Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende subkutan C1-esteraseinhibitor til behandling af arveligt angioødem - revurdering

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. subkutan C1-esteraseinhibitor til arveligt angioødem - revurdering, version 1.0
2. Forhandlingsnotat fra Amgros vedr. subkutan C1-esteraseinhibitor til arveligt angioødem
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. den sundhedsøkonomiske afrapportering
4. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. lægemidlets værdi
5. Medicinrådets vurdering vedr. subkutan C1-esteraseinhibitor til arveligt angioødem - revurdering, version 1.0
6. Ansøgers endelige ansøgning
7. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
8. Medicinrådets protokol for vurdering vedr. subkutan C1-esteraseinhibitor til arveligt angioødem, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Subkutan C1-esteraseinhibitor - revurdering

Forebyggende behandling af arveligt angioødem

Version 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.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren.

Dokumentoplysninger	
Godkendelsesdato	24. august 2021
Dokumentnummer	112815
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 24. august 2021

Indholdsfortegnelse

1. Begreber og forkortelser ... 3

2. Konklusion ... 4

3. Introduktion ... 4

3.1 Patientpopulation ... 4

3.1.1 Komparator ... 5

4. Vurdering af den sundhedsøkonomiske analyse ... 5

4.1 Antagelser og forudsætninger for model ... 5

4.1.1 Modelbeskrivelse ... 5

4.1.2 Analyseperspektiv ... 6

4.2 Omkostninger ... 6

4.2.1 Lægemiddelomkostninger ... 6

4.2.2 Omkostninger til behandling af anfald ... 7

4.2.3 Patientomkostninger ... 8

4.3 Følsomhedsanalyser ... 8

4.4 Opsummering af basisantagelser ... 9

5. Resultater ... 10

5.1 Resultatet af Medicinrådets hovedanalyse ... 10

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser ... 11

6. Budgetkonsekvenser ... 11

6.1 Ansøgers estimat af patientantal og markedsandel ... 11

6.2 Medicinrådets budgetkonsekvensanalyse ... 13

7. Diskussion ... 13

8. Referencer ... 15

9. Bilag ... 16

9.1 Resultatet af ansøgers hovedanalyse ... 16

9.2 Resultatet af ansøgers budgetkonsekvensanalyse ... 16

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
HAE	Arveligt angioødem (*hereditary angioedema*)
i.v.	Intravenøs infusion
SAIP	Sygehusapotekernes indkøbspriser
SPC	*Summary of Product Characteristics*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for subkutan C1-esteraseinhibitor ca. [redacted] DKK pr. patient sammenlignet med lanadelumab. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 12,9 mio. DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af subkutan C1-esteraseinhibitor som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 13,9 mio. DKK i år 5.

Analysen bygger på antagelsen om, at subkutan C1-esteraseinhibitor og lanadelumab ikke har forskel i effekt, og de inkrementelle omkostninger er derfor estimeret i en omkostningsminimeringsanalyse. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for subkutan C1-esteraseinhibitor, og der er stor usikkerhed forbundet med det reelle lægemiddelforbrug af subkutan C1-esteraseinhibitor. Derfor har den gennemsnitlige vægt pr. patient, spild af lægemiddel og mulighed for dosisreduktion stor betydning for analysens resultat.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af subkutan C1-esteraseinhibitor som mulig standardbehandling på danske hospitaler til patienter med arveligt angioødem (HAE).

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra CSL Behring AB. Vi modtog ansøgningen den 9. maj 2021.

3.1 Patientpopulation

HAE skyldes en genetisk defekt i det blodbaserede protein C1-esteraseinhibitor, hvilket resulterer i mangelfuld eller dysfunktionel C1-esteraseinhibitor. Der findes flere typer af HAE, hvor 90 % af tilfældene er type I, mens de sidste 10 % af tilfældene er type II. Ved begge typer af HAE kan mangel eller dysfunktionalitet af C1-esteraseinhibitor medføre en kædereaktion, der får de små blodkar til at lække væske ud i det tilstødende væv. Dette er årsagen til, at et ødem opstår [1].

Den nøjagtige forekomst af HAE er ukendt, men det anslås, at HAE påvirker ca. 1 ud af 10.000-50.000 personer verden over. Ud af de ca. 120 danske patienter anslår fagudvalget, at ca. 30-40 patienter får forebyggende behandling, heraf er hovedparten i behandling med lanadelumab.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af subkutan C1-esteraseinhibitor på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har subkutan C1-esteraseinhibitor sammenlignet med lanadelumab som forebyggende behandling for patienter med arveligt angioødem?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for subkutan C1-esteraseinhibitor sammenlignet med lanadelumab. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Sammenligningen med lanadelumab er lavet på baggrund af data fra to studier, COMPACT [2] og HELP [3]. COMPACT er et randomiseret, dobbeltblindet, placebokontrolleret fase III-studie, der sammenligner to forskellige doseringer af subkutan C1-esteraseinhibitor mod placebo hos patienter med type I eller type II HAE. HELP er et randomiseret, dobbeltblindet, placebokontrolleret fase III-studie, der sammenligner forskellige doseringer af lanadelumab overfor placebo.

Ansøger har udarbejdet en naiv sammenligning af COMPACT og HELP. Den naive sammenligning undersøger den absolutte reduktion i månedlige anfald for patienter, der er i behandling med subkutan C1-esteraseinhibitor eller lanadelumab. På baggrund af dette data antager ansøger, at subkutan C1-esteraseinhibitor er ikke-inferiør i forhold til lanadelumab.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en omkostningsminimeringsanalyse til at estimere omkostningerne forbundet med behandlingen med subkutan C1-esteraseinhibitor. Modellen estimerer omkostninger forbundet med behandling samt forhindrede anfald. Ansøger antager, at ubehandlede HAE-patienter i gennemsnit har 40 anfald om året. Da ansøger antager, at subkutan C1-esteraseinhibitor har ikke-inferiør effekt sammenlignet med lanadelumab, antages det, at både subkutan C1-esteraseinhibitor og lanadelumab reducerer anfald om

året med 84 %, hvilket var anfaldsreduktionen i COMPACT-studiet. Dette svarer til en gennemsnitlig anfaldsfrekvens på 6,4 anfald om året, når patienterne modtager enten subkutan C1-esteraseinhibitor eller lanadelumab.

Medicinrådets vurdering af ansøgers modelantagelser
Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 5 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Fagudvalget forklarer, at det kan være svært at give et bud på en gennemsnitlig behandlingsvarighed. Dette skyldes, at nogle patienter vil have behov for livslang behandling, men andre patienter stopper undervejs, da sygdommens sværhedsgrad vil variere over tid. Fagudvalget vurderer dog, at 5 år er en rimelig tidshorisont.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende er ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af subkutan C1-esteraseinhibitor sammenlignet med lanadelumab præsenteret. Ansøger har inkluderet lægemiddelomkostninger, omkostninger til anfaldsbehandling og patientomkostninger. Ansøger har ikke inkluderet bivirkningsrelaterede omkostninger, da ansøger antager, at omkostninger til bivirkninger forbundet med subkutan C1-esteraseinhibitor og lanadelumab er ens.

4.2.1 Lægemiddelomkostninger

Ansøger har jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren* estimeret lægemiddelomkostninger på baggrund af apotekets indkøbspris (AIP).

Ansøger anvender i analysen en dosis på 60 IE/kg hver 3.-4. dag for subkutan C1-esteraseinhibitor. For subkutan C1-esteraseinhibitor, som doseres efter vægt, anvender ansøger en gennemsnitsvægt på 73,1 kg baseret på kønsfordelingen fra COMPACT-studiet og den gennemsnitlige vægt i den danske befolkning.

For lanadelumab anvendes en dosis på 300 mg hver 2. uge. Ifølge produktresuméet for lanadelumab kan dosisreduktion til 300 mg hver 4. uge overvejes hos patienter, der er stabilt anfaldsfrie, især hos patienter med lav vægt.

Doser anvendt i ansøgers analyse er hentet i de respektive produkters produktresuméer (SPC'er), se Tabel 1.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 1.

Tabel 1. Anvendte lægemiddelpriser, SAIP (juni 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Subkutan C1-esteraseinhibitor (Berinert)	2000 IE	1 stk.	[redacted]	Amgros
	3000 IE	1 stk.	[redacted]	Amgros
Lanadelumab	300 mg	1 stk.	[redacted]	Amgros

Til at estimere den gennemsnitlige dosering pr. patient har ansøger valgt at anvende den gennemsnitlige vægt for den danske befolkning (73,1 kg), hvilket er lavere end 80,2 kg, som er den gennemsnitlig vægt for patienter inkluderet i COMPACT-studiet. For at undersøge betydningen af den gennemsnitlige vægt på analysens resultat, vælger Medicinrådet at udarbejde en følsomhedsanalyse, hvor den gennemsnitlige vægt fra COMPACT-studiet anvendes.

Da subkutan C1-esteraseinhibitor gives vægtbaseret, vil der være et vist spild ved hver dosering, da subkutan C1-esteraseinhibitor kun kommer i en pakning med en styrke på 2000 IE. Dette har ansøger ikke taget højde for i analysen, da ansøger anvender pris pr. IE til estimering af lægemiddelomkostningerne for subkutan C1-esteraseinhibitor. Subkutan C1-esteraseinhibitor kommer også i en styrke på 3000 IE, men denne pakning er ikke tilgængelig i Danmark. Derfor er der risiko for, at lægemiddelomkostningerne for subkutan C1-esteraseinhibitor i ansøgers analyse er underestimeret ved anvendelse af gennemsnitlig vægt, da spildet pr. patient potentielt er meget større, hvis 3000 IE ikke bliver lanceret i Danmark. Med en gennemsnitlig vægt på 73,1 kg bliver den gennemsnitlige dosering af subkutan C1-esteraseinhibitor 4.387 IE. Dette betyder, at den gennemsnitlige patient vil have behov for lidt mere end to pakninger af C1-esteraseinhibitor (Berinert). Medicinrådet vælger derfor at udarbejde en følsomhedsanalyse, der skal illustrere *best case* (forbrug på 4000 IE pr. patient) og *worst case* (forbrug på 6000 IE pr. patient), som dermed vil belyse spændet i lægemiddelomkostninger mellem de to doseringer. Ligeledes udarbejder Medicinrådet en følsomhedsanalyse, hvor forbruget er 5000 IE pr. patient, hvilket vil være en mulig dosering, hvis 3000 IE lanceres i Danmark.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger. Dog er der stor usikkerhed forbundet med det reelle lægemiddelforbrug af subkutan C1-esteraseinhibitor, og Medicinrådet vælger derfor at udarbejde følsomhedsanalyser, hvor betydningen af doseringen af subkutan C1-esteraseinhibitor undersøges.

4.2.2 Omkostninger til behandling af anfald

Ansøger antager, at der ikke er forskel i frekvensen af anfald ved behandling med subkutan C1-esteraseinhibitor og lanadelumab. Ansøger har inkluderet omkostninger til behandling af anfald i form af lægemiddelomkostninger og hospitalsomkostninger. Ansøger antager, at patienter behandles med enten i.v. C1-esteraseinhibitor (Berinert),

i.v. C1-esteraseinhibitor (Cinryze), icatibant (Firazyr) eller en kombination af icatibant (Firazyr) og i.v. C1-esteraseinhibitor (Berinert) eller i.v. C1-esteraseinhibitor (Cinryze).

Medicinrådets vurdering af ansøgers antagelser vedr. hospitalsomkostninger
Medicinrådet vælger at ekskludere omkostninger til behandling af anfald i Medicinrådets hovedanalyse, da formålet med analysen er at estimere de inkrementelle omkostninger pr. patient.

Medicinrådet ekskluderer hospitalsomkostninger i Medicinrådets hovedanalyse, da disse antages at være ens ved behandling med subkutan C1-esteraseinhibitor og lanadelumab.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administration af lægemidlerne og inkluderer patientens effektive tid på administration. Udover administration har ansøger også inkluderet patientomkostninger til behandling af anfald.

Ansøger antager, at patienten selv administrerer behandlingen med subkutan C1-esteraseinhibitor og lanadelumab i eget hjem, hvilket antages at vare 20 minutter pr. administration.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time, *jf. Medicinrådets værdisætning af enhedsomkostninger*.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid til administration af behandlingerne. Medicinrådet vælger at ekskludere patientomkostninger i forbindelse med behandling af anfald, da patientomkostningerne mellem subkutan C1-esteraseinhibitor og lanadelumab er ens.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

Tabel 2. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Administrationsfrekvens pr. uge for subkutan C1-esteraseinhibitor	± 10 %
Administrationsfrekvens for lanadelumab	Administrationer ændres til hver 4. uge fremfor hver 2. uge
Lægemiddelpris for subkutan C1-esteraseinhibitor	± 10 %

Følsomhedsanalyse	Beskrivelse
Lægemiddelpris for subkutan C1-esteraseinhibitor	[redacted] for subkutan C1-esteraseinhibitor ved anbefaling
Administrationsdosis for subkutan C1-esteraseinhibitor	40 IE/kg
Årlige anfald for lanadelumab	± 10 %
Andel af kvinder i HAE-populationen	± 10
Diskonteringsrate	0 %
Ekskludering af patientomkostninger	Patientomkostninger ekskluderes

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Ansøger informerer om, at subkutan C1-esteraseinhibitor også kan administreres i en dosis på 40 IE/kg, hvilket også er testet i COMPACT-studiet. Ansøger har valgt at inkludere en følsomhedsanalyse, hvor ansøger antager, at alle patienter modtager en dosis på 40 IE/kg. Dog foreligger der ingen retningslinjer for dosisreduktion i produktresuméet for subkutan C1-esteraseinhibitor, samtidig med at ansøger ikke giver noget bud på, hvor stor en andel af de danske patienter, som forventes at kunne dosisreduceres. Fagudvalget forventer, at nogle patienter formentlig vil kunne dosisreduceres, men ud fra nuværende datagrundlag kan fagudvalget ikke definere, hvilke patienter som kan dosisreduceres, uden at effekten af behandlingen mindskes. Fagudvalget skønner dog, at andelen som kan dosisreduceres over tid vil være af samme størrelse for subkutan C1-esteraseinhibitor som for lanadelumab. På nuværende tidspunkt er ca. 50 % af patienterne på lanadelumab i Danmark i gang med trinvis dosisreduktion fra 300 mg hver 2. uge til 300 mg hver 4. uge. Medicinrådet vælger at udarbejde en følsomhedsanalyse, hvor 50 % af både patienter på subkutan C1-esteraseinhibitor og lanadelumab reduceres efter 2 år i behandling. Dette er valgt grundet gradvis dosisreduktion på lanadelumab og manglende klinisk praksis i Danmark for dosisreduktion af subkutan C1-esteraseinhibitor.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser. Medicinrådet vælger at udarbejde egne følsomhedsanalyser, der undersøger doseringen af subkutan C1-esteraseinhibitor samt 50 % dosisreduktion på både subkutan C1-esteraseinhibitor og lanadelumab.

4.4 Opsummering af basisantagelser

I Tabel 4 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 3. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	5 år	5 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Omkostninger til anfaldsbehandling Patient- og transportomkostninger	Lægemiddelomkostninger Patient- og transportomkostninger
Dosering:		
Subkutan C1-esteraseinhibitor (Berinert)	60 IE/kg	60 IE/kg
Lanadelumab	300 mg	300 mg
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af omkostninger til anfaldsbehandling, som det fremgår af Tabel 4.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 12,9 mio. DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 5.

Tabel 4. Resultatet af Medicinrådets hovedanalyse ved sammenligning med lanadelumab, DKK, diskonterede tal

	Subkutan C1-esteraseinhibitor	Lanadelumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Patientomkostninger	38.099	16.270	21.828

	Subkutan C1-esteraseinhibitor	Lanadelumab	Inkrementelle omkostninger
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 6.

Tabel 5. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Gennemsnitlig vægt fra COMPACT: 80,2 kg	[redacted]
Gennemsnitlig dosering på 4000 IE pr. patient	[redacted]
Gennemsnitlig dosering på 5000 IE pr. patient	[redacted]
Gennemsnitlig dosering på 6000 IE pr. patient	[redacted]
50 % dosisreduktion på både subkutan C1-esteraseinhibitor og lanadelumab	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at subkutan C1-esteraseinhibitor vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Subkutan C1-esteraseinhibitor bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Subkutan C1-esteraseinhibitor bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger har estimeret, at der på nuværende tidspunkt er 31 HAE-patienter i Danmark, som modtager forebyggende behandling. Ansøger forventer, at dette patientantal vil stige til 36 patienter i år 5. På nuværende tidspunkt tilbydes patienterne forebyggende

behandling med enten lanadelumab eller i.v. C1-esteraseinhibitor. Ansøger har valgt også at inkludere i.v. C1-esteraseinhibitor (Cinryze) i budgetkonsekvensanalysen.

Ansøger antager, at subkutan C1-esteraseinhibitor vil have et markedsoptag på 10 % i år 1 stigende til 14 % i år 5 ved en anbefaling, mens subkutan C1-esteraseinhibitor vil bibeholde et markedsoptag på 3 %, hvis det ikke anbefales. Ved en anbefaling af subkutan C1-esteraseinhibitor vil patienter, der på nuværende tidspunkt behandles med i.v. C1-esteraseinhibitor (Cinryze), skifte til subkutan C1-esteraseinhibitor.

Da i.v. C1-esteraseinhibitor (Cinryze) ikke indgår som komparator i omkostningsanalyser har ansøger valgt kun at inkludere lægemiddelomkostninger for i.v. C1-esteraseinhibitor (Cinryze) i budgetkonsekvensanalyse. For i.v. C1-esteraseinhibitor (Cinryze) anvendes en dosis på 1500 IE hver 3.-4. dag.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Medicinrådet har udskiftet AIP med SAIP for i.v. C1-esteraseinhibitor (Cinryze), se Tabel 6.

Tabel 6. Anvendte lægemiddelpriser, SAIP (juni 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
i.v. C1-esteraseinhibitor (Cinryze)	500 IE	2 stk.	[redacted]	Amgros

Medicinrådet vurderer, at budgetkonsekvenserne for patienter, der behandles med i.v. C1-esteraseinhibitor (Cinryze) er underestimeret, da ansøger kun har valgt at inkludere lægemiddelomkostninger. I en tidligere vurdering af subkutan C1-esteraseinhibitor til HAE har Medicinrådet estimeret de totale omkostninger pr. patient ved forebyggende behandling med i.v. C1-esteraseinhibitor (Cinryze) [4]. Medicinrådet vælger derfor at inkludere hospitalsomkostninger og omkostningerne til behandling af anfald, således at disse omkostninger indgår for alle lægemidler inkluderet i budgetkonsekvensanalysen.

Medicinrådet accepterer ansøgers antagelser vedr. patientantal og markedsoptag, se Tabel 7.

Tabel 7. Medicinrådets estimat af antal patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Subkutan C1-esteraseinhibitor (Berinert)	3	3	3	4	5
i.v. C1-esteraseinhibitor (Cinryze)	1	1	1	1	1
Lanadelumab	27	27	28	29	30
			Anbefales ikke		

	År 1	År 2	År 3	År 4	År 5
Subkutan C1-esteraseinhibitor (Berinert)	1	1	1	1	1
i.v. C1-esteraseinhibitor (Cinryze)	3	2	2	3	4
Lanadelumab	27	28	29	30	31

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af subkutan C1-esteraseinhibitor vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 8.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 13,9 mio. DKK i år 5.

Tabel 8. Medicinrådets 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]

7. Diskussion

Behandling med subkutan C1-esteraseinhibitor er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med lanadelumab. [redacted] Sammenligningen er lavet på baggrund af antagelsen om, at der ikke er forskel i effekt mellem subkutan C1-esteraseinhibitor og lanadelumab.

Analysens resultat varierer dog meget i Medicinrådets følsomhedsanalyser grundet usikre parametre, [redacted]. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for subkutan C1-esteraseinhibitor, og der er samtidigt stor usikkerhed om det reelle lægemiddelforbrug af subkutan C1-esteraseinhibitor. Den gennemsnitlige vægt pr. patient har stor betydning for analysens resultat, da subkutan C1-esteraseinhibitor doseres efter vægt. Hvis den gennemsnitlige vægt pr. patient øges fra 73,1 kg til 80,2 kg, stiger de inkrementelle omkostninger pr. patient til ca. [redacted] DKK. Derfor er der også usikkerhed omkring analysen.

Ligeledes har spild en stor betydning for analysens resultat, da subkutan C1-esteraseinhibitor kun kommer i én pakning med en styrke på 2000 IE i Danmark. Medicinrådet har valgt at illustrere denne usikkerhed vedr. spild ved at udarbejde to scenarier, hvor alle patienterne forbruger hhv. 4000 IE pr. patient eller 6000 IE pr. patient. I de to scenarier ligger de inkrementelle omkostninger pr. patient på hhv. ca. [redacted] DKK og ca. [redacted] DKK. Hvis 3000 IE bliver markedsført i Danmark, vil den øvre grænse for de inkrementelle omkostninger pr. patient være ca. [redacted] DKK. Firmaet har tilkendegivet at en pakning med 3000 IE vil blive lanceret på det danske marked såfremt Medicinrådets anbefaler subkutan C1-esteraseinhibitor.

Derudover er der stor usikkerhed omkring andelen af patienter, der kan dosisreduceres på subkutan C1-esteraseinhibitor, da ansøger ikke giver noget bud på, hvor stor en andel af de danske patienter, som forventes at kunne dosisreduceres. I Medicinrådets følsomhedsanalyse, hvor 50 % af både patienter på subkutan C1-esteraseinhibitor og lanadelumab dosisreduceres efter 2 år i behandling, [redacted] de inkrementelle omkostninger [redacted] DKK [redacted] DKK. Andelen på 50 % bygger på fagudvalgets forventning til, hvor mange patienter der kan dosisreduceres ved behandling med lanadelumab. Fagudvalget anslår, at samme andel vil kunne dosisreduceres ved behandling med subkutan C1-esteraseinhibitor.

8. Referencer

1. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73(8):1575–96.

2. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. N Engl J Med. 2017;376(12):1131–40.

3. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108-21.

4. Medicinrådet. Baggrund for Medicinrådets anbefaling af subkutan C1-esteraseinhibitor til forebyggende behandling af arveligt angioødem.

9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 10.

Tabel 9. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Subkutan C1-esteraseinhibitor	Lanadelumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Omkostninger til anfaldsbehandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	38.099	16.270	21.828
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af subkutan C1-esteraseinhibitor vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 11.

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 I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	Skriftlig proces
Leverandør	CSL-Behring
Lægemiddel	Berinert, C1-esteraseinhibitor (human). 2000 IE + 3000 IE, SC
EMA-indikation	Berinert til subkutan injektion er indiceret til profylakse af tilbagevendende anfald af hereditært angioødem (HAE) hos unge og voksne patienter med mangel på C1-esteraseinhibitor.

Forhandlingsresultat

Amgros har opnået følgende betinget pris på Berinert ved genforhandling:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Tidligere SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Berinert	2.000 IE	1 stk.	23.320	[redacted]	[redacted]	[redacted]
Berinert	3.000 IE	1 stk.	34.980	[redacted]	[redacted]	[redacted]

Den kommende aftale er betinget af en anbefaling til indikationen. I dag er det kun 2000 IE, der er tilgængelig i Danmark men 3.000 IE vil blive markedsført, så snart lægemidlet bliver godkendt til ibrugtagning.

[redacted]

Planen er, at der igangsættes en prisregulering på lægemidlerne til profylakse behandling når berotralstat er blevet vurderet af Medicinrådet. I nærmeste fremtid vil der blive udarbejdet en behandlingsvejledningen og på baggrund af den vil Amgros publicere et udbud.

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi i denne omgang **har** opnået den bedst mulige pris på berinert. Denne vurdering baserer vi på følgende punkter:

[redacted]

Leverandøren beskriver at produktionen af Berinert er uafhængig af den samlede produktion af immunglobulinerne og derfor er produktionen ikke påvirket af den aktuelle globale mangel. Se nedenstående statement fra leverandøren:

The global challenges in plasma collection due to the pandemic has not affected Berinert. There are currently no shortages of Berinert in the Nordic region. Based upon our forward planning, we don't anticipate any impact on Berinert.

CSL Behring has further invested in additional European manufacturing capacity to avoid any shortages of Berinert that might have occurred in the past.

Konklusion

[redacted]

Relation til markedet

Medicinrådet besluttede på rådsmødet i april 2020, at der vil blive udarbejdet en behandlingsvejledning for lægemidler til behandling af HAE. Dermed vil konkurrencegrundlaget mellem lægemidlerne til profylakse behandling blive tydelig.

Aktuelle årspriser

Lægemiddel	Dosis	Doserings-frekvens	Frekvens pr. år	Årlig dosis* (IE)	SAIP pr. IE (DKK)	SAIP pr. dosis (DKK)	Pris for 52 ugers behandling (DKK)
Berinert	60 IE/kg	Hver 3,5 dag	104	4.387	[redacted]	[redacted]	[redacted]
Berinert	40 IE/kg	Hver 3,5 dag	104	2.924	[redacted]	[redacted]	[redacted]

*vægt brugt i den sundhedsøkonomiske afrapportering: 73,12 kg.

Lægemiddel	Anbefalet dosis	Doserings-frekvens	Frekvens pr år.	Årlig dosis	SAIP pr. dosis (DKK)	Pris for 52 ugers behandling
Takhzyro	300 mg	Hver 2. uge	26	7.800 mg	[redacted]	[redacted]
Takhzyro	300 mg	Hver 4. uge	13	4.800 mg	[redacted]	[redacted]

CSL Behring

2 July 2021

Cover Letter to Danish Medicines Council on Berinert® SC

Please find below comments to the Danish Medicines Council's draft reports for clinical assessment "Vurdering af human subkutan C1-esterase-inhibitor til forebyggende behandling af arveligt angioødem" and health economic assessment "Sundhedsøkonomiske afrapportering".

Clinical assessment: "Vurdering af human subkutan C1-esterase-inhibitor til forebyggende behandling af arveligt angioødem"

1) **DMC:** The report states that there are two treatment options used for prophylactic treatment in Denmark today: C1-inhibitor administered intravenously and lanadelumab.
CSL Behring: CSL Behring would like to remark that there are previous experience of using Berinert® SC i Denmark. This experience confirms efficacy and safety of the product and supports the clinical value of Berinert® SC in a Danish clinical setting.

