P* value	Description of methods used for estimation
Haem-A-QoL	Arm 1: individualized prophylaxis, (25-65 IU/kg every 3-5 days) **Pre-study prophylaxis**	34	2.0 (8.0)			Absolute changes in Haem-A-QoL scores from baseline to week 28 (A-LONG) were evaluated.

8.4 Results per PICO (clinical question)

Table 29. **Results referring to PICO question 1: Indirect Treatment Comparison of emicizumab and octocog alfa (Kovaltry®)**

Results per outcome	Results from the comparative analysis should be given in the table below, if possible.							
		Absolute difference in efficacy			Relative difference in efficacy			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Annualized bleeding rate (ABR) (ITC Calculation based on median ABR Hemlibra)[1]	HAVEN 3 LEOPOLD II	4.30			Rate Ratio: 0.13	0.12-0.15		The ITC analysis is based on the result of: 1. Result of pooling Arm A and B (prophylaxis emicizumab) compared with arm C (FVIII on demand) in HAVEN 3 study. 2. Result of pooling Low dose (2x/week) and High dose (3x/week) Arm compared with the on-demand Arm in LEOPOLD II study.
Annualized bleeding rate (ABR) (ITC calculated based on individual participant data (IPD))[2]	HAVEN 3 LEOPOLD II	2.95			Rate Ratio: 0.41	0.38-0.43		The ITC analysis is based on the result of: 1. Result of pooling Arm A and B (prophylaxis emicizumab) compared with arm C (FVIII on demand) in HAVEN 3 study. 2. Result of pooling Low dose (2x/week) and High dose (3x/week) Arm compared with the on-demand Arm in LEOPOLD II study.

1. For further information on ITC calculation please refer to excel file "*Final application Hemlibra ITC calc median ABR*"
2. For further information on ITC calculation please refer to excel file "*Final application Hemlibra ITC calc IPD*"

Table 30. **Results referring to PICO question 2: Indirect Treatment Comparison of emicizumab and efmoroctocog alfa (Elocta®)**

Results per outcome	Results from the comparative analysis should be given in the table below, if possible.							
		Absolute difference in efficacy			Relative difference in efficacy			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Annualized bleeding rate (ABR) (ITC Calculation based on median ABR Hemlibra)[1]	HAVEN 3 A-LONG	7.01			Rate Ratio: 0.06	0.05-0.06		The ITC analysis is based on the result of: 1. Result of pooling Arm A and B (prophylaxis emicizumab) compared with arm C (FVIII on demand) in HAVEN 3 study. 2. Result of rFVIIIFc (Weekly prophylaxis) Arm compared with rFVIIIFc (Episodic treatment) Arm in A-LONG study.
Annualized bleeding rate (ABR) (ITC calculated based on individual participant data (IPD))[2]	HAVEN 3 LEOPOLD II	6.17			Rate Ratio: 0.17	0.16-0.18		The ITC analysis is based on the result of: 1. Result of pooling Arm A and B (prophylaxis emicizumab) compared with arm C (FVIII on demand) in HAVEN 3 study. 2. Result of pooling Low dose (2x/week) and High dose (3x/week) Arm compared with the on-demand Arm in LEOPOLD II study.

1. For further information on ITC calculation please refer to excel file "*Final application Hemlibra ITC calc median ABR*"
2. For further information on ITC calculation please refer to excel file "*Final application Hemlibra ITC calc IPD*"

8.5 Prophylactic treatment and dose during the 6 months NIS study for patients with ABR ≥ 3

	Treatment (units)	n	mean dose	min dose	max dose
ABR >=3	ADVATE (IU)	6	23,03	10.31	34.48
ABR >=3	ADYNOVATE (IU)	1	49,08	49.08	49.08
ABR >=3	ELOCTA (IU)	1	10,71	10.71	10.71
ABR >=3	ELOCTATE (IU)	2	40,73	20.70	63.91
ABR >=3	HELIXATE (IU)	1	36,59	36.59	36.59
ABR >=3	KOGENATE (IU)	3	33,03	30.82	37.04
ABR >=3	NUWIQ (IU)	1	60	60.00	60.00
ABR >=3	REFACTO (IU)	1	20,62	20.62	20.62
ABR >=3	TRANEXAMIC ACID (mg)	1	8,66	8.66	8.66
ABR >=3	XYNTHA (IU)	1	23,33	23.33	23.33

8.6 Safety Update Hemlibra Q4-2018

THROMBOEMBOLISM

Background

Thrombus formation is a complex physiological phenomenon that serves as an appropriate response to vessel wall injury. It is a dynamic process that results when procoagulation activation overcomes the natural anticoagulant mechanisms and fibrinolytic system.[1] The three key factors contributing to

hypercoagulability are endothelial damage (abnormal vessel wall), abnormal flow (blood stasis or turbulence), and altered coagulability (abnormal blood components). Any of these three factors may lead to pathological coagulation.

Thrombotic cases in emicizumab clinical trials, other programmes and post-marketing

More than 1400 people with haemophilia A have been treated with emicizumab in the emicizumab clinical development programme and other programmes, as well as post-marketing use.

Cases of TMA and other thrombotic events (TE) were observed in the clinical development programme. Following an assessment of these events, guidance and instructions were developed as part of a detailed risk mitigation strategy, and investigators were informed about the risk of thrombotic complications in October 2016.[2] The guidance developed includes instructions on the use and dosing of bypassing agents (BPAs) in combination with emicizumab, as well as recommended medical supervision and laboratory monitoring after the administration of BPAs. These guidelines were implemented in all protocols and incorporated into informed consent forms across all emicizumab studies and programmes.

Clinical Trials & other programs	Concommitant aPCC exceeding label guidance#	Other events/risk factors	Clinical trial
TE case #2	2***	0	HAVEN 1*
TE case #1	0	1***	STASEY**
Post Marketing	**Concommitant aPCC exceeding label guidance**	**Other events/risk factors**	**Post-marketing**
TE case # 4	0	4[a]	4***

[#] Guidance on the use and dosing of BPA in combination with HEMLIBRA (emicizumab) was implemented in October 2016 and included in the label.

[*]HAVEN 1 was a phase 3 clinical study evaluating HEMLIBRA (emicizumab) in adults and adolescents with haemophilia A and FVIII inhibitors. ** STASEY a phase IIIb, single arm, international study to evaluate the safety and tolerability of emicizumab in patients with hemophilia A with inhibitors against Factor VIII (FVIII).

***Among the 3 serious thrombotic events (blood clots) that occurred in clinical trials, 1 occurred in the US and 2 occurred outside of the US. Among the 4 events that occurred in the post-marketing setting, 1 occurred in the US and 3 occurred outside of the US.

[a] In all 4 cases, all patients had pre-existing conditions for the development of thromboembolic events such as hypertension and previous history of thrombotic events.

Data cut-off date: 31 December, 2018

References

1. Tripodi A, et al. J Thromb Haemost 2009;7:906–907;
2. Data on file. Roche/Genentech; December 2018;
3. Oldenburg J, et al. N Engl J Med 2017;377:809–818.

THROMBOTIC MICROANGIOPATHY (TMA)

Background

Thrombotic microangiopathy comprises a heterogeneous group of disorders characterised by injured endothelial cells that are thickened, swollen, or detached, mainly from arterioles and capillaries.[1,2] Pathological findings include vascular damage manifesting as arteriolar and capillary thrombosis, and characteristic abnormalities in the endothelium and vessel wall. Histological and clinical features include schistocytes, microangiopathic haemolytic anaemia, thrombocytopenia, and organ injury.

TMA cases in emicizumab clinical trials and other programmes

More than 1400 people with haemophilia A have been treated with emicizumab in the emicizumab clinical development programme and other programmes, as well as post-marketing use.

Cases of TMA and other thrombotic events were observed in the clinical development programme. Following an assessment of these events, guidance and instructions were developed as part of a detailed risk mitigation strategy, and investigators were informed about the risk of thrombotic complications in October 2016.[3] The guidance developed includes instructions on the use and dosing of bypassing agents (BPAs) in combination with emicizumab, as well as recommended medical supervision and laboratory monitoring after the administration of BPAs. These guidelines were implemented in all protocols and incorporated into informed consent forms across all emicizumab studies and programmes.