2) ***DMC: The report states that the real-world data from [redacted] is limited and not representative for Danish clinical practice.***
CSLB: CSL Behring would like to emphasize that also published Spanish treatment guidelines, written by HAE experts from the Spanish Allergology Society, recommend a general starting dose of 2000 IU twice weekly. This dose will be adjusted if needed to ensure optimal disease control. Data from the usage of Berinert® SC in Spanish HAE patients were recently presented in the 12th C1-inhibitor deficiency & angioedema workshop in Budapest. Data from one poster and one oral presentation supports that patients are treated in accordance with the published treatment guidelines in Spanish clinical practice and that the majority of patients are effectively treated with doses between 20 and 40 IU/kg body weight.
To summarize, the experience from two comparable European markets supports the assumption that Berinert® SC may be used at lower doses also in Denmark.

3) ***DMC: The report confirms that few patients treated with lanadelumab in Denmark today are using the one monthly dosing regimen.***
CSL Behring: CSL Behring would like to emphasize that information from relevant HCPs in Denmark confirms that very few patients are using the one monthly dosing regimen with Takhzyro. The assumption regarding dose adjustment for Takhzyro seems unrealistic in Danish clinical setting.

Health economy: "Sundhedsøkonomiske afrapportering"

1) **DMC:** The report states there is no market authorization for Berinert® SC 3000 IU and therefore calculates treatment costs based on assumptions of waste.

CSL Behring: 3000 IU does have market authorization in Denmark but no list price yet. [redacted]
There is no waste expected in Denmark of this product resulting in higher consumption of medicines that calculated by CSL Behring.

[redacted]

Clinicians in Denmark are well aware of the value of plasma derived medicines and are expected to optimize the use in each patients.

[redacted]

2) **DMC:** The report conducts sensitivity analysis based on assumption of average body weight in line with the COMPACT study (80,2 kg).

CSL Behring:
In the COMPACT study there are a significant number of e.g. US patients included that generally have higher body weight that expected in the Danish patient population. Hence, this sensitivity analysis will not be very representative for a Danish clinical practice and the base case scenario should be more accurate.

3) **DMC:** The report conducts sensitivity analysis based on assumption that 50 % of eligible patients could adjust the dose for lanadelumab and Berinert® SC.

CSL Behring:
Please refer to CSL Behring's third comment to the clinical assessment report above.

We kindly ask you to keep all information in the application documentation marked in yellow confidential.

Kind regards,

Erik Ahlzén
Market Access Manager
CSL Behring Nordic region

Fra: Gedske Thomsen
Til: Gedske Thomsen
Emne: VS: Timeline for 7 week process of Berienert SC
Dato: 8. juli 2021 21:02:39
Vedhæftede filer: image001.png

Kære Erik

Tak for jeres høringssvar vedrørende udkast til Medicinrådets vurdering af lægemidlets værdi for subkutan C1-esteraseinhibitor og jeres høringssvar vedrørende den sundhedsøkonomiske afrapportering.
Vi har gennemgået jeres kommentarer til vurderingsrapporten og finder ikke anledning til at ændre den nuværende kategorisering.
Ligeledes har jeres kommentarer til den sundhedsøkonomiske afrapportering ikke givet anledning til ændringer i rapporten.

Dokumenter vedr. jeres lægemiddel vil blive fremsendt d.9 august til Rådet, hvorefter I kan forventer svar vedr. anbefaling indenfor 5 dage.

Det er desværre ikke muligt for os at dele, hvad vi har indstillet til Rådet.

Mvh

Gedske Thomsen
Sundhedsvidenskabelig specialkonsulent
Cand.scient.humbiol.
+45 30 34 46 43
gth@medicinraadet.dk

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

Fra: Erik.Ahlzen@cslbehring.com <Erik.Ahlzen@cslbehring.com>
Sendt: 2. juli 2021 10:50
Til: Gedske Thomsen <GTH@medicinraadet.dk>
Cc: Camilla Vels Jensen <cvj@medicinraadet.dk>; Camilla Nybo Holmberg

<CNH@medicinraadet.dk>; Katrine Jürs <KJU@medicinraadet.dk>;
Helena.Stensman@cslbehring.com
Emne: SV: Timeline for 7 week process of Berienert SC

Hej Gedske,

Vänligen se bifogat svarsdokument.

Med vänlig hälsning,
Erik Ahlzen
ust be handled in accordance with applicable privacy laws.

Medicinrådet

Medicinrådets vurdering af human subkutan C1-esterase-inhibitor til forebyggende behandling af arveligt angioødem - revurdering

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	24. august 2021
Dokumentnummer	113810
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion ... 3

2. Begreber og forkortelser ... 5

3. Introduktion ... 6

3.1 Arveligt angioødem ... 6

3.2 Subkutan C1-esteraseinhibitor ... 7

3.3 Nuværende behandling ... 7

4. Metode ... 8

5. Resultater ... 8

5.1 Klinisk spørgsmål 1 ... 8

5.1.1 Litteratur ... 8

5.1.2 Databehandling og analyse ... 12

5.1.3 Evidensens kvalitet ... 12

5.1.4 Effektestimater og kategorier ... 12

5.1.5 Fagudvalgets konklusion ... 16

6. Andre overvejelser ... 17

7. Relation til behandlingsvejledning ... 18

8. Referencer ... 19

9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet ... 21

10. Versionslog ... 22

11. Bilag ... 23

Bilag 1: Cochrane – risiko for bias ... 23

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 24. august 2021

1. Medicinrådets konklusion

Rådet vurderer på baggrund af det nuværende datagrundlag, at subkutan C1-esteraseinhibitor samlet set er lige så effektivt og sikkert til forebyggende behandling af arveligt angioødem som lanadelumab. Begge lægemidler er omtrent lige gode til at reducere anfaldsfrekvensen (subkutan C1-esteraseinhibitor: rate ratio 0,13 (0,08; 0,21) og lanadelumab: rate ratio 0,13 (0,07; 0,24)) og vurderes til at have vedvarende effekt af sammenlignelig størrelse. Begge lægemidler medfører anfaldsfrihed hos omkring 40 % af patienterne. Der er ikke registreret alvorlige bivirkninger i de kliniske studier COMPACT (subkutan C1-esteraseinhibitor) og HELP (lanadelumab). De hyppigst observerede uønskede hændelser er milde reaktioner ved injektionsstedet.

Vurderingen er baseret på en deskriptiv sammenligning af data fra studierne COMPACT og HELP, hvor hhv. subkutan C1-esteraseinhibitor og lanadelumab er sammenlignet med placebo. Der findes ikke direkte sammenlignende studier, og det har ikke været muligt at udføre indirekte sammenlignende statistiske analyser. Værdien af subkutan C1-esteraseinhibitor er ikke kategoriseret over for lanadelumab, da sammenligningen er forbundet med væsentlig usikkerhed og ikke tillader en kategorisering i henhold til Medicinrådets metode.

Rådets har noteret sig, at fagudvalget har påpeget, at subkutan C1-esteraseinhibitor er en velkommen behandlingsmulighed til forebyggende behandling hos gravide og ammende kvinder, hvorimod den anden subkutane forebyggende behandling med lanadelumab er kontraindiceret i disse patientgrupper.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

BMI: *Body-mass index*

CI: Konfidensinterval

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency)*

EPAR: *European Public Assessment Report*

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

HR: *Hazard ratio*

ITT: *Intention to treat*

OR: *Odds ratio*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*

PP: *Per Protocol*

RCT: Randomiseret kontrolleret studie *(Randomised Controlled Trial)*

RR: Relativ risiko

SMD *Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af human subkutan C1-esteraseinhibitor til forebyggende behandling af arveligt angioødem er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra CSL Behring AB. Medicinrådet modtog ansøgningen den 19. maj 2021.

Subkutan C1-esteraseinhibitor er tidligere blevet vurderet til samme indikation af Medicinrådet og blev da sammenlignet med intravenøs C1-esteraseinhibitor. Medicinrådet besluttede den 26. august 2020 ikke at anbefale subkutan C1-esteraseinhibitor. Ansøger har siden anmodet om en revurdering, hvor subkutan C1-esteraseinhibitor sammenlignes med lanadelumab, der i mellemtiden er blevet anbefalet af Medicinrådet som mulig standardbehandling. Ansøger har tilkendegivet, at subkutan C1-esteraseinhibitor, efter deres vurdering, hverken er bedre eller dårligere end lanadelumab til hele den godkendte indikation og dermed kan indgå i Medicinrådets hurtigere proces på syv uger. Medicinrådet har accepteret, at subkutan C1-esteraseinhibitor på den baggrund kan vurderes i Medicinrådets hurtigere proces.

Det kliniske spørgsmål er:

Hvilken værdi har subkutan C1-esteraseinhibitor sammenlignet med lanadelumab som forebyggende behandling for patienter med arveligt angioødem?

3.1 Arveligt angioødem

HAE er en sjælden, arvelig tilstand præget af uforudsigelige anfald af hævelser i hud og slimhinde, kaldet arveligt angioødem. HAE debuterer oftest i de første teenageår, men for nogle allerede i barndommen. Hævelserne er meget smertefulde og funktionsbegrænsende og rammer forskellige steder på kroppen. Oftest rammes ekstremiteterne, ansigtet, kønsorganerne, mave-tarm-kanalen og de øvre luftveje. Anfald, der rammer mave-tarm-kanalen, kan medføre voldsomme smerter, opkast og diarré. Et anfald kan vare op til 7 dage (gennemsnitlig 3 dage) uden behandling.

HAE kan potentielt være livstruende, hvis hævelserne f.eks. rammer de øvre luftveje, hvor et larynxødem (hævelse omkring strubehovedet og stemmelæberne) kan forårsage luftvejsobstruktion [1]. Efter tilkomsten af de nuværende behandlingsmuligheder er mortaliteten faldet drastisk, og i dag forekommer der stort set ikke dødsfald i Danmark som følge af HAE.

HAE skyldes en genetisk defekt i det blodbaserede protein C1-esteraseinhibitor, hvilket resulterer i mangelfuld eller dysfunktionel C1-esteraseinhibitor. Der findes flere typer af HAE. Hyppigst forekommer type I og type II. Type I HAE er karakteriseret ved lav produktion af normalt C1-esteraseinhibitor. Op til 90 % af patienterne har type I HAE. De resterende ca. 10 % har type II HAE, som er karakteriseret ved normal produktion, men manglende funktionalitet af C1-esteraseinhibitor. Ved begge typer af HAE kan mangel

eller dysfunktionalitet af C1-esteraseinhibitor medføre en kædereaktion, der får de små blodkar til at lække væske ud i det tilstødende væv. Dette er årsagen til, at et ødem opstår [2].

Den nøjagtige forekomst af HAE er ukendt, men det anslås, at HAE påvirker ca. 1 ud af 10.000-50.000 personer verden over [1,2]. Aktuelt er der i Danmark registreret 109 patienter, som jævnligt kontrolleres på det Nationale Kompetencecenter for HAE på Odense Universitetshospital. En opgørelse fra 2014 viste, at anfaldsfrekvensen varierede fra asymptomatiske patienter/1 anfald om året og op til 84 anfald om året. Den gennemsnitlige frekvens lå på 17 anfald om året [3].

Den uforudsigelige og potentielt livstruende sygdom påvirker patienternes livskvalitet. Selv mellem anfald, hvor patienterne ellers er symptomfri, oplever mange patienter stadig angst og begrænsninger i de daglige aktiviteter [4]. Mønstret i anfaldene og sværhedsgraden heraf er for den enkelte patient uforudsigeligt. Sygdomsbyrden mellem anfaldene fylder således rigtig meget for HAE-patienterne. Hvornår kommer det næste anfald, hvor er jeg, har jeg anfaldsmedicin i nærheden og er jeg overhovedet i stand til at administrere medicinen selv? At leve med HAE har derfor stor betydning for livskvaliteten med risiko for personlige omkostninger i forhold til familie- og arbejdsliv. Netop på grund af den store sygdomsbyrde, er det ønskeligt for HAE-patienter, at fremtidige HAE-behandlinger ikke blot holder anfaldshyppigheden nede, men at behandlingen sigter mod at gøre HAE-patienter anfaldsfrie.

3.2 Subkutan C1-esteraseinhibitor

Berinert® indeholdende C1-esteraseinhibitor er oprenset og koncentreret fra humant plasma. Subkutan administration af C1-esteraseinhibitor erstatter manglende eller dysfunktionelt C1-esteraseinhibitor hos patienten, hvorved genereringen af bradykinin bliver begrænset og risikoen for angioødemanfald mindsket.

Berinert® til subkutan injektion er indiceret til forebyggende behandling af tilbagevendende anfald af HAE hos unge og voksne med mangel på funktionelt C1-esteraseinhibitor. Den anbefalede dosis ved subkutan brug er 60 IU/kg to gange om ugen (hver 3.-4. dag).

3.3 Nuværende behandling

Behandlingsmål for HAE type I og II er at minimere anfaldshyppigheden og/eller anfaldenes sværhedsgrad. Behandlingen af HAE er opdelt i behandling af akutte anfald og forebyggende behandling.

Til behandling af akutte anfald anvendes enten intravenøs substitution af manglende funktionelt C1-esteraseinhibitor (produkterne Berinert®/Cinryze®/Ruconest) eller det bradykininblokerende præparat icatibant (Firazyr), som administreres subkutant.

Den forebyggende behandling iværksættes i henhold til den gældende internationale guideline fra World Allergy Organization og European Academy Allergy and Clinical

Immunology fra 2017 [5]. Jævnfør denne guideline eksisterer der ikke faste kriterier for, hvilke patienter der tilbydes forebyggende behandling. Behovet for forebyggende behandling vurderes under hensyntagen til patientens sygdomsaktivitet, anfalds-frekvens/sværhedsgrad/lokation, livskvalitet og eventuelt manglende sygdomskontrol ved behandling af akutte anfald. Da alle disse faktorer varierer over tid, bliver behovet for forebyggende behandling vurderet ved hvert kontrolbesøg. Patientens præferencer er også en væsentlig faktor, f.eks. i forhold til administrationsvej.

Til forebyggende behandling anvendes to behandlingsprincipper i Danmark. Det ene princip består i intravenøs substitution af manglende funktionelt C1-esteraseinhibitor, og her anvendes et af de to produkter Berinert® eller Cinryze®. Behandlingerne administreres intravenøst og oftest hver 3.-4. dag. Det andet behandlingsprincip består i at hæmme det aktive plasmakallikreins proteolytiske aktivitet, hvorved risikoen for angioødemanfald mindskes. Her anvendes lanadelumab (Takhzyro®), som er et humant monoklonalt antistof. Lanadelumab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af HAE hos patienter på ≥ 12 år og er anbefalet som mulig standardbehandling af Medicinrådet hos patienter med minimum fire anfald om måneden [6]. Den anbefalede dosis er 300 mg subkutant hver 2. uge.

De fleste patienter administrerer selv deres forebyggende behandling (eventuelt med hjælp fra pårørende). Patienter, der ikke selv behersker teknikken, behandles på lokalt sygehus. Ud af de ca. 120 danske patienter anslår fagudvalget, at ca. 30-40 patienter får forebyggende behandling, heraf er hovedparten i behandling med lanadelumab.

4. Metode

Medicinrådets protokol for vurdering af human subkutan C1-esteraseinhibitor til forebyggende behandling af arveligt angioødem beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 8 fuldtekstartikler, som rapporterer data fra 3 studier. Herudover har ansøger inkluderet

yderligere 1 fuldtekstartikel, som er publiceret, efter litteratursøgningen er udført. Fagudvalget vurderer, at studierne kan anvendes til at besvare det kliniske spørgsmål.

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer
Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor [7].	**COMPACT**	NCT01912456
Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema [8].		
Subcutaneous C1-esterase inhibitor to prevent hereditary angioedema attacks: Safety findings from the COMPACT trial [9].		
Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks [10].	**COMPACT-OLE**	NCT02316353
Long-term efficacy and safety of subcutaneous C1-inhibitor in women with hereditary angioedema: subgroup analysis from an open-label extension of a phase 3 trial [11].		
Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study [12].		
Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial [13].	**HELP**	NCT02586805
Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks [14].		
Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study [15].		

Gennemgang af studier

COMPACT er et internationalt, multicenter, randomiseret, dobbeltblindet, placebokontrolleret fase 3-studie, som har til formål at vurdere effekt og sikkerheden af

to forskellige doseringer af subkutan human C1-esteraseinhibitor hos patienter med type I eller type II HAE. Studiet har et overkrydsningsdesign, der involverer to 16-ugers behandlingsperioder. Patienterne randomiseres til én af to doser C1-esteraseinhibitor (40 IU/kg eller 60 IU/kg), som efterfølges af en tilsvarende placebobehandling (eller omvendt). Det primære effektmål var anfaldsfrekvens. De sekundære effektmål var bl.a. andelen af patienter med respons, (defineret som ≥ 50 % reduktion i antallet af anfald sammenlignet med placebo) og uønskede hændelser.

HELP er et internationalt, multicenter, randomiseret, dobbeltblindet, placebokontrolleret fase 3-studie. Studiet er et parallelgruppe studie, der inkluderer patienter på 12 år eller ældre med HAE type I eller II. De randomiseres 2:1 til lanadelumab eller placebo. Patienter i lanadelumab-armen randomiseres yderligere 1:1:1 til ét af tre forskellige dosisregimer. Det primære effektmål var anfaldsfrekvens. De sekundære effektmål var bl.a. behov for anfaldsbehandling og uønskede hændelser.

***Open-label extension* studier**
For begge lægemidler vurderes effekt og sikkerhed af langvarig forebyggende behandling i ublindede *extension* studier. Der er ikke identificeret *peer-reviewede* publicerede resultater fra HELP *extension* studiet [16]. Resultater fra studiet (*final results* efter 33 måneder) er dog præsenteret i forskellige konference abstracts [17–19]. Resultater fra COMPACT *open-label extension* (*final results* efter 88 uger) (COMPACT-OLE) er publiceret i flere *peer-reviewede* artikler [10–12]. *Extension* studierne inddrages i den samlede konklusion med henblik på at belyse den vedvarende effekt udover opfølgningstiden i de randomiserede studier.

Studiernes sammenlignelighed
Populationerne i COMPACT og HELP er sammenlignelige.

Fagudvalget vurderer i øvrigt, at patientpopulationerne i studierne er sammenlignelige med danske HAE-patienter. Det bemærkes dog, at de yngre og ældre patientpopulationer er underrepræsenterede i HELP og COMPACT. Baseret på nuværende viden forventes der ikke anderledes effekt i disse patientgrupper. Baselinekarakteristika for de behandlingsarme, som er relevante i denne vurderingsrapport, er vist i tabel 2.

Tabel 2. Baselinekarakteristika

	Subkutan C1-esteraseinhibitor (60 IU/kg hver 3.-4. dag fra COMPACT) crossover design **N= 45**	**Lanadelumab** (300 mg hver 2. uge fra HELP) parallelgruppe design Lanadelumab **N= 27**	Placebo **N= 41**
Alder (år)	36,6 ± 14,9	40,3 ± 13,3	40,1 ± 16,8
Kvinder n (%)	32 (71)	15 (55,6)	34 (82,9)
Vægt (Kg)	80,2 ± 24,6	N/A	N/A
BMI	27,7 ± 6,8	31,0 ± 7,8	27,5 ± 7,7
Type HAE, n (%)			
- Type I	37 (82)	23 (85,2)	38 (92,7)
- Type II	8 (18)	4 (14,8)	3 (7,3)
HAE-anfald før screening	8,8 ± 6,4^	20 (8-36)*	30 (17-59)*

^ Gennemsnitligt antal (SD, standardafvigelse) HAE-anfald i 3 måneder op til screening.

* Median antal (IQR, *interquartile range*) HAE-anfald i 12 måneder op til screening.

Studiernes inklusionskriterier angiver, at patienter i COMPACT-studiet har ≥ 4 anfald over en 2 måneders periode (svarende til min. 2 anfald pr. måned), mens patienter i HELP-studiet skulle have min. 1 anfald pr. måned. Begge studier har en såkaldt run-in periode, hvor anfaldsfrekvensen vurderes på hhv. 3 måneder for COMPACT og 4 uger for HELP studiet.

Det er vanskeligt at vurdere, om der er betydende forskel i anfaldsfrekvensen ved baseline mellem studierne. I COMPACT-studiet er anfaldsfrekvensen i denne periode opgjort til 4,6 anfald/måned og 4,0 anfald/måned hos patienter behandlet med hhv. 40 IU/kg og 60 IU/kg. I HELP-studiet er den månedlige anfaldsfrekvens ved baseline opgjort til 3,5 anfald/måned i gruppen behandlet med lanadelumab 300 mg hver 2. uge (4,0 anfald/måned i placebo-gruppen).

I HELP-studiet observeres en betydelig behandlingseffekt i placebo-armen, hvor anfaldsfrekvensen reduceres til 1,97 anfald/måned under studiet. Det samme ses ikke i COMPACT-studiet, hvor anfaldsfrekvensen under placebobehandling stort set er uændret fra baseline (3,6 anfald/måned i 40 IU/kg og 4,0 anfald/måned i 60 IU/kg). Fagudvalget har ikke kendskab til dokumentation, der viser, om behandlingseffekten afhænger af udgangspunktet. Baseret på fagudvalgets kliniske erfaring forventes effekten relativt at være uafhængig af udgangspunktet. Det er uvist, hvorfor der observeres en relativ stor placeboeffekt i HELP-studiet, men ikke COMPACT-studiet. Det

kan skyldes en tilfældighed, idet populationerne er små, og da det er velkendt, at der for den enkelte patient kan være væsentlige udsving i anfaldsfrekvens over tid.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Statistiske analyser

Ansøger har ikke udført formelle sammenlignende statistiske analyser mellem subkutan C1-esteraseinhibitor og komparator, da de ikke har fundet grundlag for det. Ansøger fremhæver bl.a., at der er anvendt forskellig statistisk metodik i COMPACT og HELP. Der er desuden forskelle i studiedesignet for de inkluderede studier. COMPACT er et overkrydsningsstudie, mens studiet med lanadelumab er et parallelgruppestudie. I overkrydsningsstudier kan der være problemer med bl.a. *carry-over*-effekter fra den ene behandlingsperiode til den anden. I COMPACT-studiet anvendes derfor en to ugers opstarts- eller udvaskningsperiode.

Der er også forskel i behandlingsvarigheden mellem de inkluderede studier, hvor effektestimaterne for subkutan C1-esteraseinhibitor er baseret på 16 ugers behandling (14 uger når der tages højde for udvaskning ved overkrydsning), mens effektestimater for lanadelumab baseres på 26 ugers aktiv behandling. Det er vanskeligt at vurdere, om forskellen i behandlingsvarighed har indflydelse på effektestimaterne. Fagudvalget vurderer dog, at behandlingsvarigheden formentlig ikke påvirker sammenligneligheden af estimaterne, fordi data er opgjort på det tidspunkt, hvor lægemidlerne forventes at have maksimal effekt, altså efter *steady state*-koncentrationen er opnået.

Fagudvalget har baseret deres vurdering af subkutan C1-esteraseinhibitor på en kvalitativ gennemgang af data for henholdsvis C1-esteraseinhibitor og lanadelumab overfor placebo, da det samlet set vurderes, at studierne er tilstrækkelig ens til at dette er acceptabelt, og da sammenlignende statistiske analyser ikke er tilrådelige grundet forskellig statistisk metodik.

5.1.3 Evidensens kvalitet

Medicinrådet har vurderet risikoen for bias i COMPACT og HELP. Vurderingen fremgår af Bilag 1. I begge studier er det vurderet, at risikoen for bias er lav.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle fra COMPACT og HELP, som anvendes i fagudvalgets vurdering af klinisk spørgsmål 1.

Tabel 3. Data fra COMPACT og HELP til vurdering af klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Studiearm	Subkutan C1-esteraseinhibitor vs. placebo (60 IU/kg hver 3.-4. dag fra COMPACT)			Lanadelumab vs. placebo (300 mg hver 2. uge fra HELP)		
				Mean (CI) eller % (n/N)	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)	Mean (CI) eller n/N	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)
Anfaldsfrihed	Andel af patienter som oplever en 100 % reduktion i anfaldsfrekvens fra baseline (10 %-point)	Kritisk	Intervention	40,0 % (18/45)	40,0 %-point (25,5; 54,5)	RR 37,0 (2,30; 595,7)	44,4 % (12/27)	42,0 %-point (18,1; 61,8)	RR 18,2 (2,5; 132,2)**
			Placebo	0 % (0/45)			2,4 % (1/41)		
Helbreds-relateret livskvalitet	Ændring fra baseline målt med Angioedema Quality of life Questionnaire (AE-QoL) (6 point)	Kritisk	Intervention	86,12 point* (SD 12,32)	EQ-5D-VAS* 9,96 point (1,99; 17,94)		- 21,29 point (-28,21; - 14,37)	- 16,57 point (-28,53; - 4,62)	
			Placebo	78,11 point* (SD 21,77)			- 4,72 point (-10,46; 1,02)		
	Andel af patienter som oplever en forbedring på 6 point fra baseline		Intervention				80,77 % (21/26)		OR 7,20 (2,22; 23,37)
			Placebo				36,84 % (14/38)		
Anfaldsfrekvens	Antallet HAE-anfald pr. måned (15 %-point)	Vigtigt	Intervention	0,52 (0,0; 1,04)	- 3,51 anfald (-4,21; -2,81)	Rate ratio 0,13 (0,08 - 0,21)	0,26 (0,14; 0,46)	- 1,71 anfald (-2,09; -1,33)	Rate ratio 0,13 (0,07; 0,24)
			Placebo	4,03 (3,51; 4,55)			1,97 (1,64; 2,36)		
Bivirkninger	Andel patienter der ophører behandling grundet bivirkninger (10 %-point)	Vigtigt	Intervention	2,3 % (2/45)***	1,2 %-point (-2,8; 5,0)***	RR 2,00 (0,18; 21,65)***	0 % (0/27)***	- 2,4 %-point (-9,9; 5,0)***	RR 0,50 (0,02; 11,84)***
			Placebo	1,2 % (1/45)***			2,4 % (1/41)***		

CI = konfidensinterval, OR = Odds Ratio, RR = relativ risiko, *Data fra EQ-5D-VAS score efter 14 ugers behandling. **Udregnet af Medicinrådst baseret på hændelsesfrekvenserne i interventions- og komparatorarmen. ***Data for uønskede hændelser fremfor bivirkninger baseret på tilgængelighed.