Clinical Trials & other programs	Concommitant aPCC exceeding label guidance#	Other events/risk factors	Clinical Trial
TMA case #3	3**	0	HAVEN 1*
Post-marketing	**Concommitant aPCC exceeding label guidance#**	**Other events/risk factors**	**Post-marketing**
TMA case #1	1	0	1**

Guidance on the use and dosing of BPA in combination with HEMLIBRA (emicizumab) was implemented in October 2016 and included in the label.

*HAVEN 1 was a phase 3 clinical study evaluating HEMLIBRA (emicizumab) in adults and adolescents with haemophilia A and FVIII inhibitors.

**Among the 3 TMA cases from HAVEN 1, 1 occurred in the US and 2 occurred outside of the US. The post-marketing case occurred in the US.

Data cut-off date: 31 December, 2018

References

1. Textor SC, Leung N. Vascular injury to the kidney. In: Harrison's Principles of Internal Medicine,19th ed. 2015;
2. George JN, Nester CM. N Engl J Med 2014;371:6546–66; 3. Data on file. Roche/Genentech; December 2018;
3. Oldenburg J, et al. N Engl J Med 2017;377:809–818.

FATALITIES

Background

The HEMLIBRA clinical development programme is investigating the safety and efficacy of emicizumab in people living with haemophilia A with and without FVIII inhibitors. HEMLIBRA is not approved for haemophilia A without FVIII inhibitors.

Patients who could not enrol in one of the sponsored clinical trials, and who met other criteria, were permitted to gain access to emicizumab through compassionate use. All fatalities are evaluated through Roche and Genentech drug safety and reported to regulatory authorities in strict accordance with guidelines and requirements.[1]

Fatalities* in emicizumab clinical trials and other programmes [1-3]

More than 1400 people with haemophilia A have been treated with emicizumab in the emicizumab clinical development programme and other programmes, as well as post-marketing use

	Fatalities	Clinical trial where event occurred
Clinical trials	**2**	**HAVEN 1*, STASEY****
Expanded access programme	**1**	**Not applicable**

Compassionate use programme†	**3**	**Not applicable**
Post-approval setting	**1**	**Not applicable**

*HAVEN 1 was a phase 3 clinical study evaluating HEMLIBRA (emicizumab) in adults and adolescents with haemophilia A and FVIII inhibitors
**STASEY a phase IIIb, single arm, international study to evaluate the safety and tolerability of emicizumab in patients with hemophilia A with inhibitors against Factor VIII (FVIII).

†Compassionate use is intended for patients who have a serious or life-threatening disease and are not eligible to participate in a clinical trial; they must have exhausted all therapies used to treat the disease and are either no longer responsive to them or cannot tolerate them, with no other approved treatment options remaining.

Data cut-off date: 31 December, 2018

References
1. Data on file. Roche/Genentech; December 2018;
2. Shima M et al. N Engl J Med 2016;374:2044–2053;
3. Oldenburg J, et al. N Eng

In each case, the cause of death was assessed by the investigator or treating physician as unrelated to emicizumab.

Causes of death were assessed as rectal haemorrhage (n=1), sepsis (n=1), intracranial haemorrhage (n=1), pre-existing pseudotumour associated with severe haemophilia A (n=1), sudden cardiac death (n=1), caecal perforation (n=1) and traumatic head injury (n=1).

Medicinrådet

Medicinrådets protokol for vurdering af klinisk merværdi for emicizumab til behandling af hæmofili A

Versionsnr: 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddels kliniske værdi. Den indeholder et eller flere kliniske spørgsmål, som ansøger skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	13. februar 2019
Ikrafttrædelsesdato	13. februar 2019
Dokumentnummer	41339
Versionsnummer	1.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 13. februar 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Hemlibra
Generisk navn	Emicizumab
Firma	Roche
ATC-kode	B02BX06
Virkningsmekanisme	Monoklonalt modificeret immunoglobulin G4 (IgG4).
Administration/dosis	De første 4 uger: 3 mg/kg subkutant en gang ugentlig. Herefter 1,5 mg/kg en gang ugentligt eller 3 mg hver 2. uge.
EMA-indikation	Rutineprofylakse hos patienter med svær hæmofili A (FVIII < 1 %) uden faktor VIII aktivitet.

2 Forkortelser

ABR: *Annual Bleeding Rate*

EMA: *European Medicines Agency*

EPAR: *European Public Assessment Report*

FVIII: Faktor VIII (en koagulationsfaktor)

GRADE: System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)

Haem-A-QoL: *Hemophilia-Specific Quality of Life Index*

PTP: *Previously Treated Patients*

PUP: *Previously Untreated Patients*

SD: Standardafvigelse

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af emicizumab som mulig standardbehandling af patienter med hæmofili A. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder, der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende emicizumab modtaget den 27. september 2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af emicizumab sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem emicizumab og faktor VIII (FVIII)-præparat af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

Hæmofili A er medfødt mangel på FVIII, som er vigtigt for blodets evne til at koagulere og dermed standse blødninger. Ubehandlet vil manglen på FVIII medføre spontane led- og muskelblødninger, som på sigt medfører svære ledforandringer og invaliditet. Herudover vil blødning ved traume og kirurgi være livstruende.

I 2016 var der registreret i alt 388 patienter med hæmofili A ved de to hæmofilicentre i hhv. Aarhus og København. Heraf var 132 af patienterne i profylaktisk behandling, mens 256 fik behandling efter behov (on-demand) [1].

4.1 Nuværende behandling

Hæmofili A behandles i dag med et rekombinant FVIII-præparat. Patienter med moderat og svær hæmofili tilbydes aktuelt profylaktisk behandling, som omfatter rutinemæssige infusioner af et FVIII-præparat. Valg af præparat sker iht. til Medicinrådets lægemiddelrekommandation fra februar 2018 [2]. Man skelner imellem såkaldte standardpræparater og præparater med forlænget halveringstid. Som udgangspunkt anvender man det billigste standard FVIII-præparat. Hvis patienten har vanskelig veneadgang eller har dokumenterede gennembrudsblødninger under behandling med et standard FVIII-præparat, kan man overveje at skifte til et FVIII-præparat med forlænget halveringstid (efmoroctocog alfa) [2]. Patienten håndterer selv FVIII-præparatet derhjemme 2-4 gange om ugen afhængigt af, hvilket faktorniveau der tilstræbes hos patienten samt halveringstiden for det anvendte præparat.

4.2 Emicizumab

Emicizumab er et rekombinant, humaniseret, monoklonalt modificeret immunoglobulin G4, som binder sig til faktor IXa og X, hvorved det efterligner den funktion, FVIII normalt har i koagulationskaskaden.

Medicinrådet har tidligere godkendt emicizumab som mulig standardbehandling til en snæver patientgruppe med hæmofili A, som har udviklet inhibitor mod FVIII [3]. EMA har nu godkendt en indikationsudvidelse, så emicizumab også er godkendt til rutineprofylakse hos patienter med svær hæmofili A (FVIII < 1 %) uden FVIII-aktivitet (uanset alder).

Den anbefalede startdosis er 3 mg/kg givet som subkutan injektion én gang ugentligt i de første fire uger, efterfulgt af en vedligeholdelsesdosis på 1,5 mg/kg én gang ugentligt eller 3 mg/kg hver 2. uge.

Emicizumab kan ikke anvendes til at behandle en blødning, som opstår under den profylaktiske behandling med emicizumab. Her anvendes et FVIII-præparat on-demand.

Der er endnu ingen studier af eller erfaring med emicizumab hos tidligere ubehandlede patienter (PUP). On-demandbehandling af blødninger med FVIII hos denne gruppe, som aldrig tidligere har været behandlet med FVIII, kan medføre en risiko for udvikling af inhibitor mod FVIII. Denne risiko er ikke belyst i de kliniske studier af emicizumab. Risikoen for udvikling af inhibitor mod FVIII er lille hos patienter, som har været i profylaktisk behandling med FVIII i mere end 50 behandlingsdage (PTP). Derfor forholder fagudvalget sig kun til behandling med emicizumab hos patienter, som tidligere har været i profylaktisk behandling med FVIII.

5 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde en specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

5.1 Klinisk spørgsmål 1

1. *Hvad er den kliniske merværdi af emicizumab sammenlignet med standard FVIII-præparater hos patienter med svær hæmofili A?*

Population
Patienter med svær hæmofili A (alle aldre), som tidligere har været i profylaktisk behandling med et FVIII-præparat.