Anfaldsfrihed
Som beskrevet i protokollen er effektmålet anfaldsfrihed kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det at opnå anfaldsfrihed vil fjerne den uforudsigelighed, som patienterne lever med, herunder også frygten for larynxødem, som har stor betydning for patienternes livskvalitet.

I COMPACT-studiet oplevede 40,0 % (18/45) af patienterne, at de blev anfaldsfri ved behandling med C1-esteraseinhibitor 60 IU/kg hver 3.-4. dag, mens 0 % (0/45) af patienterne behandlet med placebo oplevede anfaldsfrihed.

I HELP-studiet oplevede 44,4 % (12/27) af patienterne, at de blev anfaldsfri ved behandling med lanadelumab 300 mg q2w, mens 2,4 % (1/41) af patienterne behandlet med placebo oplevede anfaldsfrihed.

Fagudvalget vurderer, at raterne for anfaldsfrihed fra COMPACT og HELP indikerer, at subkutan C1-esteraseinhibitor og lanadelumab er lige gode, hvad dette effektmål angår. Dette baseres på observationen af, at den absolutte forskel i anfaldsfrihed er hhv. 40 % for C1-esteraseinhibitor 60 IU/kg hver 3.-4 dag og 42 %[1] for lanadelumab 300 mg q2w. Der ses altså en forskel på 2 %-point mellem de to behandlinger, hvilket er mindre end den mindste klinisk relevante forskel på 10 %-point.

Fagudvalget bemærker, at der er en relativ risiko for anfaldsfrihed på RR: 37,0 (2,30; 595,7) for subkutan C1-esteraseinhibitor og en tilsvarende RR: 18,2 (2,5;132,2) for lanadelumab. Dog er disse estimater meget sensitive overfor små ændringer, da der er meget få/ingen hændelser i placebogrupperne. Dette afspejles også i de meget brede konfidensintervaller, hvorfor de er tillagt mindre vægtning i vurderingen.

Helbredsrelateret livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet kritisk for vurderingen af lægemidlets værdi for patienterne, fordi HAE under anfald såvel som mellem anfald påvirker patientens livskvalitet.

Medicinrådet har ønsket livskvalitet belyst ved det validerede spørgeskema Angioedema Quality of Life Questionnaire (AE-QoL). Dette værktøj er dog ikke anvendt i COMPACT-studiet. Ansøger har derfor valgt at præsentere data fra EQ-5D for subkutan C1-esteraseinhibitor.

I COMPACT-studiet viste ændringen fra baseline til uge 14 på EQ-5D-VAS-scoren (patientens egen vurdering af helbred) en forbedret livskvalitet for patienter behandlet med subkutan C1-esteraseinhibitor 60 IU/kg sammenlignet med placebo (forskel mellem grupperne: 9,96 point (95 % CI 1,99; 17,94)). Forskellen i EQ-5D-indeksscore (sammenfatter de 5 dimensioner mobilitet, personlig pleje, sædvanlige aktiviteter, smerter/ubehag og angst/depression) var ikke signifikant forskellig for subkutan C1-esteraseinhibitor sammenlignet med placebo (forskel mellem grupperne: 0,04 (95 % CI 0,01; 0,08)).

I HELP-studiet oplevede patienter behandlet med lanadelumab 300 mg q2w en reduktion på AE-QoL på 21,29 point (14,37; 28,21), mens patienter i placebogruppen i gennemsnit oplevede en mindre markant forbedring, udtrykt ved en reduktion på 4,72 point (-1,02; 10,46). De gennemsnitlige ændringer fra baseline indikerer, at patienter behandlet med lanadelumab oplever en klinisk betydende forbedring af deres livskvalitet sammenlignet med placebo på 16,57 point (4,62; 28,53), hvilket er højere end den mindste klinisk relevante forskel på 6 point.

[1] 42 %: 44,4 % af patienterne er anfaldsfri og herfra fratrækkes de 2,4 % som er anfaldsfri i placeboarmen.

Resultaterne fra HELP-studiet viser i øvrigt, at en betydeligt højere andel af patienter behandlet med lanadelumab (80,77 %) oplever en forbedring på minimum 6 point sammenlignet med placebo (36,84 %). I HELP-studiet blev EQ-5D også anvendt (dog EQ-5D-5L modsat COMPACT hvor det var EQ-5D-3L). Forskellen i den gennemsnitlige ændring i EQ-5D-indeksscore og VAS score fra baseline til dag 182 mellem lanadelumab og placebo var ikke statistisk signifikant [15].

Fagudvalget vurderer, at der ses forbedret helbredsrelateret livskvalitet for begge lægemidler overfor placebo, men at de præsenterede resultater ikke kan anvendes til at afgøre om subkutan C1-esteraseinhibitor er klinisk bedre eller ringere end lanadelumab, da de anvendte værktøjer i COMPACT og HELP er forskellige.

Anfaldsfrekvens
Som beskrevet i protokollen er effektmålet anfaldsfrekvens vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det primære behandlingsmål med rutinemæssig forebyggelse er at reducere frekvensen af HAE-anfald.

Data for anfaldsfrekvens er opgjort på flere forskellige måder i studierne og efterfølgende analyser. Ser man på den absolutte reduktion i antallet af HAE-anfald, viser data fra COMPACT en reduktion på 3,51 (2,81; 4,21) anfald/måned ved behandling med 60 IU/kg sammenlignet med placebo. I HELP-studiet viser lanadelumab 300 mg hver anden uge en reduktion på 1,71 (1,33; 2,09) sammenlignet med placebo. Her bør det dog bemærkes, at placeboresponset i HELP-studiet er betydeligt større end i COMPACT-studiet [20].

I HELP-studiet er der også beregnet en relativ risikoreduktion som er baseret på en Poisson regressionsmodel. Med henblik på at gøre data fra studierne sammenlignelige har ansøger på tilsvarende vis beregnet en relativ risikoreduktion fra COMPACT-studiet. Den relative reduktion ved behandling med lanadelumab 300 mg hver anden uge sammenlignet med placebo er 0,13 (0,07; 0,24). Ved behandling med subkutan C1-estereaseinhibitor 60 IU/kg er den relative reduktion beregnet til 0,13 (0,08; 0,21).

Nedenfor følger en oversigt over sværhedsgraden af de tilbageværende anfald (gennembrudsanfald) ved de to behandlinger.

Tabel 4. Oversigt over sværhedsgrad af anfald.

	COMPACT studiet		HELP Studiet	
	Subkutan C1-esteraseinhibitor (60 IU/kg hver 3.-4. dag)	Placebo	Lanadelumab (300 mg hver 2. uge)	Placebo
Anfaldsfrie	40 % (18/45)	0 % (0/45)	44 % (12/27)	2 % (1/41)
Mild	18 % (8/45)	2 % (1/45)	11 % (3/27)	2 % (1/41)
Moderat	29 % (13/45)	22 % (10/45)	37 % (10/27)	61 % (25/41)
Svær	9 % (4/45)	69 % (31/45)	7 % (2/27)	34 % (14/41)
Ukendt	4 % (2/45)	7 % (3/45)	-	-

Af oversigten fremgår, at patienter i aktiv behandling har færre anfald end patienter behandlet med placebo, samt at ”gennembrudsanfaldene” hovedsageligt er af mild/moderat sværhedsgrad.

Der ses få svære ”gennembrudsanfald” for patienter i aktiv behandling sammenlignet med placebo.

For både subkutan C1-esteraseinhibitor og lanadelumab foreligger der *open-label* extension-studier. Patienter behandlet med subkutan C1-estraseinhibitor blev fuldt i 88 uger (ca. 20 måneder), mens patienterne behandlet med lanadelumab blev fuldt i 33 måneder. Effekten af subkutan C1-esteraseinhibitor og lanadelumab ser ud til at være vedvarende i de respektive *open-label extension* studier. Anfaldsfrekvensen forbliver på et lavt niveau med begge behandlinger (gennemsnitlig 0,5 ± 0,9 anfald/måned med subkutan C1-esteraseinhibitor og 0,25 ± 0,6 anfald/måned med lanadelumab). I begge *extension* studier oplever stort set alle patienter en reduktion på minimum 50 % i deres anfaldsfrekvens (ca. 92 % med subkutan C1-esteraseinhibitor og ca. 97 % med lanadelumab).

Fagudvalget vurderer, at de relative risikoreduktioner bedst afspejler effekten af de undersøgte behandlinger, da der her tages højde for forskellen i placeborespons i COMPACT og HELP-studierne. De relative risikoreduktioner på 0,13 (0,08; 0,21) og 0,13 (0,07; 0,24) for henholdsvis C1-estereaseinhibitor og lanadelumab viser, at de to behandlinger er sammenlignelige hvad angår anfaldsfrekvens. Det samme gør sig gældende for den vedvarende effekt af C1-estereaseinhibitor og lanadelumab på patienternes anfaldsfrekvens.

Bivirkninger
Som beskrevet i protokollen er effektmålet bivirkninger vigtigt for vurderingen af lægemidlets værdi. Medicinrådet ønsker bivirkninger opgjort som andel af patienter, der ophører behandlingen på grund af bivirkninger, og en forskel mellem grupperne på 10 %-point anses som klinisk relevant.

Ansøger har ikke udført en komparativ analyse for dette effektmål, idet der ikke findes data på bivirkninger, som medfører behandlingsophør. Der findes data på andelen af patienter, som ophører med behandling på grund af uønskede hændelser. Heller ikke for denne opgørelse har ansøger fundet grundlag for at lave en komparativ analyse.

For begge behandlinger gælder, at de er forbundet med meget få hændelser, som medfører ophør af behandlingen. I COMPACT studiet er der samlet set 2 ud af 86 patienter behandlet med subkutan C1-esteraseinhibitor, som ophører behandlingen grundet en uønsket hændelse (urticaria og forhøjede lever-aminotransferaser). For lanadelumab ophørte ingen patienter ud af de 27 patienter, behandlet med 300 mg hver anden uge, behandlingen.

Fagudvalget bemærker, at milde reaktioner ved injektionsstedet var de hyppigste forekommende uønskede hændelser for både subkutan C1-esteraseinhibitor og lanadelumab i COMPACT og HELP. Der blev ikke registreret nogen alvorlige bivirkninger for hverken C1-esteraseinhibitor eller lanadelumab.

Overordnet set vurderer fagudvalget, at begge lægemidler er yderst veltolererede, og at der ikke er betydende forskelle i sikkerhedsprofilerne.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, på det nuværende datagrundlag, at subkutan C1-esteraseinhibitor samlet set er lige så effektivt og sikkert til forebyggende behandling af arveligt angioødem som lanadelumab. Begge lægemidler er omtrent lige gode til at reducere anfaldsfrekvensen (subkutan C1-esteraseinhibitor: rate ratio 0,13 (0,08; 0,21) og lanadelumab: rate ratio 0,13 (0,07; 0,24) og

vurderes til at have vedvarende effekt af sammenlignelig størrelse. Begge lægemidler medfører anfaldsfrihed hos omkring 40 % af patienterne. Der er ikke registreret alvorlige bivirkninger i de kliniske studier COMPACT (subkutan C1-esteraseinhibitor) og HELP (lanadelumab), og de hyppigst observerede uønskede hændelser er milde reaktioner ved injektionsstedet

Vurderingen er baseret på en deskriptiv sammenligning af data fra studierne COMPACT og HELP, hvor henholdsvis subkutan C1-esteraseinhibitor og lanadelumab er sammenlignet med placebo. Der findes ikke direkte sammenlignende studier, og det har ikke været muligt at udføre indirekte sammenlignende statistiske analyser. Fagudvalget har derfor ikke kategoriseret værdien af subkutan C1-esteraseinhibitor overfor lanadelumab, da sammenligningen er forbundet med væsentlig usikkerhed og ikke tillader en kategorisering i henhold til Medicinrådets metode.

Fagudvalget ønsker at påpege, at subkutan C1-esteraseinhibitor er en velkommen behandlingsmulighed til forebyggende behandling hos gravide og ammende kvinder, da den anden subkutane forebyggende behandling lanadelumab er kontraindiceret i disse patientgrupper.

6. Andre overvejelser

Produktresuméet for lanadelumab omtaler en mulighed for at reducere doseringsfrekvensen fra 300 mg hver 2. uge til 300 mg hver 4. uge. For subkutan C1-esteraseinhibitor påpeger ansøger også, at mange patienter kan behandles med en reduceret dosis på 40 IU/kg. Produktresuméet for subkutan C1-esteraseinhibitor angiver dog ingen retningslinjer for håndtering af dosisreduktion i klinikken [21].

For begge behandlinger er det uklart, hvor mange patienter som vil opnå tilstrækkelig effekt ved en reduceret dosis. Denne uklarhed medfører betydelige usikkerheder i de sundhedsøkonomiske analyser, og derfor har fagudvalget efterspurgt, at ansøger undersøger og redegør for, om der findes evidens (gerne publiceret), som kan anvendes til at understøtte antagelserne om, at nogle af patienterne kan behandles med en reduceret dosis. Dette gælder for både intervention og komparator.

Fagudvalget har også efterspurgt, at ansøger redegør for *exposure-response* forhold for de to dosisregimer 60 IU/kg hver 3.-4. dag og 40 IU/kg hver 3.-4. dag og også gerne en redegørelse over *exposure-safety* forhold.

På baggrund heraf bør ansøger vurdere, hvor mange patienter, der forventes at kunne reduceres til en dosis på 40 IU/kg.

Ansøger har leveret følgende oplysninger som svar på fagudvalgets spørgsmål

Patientdata fra COMPACT og fra raske personer er blevet anvendt i en populations-pharmakokinetisk model [22]. Denne model understøtter, at størstedelen af patienterne behandlet med 60 IU/kg og 40 IU/kg vil have C1-inhibitor niveauer på over 38 % af normalt niveau på ethvert tidspunkt under behandlingen, hvilket er klinisk relevant, da patienter med mindre end 38 % af normalt C1-inhibitor niveau har større sandsynlig for at opleve anfald [23].

En *exposure-respons* analyse forudsiger, at 50 % (40 IU/kg) og 67 % (60 IU/kg) af patienterne vil opleve mindst 70 % reduktion i risikoen for et anfald [24].

I COMPACT oplevede 67 % af patienterne behandlet med 40 IU/kg mindst 70 % reduktion i antallet af anfald sammenlignet med placebo. Dette er flere end forventet baseret på *exposure-response* analysen. I gruppen behandlet med 60 IU/kg oplevede
83 % mindst 70 % reduktion i antallet af anfald.

Til sammenligning opnåede 66,1 % af patienterne i HELP behandlet med lanadelumab 300 mg hver 4. uge, at antallet af anfald blev reduceret med mindst 70 %. Det tilsvarende tal for 300 mg lanadelumab hver 2. uge er 79,1 %.

Ansøger oplyser, at der i visse behandlingscentre i [redacted] er klinisk praksis for at dosisreducere både lanadelumab og subkutan C1-esteraseinhibitor. Der synes ikke at foreligge en fast praksis for eller vejledning i dosisreduktion af subkutan C1-esteraseinhibitor. Målet for behandlingen er også varierende, idet det kliniske mål nogle steder er at reducere anfaldsfrekvensen, mens målet andre steder er at opnå anfaldsfrihed.

Fagudvalgets vurdering:

- Fagudvalget bemærker, at ansøger ikke giver noget bud på, hvor stor en andel af de danske patienter, som forventes at kunne dosisreduceres.
- COMPACT-studiet understøtter, at der er god effekt ved anvendelse af 40 IU/kg, om end denne er mindre end effekten ved brug af 60 IU/kg.
- Der foreligger ikke retningslinjer for dosisreduktion i produktresuméet for subkutan C1-esteraseinhibitor.
- Der findes ikke en klinisk praksis i Danmark for dosisreduktion af subkutan C1-esteraseinhibitor.
- Data præsenteret af ansøger for dosisreduktion af både lanadelumab og subkutan C1-esteraseinhibitor i [redacted] er yderst sparsomt, og ikke repræsentativt for dansk klinisk praksis, da sundhedssystemet i [redacted] fungerer væsentligt anderledes end i Danmark.
- Populationen af patienter med arveligt angioødem er yderst heterogen, idet der er stor forskel på anfaldsfrekvens, sværhedsgrad af anfaldene og hvor på kroppen anfaldene rammer. Samtidig vil alle disse faktorer også variere over tid for den enkelte patient, hvorfor behovet for forebyggende behandling også kan variere over tid. Behandlingen er derfor i høj grad individuelt tilpasset.

Fagudvalget konkluderer, at data fra COMPACT-studiet understøtter, at der kan dosisreduceres fra 60 IU/kg til 40 IU/kg. Det er dog ikke muligt på det nuværende datagrundlag at definere, hvilke patienter som kan dosisreduceres, uden at effekten af behandlingen mindskes. Der findes heller ingen evidens, som belyser, hvor stor en andel af patienterne i Danmark som vil kunne reducere dosis af subkutan C1-esteraseinhibitor. På nuværende tidspunkt er der sparsom erfaring med dosisreduktion af lanadelumab i klinikken, men det skønnes, at andelen som kan dosisreduceres, over tid vil være af samme størrelsesorden for subkutan C1-esteraseinhibitor som for lanadelumab.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

8. Referencer

1. Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med [internet]. 2008;359(10):1027–36. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/18768946

2. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy [internet]. 2018;73(8):1575–96. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/29318628

3. Bygum A. Hereditary angioedema - consequences of a new treatment paradigm in Denmark. Acta Derm Venereol [internet]. 2014;94(4):436–41. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/24202369

4. Caballero T, Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. Allergy asthma Proc [internet]. 2014;35(1):47–53. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/24268449

5. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. World Allergy Organ J [internet]. 2018;11:5. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S1939455118301583

6. Medicinrådet. Medicinrådets anbefaling vedrørende lanadelumab som mulig standardbehandling til forebyggende behandling af arveligt angioødem [internet]. 2020. Tilgængelig fra: https://medicinraadet.dk/media/ohgdhlcd/medicinraadets-anbefaling-vedr-lanadelumab-til-arveligt-angiooedem-vers-1-0_adlegacy.pdf

7. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med [internet]. 2017;376(12):1131–40. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/28328347

8. Lumry WR, Craig T, Zuraw B, Longhurst H, Baker J, Li HH, et al. Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema. J allergy Clin Immunol Pract [internet]. 2018;6(5):1733-1741.e3. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/29391286

9. Li HH, Mycroft S, Christiansen S, Wood DN, Feuersenger H, Pawaskar D, et al. Subcutaneous C1-esterase inhibitor to prevent hereditary angioedema attacks: Safety findings from the COMPACT trial. Allergy asthma Proc [internet]. 2018;39(5):365–70. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/30107868

10. Craig T, Zuraw B, Longhurst H, Cicardi M, Bork K, Grattan C, et al. Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks. J Allergy Clin Immunol Pract [internet]. 2019; Tilgængelig fra: https://doi.org/10.1016/j.jaip.2019.01.054

11. Levy DS, Farkas H, Riedl MA, Hsu FI, Brooks JP, Cicardi M, et al. Long-term efficacy and safety of subcutaneous C1-inhibitor in women with hereditary angioedema: subgroup analysis from an open-label extension of a phase 3 trial. Allergy Asthma Clin Immunol [internet]. 2020;16:8. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/32042283

12. Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet J Rare Dis [internet]. 2021;16(1):86. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/33588897

13. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA - J Am Med Assoc. 2018;320(20):2108–21.

14. Riedl MA, Maurer M, Bernstein JA, Banerji A, Longhurst HJ, Li HH, et al. Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks. Allergy [internet]. 2020;75(11):2879–87. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/32452549

15. Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. Allergy [internet]. 2020; Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/33258114

16. Riedl MA, Bernstein JA, Craig T, Banerji A, Magerl M, Cicardi M, et al. An open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention of attacks in hereditary angioedema: design of the HELP study extension. Clin Transl Allergy [internet]. 2017;7:36. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/29043014

17. Riedl M, Bernstein J, Yang W, Longhurst H, Magerl M, Hebert J, et al. LANADELUMAB REDUCES HAE ATTACK RATE: INTERIM FINDINGS FROM THE HELP OPEN-LABEL EXTENSION STUDY. Ann Allergy, Asthma Immunol [internet]. 2018;121(5):S37. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S1081120618308627

18. Banerji A, Hao J, Yu M, Bernstein J, Johnston D, Riedl M. P150 LONG-TERM EFFICACY AND SAFETY OF LANADELUMAB: FINAL RESULTS FROM THE HELP OPEN-LABEL EXTENSION STUDY. Ann Allergy, Asthma Immunol [internet]. 2020;125(5):S21. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S1081120620306529

19. Riedl M, Johnston D, Lumry W, Bernstein J, Nurse C, Yu M, et al. P157 ATTACK-FREE STATUS DURING EXTENDED TREATMENT WITH LANADELUMAB FOR HEREDITARY ANGIOEDEMA: HELP OLE STUDY FINAL RESULTS. Ann Allergy, Asthma Immunol [internet]. 2020;125(5):S23. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S108112062030658X

20. Bernstein JA, Li HH, Craig TJ, Manning ME, Lawo J-P, Machnig T, et al. Indirect comparison of intravenous vs. subcutaneous C1-inhibitor placebo-controlled trials for routine prevention of hereditary angioedema attacks. Allergy Asthma Clin Immunol [internet]. 2019;15:13. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/30899278

21. Lægemiddelstyrelsen. Berinert produktresume, pulver og solvens til injektionsvæske, opløsning 2000 IE og 3000 IE (1). 2021.

22. Pawaskar D, Tortorici MA, Zuraw B, Craig T, Cicardi M, Longhurst H, et al. Population pharmacokinetics of subcutaneous C1-inhibitor for prevention of attacks in patients with hereditary angioedema. Clin Exp Allergy. 2018;48(10):1325–32.

23. Spath PJ, Wuthrich B BR. Quantification of C1-Inhibitor functional activities by immunodiffusion assay in plasma of patients with hereditary angioedema- Evidence of a functionally critical level of C1-inhibitor concentration. Complement. 1984;1(3):147–59.

24. Zhang Y, Tortorici MA, Pawaskar Di, Pragst I, MacHnig T, Hutmacher M, et al. Exposure-response model of subcutaneous C1-inhibitor concentrate to estimate the risk of attacks in patients with hereditary angioedema. CPT Pharmacometrics Syst Pharmacol. 2018;7(3):158–65.

9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende arveligt angioødem

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Carsten Bindslev-Jensen *Professor*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke udpege en kandidat	Region Nordjylland
Kan ikke udpege en kandidat	Region Midtjylland
Shailajah Kamaleswaran *Speciallæge*	Region Syddanmark
Kan ikke udpege en kandidat	Region Sjælland
Kan ikke udpege en kandidat	Region Hovedstaden
Christina Gade *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Helle Houlbjerg Carlsen *Funktionsleder, farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Henrik Balle Boysen *Patient/patientrepræsentant*	Danske Patienter
Jørn Schultz-Boysen *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

Medicinrådet

Dampfærgevej 27-29, 3.th.

2100 København Ø

+45 70 10 36 00

medicinraadet@medicinraadet.dk

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	24. august 2021	Godkendt af Medicinrådet.

11. Bilag

Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 5. Vurdering af risiko for bias i COMPACT. NCT01912456

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomiseringen er foregået ved brug af interactive-response system, altså en central randomiseringsprocedure.
Effekt af tildeling til intervention	**Forbehold**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får. Placebomedicin er pakket på en måde, der sikrer blinding. Det er dog muligt, at patienter og personale kan ræsonnere sig frem til om patienten modtager aktiv behandling baseret på patientens anfaldsmønster.
Manglende data for effektmål	**Lav**	Alle effektivitetsanalyser er foretaget på intention to treat-populationen, svarende til alle randomiserede patienter. Sikkerhedsdatasættet bestod af alle forsøgspersoner, der modtog minimum en dosis af studiemedicin. Manglende data blev ikke forsøgt imputeret.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får. Placebomedicin er pakket på en måde, der sikrer blinding.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Analyser udført efter den offentliggjorte protokol og tilhørende statistiske analyseplan.
Overordnet risiko for bias	**Lav**	

Tabel 6. Vurdering af risiko for bias i HELP. NCT02586805

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Forbehold**	Patienterne er randomiseret 2:1 til enten placebo eller lanadelumab. For lanadelumab er patienterne randomiseret 1:1:1 til én af de tre aktive behandlingsarme. Alle patienter modtog injektioner hver 2. uge. Patienter allokeret til aktiv behandling hver 4. uge fik placebo mellem de aktive behandlinger. Randomisering foregik via et interaktivt webbaseret randomiseringssystem (Rho Inc) af blindet studiepersonale. Randomiseringen var stratificeret på den normaliserede anfaldsfrekvens. Det er muligt, at patienter og personale kan ræsonnere sig frem til, om patienten modtager aktiv behandling baseret på patientens anfaldsmønster. Der er tendens til forskelle i visse baselinekarakteristika, f.eks. den historiske anfaldsfrekvens, kønsfordeling og anvendelse af forebyggende behandling op til studiets start.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får.
Manglende data for effektmål	**Lav**	Alle effektivitetsanalyser blev udført på intention to treat-population, defineret som alle randomiserede patienter eksponeret for aktiv behandling eller placebo. Sikkerhedsanalyser blev udført på sikkerhedspopulationen, som omfattede alle patienter, der modtog en eller flere doser af studiemedicin; analyser blev udført i henhold til den faktiske modtagne behandling. Der er transparent og sammenligneligt frafald i alle behandlingsarme.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Analyser udført efter den statistiske analyse plan.
Overordnet risiko for bias	**Lav**	Den samlede risiko for bias vurderes som lav, selvom ubalance i visse baselinekarakteristika medfører forbehold i forhold til randomiseringen.