Intervention
Emicizumab.

Komparator
Profylakse med standard FVIII-præparater: Kovaltry[1] vælges som repræsentant for gruppen.

Effektmål
Se tabel 1 (effektmål) og afsnit 6 (andre overvejelser).

[1] Indholdsstoffet i Kovaltry er octocog alfa, som indgår i flere andre FVIII-præparater, herunder ældre præparater. Derfor er der specifikt angivet handelsnavn her.

5.2 Klinisk spørgsmål 2

2. *Hvad er den kliniske merværdi af emicizumab sammenlignet med FVIII-præparater med forlænget halveringstid hos patienter med svær hæmofili A?*

Population
Patienter med svær hæmofili A, som tidligere har været i profylaktisk behandling med et FVIII-præparat.

Intervention
Emicizumab.

Komparator
Profylakse med FVIII-præparater med forlænget halveringstid (efmoroctocog alfa).

Effektmål
Se tabel 1 (effektmål og afsnit 6 (andre overvejelser)).

Baggrund for valg af de kliniske spørgsmål
FVIII med forlænget halveringstid anvendes fortrinsvis til patienter, som har vanskelig veneadgang eller har dokumenterede gennembrudsblødninger under behandling med et standard FVIII-præparat. Da den subkutane administration af emicizumab er en fordel for patienter med vanskelig veneadgang, er FVIII med forlænget halveringstid en relevant komparator. Da den godkendte indikation omfatter den brede population, har fagudvalget valgt at sammenligne emicizumab med både standard FVIII og FVIII med forlænget halveringstid.

Der er ikke randomiserede eller kontrollerede studier, hvor emicizumab er direkte sammenlignet med FVIII.

RADS har vurderet de syv tilgængelige standard FVIII-præparater som ligeværdige. Fagudvalget finder det derfor tilstrækkeligt at sammenligne emicizumab med ét præparat, som er repræsentativt for gruppen af standard FVIII-præparater. En del af standard FVIII-præparaterne er godkendt for år tilbage, hvor der ikke var samme dokumentationskrav og behandlingspraksis som i dag. Det kan derfor medføre yderligere bias, hvis data fra nye studier af emicizumab sammenlignes med data fra ældre studier af FVIII. Kovaltry er det senest godkendte præparat. Fagudvalget ønsker derfor, at data fra kliniske studier af Kovaltry anvendes i sammenligningen med emicizumab.

Der er aktuelt markedsført to FVIII-præparater med forlænget halveringstid: efmoroctocog alfa (Elocta) og rurioctocog alfa pegol (Adynovi). Rurioctocog alfa pegol er ikke godkendt til børn under 12 år. Da emicizumab er godkendt til børn i alle aldre, er efmoroctocog alfa en mere relevant komparator. Fagudvalget ønsker derfor, at data for emicizumab sammenlignes med data fra kliniske studier af efmoroctocog alfa.

5.3 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.
For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko, odds ratio eller hazard ratio. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikkealvorlige symptomer og bivirkninger).

Effektmål*	Vigtighed	Kategori	Måleenhed	Mindste klinisk relevante forskelle (absolutte værdier)
Årlig blødningsrate (ABR)	Kritisk	Alvorlige symptomer og bivirkninger	Median antal blødninger per patient i studiet omregnet til per år	3 blødninger per år per patient
Ophør pga. bivirkninger	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter, som ophører pga. bivirkning	5 %
Alvorlig venøs tromboemboli	Vigtig	Alvorlige symptomer og bivirkninger	Antal hændelser	Forskel på 2 hændelser mellem hvert studie
Livskvalitet	Vigtig	Helbredsrelateret livskvalitet	Haem-A-QoL (voksne), Haem-A-QoL-SF (unge)	0,5 SD eller 5 point

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Kritiske effektmål

Blødningsrate (median ABR)
Målet med profylaktisk behandling er at undgå livstruende blødning samt at forebygge gentagne ledblødninger, som medfører ledskader (hæmofiliartropati) og senere invaliditet. Ledskader udvikles over årtier og er derfor ikke et realistisk effektmål i prospektive studier. I stedet anvender man det af EMA accepterede surrogatmål: ABR. ABR dækker det samlede antal blødninger (spontane, led- og livstruende), som patienten rapporterer i studieperioden og omregnes til en gennemsnitlig eller median årlig blødningsrate per patient.

Da studierne som oftest er baseret på et lille patientantal, vil få patienter med meget høj ABR have stor indflydelse på gennemsnittet. Fagudvalget finder derfor, at den mediane ABR skal anvendes fremfor den gennemsnitlige ABR. Den mediane ABR i kliniske studier af profylaktisk behandling ligger typisk på 2-3. Da rapporteringen af blødninger i praksis foretages af patienten selv, kan der være en vis usikkerhed i opgørelsen.

Fagudvalget finder på baggrund af den forventede ABR, det lille antal patienter og den indirekte sammenligning, at en forskel i median ABR på 3 mellem studierne er klinisk relevant.

Vigtige effektmål

Behandlingsophør pga. bivirkninger
Da typen af bivirkninger er forskellig mellem emicizumab og FVIII-præparater, er det relevant at anvende et mål, som opgør den samlede byrde af klinisk relevante bivirkninger. Behandlingsophør pga. bivirkninger afspejler, hvorvidt bivirkninger er af betydning for patienten i en sådan grad, at behandlingen ikke kan fortsætte. Fagudvalget finder derfor, at behandlingsophør pga. bivirkninger er et vigtigt effektmål. Der er tale om indirekte sammenligning af studier med få patienter, hvorfor mindre forskelle (< 5 %) kan være helt tilfældige. Fagudvalget har drøftet, hvor stor forskellen skal være, for at man vil begynde at blive betænkelig ved at anvende lægemidlet. På den baggrund er den mindste klinisk relevante forskel fastsat til 5 %.

Alvorlig venøs tromboemboli
Der er i tidligere studier set tilfælde af alvorlig venøs tromboemboli (proksimal dyb venetrombose, lungeemboli, trombose i centralnervesystemet eller andre vitale organer), når emicizumab blev givet i kombination med høje doser af *activated prothrombin complex concentrate* (Feiba). Der var derimod ingen tilfælde, hvor emicizumab blev givet i monoterapi.

Behandling med FVIII-præparater er sjældent forbundet med tromboemboliske episoder. En forskel på ét tilfælde vil derfor umiddelbart vække bekymring. Patientgruppen i studier af lægemidler til behandling af hæmofili er oftest lille (< 100 patienter), observationstiden kort og lægemidlerne ikke direkte sammenlignet. Det kan derfor være tilfældigt, at ét tilfælde af alvorlig venøs tromboemboli forekom i det ene studie, men ikke det andet. Fagudvalget vurderer derfor, at en forskel på to tilfælde af alvorlig venøs tromboemboli mellem de aktuelle studier er klinisk relevant.

Livskvalitet
Livskvalitetsdata for FVIII-præparater reflekterer ofte resultatet af en bedre blødningskontrol, fordi patienterne er skiftet fra on-demand behandling (med mange blødninger) til en profylaktisk behandling (med få blødninger). En forbedring af livskvaliteten skyldes dermed mere et bedre behandlingsregime end effekten af det undersøgte FVIII-præparat.

Der er ikke randomiserede eller kontrollerede sammenlignende studier imellem emicizumab og profylakse med FVIII, derfor reflekterer målingen patientens livskvalitet før og efter behandlingen i studiet.

Det er derfor kun relevant at inkludere studier, hvor patienterne var i profylaktisk behandling forud for studiet. Der er ikke umiddelbart kendskab til publicerede data for standard FVIII-præparaterne, som opfylder dette kriterium. Da både effekt, bivirkninger og doseringsinterval er ens imellem standard FVIII-præparaterne [1], vil man ikke forvente, at skift imellem disse vil medføre målbare ændringer i livskvalitet.

I studierne af både emicizumab og efmoroctocog alfa er der anvendt det sygdomsspecifikke redskab Haem-A-QoL til voksne patienter og det tilsvarende Haem-A-QoL-SF til børn og unge (4-16 år). Den samlede livskvalitet scores på en skala fra 0 til 100. Denne skala vil derfor blive anvendt i sammenligning med efmoroctocog alfa.