Medicinrådet

Application for the assessment of Berinert® SC for prevention of attacks in severe Hereditary Angioedema (HAE)

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

1. Contents

1. Contents 2

2. Basic information 4

3. Abbrevations 5

4. Summary 6

5. Literature search 7
5.1 Relevant studies 11
5.2 Main characteristics of included studies 12

6. Clinical questions 18
6.1 Clinical question 1: Attack free (Anfaldsfrihed) 18
6.1.1 Presentation of relevant studies 18
6.1.2 Results per study 19
6.1.3 Comparative analyses 19

6.2 Clinical question 2: Health Related Quality of Life (Helbredsrelateret livskvalitet) 20
6.2.1 Presentation of relevant studies 20
6.2.2 Results per study 21
6.2.3 Comparative analyses 22

6.3 Clinical question 3: Attack frequency (Anfaldsfrekvens) 22
6.3.1 Presentation of relevant studies 22
6.3.2 Results per study 23
6.3.3 Comparative analyses 25

6.4 Clinical question 4: Side effects (Bivirkninger) 25
6.4.1 Presentation of relevant studies 26
6.4.2 Results per study 26
6.4.3 Comparative analyses 27

6.5 Other considerations: Exposure-response relationship 27

7. References 29

8. Appendices 31
8.1 Literature search 31
8.2 Main characteristics of included studies 32
8.3 Results per study 40
8.4 Results per PICO (clinical question) 50

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

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

2. Basic information

Kontaktoplysninger	
Navn	**Stina Johansson**
Titel	Market Access Manager, Nordics
Ansvarsområde	Market Access and Health Economics
Telefonnummer	+46 (0)70 252 00 08
E-mail	Stina.johansson@cslbehring.com
Navn	**Helena Stensman**
Titel	Scientific Advisor, Nordics
Ansvarsområde	Medical
Telefonnummer	+46 (0)736 56 74 08
E-mail	Helena.stensman@cslbehring.com

Overview of the pharmaceutical	
Proprietary name	Berinert® 2000 IU and 3000 IU for subcutaneous injection (SC)
Generic name	C1-esterase inhibitor (human) subcutaneous
Marketing authorization holder in Denmark	CSL Behring GmbH
ATC code	B06AC01
Pharmacotherapeutic group	Medicines used in hereditary angioedema: C1-inhibitor, plasma derived
Active substance(s)	C1-esterase inhibitor (human)
Pharmaceutical form(s)	Subcutaneous use
Mechanism of action	Substitution of the deficient C1-esterase inhibitor activity

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

Overview of the pharmaceutical	
Dosage regimen	The recommended dose of Berinert® SC is 60 IU/kg body weight twice weekly (every 3-4 days) (1, 2) [redacted] **- Real world data from* [redacted] *- Clinical trial COMPACT (Berinert® SC vs Placebo) shows that 40 IU/kg is used in 50% of the study population with similar efficacy and safety results as 60 IU/kg ((4) published). The information about the 40 IU/kg dose has also been added to section 5.1 in the SmPC, and the Danish SmPC has recently been updated.* *- Clinical recommendation in Spain shows that similar low doses are recommended for Berinert® SC ((5) published)* [redacted]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Berinert® for subcutaneous injection is indicated for prevention of recurrent Hereditary Angioedema (HAE) attacks in adolescent and adult patients with C1-esterase inhibitor deficiency.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	BEGR - kun til sygehuse
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Vials: 1 x 2000 IU, 5 x 2000 IU and 20 x 2000 IU 1 x 3000 IU, 5 x 3000 IU and 20 x 3000 IU
Orphan drug designation	No

3. Abbrevations

Abbreviation	Definition
AE	Adverse event
AE-QoL	Angioedema Quality of Life
BMI	Body mass index
BW	Body weight
C1-INH	C1-esterase inhibitor
DMC	Danish Medicines Council
EMA	European Medicines Agency

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

EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
HSV	Health State Value
ISR	Injection site reactions
IV	Intravenous
LTP	Long-term prophylactic treatment
OLE	Open-label extension
PICO	Population Intervention Comparator Outcome
RCT	Randomized controlled trial
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TSQM	Treatment Satisfaction Questionnaire for Medication
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment

4. Summary

This application describes the literature search, the selection of publications and the assessment of safety and efficacy of Berinert® 2000 IU and 3000 IU for subcutaneous injection (in this report referred to as Berinert® SC) versus lanadelumab (Takhzyro®) 300 mg for subcutaneous administration for prevention of attacks in severe Hereditary Angioedema (HAE) based on the PICO and pre- defined clinical outcomes in the Medicines Council protocol from January 2021 (2).

Data from two randomized clinical trials (RCTs) (4, 7) and two indirect comparisons on individual patient data from the same trials (8)[1] and [redacted] demonstrated similar safety and efficacy of Berinert® SC versus Takhzyro® in routine prophylaxis of HAE attacks with reference to the defined critical clinical outcomes related to reduction of HAE attacks.

This application also presents long-term efficacy of Berinert® SC related to reduction of attack frequency (10) and long-term quality of life data from the COMPACT open-label extension (OLE) study of Berinert® SC that was published after the performance of the literature search (11).

There were not sufficient data to assess differences in effect with regards to the other critical clinical outcomes defined by the Medicines Council protocol, i.e., 100% attack free, safety, and health-related Quality of Life (HRQoL). However, HRQoL outcome data from pivotal studies of Berinert® SC and Takhzyro® are presented and further discussed in this application. An indirect comparison of HRQoL outcomes was not possible since different HRQoL tools were used in the different clinical studies on Berinert® SC and Takhzyro® 300 mg.

Berinert® SC has demonstrated a very beneficial short and long-term safety profile and tolerability which is expected since C1-esterase inhibitor (C1-INH) as an active ingredient has be used for more than 40 years in clinical practice. The beneficial outcomes of Berinert® SC are assumed similar to the safety and efficacy outcomes of Takhzyro®. This is based

[1] Published poster at the ISPOR conference 2020

[redacted]

on the preliminary outcomes from [redacted] showing similar attack rates in patients using Takhzyro® vs Berinert® SC. In addition, there are patient groups in which some of the available treatments are not indicated, e.g., Takhzyro® for pregnant and lactating women.

The clinical outcomes in terms of monthly attack rate reductions have been shown in indirect comparisons to be similar for both Berinert® SC 60 IU/kg and 40 IU/kg vs. Takhzyro® respectively. Some naïve indirect comparisons have been presented in table A4 (e.g., withdrawals due to adverse events). Overall, the general safety profile and the increase in HRQoL among patients receiving treatment with Berinert® SC and Takhzyro® are considered good, where significant differences are not expected.

The conclusion is that Berinert® SC generates a high, added clinical value for reduction of attack frequency, which is considered the most relevant treatment goal in a very severe and potentially life-threatening disease.

5. Literature search

A literature search was performed by CSL Behring on January 22, 2021, following the search strategy defined by the Medicines Council protocol for Berinert® SC for severe hereditary angioedema (Document number 97666, approved Jan 11, 2021) (2).

Inclusion and exclusion criteria have been explained in detail in Appendices (Table A1).

Inclusion criteria: The Danish Medicines Council (DMC) requests data from full-text articles published in scientific, peer-reviewed journals and data from the European Medicines Agency's (EMAs) European Public Assessment Reports (EPAR). The data will comply with the descriptions in the protocol (2).

Unpublished data and abstracts/posters on indirect comparisons between Berinert® SC and Takhzyro® have also been included in the analysis. Since there are no studies on direct comparisons between Berinert® SC and Takhzyro®, studies on indirect comparisons have been added to the full-text review. In addition, EMA's EPAR for its comparator Takhzyro® has also been investigated (12). There is no EPAR for the current medical product Berinert® SC since Berinert® SC was not market approved through the centralized process at EMA. The summary of product characteristics of Berinert® SC has been assessed (1). Additional articles/posters/unpublished data outside the search string and pre-defined PICO from the Medicines Council that might be of interest for the final discussion have also been added to the initial search.

Exclusion criteria: Articles with populations other than those specified in the Medicines Council protocol and articles that do not report at least one of the critical or important outcomes from section Clinical questions have been excluded (2). Abstracts and posters were excluded unless they presented an indirect comparison with relevant clinical outcomes between Berinert® SC and Takhzyro®.

Some adjustments in the search strings have been made to include conference abstracts and grey literature. The rationale behind this inclusion was the potential identification of ongoing unpublished studies on indirect comparisons between Berinert® SC and Takhzyro®.

Searches were performed in Medline (PubMed) and CENTRAL Database (Cochrane Library) (Table 1).

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

Table 1 Databases used in the search for relevant studies

Database	Platform	Date of search completion
CENTRAL	Cochrane Library	2021-01-22
Medline	PubMed (NCBI)	2021-01-22

Search strings for both databases are presented below.

Table 2 Search string PubMed according to Medicines Council protocol (2), conducted on Jan 22, 2021

#	Search string	Hits
#1	"Angioedemas, Hereditary"[Mesh]	1162
#2	(C1[tiab] AND Inhibitor*[tiab] AND Deficienc*[tiab]) OR (hereditary[tiab] AND (edema*[tiab] OR oedema*[tiab] OR angioedema*[tiab] OR angiooedema*[tiab]))	3511
#3	#1 OR #2	3597
#4	prophyl*[tiab] OR prevent*[tiab]	1 612 670
#5	#3 AND #4	686
#6	lanadelumab[nm] OR DX-2930[tiab] OR Takhzyro[tiab] OR lanadelumab[tiab]	46
#7	"Complement C1 Inhibitor Protein"[Mesh]	1 161
#8	(C1*[tiab] AND Inhibitor*[tiab]) OR Cinryze[tiab] OR Berinert[tiab] OR C1NH[tiab] OR C1IN[tiab]	6 365
#9	#7 OR #8	6 598
#10	#6 OR #9	6 618
#11	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans [mh])	1 282 310
#12	#5 and #10 and #11	78
#13*	(conference*[tiab] OR congress*[tiab])	107 553
#14*	#11 OR #13	1 380 808
#15*	#5 and #10 and #14	78

*Additional search strings to check conference/congress abstracts on indirect comparisons between Berinert® SC and Takhzyro®.

Table 3 Search string CENTRAL (via Cochrane Library) according to Medicines Council protocol (2), conducted on Jan 22, 2021

#	Search string*	Hits
#1	[mh "Angioedemas, Hereditary"]	116
#2	(C1 AND Inhibitor* AND Deficienc*):ti,ab,kw	85

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

#	Search string*	Hits
#3	(hereditary AND (edema* or oedema* or angioedema* or angiooedema*)):ti,ab,kw	396
#4	(13-#3)	401
#5	(prophyl* or prevent*):ti,ab or prophylaxis:kw	173 794
#6	#4 AND #5	206
#7	(DX-2930 OR Takhzyro OR lanadelumab):ti,ab,kw	56
#8	[mh "Complement C1 Inhibitor Protein"]	83
#9	((C1* AND Inhibitor*) OR Cinryze OR Berinert OR C1NH OR C1IN):ti,ab,kw	1 062
#10	#8 OR #9	1 062
#11	#7 OR #10	1 104
#12	#6 AND #11	168

*Abstracts and posters were already included in the initial search string, so no additional search string was needed.

Articles were screened and reviewed, following the clinical questions defined in the Medicines Council protocol as well as criteria for study and publication types. Articles with populations other than those specified in the protocol and articles that did not report at least one of the critical or important clinical questions and outcomes were excluded. The exact measurement of the clinical outcomes was sometimes presented in a different way as what was requested by the Medicines Council due to the differences in presentation format from each clinical trial.

The first exclusion was at the title and abstract level. The second exclusion was for full-text articles. Articles that were excluded by full-text reading are presented in an inclusion/exclusion list in section Appendices (Table A6), where the reason for inclusion/exclusion was justified. The overall selection process has been presented in a PRISMA flow chart below (Figure 1).

In total 246 publications were identified in the search. After removing duplicates and reviewing the abstracts, 9 of the studies were selected to be reviewed in full text. After reviewing the full-text articles, 8 publications were included in the final assessment. Inclusion and exclusion criteria have been presented in the section Literature search.

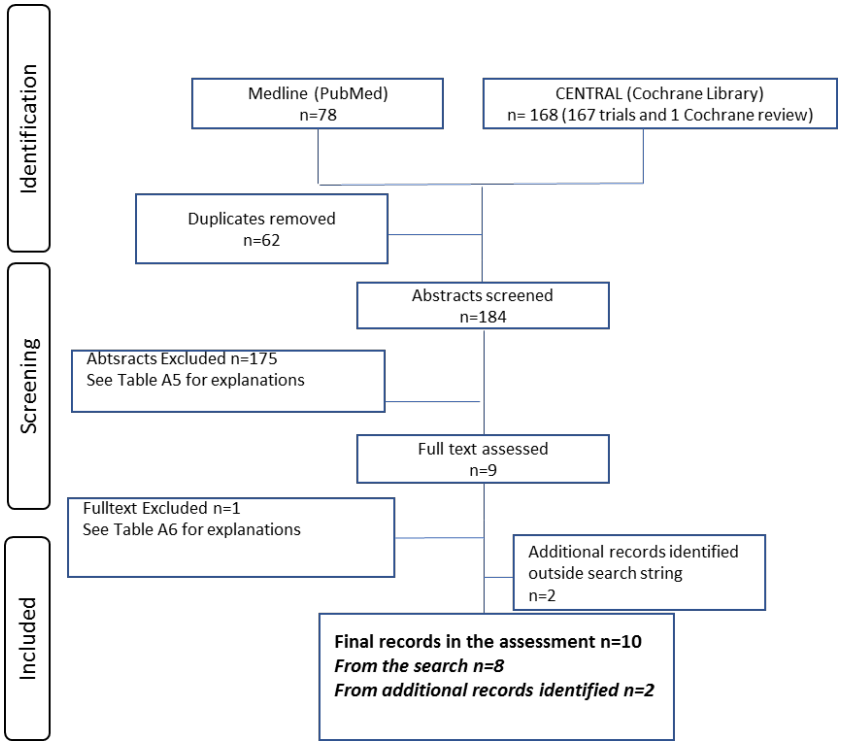
Table 4 Number of identified articles

	Medline (PubMed)	CENTRAL (Cochrane Library)
Records found	78 records	1 Cochrane review 167 Trials
Duplicates	62 duplicates	
Records excluded	237 excluded	
Records remaining	8	

The identification of relevant full text articles, with inclusion/exclusion criteria for each inclusion/exclusion step has been presented in a PRISMA flow chart below.

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

Figure 1 PRISMA flow diagram of literature search



Hereditary angioedema is a rare disease, and the evidence level of published studies is generally quite low, with only a few randomized controlled studies conducted. None if the studies identified were direct comparisons between Berinert® SC and Takhzyro®. In addition, only one published poster of an indirect comparison between Berinert® SC and Takhzyro® was identified in the search.

The PICO criteria and the selected clinical outcomes (section Clinical questions and Table 5) specified in the Medicines Council protocol (2) were used to select and discard among the remaining 8 full text records. There were no direct nor published full text on an indirect study comparison on Berinert® SC vs Takhzyro® identified. Therefore, abstracts and posters on potential indirect comparisons between Berinert® SC vs Takhzyro® were selected and included in the final assessment.

In addition to the identified studies and abstract posters on indirect comparisons between Berinert® SC vs Takhzyro® from the search databases Medline and Cochrane Library, two additional unpublished studies (grey literature) on indirect comparisons of relevance were added to the final assessment. This resulted in total 10 records (8 from the literature search and 2 additional unpublished studies outside the search) that were finally included in the assessment.

Table 5 Selected clinical outcomes in the Medicines Council protocol (copy-paste from DMC protocol on Berinert® SC (2))

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Retningsgivende mindste klinisk relevante forskel
Anfaldsfrihed	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel af patienter som oplever en 100 % reduktion i anfaldsfrekvens (symptomfrihed) fra baseline	10 %-point
Helbredsrelateret livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Ændring fra baseline målt med Angioedema Quality of life Questionnaire (AE-QoL)	6 point
			Andel af patienter som oplever en forbedring på 6 point fra baseline	Anvendes til bestemmelse af den relative effektforskel. Der er derfor ikke fastsat en MKRF
Anfaldsfrekvens	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Procentvis reduktion i antallet HAE-anfald pr. måned	15 %-point
			Gennemgang af sværhedsgraden af de tilbageværende anfald (gennembruds-anfald) ved de to behandlinger† .	-
Bivirkninger	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter der ophører behandling grundet bivirkninger	10 %-point
			Kvalitativ gennemgang af lægemidlernes bivirkningsprofil	-

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
† Foruden opgørelsen af den gennemsnitlige reduktion i anfaldsfrekvens ønsker fagudvalget også en gennemgang af sværhedsgraden af de tilbageværende anfald (gennembrudsanfald) ved de to behandlinger. Se mere under beskrivelsen af effektmålet.

5.1 Relevant studies

A total of 10 relevant studies was identified in the assessment.

Table 6 Relevant studies included in the assessment (n=10)

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Longhurst H et al., 2017 (4)	COMPACT	NCT01912456	From Dec 2013 through Oct 2015	Attack frequency and Safety
Craig T et al., 2019 (10)	COMPACT OLE	NCT02316353	From Dec 2014 through Dec 2017	Attack frequency and Safety
Li HH et al., 2018 (14)	COMPACT	NCT01912456	Based on COMPACT	Safety
Lumry et al., 2018 (15)	COMPACT	NCT01912456	Based on COMPACT	HRQoL
Banerji et al., 2018 (7)	HELP	NCT02586805	From March 3 2016, through September 9 2016	Attack frequency and Safety

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

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Riedl et al., 2020 (16)	HELP	NCT02586805	Based on HELP	Attack frequency and Safety
Lumry et al., 2020 (17)	HELP	NCT02586805	Based on HELP	HRQoL
Fridman M et al. 2020 (8)	ISPOR 2020 Poster Poster Number: PRO65	NCT01912456 and NCT02586805	Based on HELP and COMPACT	Attack frequency and indirect comparison
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

After the systematic literature search was performed in Jan 22, 2021, an additional relevant study was identified and chosen to be included in the final assessment (Table 7).

Table 7 Additional relevant study included in the analysis after the systematic literature search in Jan 22, 2021.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Lumry et al., 2021 (11)	COMPACT OLE	NCT02316353	Based on COMPACT OLE	HRQoL

5.2 Main characteristics of included studies

The main characteristics of included studies are presented below. A complete description of main study characteristics of the two RCTs, COMPACT (4) and HELP (7) are presented in Appendices (Table A2). Results of the two RCTs, COMPACT and HELP are presented in Appendices Table A3a-c.

With reference to the selected clinical outcomes specified by the Medicine Council protocol (2), e.g., attack frequency, complete reduction of attacks and discontinuation due to adverse events, there are sufficient data identified in the COMPACT study on Berinert® SC (4). For the clinical outcome HRQoL, the requested questionnaire AE-QoL is not used in the COMPACT trial. In the COMPACT open-label extension trial COMPACT OLE (10), the AE-QoL was assessed only in US patients entering the extension period of the OLE trial. There are however other HRQoL tools assessing quality of life in the COMPACT and COMPACT OLE studies. In addition to the COMPACT trial, the open-label extension study following the COMPACT trial (i.e., COMPACT OLE) was included since it presents long-term data for the use of Berinert® SC.

Two secondary manuscripts from the COMPACT study describing safety and HRQoL respectively have been included (14, 15). In addition, after the finalization of the search on January 22, 2021, additional long-term quality of life data from COMPACT OLE was identified (11). The results from this study have been chosen to be interpreted since the study presents relevant long-term HRQoL data from the COMPACT OLE trial.

Two secondary manuscript from the HELP study were included, one presenting efficacy results during steady state (18) and one study describing HRQoL data (17). Since there are no head-to-head studies comparing the efficacy between

Berinert® SC and Takhzyro®, [redacted]

Hence, of the 10 studies identified from the literature search, 8 studies and additional 2 studies outside the literature search were selected after full text review. Moreover, one additional recently published study on HRQoL from COMPACT OLE trial was also selected for full text review.

See appendices in Table A5 and Table A6 for complete overview of included and excluded publications from the literature search.

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

Table 8 Main characteristics of included studies (n=10)

Study	Study type	Design	Intervention	Endpoints	Results
Longhurst H et al. 2017 (4)	RCT (primary manuscript) COMPACT	Pts≥12 y age, HAE I and II, n=90, double-blind, RCT, crossover	Berinert® SC 40 IU/kg bw and 60 IU/kg bw, twice weekly vs volume-matched placebo	(1st) Number of attacks of angioedema (2nd) percentage of patients who had a response and the number of times that rescue medication was used.	Attack reduction: 95 % (median) with 60 IU/kg bw 2x weekly and 89% (median) with 40 IU/kg bw 2x weekly
Craig T et al. 2019 (10)	Open label	N=126, follow up mean 1.5 years	Berinert® SC 40/60 IU/kg bw twice weekly, up/down titration allowed	(1st) safety, (2nd) Number of attacks, duration, severity, rescue medication, PK	Low incidence of AE, the percentage of patients achieving an attack rate of less than 1 attack per month was 86% in the 60 IU/kg bw group and 79% in the 40 IU/kg bw group.
Li HH et al. 2018 (14)	RCT (2nd manuscript)	Safety data from Ph III study (Longhurst et al.)	See Longhurst et al.	See Longhurst et al.	No dose-dependent safety concerns. Local injection site reactions most common AE, mild/moderate, none lead to discontinuation
Lumry et al. 2018 (15)	RCT (2nd manuscript)	HRQoL data from Ph III study (Longhurst et al.)	See Longhurst et al.	See Longhurst et al.	Berinert® SC was associated with better EQ-5D visual analog scale general health, less HADS anxiety and improvements in additional HRQoL outcomes
Banerji et al. 2018 (7)	RCT (primary manuscript) HELP	Pts≥12 y age, HAE I and II, n=125, double-blind, parallel-group, RCT	Takhzyro® 150 mg Q4W, 300 mg Q4W, 300 mg Q2W vs placebo	(1st) Number or attacks during the treatment period (2nd) number of attacks requiring acute treatment, number of moderate or severe attacks, number of attacks from days 14 through 182	There were statistically significant reductions in attack rates per month in the Takhzyro® groups versus placebo.
Riedl et al. 2020 (16)	RCT (secondary manuscript)	Efficacy and safety data from Ph III study (Banerji et al)	See Banerji et al.	See Banerji et al.	The mean monthly attack rate was significantly lower with Takhzyro® vs placebo during days 0-69 as well as at steady state (days 70-182)
Lumry et al.	RCT	HRQoL data	See Banerji et	See Banerji et	The Takhzyro® total

Study	Study type	Design	Intervention	Endpoints	Results
2020 (17)	(secondary manuscript)	from Ph III study (Banerji et al)	al.	al.	group demonstrated significantly greater improvements in AE-QoL total and domain scores with the largest improvement in functioning. Mean EQ-5D-5L scores at day 0 were high in all groups and did change significantly at day 182.
Fridman M et al. 2020 (8)	Pairwise indirect comparison COMPACT vs HELP	Pairwise indirect comparison of the primary RCT endpoint results for Berinert® SC 60 IU/kg vs Takhzyro®	Berinert® SC 60 IU/kg bw vs placebo and Takhzyro® 150 mg q4w, 300 mg q4w, and 300 mg q2w vs placebo	Absolute and relative attack rate reduction over placebo.	The absolute reduction in monthly attacks was 3.29 for Berinert® SC 60 IU/kg bw vs placebo and 1.71 for Takhzyro® 300 mg q2w vs placebo. The relative reduction was 0.12 for Berinert® SC 60 IU/kg bw vs placebo and 0.13 for Takhzyro® 300 mg q2w vs placebo.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Study	Study type	Design	Intervention	Endpoints	Results
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

There are meaningful differences in the pivotal studies of Berinert® SC and Takhzyro®, e.g. study designs and study durations, which may challenge the possibility to make indirect comparisons between the products.

Differences and similarities between the COMPACT and HELP trials have been summarized in Table 9 with comments below [redacted]

	COMPACT Trial	HELP Trial	Comments
Study Type	Randomized Controlled Trial (primary manuscript)	Randomized Controlled Trial (secondary manuscript)	Similar in both trials
Study Design	Double-blind, crossover, RCT	Double-blind, parallel-group, RCT	The influence of confounding covariates is decreased with crossover studies.
Study duration	Two periods of 16 weeks	26 weeks	To account for a run-in or washout period in COMPACT, the efficacy data were included from the beginning of week 3 for each 16w treatment period
Patient population	Pts≥12 y age, HAE I and II	Pts≥12 y age, HAE I and II	Similar in both trials

Number of patients	n=90	n=125	Crossover studies (COMPACT) are statistically efficient and thus require fewer subjects than non-crossover designs (HELP)
Patients receiving SmPC dose	45 patients receiving Berinert® SC 60 IU/kg bw	27 patients receiving receiving 300 mg Takhzyro® twice weekly	Small sample sizes decrease statistical power and decrease the flexibility of the effect size. Large studies produce narrow intervals and, therefore, more precise results.
Primary endpoint*	Number of attacks of angioedema	Number or attacks during the treatment period	The primary efficacy endpoint in the COMPACT trial was the time-normalized number of HAE attacks, as reported by the investigator. In the HELP study, there was a statistically significant reduction in attack rate per month
Secondary endpoint	Percentage of patients who had a response and the number of times that rescue medication was used	Number of attacks requiring acute treatment, number of moderate or severe attacks, number of attacks from days 14 through 182	Different efficacy outcome measurements, definitions and study lengths make the comparisons between trials not applicable.
Mean age	36.8±14.9 years in the 60 IU/kg bw group	40.3±13.3 years in the Takhzyro® 300 mg twice weekly group	Similar in both trials
Proportion women	71%	55.6%	Similar in both trials
BMI	27.7±6.8 in the Berinert® SC 60 IU/kg bw group	31.0±7.8 in the Takhzyro® 300 mg twice weekly group	Similar in both trials
Mean number of attacks per month during the run-in period	4.0±2.2 for the 60 IU treatment sequence group	3.5±2.3 for patients in the group receiving 300 mg Takhzyro® twice weekly	Similar in both trials

* [redacted]

The dosage of Takhzyro® is not dependent on patient weight where adults with meny re-occuriing HAE attacks are recommended to receive 300 mg every 2 weeks. In patients who are stable and attack free on treatment, a dose reduction of 300 mg Takhzyro® every 4 weeks may be considered, especially in patients with low weight. In the DMC assessment protocol of Takhzyro®, there are assumptions that a proportion of patients in Denmark could reduce their dose interval to every 4 weeks with lanadelumab [redacted]

[redacted]

In addition, In the HELP-study, only 4 patients had 1.4 or more seizures per week which makes the effect of Takhzyro® among the most severely ill patients very uncertain. The HELP study can therefore not demonstrate that any patients in this severely ill group can reduce their dose interval to every 4 weeks instead of every 2 weeks.