Der er ikke fundet studier, som specifikt redegør for størrelsen af den mindste klinisk relevante forskel hos patienter med hæmofili A. For flere andre sygdomme har man fundet, at en forskel på 5 point på en skala fra 0-100 er mindste klinisk relevante forskel. En standardafvigelse (SD) på 0,5 har historisk vist sig at have relevans som mindste klinisk relevante forskel på helbredsrelateret livskvalitet [4]. Fagudvalget har derfor valgt en absolut forskel på 0,5 SD på samme skala, som den mindste klinisk relevante forskel til sammenligningen mellem emicizumab og de valgte komparatorer. I fald det ikke er muligt at beregne denne, vil en forskel på 5 point vurderes som værende den mindste klinisk relevante forskel.

Mindre vigtige effektmål

Inhibitor (neutraliserende antistoffer)
Udvikling af inhibitor er dannelse af neutraliserende antistoffer mod lægemidlet, som gør, at behandlingen ikke længere virker. Det er en kendt bivirkning til behandling med FVIII. Patienter i profylakse med emicizumab behandles med FVIII on demand ved blødning eller traume. Derfor er der en teoretisk risiko for udvikling af inhibitor mod FVIII under emicizumabbehandling. Rapportering af hændelsen i kliniske studier er sjælden pga. små studier, kort observationstid og en ofte selekteret patientpopulation med lav risiko for

inhibitor mod FVIII. Derfor finder fagudvalget, at man vanskeligt kan foretage en relevant sammenligning mellem emicizumab og FVIII-præparater på denne parameter ud fra de kliniske studier.

For emicizumab er der i det tidligere HAVEN 2-studie set ét enkelt tilfælde af neutraliserende antistoffer mod emicizumab hos børn, som havde udviklet inhibitor mod FVIII [3].

Langtidsbivirkninger
Der er ikke langtidsdata for emicizumab. Derfor vil langtidsbivirkninger ikke indgå som et egentligt effektmål. Overvejelser om mulige langtidsbivirkninger er ikke desto mindre meget relevante, da der er tale om en ny og potentielt livslang behandling, som kun er afprøvet i korttidsstudier med relativt få patienter. Fagudvalget vil derfor have risikoen for mulige langtidsbivirkninger in mente, når man afvejer fordele og ulemper ved behandlingen sammenlignet med FVIII-præparater.

6 Litteratursøgning

Databaser for søgningen
Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer
Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen.

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der er angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

Lægemiddel/komparator(er)	**Indikation**
emicizumab	Hemophilia A Haemophilia A
Faktor VIII, FVIII Kovaltry, octocog alfa, BAY 81-8973 Elocta, efmoroctocog alfa	

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur
Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier: Alle prospektive interventionsstudier af intervention og komparator publiceret 5 år tilbage skal inkluderes, såfremt de er gennemført hos den i protokollen specificerede

population og rapporterer mindst ét af de præspecificerede effekt- eller bivirkningsmål. Studier, som alene omfatter on-demand behandling (og ikke profylakse), kan ekskluderes.

Vurderingen af klinisk merværdi baseres i udgangspunktet på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser.

7 Databehandling/analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat, per-protocol) samt metode. Resultater for intention-to-treat-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængeligt for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (fx bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

8 Andre overvejelser

Fordele

Emicizumab administreres som subkutan injektion hver eller hver anden uge, hvilket generelt er en fordel for patienterne ift. FVIII, der administreres som intravenøs infusion 2-4 gange om ugen.

Det intravenøse regime er en udfordring hos patienter med vanskelig veneadgang. Hos små børn eller andre med vanskelig veneadgang kan der være behov for en intravenøs port med deraf følgende risiko for infektion og nedsat adhærens til behandlingen. Fagudvalget finder derfor, at den subkutane administrationsvej især er en fordel hos patienter med vanskelig veneadgang, hvilket bør vægte positivt i kategoriseringen af den klinisk merværdi.

Det lange doseringsinterval på op til 2 uger mindsker behandlingsbyrden betydeligt. De hyppige doseringer af FVIII med dårligere beskyttelse ved glemt eller udskudt infusion er især en ulempe hos patienter med dårlig adhærens. Fagudvalget finder derfor, at det lange doseringsinterval med stabil plasmakoncentration bør vægte positivt i vurderingen af den kliniske merværdi.