The recommended dose of Berinert® SC is 60 IU/kg body weight twice weekly. However, a dose of 40 IU/kg has been evaluated together with the 60 IU/kg dose in the clinical study program of COMPACT, and the Danish SmPC has recently been updated to also include the information about the 40 IU/kg dose (see section 5.1 in the SmPC).

Moreover, real world evidence has also shown that lower dosing corresponding to around 40 IU/kg body weight have been used in several clinics in Europe.

[redacted]

- A clinical protocol for the introduction of Berinert® SC in Spain, recommended a treatment regimen where the general starting dose of Berinert® SC is 2000 IU twice weekly and if the patient's response is satisfying after 3 months follow-up, the dose interval may increase from twice a week to every 4-5 days. This corresponds to around 30 IU/kg for a 70 kg patient.

6. Clinical questions

6.1 Clinical question 1: Attack free (Anfaldsfrihed)

Proportion of patients who achieve a 100% reduction in seizure frequency is a critical measurement for DMC. The Danish Medicines Council wants the effect measure to be calculated as a difference in the proportion of patients who achieve a 100% reduction in seizure frequency from baseline. The professional committee (Fagudvalget) assesses that a difference of 10 percentage points in the proportion who achieve freedom from seizures is clinically relevant.

6.1.1 Presentation of relevant studies

COMPACT

The proportion of patients experiencing a 100% attack-reduction is reported in the COMPACT study (4) and in the COMPACT OLE study (10). In the COMPACT study, complete reduction of attacks was evaluated at the end of the study at 16 weeks. In the COMPACT OLE study, the percentage of patients being completely attack-free was presented as a post-hoc analysis of six-month periods with a subset of patients being treated for up to 35 months.

HELP

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

In the HELP study, the proportion of attack-free patients is presented as a pre-specified exploratory endpoint (7). In an ad-hoc analysis, results from patients being attack-free days 0-69 are presented (16).

STUDY DIFFERENCES

In both the COMPACT study and the HELP study the statistical analyses were performed in the intention-to-treat population, defined as all randomized patients exposed to study treatment. All safety analyses were evaluated in the safety population, which included all patients who received at least one dose of study treatment. In the COMPACT study there were 45 patients in the treatment arm receiving Berinert® SC 60 IU/kg bw compared to 27 patients in the HELP study receiving 300 mg Takhzyro® twice weekly.

The COMPACT study is a cross-over study running over two periods of 16 weeks each. To account for a run-in or washout period, the efficacy data were included from the beginning of week 3 for each treatment period. The HELP study is a parallel group study running over 26 weeks.

The study populations are similar between the COMPACT and the HELP study. The mean age in the COMPACT study is 36.8±14.9 years in the 60 IU/kg bw group compared to 40.3±13.3 years in the Takhzyro® 300 mg twice weekly group. 71% of the patients are women and the mean BMI is 27.7±6.8 in the Berinert® SC 60 IU/kg bw compared to 55.6% women and a mean BMI of 31.0±7.8 in the Takhzyro® 300 mg twice weekly group. The mean number of attacks per month during the run-in period was 4.0±2.2 for the 60 IU treatment sequence group. In the HELP study, the attack rate in the run-in period was 3.5±2.3 for patients in the group receiving 300 mg Takhzyro® twice weekly.

6.1.2 Results per study

COMPACT

In the COMPACT study, 40% of patients treated with 60 IU/kg bw Berinert® SC were HAE attack-free compared to 0% of the patients treated with placebo in this treatment sequence. In the 40 IU/kg bw Berinert® SC treatment sequence 38% in the Berinert® SC group and 9% in the placebo group were completely attack-free throughout the study (4). In the COMPACT OLE study, 23 patients were treated with the 60 IU/kg bw dose for over two years and of those 82.3% were attack-free during months 25 to 30 of treatment. Of the 21 patients that were treated with 40 IU/kg bw Berinert® SC, 76.2% were attack-free during the same treatment period (10).

HELP

In the HELP study, 44.4% of patients treated with 300 mg Takhzyro® every two weeks were attack-free compared to 2.4% of the patients treated with placebo. In the group treated with 300 mg Takhzyro® every four weeks, 31% of the patients were attack-free during the course of the study (7). In an ad-hoc analysis assessing data days 0-69, 48.1% of patients treated with 300 mg Takhzyro® every 2 weeks were attack-free, compared to 37.9% of the patients treated with 300 mg every four week and 7.3% of patients treated with placebo (16).

6.1.3 Comparative analyses

From the data available from the publications, it is not possible to do an indirect comparison on number of patients who are 100% attack-free and it is thus not possible to claim that there are differences in the attack-free rates between treatment arms. In the HELP study, the proportion of attack-free patients is presented as a pre-specified exploratory endpoint and in the COMPACT study, the proportion of patients experiencing a 100% attack-reduction is reported. In addition, the definition of 100% attack-free and the study designs between COMPACT and HELP differ. The COMPACT study is a cross-over study running over two periods of 16 weeks each and the HELP study is a parallel group study running over 26 weeks. In the HELP study where the proportion of attack-free patients is presented with the pre-

specified exploratory endpoint, results from patients being attack-free days 0-69 are presented. In the COMPACT study, the proportion of patients experiencing a 100% attack-reduction in each treatment sequence is presented. In conclusion, differences in the study designs such as follow-up of the patients in the studies and differences in the disease-severity prevent indirect comparisons of complete freedom of attacks.

[redacted]

See appendices in Table A4 for full description of the comparisons based on clinical questions stated by DMC.

6.2 Clinical question 2: Health Related Quality of Life (Helbredsrelateret livskvalitet)

Health-related quality of life (HRQoL) is a critical endpoint in the assessment of subcutaneous C1-esterase inhibitor, as HAE during seizures as well as between seizures affects patient's quality of life.

The Danish Medicines Council wants quality of life to be elucidated from the validated questionnaire Angioedema Quality of Life Questionnaire (AE-QoL). In AE-QoL the score goes from 0-100, where a higher score indicates a poorer quality of life.

The Danish Medicines Agency wants the assessment to be based on the overall score, and the smallest clinically relevant difference is set at 6 points, as this difference has been found to be clinically significant when using AE-QoL.

The Danish Medicines Council wants the relative effect difference for AE-QoL total score to be calculated as the proportion of patients who achieve a reduction of 6.0 points from baseline.

6.2.1 Presentation of relevant studies

COMPACT

The AE-QoL was not validated at the time when the COMPACT study was established, and it is therefore not possible to present data of that as requested by the Medicines Council. Instead, other commonly used and validated generic HRQoL tools were included in the study.

In the COMPACT study, several HRQoL assessments were included and analyzed at baseline and at various time points throughout the study. General health and health status were measured with the European Quality of Life-5 Dimension Questionnaire (EQ-5D-3L), including Health State Value (HSV) and Visual Analogue Scale (VAS). Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) and health-related work productivity and activity impairment were evaluated with the Work Productivity and Activity Impairment Questionnaire (WPAI). Lastly, the study subjects' satisfaction with medication was measured with Treatment Satisfaction Questionnaire for Medication (TSQM) (15).

COMPACT OLE

In the COMPACT OLE study, HRQoL was evaluated at the beginning of the open-label study and at various time points using the EQ-5D scores (including HSV and VAS), HADS anxiety and depression scores, WPAI-assessed presenteeism, work productivity loss and activity impairment and TSQM for treatment satisfaction. In addition, the disease-specific AE-QoL and HAE-QoL total and domain scores were assessed in US patients during the additional 88-week extension period (11).

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

HELP

In the HELP study, the AE-QoL consisting of four domains and total score, was administered monthly. In addition, the generic EQ-5D-5L questionnaire was administered on days 0, 98, and 182 (17).

6.2.2 Results per study

COMPACT

For each HRQoL assessment, the effect of Berinert® SC was evaluated by the mean and median difference in within-subject scores between active treatment (both doses combined) and placebo treatments at week 14. For each or the patient-reported outcome measures in the trial, a greater proportion of patients had last visit scores reflecting minimal clinically important improvements with Berinert® SC as compared with placebo use (15).

Baseline mean and median scores for EQ-5D and HADS instruments indicated a good general health and little anxiety and depression. The mean EQ-5D at screening was high, yet both doses of Berinert® SC was associated with a significantly better mean EQ-5D VAS scores as compared with on-demand (placebo) treatment after 14 weeks of treatment. EQ-5D VAS score changed between Berinert® SC and placebo at the last visit indicated a treatment benefit with Berinert® SC (mean treatment difference, 8.53; 95% CI 4.10, 12.97). Changes in HSV scores from baseline to the last visit were small (mean treatment difference, 0.04; 95% CI -0.01, 0.08) and did not suggest a treatment benefit with Berinert® SC vs placebo. Similar, the COMPACT study population had low anxiety and depression scores at screening. Yet, the study demonstrated a treatment benefit of Berinert® SC compared to placebo in the HADS anxiety score (mean treatment difference, -1.05; 95% CI -1.79, -0.31) from screening to the last visit. The depression score assessed with HADS depression score were numerically lower (direction of improvement) for Berinert® SC vs placebo at the last visit but the mean difference (-0.55; 95% CI – 1.11, 0.01) did not demonstrate a beneficial treatment effect. There were no meaningful differences observed for WPAI absenteeism between Berinert® SC and placebo at last visit. In contrast, a treatment benefit in favor of Berinert® SC vs placebo for presenteeism, work productivity loss, and activity impairment was observed after 14 weeks of treatment. For the TSQM domains, the mean TSQM scores during treatment with Berinert® SC were markedly improved compared with baseline and compared with placebo at the last visit (15).

COMPACT OLE

Mean baseline EQ-5D scores (Health State Value, 0.90; Visual Analog Scale, 81.32) were slightly higher (better) than United States population norms (0.825, 80.0, respectively) and mean HADS anxiety (5.48) and depression (2.88) scores were within "normal" range (0-7). Yet, patients using C1-INH(SC) 60 IU/kg demonstrated significant improvement from baseline to end-of-study on the EQ-5D Health State Value (mean change [95% CI], 0.07 [0.01, 0.12] and Visual Analog Scale (7.45 [3.29, 11.62]). In the C1-INH(SC) 60 IU/kg group, there were significant improvements in the HADS anxiety scale (mean change [95% CI], - 1.23 [- 2.08, - 0.38]), HADS depression scale (- 0.95 [- 1.57, - 0.34]), and WPAI-assessed presenteeism (mean change [95% CI], - 23.33% [- 34.86, - 11.81]), work productivity loss (- 26.68% [- 39.92, - 13.44]), and activity impairment (- 16.14% [- 26.36, - 5.91]). Clinically important improvements were achieved in ≥ 25% of patients for all domains except WPAI-assessed absenteeism (which was very low at baseline) (11).
Mean AE-QoL total score by visit ranged from 13.39 to 17.89 (scale 0-100; lower scores = less impairment). Mean HAE-QoL global scores at each visit (115.7-122.3) were close to the maximum (best) possible score of 135.
(11).

HELP

In the HELP study, the patient group treated with 300 mg Takhzyro® q2w and q4w had a reduction in the AE-QoL of 21.29 and 17.38 points respectively from baseline to the end of study at week 26. In the placebo group the

corresponding number was a reduction of 4.72 points. Mean EQ-5D-5L score and VAS scores at day 0 were high in all groups, indicating low impairment, with no significant changes at day 182. In the Takhzyro® group, 81% of the patients treated twice weekly and 63% of patients treated once monthly achieved a clinically meaningful improvement (MCID = 6) in AE-QoL total score compared to 37% in the placebo group (17).

6.2.3 Comparative analyses

Due to different HRQoL instruments used in COMPACT and HELP studies, it is not feasible to do an indirect comparison of HRQoL outcome data. COMPACT used EQ-5D and HADS instruments and HELP used mainly the AE-QoL instrument. However, in the recently published HRQoL data from COMPACT OLE the AE-QoL instrument was assessed (11). The reduction in AE-QoL could still not be retrieved from the COMPACT OLE trial since the AE-QoL instrument was not used from the trial start.

In addition, in the COMPACT study, EQ-5D-3L was included and in the HELP study EQ-5D-5L was included (both questionnaires with different instrument designs) and in both studies general health status was evaluated using the VAS-scale (visual analogue scale from 0-100). In both studies the baseline mean VAS scores were high for all treatment groups, indicating a generally good self-reported quality of life. The study designs of COMPACT and HELP differ and with different HRQoL instruments an indirect comparison is therefore not applicable.

Since most of the HRQoL instruments and evidence for quality of life between Berinert® SC and Takhzyro® differ, it is not possible to perform a comparative analysis between the treatments.

See appendices in Table A4 for full description of the comparisons based on clinical questions stated by DMC.

6.3 Clinical question 3: Attack frequency (Anfaldsfrekvens)

Attack frequency is an important endpoint in the assessment of subcutaneous C1 esterase inhibitor. The primary treatment goal with routine prevention is to reduce the frequency of HAE seizures, and seizure frequency is therefore an important efficacy measure. The Danish Medicines Council will shed light on seizure frequency by looking at the difference in the average number of HAE seizures per month. The subject committee has chosen an average percentage change as the least clinically relevant difference to take into account that there is great variation in seizure frequency from patient to patient. The Technical Committee considers a difference of 15 percentage points in the average seizure frequency to be the smallest clinically relevant difference.

In addition to the calculation of the average reduction in seizure frequency, the specialist committee also wants a review of the severity of the remaining seizures (breakthrough seizures) in the two treatments. Specifically, a statement of the proportion of seizures characterized by mild, moderate, and severe severity, respectively, is desired.

6.3.1 Presentation of relevant studies

COMPACT

The time-normalized attack rate of angioedema and severity of breakthrough attacks per month in patients treated with Berinert® SC is presented in the COMPACT study (4).

COMPACT OLE

For long-term data, the time-normalized number of angioedema attacks per month is presented in the COMPACT OLE study (10).

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

HELP

In the HELP study, the number of attacks per month and the severity of breakthrough attacks were evaluated in patients treated with Takhzyro® for 26 weeks (7). In an ad-hoc analysis, these endpoints were assessed from day 0-69 and compared with steady state (days 70-182) (16).

Fridman 2020 Indirect comparison (Berinert® SC 60 IU/kg vs Takhzyro® - published poster)

In the absence of head-to-head studies comparing the efficacy between Berinert® SC and Takhzyro®, an indirect comparison between the treatments has been performed. In this indirect comparison, the statistical methods used in the COMPACT trial and HELP trial respectively were standardized to allow for indirect comparison between the absolute and relative monthly attack rate reduction of 60 IU/kg Berinert® SC vs placebo and Takhzyro® vs placebo (8).

[redacted]

[redacted]

6.3.2 Results per study

COMPACT

The primary efficacy endpoint in the COMPACT trial was the time-normalized number of HAE attacks, as reported by the investigator. The mean difference, as compared with placebo, was -2.42 attacks per month (95% CI, -3.38 to -1.46) with 40 IU/kg and -3.51 attacks per month (95% CI, -4.21 to -2.81) with 60 IU/kg (P<0.001 for both comparisons). In patients with data that could be evaluated at both doses, the median reduction in the normalized number of attacks versus placebo was 88.6% (interquartile range, 69.6 to 100.0) with 40 IU/kg bw and 95.1% (interquartile range, 79.0 to 100.0) with 60 IU/kg bw (4).

In the COMPACT trial, thirteen patients who received either dose of Berinert® SC had a total of 52 severe attacks, and 64 patients who received placebo had a total of 252 severe attacks. The average severity of attacks was lower in the patients who received Berinert® SC than in those who received placebo. Of the 45 patients treated with 60 IU/kg bw, 18%, 29% and 9% experienced mild, moderate, and severe attacks respectively. The corresponding numbers in the placebo group in this treatment sequence was 2%, 22% and 69% respectively. Of the 45 patients treated with 40 IU/kg bw, 11%, 27% and 20% experienced mild, moderate, and severe attacks respectively. The corresponding numbers in the placebo group in this treatment sequence was 2%, 13% and 73% respectively (4).

COMPACT OLE

In the long-term follow-up of the COMPACT study, the median number of attacks per month was 0.1 (0.0 to 3.4) for patients treated with 40 U/kg bw and 0.1 (0.0 to 4.0) for the 60 IU/kg bw groups (10).

HELP

In the HELP study, there was a statistically significant reduction in attack rate per month with a mean difference of -1.71 (95% CI, -2.09 to -1.33, p<0.001) in Takhzyro® 300 mg twice weekly vs placebo and -1.44 (95% CI, -1.84 to -1.04) in

Takhzyro® 300 mg every four weeks vs placebo. The mean rate ratio relative to placebo was 0.13 (95% CI, 0.07 to 0.24, p<0.001) for the Takhzyro® 300 mg twice weekly group and 0.27 (95% CI, 0.18 to 0.41) in the group treated with Takhzyro® 300 mg every four weeks. For moderate or severe attacks, the mean difference vs placebo was -1.01 (95% CI, -1.32 to -0.71) for the Takhzyro® 300 mg twice weekly group and -0.89 (95% CI, -1.20 to -0.58) for the Takhzyro® 300 mg every four weeks group (7). Patients who received Takhzyro® 300 mg every four weeks also included patients who are not severely ill with several HAE attacks per month at baseline, i.e., patients who are not recommended to receive Takhzyro® as standard treatment in Denmark.

Fridman 2020 Indirect comparison (Berinert® SC 60 IU/kg vs Takhzyro® - published poster)

An indirect comparison was also conducted for Berinert® SC 60 IU/kg and Takhzyro® using the Phase III clinical trials COMPACT and HELP (4, 7). Because the respective clinical trials differed in design, individual patient data from COMPACT were reanalyzed using a generalized estimating equation model for Poisson multiple regression in the HELP trial. For the COMPACT trial, the least squares mean difference was estimated with 95% confidence intervals with the use of a mixed-model accounting for the within patient correlation. For the HELP trial, a Poisson regression model including a covariate for the normalized run-in period attack rate and accounting for potential overdispersion was applied. Following Bucher's method, the authors indirectly compared attack reduction outcomes (mean number of monthly HAE attacks over placebo) between the two treatments. The absolute reduction in monthly attacks for patients treated with Berinert® SC 60 IU/kg compared with placebo in COMPACT was 3.29 (CI 2.65–3.98) attacks per month compared to an absolute reduction of 1.71 (CI 1.33–2.09) attacks per month for patients treated with Takhzyro® 300 mg every 2 weeks compared with placebo in the HELP trial. Patients saw similar relative reductions in monthly attacks while using both Berinert® SC 60 IU/kg and Takhzyro® 300 mg every 2 weeks of 0.12 and 0.13 respectively (8).

[redacted]

[redacted]

6.3.3 Comparative analyses

There are three comparative analyses that have been chosen to be presented here, i.e., [redacted]

See appendices in Table A4 for full description of the comparisons based on clinical questions stated by DMC.

Fridman 2020 Indirect comparison (Berinert® SC 60 IU/kg vs Takhzyro® - published poster)

An indirect comparison was conducted for Berinert® SC 60 IU/kg and Takhzyro® using the Phase III clinical trials COMPACT and HELP (8). Because the respective clinical trials differed in design, individual patient data from COMPACT were reanalyzed using a generalized estimating equation model for Poisson multiple regression in the HELP trial. The absolute reduction in monthly attacks for patients treated with Berinert® SC 60 IU/kg compared with placebo in COMPACT was 3.29 attacks per month compared to an absolute reduction of 1.71 attacks per month for patients treated with Takhzyro® 300 mg every 2 weeks in HELP compared with placebo. Patients saw similar relative reductions in monthly attacks while using both Berinert® SC 60 IU/kg and Takhzyro® 300 mg every 2 weeks of 0.12 and 0.13 respectively.

[redacted]

[redacted]

6.4 Clinical question 4: Side effects (Bivirkninger)

Side effect is an important endpoint in the assessment of subcutaneous C1 esterase inhibitor. Side effects can have an impact on the individual patient's quality of life and can lead to discontinuation of treatment. As the treatment is expected to be given continuously for many years, the Danish Medicines Council wants side effects to be included as an important effect measure.

The Danish Medicines Council wants side effects to be calculated as a proportion of patients who discontinue treatment due to side effects, and a difference between the groups of 10 percentage points is considered clinically relevant.

The Danish Medicines Council also wants the applicant to provide an approved summary of product characteristics (SmPC) for subcutaneous C1 esterase inhibitor Berinert® SC and comparator Takhzyro® (1, 19). Both SmPC have been attached to the application report.

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

6.4.1 Presentation of relevant studies

COMPACT
Safety and the side-effect profile are presented in the COMPACT trial (4).

In Li and colleagues from 2018 (14), the relationship of the Berinert® SC dose regimens was tested in the COMPACT trial (40 IU/kg and 60 IU/kg twice weekly) and the occurrence of adverse events were evaluated.

COMPACT OLE
Long-term safety was assessed in the COMPACT OLE trial (10). The primary pre-specified endpoints were person-time incidence rate of related serious adverse events, adverse events leading to premature discontinuation, adverse events of special interest (thromboembolic events and anaphylaxis), HAE attacks resulting in hospitalization, injection-site reactions graded severe by the investigator, and the development of neutralizing anti-C1-INH antibodies.

Secondary safety endpoints parameters included types of adverse events, suspected drug-related adverse events, and thromboembolic, anaphylaxis, sepsis, and bacteremia events.

HELP
In the HELP study, adverse events following repeated subcutaneous Takhzyro® administrations were analyzed (7).

6.4.2 Results per study

COMPACT
In the COMPACT trial, adverse events were reported by similar proportions of patients in the Berinert® SC groups and the placebo groups. The majority of reported adverse events were mild in 95%, 76% and 83% of the patients in the 40 IU/kg, 60 IU/kg and the combined placebo groups respectively. In 98%, 94%, and 96% of the patients in the 40 IU/kg, 60 IU/kg and combined placebo group respectively the adverse events were resolved at the end of the trial as reported by the investigator. There were no anaphylactic reactions or serious hypersensitivity, thromboembolic events, sepsis or bacteremia events or any inhibitory antibodies to C1-INH observed during the study (4).

Most reported adverse events were injection-site reactions (ISRs). ISRs were reported in 28%, 35%, and 24% of patients treated with 40 IU/kg, 60 IU/kg and combined placebo groups, respectively. Of the ISRs, 95% in the combined Berinert® SC groups and 95% in the placebo groups were mild and 83% in the combined Berinert® SC groups and 90% in the placebo groups resolved within one day from onset. ISRs reported by >5% of patients during treatment with Berinert® SC were injection-site erythema, pain, edema, induration, bruising, and swelling (14).

Three adverse events led to trial discontinuation: pulmonary embolism in a patient who received placebo, urticaria in a patient who received Berinert® SC 60 IU/kg, and an increase in liver aminotransferase levels in a patient who received Berinert® SC 60 IU/kg. Four serious adverse events were reported in three patients: one event (urosepsis) in a patient who received Berinert® SC 40 IU/kg and three events (pulmonary embolism, attack for angioedema, and syncope) in patients who received placebo. None of the withdrawals or serious adverse events with Berinert® SC were related to the study drug (4).

COMPACT OLE
The long-term safety was further supported in the COMPACT OLE study with similar adverse event profiles reported in both treatment arms of the study. The most frequently observed adverse event was injection-site reactions. Overall

incidence rates of ISRs were 0.06 and 0.08 events per injection for 60 IU/kg and 40 IU/kg respectively, but four patients, who were administered approximately 3% of all injections delivered during the study, accounted for more than 50% of all solicited adverse events (10).

Twelve serious adverse events were experienced by 9 (7.1%) patients. Most serious adverse events were moderate or severe in intensity and resolved. None was deemed to be related to the study drug. Four (3%) adverse events led to study discontinuation, including an unrelated serious adverse event of myocardial infarction. The nonserious adverse events leading to discontinuation were headache, myalgia, and arthralgia and none of these events were related to study drug (10).

HELP

In the HELP study, none of the patients treated with Takhzyro® 300 mg q2w withdrew from the study because of adverse events. The most common adverse events were injection-site reactions reported by 51.9% and 29.3% of the patients in the Takhzyro® 300 mg q2w and placebo groups respectively (7).

Two patients in the placebo group withdrew from the study due to treatment-emergent adverse events of tension headache and hereditary angioedema attack (related), which were of moderate severity. One patient in the Takhzyro® 300 mg q4w group withdrew due to a related, isolated, asymptomatic, and transient elevation of alanine transaminase and aspartate transaminase. Overall, there were four (4.8%) patients in the combined Takhzyro® groups that had a serious adverse event compared to 0 (0%) in the placebo group (7).

6.4.3 Comparative analyses

From the data available from the publications, it is not possible to do an indirect comparison of withdrawals due to adverse events and it is thus not possible to claim that there are differences in the tolerability of the different products. A significant difference is not expected, and the general safety profile is good.

See appendices in Table A4 for full description of the comparisons based on clinical questions stated by DMC.

6.5 Other considerations: Exposure-response relationship

Under 'other considerations' in section 7 in the protocol, the Medicine Council asks CSL Behring to expound the exposure-response relationship for 40 IU/kg and 60 IU/kg and if possible, estimate how many patients is expected to be sufficiently treated with the low dose regimen.

A population pharmacokinetic model of subcutaneous C1-inhibitor in healthy individuals and HAE patients has been developed where simulations based on the final population PK model to support dosing of Berinert SC were evaluated (20). Data were obtained and pooled from 3 clinical studies: 1 study in healthy volunteers and 2 studies in patients with HAE following either IV or SC administration of C1-INH. Based on the final model, mean C_{trough} was 40.2% for 40 IU/kg and 48.0% for 60 IU/kg. These numbers are higher than the C_{trough} value calculated for C1-INH IV 1000 IU that was 29.5%. These results suggest that the majority of patients treated with Berinert SC 40 IU/kg or 60 IU/kg will have C_{trough} values above the clinically meaningful 38% threshold, below which patients are more likely to experience attacks (21, 22).

In an exposure-response analysis of the relationship between C1-INH functional activity and risk of HAE attacks it was further confirmed that increasing C1-INH functional activity correlates with a greater reduction in the relative risk of an HAE attack (23). In the exposure-response model, data from the COMPACT study were utilized. Based on trough

functional C1-INH values, which are above the clinically meaningful 40% threshold, both for the 40 IU/kg and 60 IU/kg dosing regimen of Berinert SC, the model predicted that 50% and 67% of the population respectively, would see at least a 70% decrease in the risk of an attack. Overall, the 40 IU/kg and 60 IU/kg doses may both achieve ≥50% reductions in the relative risk of an HAE attack in over 72% of the subjects.

As discussed previously in the application, HAE patients belong to a heterogeneous patient population and treatment should be individualized. Patients should be evaluated regarding which dose of Berinert SC that is sufficient to prevent attacks. From the phase III COMPACT study, it is shown that 67% of the patients have ≥70% reduction in attacks vs placebo when treated with 40 IU/kg Berinert SC which is even higher than predicted in the exposure-response analysis described by Zhang et al (23). The corresponding number for patients treated with 60 IU/kg Berinert SC is 83% (4). The response rate in the COMPACT study is compared to the corresponding numbers in the HELP study with 79.1% of the patients have ≥70% reduction in attacks vs placebo when treated with 300 mg lanadelumab every two weeks and 66.1% of patients had ≥70% reduction in attacks vs placebo when treated with 300 mg lanadelumab every 4 week (7).

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

7. References

1. Laegemiddelstyrelsen. PRODUKTRESUMÉ for Berinert, pulver og solvens til injektionsvæske, opløsning 2000 IE og 3000 IE. 2021.
2. Medicinrådet. Medicinrådets protokol for vurdering vedrørende C1-esterase-inhibitor til forebyggende behandling af arveligt angioødem. Medicinrådet: Medicinrådet, Medicinrådet; 2021. Contract No.: Dokumentnummer 97666.
3. [redacted]
4. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med. 2017;376(12):1131-40.
5. Caballero Molina GQT, Lleonart Bellfill, Baeza Ochoa de Ocariz,, Almero Ves GC. Propuesta del GEAB para el inicio de concentrado plasmático de C1-Inhibidor (cpC1INH) (Berinert®) subcutáneo como profilaxis a largo plazo en AEH-C1-INH. Investigational Allergology and Clinical Immunology. 2020;30.
6. [redacted] use only). In: Dr Martina Witzaer CB, editor. Frankfurt, Germany2020. p. 2.
7. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108-21.
8. Moshe Fridman DS, Subhransu Prusty, John-Philip Lawo. Indirect comparison between human C1-inhibitor (C1-INH) subcutaneous treatment and lanadelumab for routine prevention of hereditary angioedema (HAE) attacks. Presented at the ISPOR US annual meeting May 18–20, 2020. 2020;Poster Number: PRO65.
9. [redacted]
10. Craig T, Zuraw B, Longhurst H, Cicardi M, Bork K, Grattan C, et al. Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks. J Allergy Clin Immunol Pract. 2019;7(6):1793-802 e2.
11. Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet J Rare Dis. 2021;16(1):86.
12. EMA. Assessment Report Takhzyro. Committee for Medicinal Products for Human Use (CHMP); 2018.
13. Bock SC, Skriver K, Nielsen E, Thogersen HC, Wiman B, Donaldson VH, et al. Human C1 inhibitor: primary structure, cDNA cloning, and chromosomal localization. Biochemistry. 1986;25(15):4292-301.
14. Li HH, Mycroft S, Christiansen S, Wood DN, Feuersenger H, Pawaskar D, et al. Subcutaneous C1-esterase inhibitor to prevent hereditary angioedema attacks: Safety findings from the COMPACT trial. Allergy Asthma Proc. 2018;39(5):365-70.
15. Lumry WR, Craig T, Zuraw B, Longhurst H, Baker J, Li HH, et al. Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2018;6(5):1733-41 e3.
16. Riedl MA, Maurer M, Bernstein JA, Banerji A, Longhurst HJ, Li HH, et al. Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks. Allergy. 2020;75(11):2879-87.
17. Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. Allergy. 2020.
18. Riedl MA, Bernstein JA, Craig T, Banerji A, Magerl M, Cicardi M, et al. An open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention of attacks in hereditary angioedema: design of the HELP study extension. Clin Transl Allergy. 2017;7:36.
19. EMA. EPAR Takhzyro product information - ANNEX I - SUMMARY OF PRODUCT CHARACTERISTICS. 2018.
20. Pawaskar D, Tortorici MA, Zuraw B, Craig T, Cicardi M, Longhurst H, et al. Population pharmacokinetics of subcutaneous C1-inhibitor for prevention of attacks in patients with hereditary angioedema. Clin Exp Allergy. 2018;48(10):1325-32.

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

21. Spath PJ, Wuthrich B, Butler R. Quantification of C1-inhibitor functional activities by immunodiffusion assay in plasma of patients with hereditary angioedema--evidence of a functionally critical level of C1-inhibitor concentration. Complement. 1984;1(3):147-59.
22. Hack CE, Relan A, van Amersfoort ES, Cicardi M. Target levels of functional C1-inhibitor in hereditary angioedema. Allergy. 2012;67(1):123-30.
23. Zhang Y, Tortorici MA, Pawaskar D, Pragst I, Machnig T, Hutmacher M, et al. Exposure-Response Model of Subcutaneous C1-Inhibitor Concentrate to Estimate the Risk of Attacks in Patients With Hereditary Angioedema. CPT Pharmacometrics Syst Pharmacol. 2018;7(3):158-65.
24. Bernstein JA, Schwartz L, Yang W, Baker J, Anderson J, Farkas H, et al. Long-term safety and efficacy of subcutaneous C1-inhibitor in older patients with hereditary angioedema. Ann Allergy Asthma Immunol. 2020;125(3):334-40 e1.
25. Levy D, Caballero T, Hussain I, Reshef A, Anderson J, Baker J, et al. Long-Term Efficacy of Subcutaneous C1 Inhibitor in Pediatric Patients with Hereditary Angioedema. Pediatr Allergy Immunol Pulmonol. 2020a;33(3):136-41.
26. Levy DS, Farkas H, Riedl MA, Hsu FI, Brooks JP, Cicardi M, et al. Long-term efficacy and safety of subcutaneous C1-inhibitor in women with hereditary angioedema: subgroup analysis from an open-label extension of a phase 3 trial. Allergy Asthma Clin Immunol. 2020b;16:8.
27. Li HH, Zuraw B, Longhurst HJ, Cicardi M, Bork K, Baker J, et al. Subcutaneous C1 inhibitor for prevention of attacks of hereditary angioedema: additional outcomes and subgroup analysis of a placebo-controlled randomized study. Allergy Asthma Clin Immunol. 2019;15:49.

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

8. Appendices

8.1 Literature search

Table A1 Inclusion and exclusion criteria	
Inclusion criteria	Population*: Børn ≥ 12 år og voksne med HAE type I eller II. Intervention(s)*: Berinert® (C1-esteraseinhibitor) s.c. 60 enheder/kg hver 3.-4. dag.** Comparator(s)*: Takhzyro 300 mg hver 2. uge.** Outcomes*: Effect parameters outlined in section Clinical questions (following Table 1 in Medicines Council protocol (Document number 97666) and also attached below. Settings (if applicable): N/A Study design: • Full-text articles published in scientific, peer-reviewed journals and data from the European Medicines Agency's (EMAs) European Public Assessment Reports (EPAR) • Conference abstracts and non-published studies (grey literature) on indirect comparisons between Berinert® SC and Takhzyro® with relevant clinical outcomes • Additional non-published data on indirect comparisons between Berinert® SC and Takhzyro® (outside literature search) Language restrictions: None Other search limits or restrictions applied: Search hits until Jan 22, 2021Ω
Exclusion criteria	Population: Other than mentioned in Inclusion criteria above Intervention(s): Other than mentioned in Inclusion criteria above Comparator(s): Other than mentioned in Inclusion criteria above Outcomes: Other than mentioned in Inclusion criteria above Settings (if applicable): N/A Study design: Other than mentioned in Inclusion criteria above Language restrictions: None Other search limits or restrictions applied: Search hits after Jan 22, 2021Ω

* According to Medicines Council protocol (Document number 97666, approved Jan 11, 2021) (2); ** Alternative dose of Berinert® SC 40 IU/kg and Takhzyro® 300 mg every 4 week were also included and presented in the final assessment.; Ω One study on HRQoL from the COMPACT OLE trial was identified after the literature search day (Jan 22, 2021) and was chosen to be included in the final assessment.

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

Tabel 1 Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Retningsgivende mindste klinisk relevante forskel
Anfaldsfrihed	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel af patienter som oplever en 100 % reduktion i anfaldsfrekvens (symptomfrihed) fra baseline	10 %-point
Helbredsrelateret livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Ændring fra baseline målt med Angioedema Quality of life Questionnaire (AE-QoL)	6 point
			Andel af patienter som oplever en forbedring på 6 point fra baseline	Anvendes til bestemmelse af den relative effektforskel. Der er derfor ikke fastsat en MKRF
Anfaldsfrekvens	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Procentvis reduktion i antallet HAE-anfald pr. måned	15 %-point
			Gennemgang af sværhedsgraden af de tilbageværende anfald (gennembruds-anfald) ved de to behandlinger†.	-
Bivirkninger	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter der ophører behandling grundet bivirkninger	10 %-point
			Kvalitativ gennemgang af lægemidlernes bivirkningsprofil	-

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
† Foruden opgørelsen af den gennemsnitlige reduktion i anfaldsfrekvens ønsker fagudvalget også en gennemgang af sværhedsgraden af de tilbageværende anfald (gennembrudsanfald) ved de to behandlinger. Se mere under beskrivelsen af effektmålet.

8.2 Main characteristics of included studies

Table A2 Main study characteristics COMPACT	
Trial name	COMPACT
NCT number	NCT01912456
Objective	The objective of the study was to test the hypothesis that twice-weekly subcutaneous administration of Berinert® SC 2000/3000, as compared with placebo, could reduce the frequency of HAE attacks in patients with frequent attacks.
Publications – title, author, journal, year	Prevention of hereditary angioedema attacks with a subcutaneous s C1 inhibitor, Longhurst et al. NEJM. 2018;376(12)1131-114

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

Table A2 Main study characteristics COMPACT	
Study type and design	COMPACT is an international, prospective, multicenter, dose-ranging phase 3 trial that was conducted from December 2013 through October 2015. Patients were randomly assigned in a 1:1:1:1 ratio by means of an interactive-response system to receive Berinert® SC 2000/3000 at a dose of 40 IU/kg bw during the first 16-week treatment period followed by placebo for the second 16-week treatment period or vice versa; or Berinert® SC 2000/3000 at a dose of 60 IU/kg bw followed by placebo or vice versa. Berinert® SC 2000/3000 or placebo was administered by the patient twice weekly in a double-blind crossover manner during each treatment period. To maintain the blinding, a high-volume placebo (matching the volume of the 60 IU dose of Berinert® SC 2000/3000) was provided to patients who received the 40 IU dose of Berinert® SC 2000/3000 and a low-volume placebo to patients receiving the 60 IU dose of Berinert® SC 2000/3000.
Follow-up time	Patients received placebo and active treatment for 16 weeks respectively. The mean duration of exposure was 16.3±1.6 weeks for 40 IU, 16.0±2.1 weeks for 60 IU, and 15.3±3.3 weeks for combined placebo.

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

Table A2 Main study characteristics COMPACT	
Population (inclusion and exclusion criteria	**Run-In Period Inclusion Criteria:** • Males or females aged 12 years or older. • A clinical diagnosis of hereditary angioedema type I or II. • Experienced ≥4 hereditary angioedema attacks over a consecutive 2-month period that required acute treatment, medical attention, or caused significant functional impairment within three months prior to screening. • For subjects who have used oral therapy for prophylaxis against HAE attacks within 3 months of screening: use of a stable regimen within 3 months of screening. **Eligibility Criteria for Entering Treatment Period 1**: • Laboratory confirmation of type I or type II hereditary angioedema, including C1-esterase inhibitor functional activity less than 50% AND C4 antigen level below the laboratory reference range. • No clinically significant abnormalities as assessed using laboratory parameters. • During participation in the run-in period, subjects must have experienced ≥2 hereditary angioedema attacks within any consecutive 4-week period or ≥1 attack during the first 2 weeks that required acute treatment, required medical attention, or caused significant functional impairment. **Run-In Period Exclusion Criteria**: • History of clinically significant arterial or venous thrombosis, or current history of a clinically significant prothrombotic risk. • Incurable malignancies at screening. • Any clinical condition that will interfere with the evaluation of C1-esterase inhibitor therapy. • Clinically significant history of poor response to C1-esterase therapy for the management of hereditary angioedema. • Receiving therapy prohibited by the protocol, including medications for hereditary angioedema prophylaxis. • Female subjects who started taking or changed dose of any hormonal contraceptive regimen or hormone replacement therapy (i.e., estrogen/progesterone-containing products) within 3 months prior tothe screening visit. • For additional exclusion criteria, please see Table S1 in Supplementary appendix [3]

[3] Supplement to: Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. N Engl J Med 2017; 376:1131-40. DOI: 10.1056/NEJMoa1613627

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

Table A2 Main study characteristics COMPACT		
Intervention	Overall, 115 patients were screened and of those 23 patients were randomized to receive Berinert® SC twice weekly at a dose 40 IU/kg bw for 16 weeks followed by placebo treatment for 16 weeks and 22 patients were treated vice versa. 22 patients were randomized to Berinert® SC 60 IU/kg bw followed by placebo treatment for 16 weeks and 23 patients were treated vice versa. Patients were permitted to use intravenous C1 inhibitor concentrate, icatibant, ecallantide or fresh-frozen plasma as a rescue medication for on-demand treatment of attacks at any time during the trial or for preprocedural prophylaxis.	
Baseline characteristics Baseline characteristics of patients in the intention-to-treat population (mean±SD)	Age (years): Female sex (no. (%): Body weight (kg): Body-mass index: No of attacks of angioedema in 3 months before screening:	39.6±14.9 60 (67) 81.6±23.7 28.6±7.1 9.8±6.6
Primary and secondary endpoints	**Primary efficacy endpoint** was the number of attacks of angioedema. **Secondary efficacy endpoints** were the percentage of patients who had a response (≥50% reduction vs. placebo in the number of attacks) and the number of times that rescue medication was used. ***Exploratory endpoints*** included the number of days of angioedema symptoms, severity of attacks, and proportion of patients in whom the number of attacks was reduced to less than one attack per 4-week period with placebo. The number of attacks and uses of rescue medication were normalized for the number of days that the patient received the corresponding treatment.	
Method of analysis	All efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization. Efficacy data were included from the beginning of week 3 for each treatment period to account for a run-in or washout period. The primary efficacy analysis was conducted without imputation for missing data. Safety analysis were based on the safety population, which included all the patients in the intention-to treat population who had received at least one dose of a study drug. Descriptive statistics were used. For the comparison of the number of attacks and the number of times that rescue medication was used, normalized for the number of days that the patient received the corresponding treatment, a least-square mean difference was estimated with 95% confidence intervals and P values with the use of a mixed-model accounting for the within-patient correlation. All statistical tests were two-sided. Statistical analyses were conducted with the use of SAS software version 9.1.3 (SAS Institute).	

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

Table A2 Main study characteristics COMPACT	
	Bernstein, J. A., L. Schwartz, W. Yang, J. Baker, J. Anderson, H. Farkas, E. Aygoren-Pursun, A. Bygum, I. Jacobs, H. Feuersenger, I. Pragst, and M. A. Riedl. 2020. 'Long-term safety and efficacy of subcutaneous C1-inhibitor in older patients with hereditary angioedema', Ann Allergy Asthma Immunol, 125: 334-40 e1. (24)
	Levy, D., T. Caballero, I. Hussain, A. Reshef, J. Anderson, J. Baker, L. B. Schwartz, M. Cicardi, S. Prusty, H. Feuersenger, I. Pragst, and M. E. Manning. 2020a. 'Long-Term Efficacy of Subcutaneous C1 Inhibitor in Pediatric Patients with Hereditary Angioedema', Pediatr Allergy Immunol Pulmonol, 33: 136-41. (25)
Subgroup analyses	Levy, D. S., H. Farkas, M. A. Riedl, F. I. Hsu, J. P. Brooks, M. Cicardi, H. Feuersenger, I. Pragst, and A. Reshef. 2020b. 'Long-term efficacy and safety of subcutaneous C1-inhibitor in women with hereditary angioedema: subgroup analysis from an open-label extension of a phase 3 trial', Allergy Asthma Clin Immunol, 16: 8. (26)
	Li, H. H., B. Zuraw, H. J. Longhurst, M. Cicardi, K. Bork, J. Baker, W. Lumry, J. Bernstein, M. Manning, D. Levy, M. A. Riedl, H. Feuersenger, S. Prusty, I. Pragst, T. Machnig, T. Craig, and Compact Investigators. 2019. 'Subcutaneous C1 inhibitor for prevention of attacks of hereditary angioedema: additional outcomes and subgroup analysis of a placebo-controlled randomized study', Allergy Asthma Clin Immunol, 15: 49. (27)

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

Table A2 Main study characteristics HELP	
Trial name	HELP
NCT number	NCT02586805
Objective	The objective of the study was to assess the efficacy of Takhzyro® compared with placebo for preventing hereditary angioedema attacks.
Publications – title, author, journal, year	Effect of Takhzyro® compared with placebo on prevention of hereditary angioedema attacks. A randomized clinical trial. Banerji et al. JAMA. 2018;320(20):2108-2121 (7)
Study type and design	HELP was an international, randomized, double-blind, parallel-group, placebo-controlled phase 3 trial that was conducted from March 2016 through April 2017. Patients were randomized 2:1 to receive subcutaneously injected Takhzyro® or placebo. Patients randomized to receive Takhzyro® were assigned in a 1:1:1 ratio to 150 mg every 4 weeks, 300 mg every 4 weeks, or 300 mg very 2 weeks respectively. All patients received injections every 2 weeks, with those in the every-4-week groups receiving placebo in between active treatments. Patients were enrolled and assigned to interventions using an interactive web-based randomization system and was stratified by normalized number of attacks during the run-in period.
Follow-up time	The follow-up time was 26 weeks.

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

Table A2 Main study characteristics HELP	
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Males or females aged 12 years or older. • A clinical diagnosis of hereditary angioedema type I or II. • Experienced ≥1 investigator-confirmed hereditary angioedema attack per 4 week in the run-in period over a consecutive 2-month period that required acute treatment, medical attention, or caused significant functional impairment within three months prior to screening. • For subjects who have used oral therapy for prophylaxis against HAE attacks within 3 months of screening: use of a stable regimen within 3 months of screening. • Males and females who were fertile and sexually active must have adhered to contraception requirements. **Exclusion criteria:** • Concomitant diagnosis of another form of chronic recurrent angioedema • Participated in a prior Takhzyro® study • Liver function test abnormalities • Pregnant or breast-feeding • For additional exclusion criteria, please see eMethods 1 in Supplmentary Online Content (7)
Intervention	Overall, 159 patients were assessed for eligibility. Of these, 29 patients were randomized to receive 150 mg of Takhzyro® every 4 weeks, 29 patients were randomized to receive 300 mg Takhzyro® every 4 weeks, 27 patients were randomized to receive 300 mg of Takhzyro® every 2 weeks and 41 patients were randomized to receive placebo. Treatment of attacks followed the site investigator's standard of care, which could include intravenous C1 inhibitor, icatibant, or ecallantide.

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

Table A2 Main study characteristics HELP					
Baseline characteristics		**150 mg Q4W**	**300 mg Q4W**	**300 mg Q2W**	**Placebo**
	Age, mean (SD), years	43.4 (14.9)	39.5 (12.8)	40.3 (13.3)	40.1 (16.8)
	Females	20 (71.4)	19 (65.5)	15 (55.6)	34 (85.4)
	BMI, mean (SD)	26.9 (4.7)	28.1 (5.1)	31.0 (7.8)	27.5 (7.7)
	Run-in HAE attack rate, mean (SD), attacks per month	3.2 (1.8)	3.7 (2.5)	3.5 (2.3)	4.0 (3.3)
Primary and secondary endpoints	**Primary efficacy endpoint** was the number of attacks of angioedema during the 26-week treatment period. **Secondary efficacy endpoints** included the number of attacks requiring acute treatment during the 26-week treatment period, number of moderate or severe attacks during the 26-week treatment period, and number of attacks from days 14 through 182. ***Prespecified exploratory endpoints*** included the percentage of patients who were attack-free, number of attack-free days, responders, and number of high-morbidity attacks.				
Method of analysis	All efficacy analyses were conducted using SAS version 9.4. The primary and secondary efficacy end points for each active treatment group were compared with placebo using a Poisson regression model. All available data were included in the primary and secondary efficacy analyses. eMethods 5 in Supplement 2 provides a detailed description of the statistical methods.				
Subgroup analyses	No				

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

8.3 Results per study

Table A3a Results of study COMPACT 60 IU/kg											
Trial name:	COMPACT										
NCT number:	NCT01912456										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
% of patient with 100% reduction of HAE attacks*	Berinert ® SC 60 IU/kg vs low volume placebo	45 vs 45	Berinert ® SC 60 IU/kg 18 patients attack free vs 0 in placebo: 40%	Berinert® SC 60 IU/kg vs placebo = 18 patients 100% attack free	25.69 to 54.31%	<0.001	RR: 37	2.30 to 595.69	0.0054	Absolute difference: Post hoc Wald test including superiority testing (margin=0) Relative risk: Post hoc modified Wald test including superiority testing (margin=1)	Longhurst 2017 (4)

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

Table A3a Results of study COMPACT 60 IU/kg											
Number of attacks of angioedema per month*	Berinert® 60 IU/kg vs placebo	43 vs 42	0.52 (0.00 to 1.04) vs 4.03 (3.51 to 4.55)	Berinert® 60 IU/kg vs Placebo -3.51	–4.21 to –2.81	P<0.001	0.1282	0.07802 to 0.2106	<0.0001	No. of time-normalized attacks per month — mean (95% CI) For relative effect: post hoc analysis using poisson model for repeated measures with period and sequence as fixed effects and log(monthly duration) as offset	Longhurst 2017 (4)
Change from baseline assessed with AE-QoL*	Berinert® SC 60 IU/kg and placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	Since AE-QoL was not validated at the time when the COMPACT study was established, it is not possible to evaluate this assessment.	Lumry 2018 (15)

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

Table A3a Results of study COMPACT 60 IU/kg										
Patients that withdraw from the study due to adverse events*	Berinert® SC (60 IU/kg bw) twice weekly Placebo	86 86	Berinert® SC 60 IU/kg group 2 Placebo group 1	Berinert® SC vs placebo = 1	N/A	N/A	N/A	N/A	N/A	One adverse event in the placebo group and two in the Berinert® SC 60 IU/kg group led to the withdrawal from the study. None of the adverse events were related to study drug. From a statistical perspective, an analysis of 1 case difference in these small numbers is not feasible.	Longhurst 2017 (4)
Percentage of patients who had a response (≥50% reduction vs. placebo in the number of attacks)	Berinert 60 IU/kg vs placebo	40	90% (77 to 96)	N/A	N/A	N/A	N/A	N/A	N/A	Patients with a response — % (95% CI) ≥50% reduction in attacks vs. placebo. Not feasible to do any more comparison as This is a within patient comparison already.	Longhurst 2017 (4)

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

Table A3a Results of study COMPACT 60 IU/kg											
Use of rescue medication per month	SC Berinert (60 IU/kg bw) twice weekly	43	0.32 (-0.33 to 0.97)	-3.57	-4.50 to -2.64	<0.001	0.07583	0.03662 to 0.1570	<0.0001	*A least-square mean difference was estimated with 95% confidence intervals and P values with the use of a mixed-model accounting for the within-patient correlation.* *For relative effect: pot hoc analysis using poisson model for repeated measures with period and sequence as fixed effects and log(monthly duration) as offset*	Longhurst 2017 (4)
	Placebo	42	3.89 (3.23 to 4.55)								

Table A3b Results of study COMPACT 40 IU/kg	
Trial name:	COMPACT
NCT number:	NCT01912456

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

Table A3b Results of study COMPACT 40 IU/kg

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
% of patient with 100% reduction of HAE attacks*	Berinert® SC 40 IU/kg vs low-volume placebo	45 vs 45	Berinert® SC 40 IU/kg 17 patients attack free vs 4 in placebo	Berinert® SC 40 IU/kg vs placebo = 13 patients 100% attack free: 28.9%	12.46 to 45.31%	0.0003	RR: 4.25	1.5514 to 11.6428	0.0024	Absolute difference: Post hoc Wald test including superiority testing (margin=0) Relative risk: Post hoc modified Wald test including superiority testing (margin=1)	Longhurst 2017 (4)
Number of attacks of angioedema per month*	Berinert® 40 IU/kg vs placebo	43 vs 44	1.19 (0.54 to 1.85) vs 3.61 (2.96 to 4.26)	Berinert® 40 IU/kg vs Placebo	–3.38 to –1.46	P<0.001	0.2781	0.1729 to 0.4473	<0.0001	No. of time-normalized attacks per month — mean (95% CI) For relative effect: post hoc analysis using	Longhurst 2017 (4)

Table A3b Results of study COMPACT 40 IU/kg										
				-2.42					poisson model for repeated measures with period and sequence as fixed effects and log(monthly duration) as offset	
Change from baseline assessed with AE-QoL*	Berinert® SC 40 IU/kg and placebo		N/A	N/A	N/A	N/A	N/A	N/A	Since AE-QoL was not validated at the time when the COMPACT study was established, it is not possible to evaluate this assessment.	Lumry 2018 (15)
Patients that withdraw from the study due to adverse events*	Berinert 40 IU/kg vs placebo	43 vs 42	90 (77 to 96)	Berinert® SC vs placebo = -1	N/A	N/A	N/A	N/A	One adverse event in the placebo group and none in the Berinert® SC 40 IU/kg group led to the withdrawal from the study. None of the adverse events were related to study drug. From a statistical perspective, an analysis of 1 case difference in these small numbers is not feasible.	Longhurst 2017 (4)

Table A3b Results of study COMPACT 40 IU/kg										
Percentage of patients who had a response (≥50% reduction vs. placebo in the number of attacks)	Berinert 40 IU/kg vs placebo	42	76% (62 to 87)	N/A	N/A	N/A	N/A	N/A	N/A	Patients with a response — % (95% CI) ≥50% reduction in attacks vs. placebo. Not feasible to do any more comparison as This is a within patient comparison already.	Longhurst 2017 (4)
Use of rescue medication per month	SC Berinert (40 IU/kg bw) twice weekly	43	1.13 (-1.44 to 3.69)	-4.42	-8.03 to -0.81	0.02	0.2460	0.1242 to 0.4872	0.0002	A least-square mean difference was estimated with 95% confidence intervals and P values with the use of a mixed-model accounting for the within-patient correlation. For relative effect: pot hoc analysis using poisson model for repeated measures with period and sequence as fixed effects and log(monthly duration) as offset	
	Placebo	44	5.55 (3.10 to 8.00)								

Table A3c Results of study HELP												
Trial name:	HELP											
NCT number:	NCT02586805											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
% of patient with 100% reduction of HAE attacks*		27 41	44% 2.4%	42%	18.1%-61.8%	<0.001	N/A	N/A	N/A	The treatment period included days 70 through 182. The difference vs placebo was analyzed using Fisher exact test	Banerji 2018 (7)

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

Table A3c Results of study HELP										
Number of attacks of angioedema per month*	Takhzyro® 300 mg every 2w Placebo	27 41	Takhzyro® 0.26 (0.14-0.46) attacks Placebo 1.97 (1.64-2.36) attacks	-1.71	-2.09-1.33	<0.001	0.13	0.07-0.24	0.001	Attack rates are model-based mean attacks per month, defined as 4 weeks. A Poisson regression model accounting for overdispersion was used. All P values (Wald test) are reported vs placebo. The difference in absolute number of attacks was estimated from a nonlinear function of the model parameters.	Banerji 2018 (7)
Change from baseline assessed with AE-QoL*	Takhzyro® 300 mg every 2w Placebo	27 41	-21.29 ±3.53 -4.72 ±2.93	16.57	N/A	N/A	N/A	N/A	The Takhzyro® total group and placebo group were compared using analysis of covariance, adjusting for baseline scores.	Lumry 2020 (17)
Change from baseline assessed with VAS score	Takhzyro® 300 mg every 2w Placebo	27 41	-2.0 -2.3		Not significant	N/A	N/A	N/A	The Takhzyro® total and individual group and placebo group were compared using analysis of covariance, adjusting for baseline scores.	