Ulemper

Emicizumab kan ikke anvendes til at behandle blødninger, som opstår spontant eller ved traume eller kirurgi.

For patienten betyder det, at man skal have både emicizumab og et FVIII-præparat på lager (have to præparater med på rejse, holde øje med udløbsdato mv.).

Patienter, som tidligere har været i behandling med et FVIII-præparat, kan miste rutine i administration af FVIII-præparatet, hvilket kan betyde, at man i tilfælde af blødning er nødt til at søge skadestue. For små børn, som ikke tidligere er behandlet med et FVIII-præparat (PUP), vil behandling med emicizumab i praksis betyde, at forældrene ikke lærer at administrere FVIII, hvorfor man altid vil skulle søge skadestue i tilfælde af opstået blødning.

Der er sparsom erfaring med kirurgi under emicizumab-profylakse og usikkerhed om dosering af FVIII. Hvis patienten eller forældrene ikke selv kan administrere FVIII-præparatet, kan det resultere i forlænget indlæggelse eller ekstra ambulante besøg.

Emicizumabbehandlingen kan ikke monitoreres biokemisk, sådan som behandlingen med FVIII kan, hvilket er en ulempe. Dertil kommer, at monitorering af FVIII-behandlingen i forbindelse med f.eks. kirurgi eller behandling af større blødninger kun kan foretages med helt specifikke FVIII assays og ikke almindelige FVIII clot-analyser. Den samlede hæmostatiske effekt ved kombinationsbehandling med emicizumab og FVIII kan ikke måles med de eksisterende analyser, og erfaringen er begrænset.

Andre lægemiddelrelaterede forhold

Fagudvalget har i forbindelse med den tidligere vurdering af emicizumab til patienter med inhibitor mod FVIII foretaget en struktureret gennemgang af lægemiddelhåndteringsmæssige forhold (såsom opbevaring, holdbarhed mv.). Der blev ikke fundet andre forhold af betydning for den kliniske merværdi [3].

9 Referencer

1. Baggrundsnotat for behandling af hæmofili. RADS november 2016. http://rads.dk/media/4111/bgnhaemofili-m-bilag-2016-12.pdf

2. Behandlingsvejledning inklusiv lægemiddelrekommandation for behandling af hæmofili. Februar 2018 www.medicinraadet.dk/media/7027/laegemiddelrekommandation-haemofili-vers-12.pdf

3. Medicinrådets anbefaling vedrørende emicizumab som mulig standardbehandling til hæmofili A med inhibitor mod Faktor VIII. Juni 2018. http://www.medicinraadet.dk/media/9281/medicinraadets-anbefaling-vedr-emicizumab-bloedersygdom-10.pdf

4. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41:582–92.

10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende blødersygdom

Forvaltningslovens § 4, stk. 2 har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	***Indstillet af***
Eva Funding Overlæge	Lægevidenskabelige Selskaber og Region Hovedstaden
Medlemmer	***Udpeget af***
Afventer ny udpegning	Region Nordjylland
Anne-Mette Hvas Professor, overlæge, ph.d.	Region Midtjylland
Lone Hvitfeldt Poulsen Overlæge	Region Midtjylland
Jesper Farup Revsholm Afdelingslæge	Region Syddanmark
Rune Larsen Overlæge	Region Sjælland
Marianne Hutchings Hoffmann Overlæge	Dansk Pædiatrisk Selskab
Peter Kampmann Overlæge, lægefaglig teamleder	Dansk Selskab for Trombose og Hæmostase
Marie Louise Schougaard Christiansen Afdelingslæge, klinisk farmakolog, ph.d.	Dansk Selskab for Klinisk Farmakologi (DSKF)
Afventer ny udpegning	Dansk Selskab for Sygehusapoteksledelse (DSS)
Finder det ikke længere relevant at have en kandidat i fagudvalget	Dansk Selskab for Anæstesiologi og Intensiv Medicin
Kan ikke udpege en kandidat	Dansk Selskab for Klinisk Biokemi
To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe Dorte Glintborg (projekt- og metodeansvarlig) Mette Hollensted (projektdeltager) Anne Sofie Gram (projektdeltager) Ilse Linde (koordinator) Kirsten Holdt Henningsen (teamleder)