Table A3c Results of study HELP										
Patients that withdraw from the study due to adverse events*	Takhzyro® 300 mg every 2w Placebo	27 41	N/A	N/A	N/A	N/A	N/A	N/A	None of the patients treated with Takhzyro® 300 mg q2w withdrew from the study because of adverse events.	Banerji 2018 (7)
Percentage of patients who had a response (≥50% reduction vs. placebo in the number of attacks)	Takhzyro® 300 mg every 2w vs placebo	27 vs 41	68.3%	47.9 to 83.8	<0.001	N/A	N/A	N/A	Achievement of a prespecified reduction from the run-in period in the hereditary angioedema attack-rate. The percentage reduction was calculated as the run-in period attack rate minus the treatment period attack rate divided by the run-in period attack rate, multiplied by 100. The difference vs placebo was analyzed using Fisher exact test.	Banerji 2018 (7)

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

Table A3c Results of study HELP											
Use of rescue medication per month	Takhzyro® 300 mg every 2w	27	0.21 (0.11 to 0.40)	-1.43	-1.78 to -1.07	<0.001	0.13	0.07 to 0.25	<0.001	Attack rates are model-based mean attacks per month, defined as 4 weeks. A Poisson regression model accounting for overdispersion was used. All P values (Wald test) are reported vs placebo. The difference in absolute number of attacks was estimated from a nonlinear function of the model parameters.	Banerji 2018 (7)
	Placebo	41	1.64 (1.34 to 2.00)								

*Clinical questions requested by DMC (2)

8.4 Results per PICO (clinical question)

Results referring to the 4 clinical questions requested by the Danish Medicines Council (2)

Table A4 Results referring to Clinical question				
Results per outcome:		**Absolute difference in effect**	**Relative difference in effect**	**Methods used for quantitative synthesis**

Table A4 Results referring to Clinical question								
		Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**
1)	**Attack free**	Longhurst 2017 (COMPACT) Craig 2019 (COMPACT OLE) Banerji 2018 (HELP)	N/A	N/A	N/A	N/A	N/A	N/A

From the data available from the publications, it is not possible to do an indirect comparison on number of patients who are 100% attack free and it is thus not possible to claim that there are differences in the attack free rates between treatment arms. In the HELP study, the proportion of attack-free patients is presented as a pre-specified exploratory endpoint and in the COMPACT study, the proportion of patients experiencing a 100% attack-reduction is reported. In addition, the definition of 100% attack-free and the study designs between COMPACT and HELP differ. The COMPACT study is a cross-over study running over two periods of 16 weeks each and the HELP study is a parallel group study running over 26 weeks.

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

Table A4 Results referring to Clinical question							
2) HRQoL	Lumry 2018 (COMPACT) Lumry 2021* (COMPACT OLE) Lumry 2020 (HELP)	N/A	N/A	N/A	N/A	N/A	N/A	Due to different HRQoL instruments used in COMPACT and HELP studies, it is not feasible to do an indirect comparison of HRQoL outcomes. In the COMPACT study EQ-5D-3L was included and in the HELP study EQ-5D-5L was included and in both studies general health status was evaluated using the VAS-scale. The study designs of COMPACT and HELP differ and with different HRQoL instruments an indirect comparison is therefore not applicable.

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

Table A4 Results referring to Clinical question								
3a) Attack frequency (absolute and relative reduction in monthly attacks)	Berinert® SC (COMPACT) vs Takhzyro® (HELP)	Berinert® SC 60 IU/kg 3.29 Takhzyro® 300 mg 2w 1.71	2.65-3.98 1.33-2.09	N/A	Berinert® SC 60 IU/kg 0.12 Takhzyro® 300 mg 2w 0.13	0.07-0.20 0.07-0.24	N/A	From indirect comparison Fridman 2020 (ISPOR Poster COMPACT vs HELP) Because the respective clinical trials differed in design, individual patient data from COMPACT (on Berinert® SC 60 IU/kg) were reanalyzed using a generalized estimating equation model for Poisson multiple regression in the HELP trial. For the COMPACT trial, the least squares mean difference was estimated with 95% confidence intervals with the use of a mixed-model accounting for the within patient correlation. Following Bucher's method, they indirectly compared attack reduction outcomes (mean number of monthly HAE attacks over placebo) between the two treatments.

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

Table A4 Results referring to Clinical question

	[redacted]				
3b) Attack frequency (average number of attacks per year	[redacted]				

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

Table A4 Results referring to Clinical question								
4) Side effects (withdrawals due to adverse events)	Longhurst 2017 (COMPACT) Li 2018 (COMPACT) Craig 2019 (COMPACT OLE) Banerji 2018 (HELP)	Berinert® SC = 2 Takhzyro® = 0	N/A	N/A	2	N/A	N/A	COMPACT: Three adverse events led to trial discontinuation: pulmonary embolism in a patient who received placebo, urticaria in a patient who received Berinert® SC 60 IU/kg, and an increase in liver aminotransferase levels in a patient who received Berinert® SC 60 IU/kg (both Berinert® SC 60 IU/kg not related to the study drug). HELP: None of the patients treated with Takhzyro® 300 mg q2w withdrew from the study because of adverse events. Two patients in the placebo group withdrew from the study due to treatment-emergent adverse events of tension headache and hereditary angioedema attack (related), which were of moderate severity. Overall, there are very few withdrawals due to adverse events in the studies and a significant difference is not expected. The general safety profile is considered good. From the data available from the publications, it is not possible to do an indirect comparison of withdrawals due to adverse events. The study designs and definitions of adverse events of COMPACT and HELP differ, and it is thus not possible to claim that there are differences in the tolerability of the different products.

*Additional finding not identified in the initial search since it was published on Feb 15, 2021 and the literature search was performed on Jan 22, 2021.

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

Table A5 Included publications (full text reviews) from literature search n=9 (among included title/abstracts)

No	Reference	Comment
1	Longhurst H et al. 2017 (4)	COMPACT RCT Trial
2	Craig T et al. 2019 (10)	COMPACT OLE Trial
3	Li HH et al. 2018 (14)	COMPACT Safety Trial
4	Lumry et al. 2018 (15)	COMPACT HRQoL
5	Banerji et al., 2018 (7)	HELP RCT Trial
6	Riedl et al., 2020 (16)	HELP Subanalysis
7	Lumry et al., 2020 (17)	HELP HRQoL
8	Fridman M et al. 2020 (8)	ISPOR Poster on indirect comparison between Berinert® SC 60 IU/kg and Takhzyro®
9	Riedl et al., 2017 (18)	Open-label extension trial of HELP

Table A6 Included and excluded publications from literature search (n=9) (among included full text reviews), and additional findings (n=2) outside literature search

Author	Title	Reference	Comment	Decision
From literature search (n=9)				
Craig T et al. 2019 (10)	Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks	J Allergy Clin Immunol Pract. 2019 Feb 15. pii: S2213-2198(19)30163-1	Open label, but outcome and safety data relevant. P, I relevant.	**Included**

Author	Title	Reference	Comment	Decision
Li HH et al. 2018 (14)	Subcutaneous C1-esterase inhibitor to prevent hereditary angioedema attacks: Safety findings from the COMPACT trial	Allergy Asthma Proc. 2018 Sep 14;39(5):365-370	RCT. P, I, O relevant.	**Included**
Longhurst H et al. 2017 (4)	Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor	N Engl J Med. 2017 Mar 23;376(12):1131-1140	RCT. P, I, O relevant	**Included**
Lumry WR et al. 2018 (15)	Health-Related Quality of Life with Subcutaneous C1- Inhibitor for Prevention of Attacks of Hereditary Angioedema	J Allergy Clin Immunol Pract. 2018 Sep - Oct;6(5):1733-1741.e3	RCT. P, I relevant, O – relevant QoL instrument but not correct according to what's specified in Medicines Council protocol	**Included**
Banerji et al., 2018 (7)	Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks A Randomized Clinical Trial	JAMA. 2018;320(20)	RCT. P, C, O relevant	**Included**
Lumry et al., 2020 (17)	Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study	Allergy. 2020 Nov 30.	RCT. P, C relevant, O – relevant QoL instrument	**Included**
Riedl et al., 2020 (16)	Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks	Allergy. 2020 Nov	RCT. P, C, O relevant	**Included**

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

Author	Title	Reference	Comment	Decision
Fridman M et al. 2020 (8)	Indirect comparison between human C1-inhibitor (C1-INH) subcutaneous treatment and lanadelumab for routine prevention of hereditary angioedema (HAE) attacks	Presented at the ISPOR US annual meeting. May 18–20, 2020. Poster Number: PRO65	P, I, C, O relevant, indirect comparison	**Included**
Riedl et al., 2017 (18)	An open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention of attacks in hereditary angioedema: design of the HELP study extension	Clin Transl Allergy (2017) 7:36	Open label extension trial of HELP – only a study protocol on a phase 1b trial. P, C, O relevant	**Discarded**
Outside literature search (n=2)				
[redacted]	[redacted]	[redacted]	[redacted]	**Included**
[redacted]	[redacted]	[redacted]	[redacted]	**Included**

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

Berinert® SC 2000/3000 IU

Cost comparison between Berinert® SC and Takhzyro® 300 mg in Denmark

Stockholm, Sweden

May 18, 2021

CSL Behring

Summary

Hereditary Angioedema (HAE) is a rare, inherited disease characterized by unpredictable and recurrent attacks of edema.

The exact occurrence of HAE is unknown, but it is estimated that HAE affects approximately 1 in 10,000 to 50,000 people worldwide. In Denmark, 120 patients with HAE are registered at the National Competence Centre for HAE at Odense Universitetshospital (OUH), but there are probably more patients affected by the disease.

International guidelines recommend that all HAE attacks shall be treated on-demand. Consensus treatment guidelines state that long-term prophylaxis should be individualized and considered in all severe, symptomatic HAE-patients.

Currently there are C1-esterase inhibitors (C1-INH), administered intravenously (IV) (Cinryze® IV) and subcutaneously (SC) (Berinert® SC), and a recombinant fully human IgG1 monoclonal antibody inhibitor, administered subcutaneously (SC) (Takhzyro® SC 300 mg) available on the Danish market for prophylactic treatment.

Hereditary Angioedema remains a serious clinical condition with a high, unmet medical need for better prophylactic treatment. The purpose of this report and cost and budget impact analysis is to illustrate the financial impact of Berinert® SC. Despite the availability of prophylactic treatments, there is a medical need for additional prophylactic treatment in patients that do not have an effect or cannot use available treatments because of safety and tolerability issues. In addition, there are patient groups in which some of the available treatments are not indicated, e.g., Takhzyro® for pregnant and lactating women.

A cost analysis was conducted comparing long-term prophylactic treatment with Berinert® SC versus Takhzyro®, using Danish unit costs and resources.

The cost inputs to the analysis were categorized as medicine costs, hospital costs and patient costs and was conducted from a restricted societal perspective in Denmark. Annual attack frequency reduction was applied to the cost analysis as a clinical input and was assumed similar in both treatment arms.

Differences in costs between treatment arms were related to the differences in medicine costs and patient costs for treatment administration. All other costs (e.g., for on-demand treatment and hospital costs for treating HAE attacks) remained the same in both treatment arms. Follow-up costs and costs for drug prescriptions were not included in the analysis since there was no difference between treatment arms.

The base case results suggest that treatment with Berinert® SC 60 IU/kg is 2,570,000 DKK more costly per patient per year in average, compared to Takhzyro® 300 mg. The difference in medicine costs is 2,567,000 DKK higher and patient costs for drug administration 4,366 DKK higher for Berinert® SC compared to Takhzyro® 300 mg. Other costs (e.g., hospital and patient costs for HAE treatment and on-demand medicine costs) are similar in both treatment arms.

A lower dose for Berinert® SC of 40 IU/kg depending on patient body weight are [redacted] and recommended in Spain. The information about the 40 IU/kg dose has also been added to section 5.1 in the SmPC, and the Danish SmPC has recently been updated (18). In comparison to Berinert® SC of 60 IU/kg, treatment with Berinert® SC 40 IU/kg is only 900,000 DKK more costly compared to Takhzyro® 300 mg.

The model is sensitive to price, dose of Berinert® SC and dose intervals of Takhzyro® 300 mg. [redacted]

[redacted]

The total patient population subject for prophylactic treatment of HAE in Denmark (i.e., patients who suffer from severe and high/ultra-high attack rates) is estimated to be 31-36 patients from year 1 to year 5. Most of these patients are currently receiving Takhzyro® 300 mg (i.e., 27-31 from year 1 to year 5). If Berinert® SC is recommended in Denmark, the total patient population receiving Berinert® SC is expected to increase from 1 (current patient who receive Berinert® SC today when Berinert® SC is not recommended as standard treatment in Denmark) to 5 at year 5 (if Berinert® SC gets recommended as standard treatment in Denmark).

As a low-volume, subcutaneously administered C1-INH replacement therapy, Berinert® SC represents a major advance in the prophylactic treatment of HAE attacks with its efficacy, safety, and route of administration. There is a medical need for additional prophylactic treatment in patients that do not have an effect or cannot use available treatments because of safety and tolerability issues and there are patient groups in which Takhzyro® is not indicated, e.g., for pregnant and lactating women. In addition, limitations of existing intravenously (IV) administered C1-INH prophylaxis include the frequency of breakthrough attacks and the burden of venous access.

Berinert® SC is most appreciated for its physiological mode of action and long history of safe use, allowing use in patients with comorbidities and for HAE patients intending to conceive or already pregnant.

Table of contents

Summary 2
Tables & Figures 6
Confidentiality 8
Abbreviations 8
1. Introduction 8
1.1 Hereditary Angioedema 9
1.2 Diagnosis 9
1.3 Treatment recommendations 9
1.3.1 Prophylactic treatment 10
1.3.2 Unmet need 12
1.4. Berinert® 12
1.4.1 Berinert® 2000/3000 IU SC 13
Cost analysis 14
2.1 Patient population 15
2.2 Intervention 15
2.3 Comparator(s) 16
2.3.1 Dose intervals for Takhzyro® 16
2.3.2 Other treatments 17
2.4 Reduction in HAE attacks 17
2.4.1. HAE attack rate used in model 18
2.4.2. COMPACT study 18
2.4.3. COMPACT Ole 19
2.4.3. HELP study 19
2.4.5. Indirect comparison 19
2.4.6. Conclusion on clinical outcomes 20
2.4.7. Clinical inputs to the model 20
2.5 Cost perspective 21
2.6 Time horizon 21
2.7 Model assumptions 21
2.7.1 Costs not included in the analysis 21
2.8 Resource use and unit cost 22
2.8.1 Medicine costs 22
2.8.2 Hospital costs 23
2.8.3 Patient costs 24
2.9 Results 25

2.10 Sensitivity analysis 26
3. Budget impact 28
3.1 Annual treatment costs in budget impact model 28
4. Discussion 31
4.1 Relevance of the analysis 32
4.2 Model structure 32
4.3 Cost data 32
5 Conclusion 33
References 34

Table 1 Lægemidlets oplysninger (in Danish)

Lægemidlets oplysninger	
Handelsnavn	Berinert® SC
Generisk navn	C1-esterase-inhibitor (human)
Firma	CSL Behring AB
ATC-kode	B06AC01
Virkningsmekanisme	Berinert® SC består af oprenset og koncentreret C1-esterase-inhibitor fra humant plasma. Administrationen af Berinert® erstatter manglende eller dysfunktionelt C1-esterase-inhibitor hos patienten, hvorved genereringen af bradykinin begrænses.
Administration/dosis	Berinert® SC er beregnet til subkutan administration. Den anbefalede dosis er 60 IU/kg, to gange om ugen (hver 3.-4. dag).[1]
Indikation	Berinert® SC til subkutan injektion er indiceret til profylakse af tilbagevendende anfald af hereditært angioødem (HAE) hos unge og voksne patienter med mangel på C1-esterase-inhibitor.[2]

Source: Danish Medicines Council Protocol on Berinert® SC, Jan 2021 (1)

Table 2 Cost analysis in PICO format

Cost analysis in PICO format	
Population	Children ≥ 12 years and adults with hereditary angioedema type I or II* and who suffer from high/ultrahigh attack frequency of ≥ 40 attacks annually if left untreated**

[1] 40 IU/kg body weight twice weekly has also been used in the clinical trial COMPACT with similar efficacy results as with 60 IU/kg. The information about the 40 IU/kg dose has also been added to the new recently updated version of the Danish SmPC (see Section 5.1 in SmPC). [redacted]

[2] The target patient population in this report is for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older who suffer from high/ultrahigh attack frequency and/or in patients who do not tolerate existing treatment.

Intervention	Berinert® subcutaneous administration in 60 international units per kilogram twice weekly*[1]
Comparator	Prophylactic treatment with subcutaneous administered human IgG1 monoclonal antibody inhibitor, Takhzyro® 300 mg every 2nd week in adults*
Outcomes (in the cost analysis)	Differences in medicine and administration costs and similar hereditary angioedema attack reduction in both treatment arms***

* Danish Medicines Council Protocol on Berinert® SC, Jan 2021 (1)** Also an alternative treatment in patients who do not tolerate existing treatment; ***Fridman et al., 2020 and [redacted][3] (2, [redacted]) [3]

Tables & Figures

Table 1 Lægemidlets oplysninger (in Danish) 5
Table 2 Cost analysis in PICO format 5
Table 3 Distribution of patients receiving on-demand treatment 10
Table 4 No. of patients receiving prophylactic treatment today (year 1, if Berinert® SC 2000/3000 IU is recommended) 12
Table 5 Patient weight in the model 15
Table 6 Annual reduction of attacks with prophylactic C1-INH treatments (used in model) 20
Table 7 Unit costs and calculated costs for on-demand treatment 23
Table 8 Medicine resource utilizations for intervention, comparator, and on-demand medicine 23
Table 9 Hospital unit costs for intervention and comparator medicine 24
Table 10 Hospital resource utilizations for intervention and comparator medicine 24
Table 11 Patient unit costs for intervention and comparator medicine 24
Table 12 Patient resource utilizations for intervention and comparator medicine 24
Table 13 Base case results on Berinert® SC 60 IU/kg in average per patient per year and per patient in 5 years (in DKK, discounted) 25
Table 14 Scenario analysis results on Berinert® SC 40 IU/kg in average per patient per year and per patient in 5 years (in DKK, discounted) 25
Table 15 One-way sensitivity analysis 27
[redacted] 27
Table 17 Number of patients per year 29
Table 18 Base case budget impact results (undiscounted, excl patient costs, in DKK) 30
Table 19 Budget impact sensitivity analyses (undiscounted, excl patient costs, in DKK) 30
[redacted] .. 31

Figure 1 Tornado diagram with ±10% variation 26

[redacted]

Confidentiality

References, texts and footnotes that are confidential, unpublished and for internal use only have been [redacted] throughout this report.

In case of unclarity, please contact Stina Johansson or Helena Stensman, see contact information below:

Kontaktoplysninger	
Navn	Stina Johansson
Titel **Ansvarsområde** **Telefonnummer** **E-mail**	Market Access Manager, Nordics Market Access and Health Economics +46 (0)70 252 00 08 Stina.johansson@cslbehring.com
Navn	Helena Stensman
Titel **Ansvarsområde** **Telefonnummer** **E-mail**	Scientific Advisor, Nordics Medical +46 (0)736 56 74 08 Helena.stensman@cslbehring.com

Abbreviations

Abbreviation	**Definition**
C1-INH	C1-esterase inhibitor
DMC	Danish Medicines Council
DKK	Danish krone
HAE	Hereditary angioedema
IgG1	Immunoglobulin G1 Antibodies
ISR	Injection-site reactions
IU	International unit
IV	Intravenous
LTP	Long-term prophylaxis
MAH	Market Authority Holder
pdC1-INH	plasma derived C1-esterase inhibitor
PICO	Population Intervention Comparator Outcomes
PPP	Pharmacy Purchasing Price
RCT	Randomized controlled trial
SC	Subcutaneous
SmPC	Summary of product characteristics
VAT	Value added tax
WAO	World Allergy Organization

1. Introduction

Hereditary Angioedema (HAE) is a rare, inherited disease characterized by unpredictable and recurrent attacks of edema. The most dangerous swelling episodes are laryngeal attacks, and they are potentially life threatening. Because of the rarity of the disease, diagnosis is often delayed.

Although effective on-demand treatment is available on the Danish market, HAE remains a serious clinical condition with a high, unmet medical need for better prophylactic treatment in certain patient

groups. For instance, there is a medical need for additional prophylactic treatment in patients that do not have an effect or cannot use available treatments because of safety and tolerability issues, and in patient groups in which some of the available treatments are not indicated, e.g. Takhzyro® for pregnant and lactating women.

The purpose with this report and cost- and budget impact analysis is to illustrate the financial impact of giving access to the subcutaneously administered C1-esterase inhibitor (C1-INH) Berinert® SC to Danish patients with severe HAE (i.e., high/ultrahigh attack frequency of ≥ 40 attacks annually if left untreated, and/or in patients who do not tolerate existing treatment).

Patient groups with unmet medical need could have access to long-term prophylactic treatment with Berinert® subcutaneous (SC) administration. Berinert® 2000/3000 international units (IU) SC has demonstrated excellent efficacy, safety and preferred route of administration in large phase III clinical trials as well as proven safety profile from 40 years of use of C1-INH in the concerned patient group (4, 5).

1.1 Hereditary Angioedema

Hereditary Angioedema is a rare, inherited, autosomal, dominant disease caused by mutations in the gene coding for C1-INH. C1-INH is a serine protease inhibitor (serpin) that regulates activation of the complement, contact, and coagulation systems. Dysregulation of these systems due to C1-INH deficiency results in the uncontrolled production of vasoactive peptides (e.g. bradykinin) that promote inflammation through increased vascular permeability and excessive fluid accumulation in body tissues (6).

Clinically, HAE is characterized by unpredictable and recurrent attacks of edema affecting any part of the body. The attacks are localized, non-itchy swellings of the skin and mucosa associated with the absence of urticarial. The most common sites are hands, feet, face, or gastrointestinal tract and the attacks can be painful, disfiguring, disabling and sometimes fatal. Swellings of the mucous membrane of the larynx are rare but if left untreated it can lead to death by asphyxiation. The symptoms are temporary and usually lasting 2-5 days if left untreated. The potential life-threatening laryngeal attacks is the most serious concern in HAE patients (6).

Patients with HAE bear a significant burden of disease. The unpredictable nature and severity of HAE attacks routinely impact patients' quality of life (6).

1.2 Diagnosis

The diagnosis of HAE is confirmed by low complement component 4 (C4) antigen and absent or greatly reduced C1-INH antigen (protein) or C1-INH functional activity. Typical C1-INH functional activity in untreated HAE patients is between 5% and 30% of normal (6).

For most individuals, acute attacks begin to occur in the first or second decade of life (7). Because of the rarity of the disease, delay in diagnosis is common. Symptoms of HAE are often mistaken for those of other acute abdominal disorders and many patients have a history of unnecessary surgery (6).

The exact occurrence of HAE is unknown, but it is estimated that HAE affects approximately 1 in 10,000 to 50,000 people worldwide. Currently, 120 patients are assumed to suffer from HAE in Denmark (1).

1.3 Treatment recommendations

International guidelines recommend that all attacks shall be treated on-demand. It is recommended that either C1-INH intravenous (IV) (Berinert®/Cinryze®/Ruconest®) or Firazyr® subcutaneous (SC) is given to the patient (1).

For the medicine to have optimal effect, it should preferably be used at the earliest possible stage in the development of the attack. However, it will vary which on-demand treatment that benefits the patient the most. At the onset of attacks, the patient cannot assess for himself whether the attack develops to a mild, moderate or severe degree. The recommendation is for all patients to have their on-demand treatment medicine available at home for self-administration. The Danish Medicines Council estimates based on their clinical experts that around 85% of the HAE attacks require on-demand treatment (8).

In Denmark, the following treatments are approved for on-demand treatment (1):

- Firazyr® 30 mg by subcutaneous injection for adults
- Berinert® 20 IU/kg by slow intravenous injection
- Cinryze® 1000 IU by slow intravenous injection for adults
- Ruconest® 50 IU/kg or 4200 IU (weight > 84 kg) by slow intravenous injection for adults

According to CSL Behring's clinical experts at the hospital clinics and internally, the distribution of patients receiving on-demand treatment is approximately as follows:

Table 3 Distribution of patients receiving on-demand treatment

On-demand treatment (dose and administration)	Proportion (%)
Firazyr® (30 mg SC)	17
Berinert® (1500 IU IV)	75
Cinryze® (1000 IU IV)	0
Ruconest® IV	0
Firazyr® SC + Berinert® IV/Cinryze® IV	8
Total	**100%**

1.3.1 Prophylactic treatment

The treatment goals of routine prophylaxis are to minimize the number and severity of HAE attacks and reduce the burden of HAE symptoms in daily life (6).

The preventive treatment is implemented according to the applicable international guideline of the World Allergy Organization (WAO) and the European Academy Allergy and Clinical Immunology of 2017 (9). A recent update to the 2014 Canadian Hereditary Angioedema Guideline was published in 2019 (10), showing that there is a high and strong recommendation of subcutaneous C1-INH (Berinert® SC) or lanadelumab (Takhzyro®) to be used as first-line therapy for long-term prophylaxis in patients with HAE I and II. Although there have not been any head-to-head comparisons of long-term prophylactic agents, hence a consensus level of evidence for efficacy, the authors agreed that either Berinert® SC or Takhzyro® are appropriate as first-line long-term prophylaxis (LTP). For pregnant women and paediatric patients, pdC1-INH (plasma derived C1-INH) is the treatment of choice for LTP.

Consensus treatment guidelines state that long-term prophylaxis should be individualized and considered in all severe, symptomatic HAE-patients taking into consideration the activity of the disease, frequency of attacks, patient's quality of life, availability of healthcare resources, and failure to achieve adequate control by appropriate on-demand therapy. Since all these factors can vary over time, all patients should be evaluated for long-term prophylaxis at every visit, at least once a year (6).

[redacted]

Two C1-INH medicines that are currently used for prophylactic treatment in Denmark are Berinert® SC and Cinryze® IV. Cinryze® is administered intravenously and is most used at a fixed dose of 1500 IU every 3rd day (1), and Berinert® SC is administered subcutaneously every 3rd to 4th day (1).

The third prophylactic treatment that is currently used for prevention of HAE attacks in Denmark is Takhzyro® 300 mg (Takhzyro®), a human monoclonal antibody indicated for the routine prevention of recurrent seizures of HAE in patients ≥ 12 years of age. Takhzyro® is recommended as standard treatment by the Danish Medicines Council (DMC) in patients with a minimum of four seizures per month (i.e., similar high attack frequency as in patients expected for treatment with Berinert® SC). The recommended dose of Takhzyro® is 300 mg subcutaneously every 2 weeks (1). However, the Danish Medicines Council and the Market Authority Holder (MAH) of Takhzyro® Takeda have both assumed that a proportion of patients in Denmark could reduce their dose interval to every 4 weeks (11).

Takhzyro® has been recommended for prophylactic treatment in Denmark in patients who have frequent HAE attacks and who are seriously ill, and the drug has been studied in a randomized controlled trial, the HELP study, compared to placebo (12). In the HELP-study, only 4 patients had 1.4 or more seizures per week which makes the effect of Takhzyro® [redacted]

[redacted]

Berinert® C1-INH administered intravenously (IV) is only indicated for treatment and pre-procedure prevention of acute episodes and is not used for prophylactic treatment in HAE patients in Denmark. Berinert® IV is administered by patient weight, with a standard dose of 20 IU/kg. A patient of 75 kg is thus treated with 1 500 IU every 3rd day (1).

In Denmark, patients in need for a prophylactic treatment may also be treated with the following (1):

- Cyklokapron® (tablets containing tranexamic acid): This is primarily for children and for patients with milder HAE attacks.
- Danol® (capsules containing danazol): This is primarily used in adult men with many or severe attacks. HAE patients are rarely started on long-term treatment with Danol®® today. However, some HAE patients have been on long-term treatment with Danol® at low dose with good efficacy and few side effects and will therefore remain on this treatment.

Cyklokapron® and Danol® have not been included in the budget impact calculation of Berinert® SC since these treatments are assumed to be provided to a similarly low number of patients over time. This was also agreed by DMC in their previous assessment of Berinert® SC (8).

The Danish Medicine Council estimates that around 120 patients are currently suffering from HAE in Denmark and approximately 30-40 of these patients are severe cases with several HAE attacks who also currently receive prophylactic treatment in Denmark (1).

Most patients administer their on-demand and prophylactic treatment at home (1).

Number of patients who receive the different prophylactic treatments is presented below and has been estimated by CSL Behring with guidance from health care professionals from the national competence center in Denmark, Danish clinical experts, and internal clinical experts at the company (Table 4).

Table 4 No. of patients receiving prophylactic treatment today (year 1, if Berinert® SC 2000/3000 IU is recommended)

Prophylactic treatment	No. of patients	Comments
C1-INH IV	1	Cinryze® IV for prophylactic treatment, currently one patient on Cinryze® IV in Denmark
Cyklokapron®	7	[redacted]
Danol®	5	[redacted]
Berinert® SC 2000/3000 IU	3	[redacted]
Takhzyro® 300 mg	27	[redacted]
Total	**43 (when excl Danol® and Cyklokapron® in the Budget Impact analysis, then total n=31)**	

1.3.2 Unmet need

Despite the availability of prophylactic treatments, such as intravenously administered C1-INH therapy, oral attenuated androgens and monoclonal antibodies, there is a medical need for additional prophylactic treatment in patients that do not have an effect or cannot use available treatments because of safety and tolerability issues. In addition, there are patient groups in which some of the available treatments are not indicated, e.g. Takhzyro® for pregnant and lactating women. Since women are often having more frequent and severe attacks it is therefore of extra importance to have effective and safe treatments available for this patient group.

Limitations of intravenously (IV) administered C1-INH prophylaxis include the frequency of breakthrough attacks and the burden of venous access (13).

Moreover, real-world data suggest that a subset of patients with HAE requiring long-term prophylaxis with C1-INH IV continue to experience considerable disease and treatment burden (14).

Long-term use of attenuated androgens is associated with substantial safety and tolerability issues, and the effectiveness of androgens diminishes over time (7, 15-17).

As a low-volume, subcutaneously administered C1-INH replacement therapy, Berinert® SC represents a major advance in the prophylactic treatment of HAE attacks with its efficacy, safety, and route of administration. Berinert® SC is most appreciated for its physiological mode of action and long history of safe use, allowing use in patients with comorbidities and for HAE patients intending to conceive or already pregnant. Its subcutaneous formulation is also of major importance in patients with poor veins, repeated bacterial infections in their shunts or poor eyesight.

1.4. Berinert®

Berinert® is purified and concentrated human C1-esterase inhibitor (C1-INH) derived from human plasma. Administration of Berinert® to patients with C1-inhibitor deficiency replaces the missing or malfunctioning protein in patients. Treatment results are an increase of the plasma levels of C1-inhibitor and help to regulate all cascade systems involved in the production of bradykinin during attacks (6).

Berinert® targets the root cause of HAE by replacing the missing or dysfunctional C1-INH, while other HAE treatments may only target on step in the kallikrein-kinin cascade. Berinert® also restores the body's natural ability to regulate other physiological pathways such as those belonging to complement, coagulation and the fibrinolytic systems (6).

1.4.1 Berinert® 2000/3000 IU SC

Berinert® 2000 IU and 3000 IU SC contains 500 IU/ml C1-esterase inhibitor (lyophilized powder) after reconstitution with 4 ml or 6 ml water for injections. Berinert® SC is indicated for prevention of recurrent HAE attacks in adolescent and adult patients with C1-esterase inhibitor deficiency.

Berinert® in COMPACT trial

Berinert® SC has been studied in the clinical program COMPACT (5). COMPACT trial is an international, prospective, multicentre, randomized, double-blind, placebo-controlled, dose-ranging, phase 3 trial that evaluate the efficacy and safety of self-administered subcutaneous Berinert® SC in patients with type I or type II hereditary angioedema. Patients in the study were randomly assigned to one of four treatment sequences in a crossover design, each involving two 16-week treatment periods: either 40 IU or 60 IU of Berinert® SC per kilogram of body weight twice weekly followed by placebo, or vice versa. The primary efficacy end point was the number of attacks of angioedema. Both doses of Berinert® SC (40 IU and 60 IU), as compared with placebo, reduced the rate of attacks of hereditary angioedema (mean difference with 40 IU, –2.42 attacks per month; 95% confidence interval [CI], –3.38 to –1.46; and mean difference with 60 IU, –3.51 attacks per month; 95% CI, –4.21 to –2.81; P<0.001 for both comparisons).

Berinert® SC Usage

The pharmaceutical form of C1-INH Berinert® SC is a powder and solvent for solution for injection. C1-INH concentrate was first licensed in Germany in 1979, and its long-term efficacy and safety for treatment of HAE attacks is well established.

Berinert® SC is intended for self-administration by subcutaneous injection. The patient or caregiver should be trained on how to administer Berinert® as needed (5).

Out of 120 patients who are currently suffering from HAE in Denmark (1), around 30 patients are currently receiving prophylactic treatment. These patients are considered a target population subject for prophylactic treatment with Berinert® SC and its relevant comparator Takhzyro® SC 300 mg. In addition, Berinert® SC is also relevant in patients who do not tolerate existing prophylactic treatments, e.g., Takhzyro® is not indicated for pregnant women and Cinryze® IV is not well tolerated in patients with burden of venous access.

Similar efficacy for Berinert® SC 60 IU/kg and Berinert® SC 40 IU/kg

The recommended dose of Berinert® SC is 60 IU/kg body weight twice weekly (5). This is the recommended dose in the SmPC of Berinert® SC and stated by the DMC (1).

However, a dose of 40 IU/kg has been evaluated together with the 60 IU/kg dose in the clinical study program of COMPACT (5), and the Danish SmPC has recently been updated to also include the information about the 40 IU/kg dose (see section 5.1 in the SmPC) (18).

The primary efficacy endpoint in the COMPACT trial was the time-normalized number of HAE attacks, as reported by the investigator. The mean difference, as compared with placebo, was -2.42 attacks per month (95% CI, -3.38 to -1.46) with 40 IU/kg and -3.51 attacks per month (95% CI, -4.21 to -2.81) with 60 IU/kg (P<0.001 for both comparisons).

In the COMPACT OLE extension trial, for 40 IU/kg and 60 IU/kg, median annualized attack rates were 1.3 and 1.0, respectively, and median rescue medication use was 0.2 and 0.0 times per year, respectively (4).

[redacted]

In conclusion, there were similar efficacy for the higher 60 IU and lower 40 IU dose of Berinert® SC in attack rate reduction and the efficacy remained for a mean of 1.5 years.

Low dose of Berinert® SC in real practice

[redacted]

Moreover, a clinical protocol for the introduction of Berinert® SC in Spain, recommended a treatment regimen where the general starting dose of Berinert® SC is 2000 IU twice weekly and if patients respond satisfying to the treatment after 3 months follow-up, the dose interval increases from twice a week to every 4-5 days. This corresponds to around 30 IU/kg for a 70 kg patient[4].

Cost analysis

A cost analysis was conducted to identify the potential cost consequences of introducing Berinert® SC for prophylactic treatment of severe HAE on the Danish market. The analysis compares costs of C1-INH Berinert® SC to Takhzyro® SC 300 mg, using Danish unit costs, inputs from clinical experts and Danish resources. Takhzyro® SC 300 mg is already used in Denmark and has the same target population of severe HAE cases as Berinert® SC.

Unit costs were multiplied with identified resources and total costs were assessed and compared in severe HAE patients with high/ultra-high attack frequency of ≥40 attacks per year if left untreated.

[4] GEAB proposal for the start of subcutaneous C1-Inhibitor plasma concentrate (cpC1INH) (Berinert®) as long-term prophylaxis in HAE-C1-INH. GEAB is the Group of experts on HAE from the Spanish Allergology Society.

Costs were reported in Danish krone (DKK) discounted at 3,5% annually, following the DMC Guidelines from 2020 (i.e., still following the guideline before Jan 1, 2021, as agreed with DMC prior to commencing this work (22)). The cost analysis was conducted from a restricted societal perspective in Denmark, including both health care costs and potential costs for patient time and transportation.

The cost inputs to the analysis are categorized as medicine costs, hospital costs and patient costs (i.e., costs incurred by patients, e.g., production loss and transportation).

2.1 Patient population

The relevant patient population subject for treatment with Berinert® SC is children ≥12 years and adults diagnosed with HAE type I or type II with high/ultra-high attack frequency, i.e., who experience ≥40 attacks per year if left untreated, and/or in patients who do not tolerate existing treatment (1).

Consensus treatment guidelines state that long-term prophylaxis should be individualized and considered in all severe, symptomatic HAE-patients taking into consideration the activity of the disease, frequency of attacks, patient's quality of life, and failure to achieve adequate control by appropriate on-demand therapy (1).

The patient population in the cost analysis was retrieved from the Berinert® SC RCT COMPACT study (5). The study population consisted of patients 12 years of age or older and had a clinical and central laboratory diagnosis of type I or II HAE (functional C1 inhibitor activity of <50% and C4 antigen level below the normal level). All patients had had four or more attacks requiring immediate treatment or medical attention or causing clinically significant functional impairment over a 2-month period within 3 months before screening. The mean (±SD) number of attacks per month during the run-in period, normalized for the number of days that the patient received the corresponded drug or placebo, was 4.6±2.2 for the 40 IU treatment sequences and 4.0±2.0 for the 60 IU treatment sequences. For all patients who received Berinert® SC this corresponds to 39.2 (rounded up to 40) attacks per year and covers approximately 30 patients with severe HAE in Denmark.

The patient start age in the model is 39.6 years (rounded up to 40 years) (5).

2.2 Intervention

The intervention is Berinert® (C1-INH) 2000/3000 IU SC, in a dosage of 60 IU/kg 3-4 days a week (twice weekly) (1, 18).

Berinert® SC is administered based on patient weight. The average weight in the model is 73.12 kg, which result in a total IU per patient weight of 4,387 IU per administration.

The average weight in the model is calculated based on the weight of the general population females and males in Denmark. Males have a general weight of 83.5 kg and females 68 kg (23). The gender distribution between males and females were further retrieved from the patient characteristics in the Berinert® SC RCT COMPACT study, where 67% of the study population were females (5). A gender distribution of 50% has been tested in a sensitivity analysis, based on assumptions from Danish clinical experts.

Table 5 Patient weight in the model

	Males	**Females**	**Source**
Gender distribution (%)	33%	67%	Longhurst 2017 (COMPACT) (5)
Weight distribution (kg)	83.5	68	Statens Institut for Folkesundhed 2019 (23)
Average weight (kg)			**73.12**

In addition, a lower dose of 40 IU/kg has also been tested in a sensitivity and scenario analysis. A dose of 40 IU/kg is evaluated in the clinical study programme COMPACT with similar favourable outcomes and safety data as for the higher dose of 60 IU/kg. The information about the 40 IU/kg dose has also been added to section 5.1 in the recently updated Danish SmPC [redacted] and recommended in Spain.

The clinical study programme COMPACT also showed that around 50% of the patients in the phase III study and the long-term follow-up study COMPACT OLE received a dose of 40 IU/kg body weight twice weekly (24).

[redacted]

Moreover, clinical recommendation for the introduction of Berinert® SC at Spanish hospital clinics have published dose recommendations that correspond to around 40 IU/kg in a Spanish clinical recommendation report [6]. The Spanish clinical recommendation has been retrieved from a society congress publication where Dr. Caballero and his colleagues have investigated 10 patients that were treated with HAE-C1-INH (6/4 women / men): 9 with cpC1INH SC (doses between 1500U / 3 days and 1500U 2 times / week), of which 7 improved (6: 100%; 1: 85%), 2 did not improve; one patient combined cpC1INH IV and SC with 80% improvement. Based on this investigation, the GAB group of experts on HAE from the Spanish Allergology Society, proposed a treatment regimen, with a general starting dose of Berinert® SC 2000 IU twice a week, which corresponds to 40 IU/kg body weight in a 70 kg patient. If the patients receive a satisfying response after 3 months, the interval between doses are decreased to every 4-5 days, which corresponds to around 30 IU/kg for a 70 kg patient. If the patients receive an unsatisfying response, the interval between doses are increased to every 3rd day.

2.3 Comparator(s)

The relevant comparator(s) to C1-INH Berinert® SC is Takhzyro® (Takhzyro®) (1). Takhzyro® is a fully human monoclonal antibody that binds and inhibits active plasma kallikrein, thereby preventing the cleavage of high-molecular-weight kininogen and the generation of bradykinin.

2.3.1 Dose intervals for Takhzyro®

The dosage for Takhzyro® is not dependent on patient weight where adults with many HAE attacks are recommended to receive 300 mg every 2 weeks. In patients who are stable and attack free on

treatment, a dose reduction of 300 mg Takhzyro® every 4 weeks may be considered, especially in patients with low weight (1, 25).

The Danish Medicines Council published an assessment protocol of Takhzyro® in December 2019 (11). Based on the SmPC of Takhzyro® where dose reduction may be considered in patients who are stable, seizure-free, and especially in patients with low weight, the DMC might expect a dose reduction in a proportion of Danish Takhzyro® patients. Not all patients expect to be treated at full dose every 2 weeks. However, due to limited knowledge of the real-world usage of Takhzyro®, the DMC concluded that it is not possible to assess the proportion of patients who will reduce the dosing frequency to every 4 weeks and also how many patients who will benefit adequately from treatment every 4 weeks.

[redacted]

[redacted]

In the model, the patient start age is 40 years and all suffer from high/ultra-high attack frequency. This is a combination of the baseline mean age in the Berinert® SC RCT trial COMPACT (5) and the Takhzyro® RCT trial HELP (12). The base case administration of Takhzyro® in the model is 300 mg every 2 weeks. The unlikely dose interval for Takhzyro® of 300 mg every 4 weeks has been tested in a sensitivity analysis.

[redacted]

2.3.2 Other treatments

According to the Danish Medicine Council, Cyklokapron® and Danol® (danazol on license) are also available for prophylactic treatment in HAE patients (1).

Cyklokapron® is mainly used among children and for milder HAE attacks and are therefore not a relevant comparator to the target population for Berinert® SC. Danol® is primarily used for adult men. Patients are very rarely started on long-term treatment with Danol®, and there are only very few that remain on this treatment today. Danol® is therefore also not a relevant comparator to Berinert® SC.

2.4 Reduction in HAE attacks

The reduction in HAE attacks were assumed similar for both Berinert® SC and Takhzyro® 300 mg.

Data from two randomized clinical trials (RCTs), the COMPACT study (5) and the HELP study (12), demonstrate superior efficacy of C1-INH SC Berinert® and Takhzyro® 300 mg over placebo in reduction of HAE attacks (1).

The results have been further analysed in [redacted] indirect comparisons. The first one is a published poster on Berinert® SC 60 IU/kg vs Takhzyro® (2), [redacted]

[redacted]

The absolute reduction in monthly attacks for patients treated with Berinert® SC 60 IU/kg compared with placebo in COMPACT was 3.29 (CI 2.65–3.98) attacks per month compared to an absolute reduction of 1.71 (CI 1.33–2.09) attacks per month for patients treated with Takhzyro® 300 mg every 2 weeks in HELP compared with placebo. Patients saw similar relative reductions in monthly attacks while using both Berinert® SC 60 IU/kg and Takhzyro® 300 mg every 2 weeks of 0.12 and 0.13 respectively (2).

[redacted]

[redacted]

2.4.1. HAE attack rate used in model

Based on the existing evidence on Berinert® SC and Takhzyro®, the reduction in HAE attacks were assumed similar for both treatment arms.

The model base case assumed similar attack rate reduction of 84% in both treatment arms. The attack rate of 84% was retrieved from previous data showing an 84% attack rate reduction for patients treated with Berinert® SC (26). The model was initially used in the previous application when Berinert® SC was compared to Cinryze® IV. For the simplicity of the model calculations, a similar attack rate reduction in the comparator arm Takhzyro® was used in the model base case.

2.4.2. COMPACT study

The COMPACT trial (5) was a randomized, double-blind, placebo-controlled, dose-ranging phase 3 study designed to evaluate the efficacy and safety of self-administered subcutaneous C1-inhibitor in patient with HAE type I or type II who had had four or more attacks in a consecutive 2-month period within 3 months before screening. 90 patients were randomly assigned in a 1:1:1:1 ratio to receive Berinert® SC at a dose of 40 IU/kg bw twice weekly during the first 16-week treatment period followed by placebo for the second 16-week treatment period or vice versa; or Berinert® SC at a dose of 60 IU/kg bw twice weekly followed by placebo or vice versa. Berinert® SC or placebo was administered by the patient twice weekly in a double-blind crossover manner during each treatment period.

The primary efficacy endpoint was the number of attacks and response rate was one of the secondary endpoints.

The results showed an attack reduction of 95 % (median) with 60 IU/kg bw 2 times weekly and 89% (median) with 40 IU/kg bw twice weekly.

2.4.3. COMPACT Ole

The COMPACT Ole trial (4) is an open-label, randomized, parallel-arm extension of the COMPACT trial designed to assess the long-term safety, occurrence of angioedema attacks, and use of rescue medication with C1-inhibitor. Patients who completed the placebo-controlled COMPACT trial and study treatment-naïve patients who had a history of experiencing at least 4 attacks within 2 consecutive months before enrolment into the COMPACT program were eligible. Patients were randomly assigned to receive 40 IU or 60 IU/kg bw twice of Berinert® SC twice per week for at least 52 weeks.

The primary objective was to determine the long-term safety of Berinert® SC. Secondary endpoints assessed additional safety endpoints as well as efficacy endpoints including the percentage of patients with a time-normalized attack frequency of less than 1 attack per 4-week period and the percentage of responders.

The results showed that there were a low incidence of AEs and 83 % of the patients in the 60 IU/kg group were attack free during month 25-30 of treatment. Furthermore, 87% did not use any rescue medication in the 60 IU/kg group. The corresponding results in the group receiving 40 IU/kg were 76.2% of the patients being completely attack-free and 76.2% not using any rescue medication.

2.4.3. HELP study

The HELP study (12) was a randomized, double-blind, parallel-group, placebo-controlled phase 3 trial conducted at 41 different sites. The objective of the Hereditary Angioedema Long-term Prophylaxis (HELP) clinical trial was to determine the efficacy of Takhzyro® compared with placebo for preventing hereditary angioedema attacks. Patients were 12 years or older at screening with a confirmed diagnosis of hereditary angioedema type I or II. Patients underwent a 4-week run-in period (preceded by a ≥2-week washout of any long-term prophylactic therapy if applicable) to determine their baseline attack rate. Patients with 1 or more investigator-confirmed attack per 4 weeks were eligible for enrolment. Eligible patients were randomized 2:1 to receive subcutaneously injected Takhzyro® or placebo. Patients randomized to receive Takhzyro® were assigned in a 1:1:1 ratio to 1 of 3 Takhzyro® dose regimens: 150 mg every 4 weeks, 300 mg every 4 weeks, or 300 mg every 2 weeks.

The primary efficacy end point was the number of attacks during the 26-week treatment period. Secondary end points included the number of attacks requiring acute treatment during the 26-week treatment period, number of moderate or severe attacks during the 26-week treatment period, and number of attacks from days 14 through 182.

The results showed that the mean number of attacks per month from days 0 through 182 was 1.97 (95% CI, 1.64-2.36) in the placebo group compared with 0.48 (95% CI,0.31-0.73) in the 150-mg every-4-week group, 0.53 (95%CI, 0.36-0.77) in the 300-mg every-4-week group, and 0.26 (95% CI,0.14-0.46) in the 300-mg every-2-week group.

2.4.5. Indirect comparison

An indirect comparison was conducted for Berinert® SC 60 IU/kg and Takhzyro® using the Phase III clinical trials COMPACT and HELP (5, 12). Because the respective clinical trials differed in design, individual patient data from COMPACT were reanalysed using a generalized estimating equation model for Poisson multiple regression in the HELP trial. The absolute reduction in monthly attacks for patients treated with Berinert® SC 60 IU/kg compared with placebo in COMPACT was 3.29 attacks per month compared to an absolute reduction of 1.71 attacks per month for patients treated with Takhzyro® 300 mg every 2 weeks in HELP compared with placebo. Patients saw similar relative reductions in monthly attacks while using both Berinert® SC 60 IU/kg and Takhzyro® 300 mg every 2 weeks of 0.12 and 0.13

respectively (2). [redacted]

[redacted]

2.4.6. Conclusion on clinical outcomes

There was a similar attack rate reduction (absolute and relative) of Berinert® SC in the COMPACT trial vs Takhzyro® 300 mg in the HELP trial.

In the published indirect comparison from the ISPOR conference 2020, results from Fridman and colleagues demonstrated similar efficacy of Berinert® SC 60 IU/kg versus Takhzyro® with regards to the pre-defined clinical outcome relative reductions in monthly attacks (2). [redacted]

[redacted]

2.4.7. Clinical inputs to the model

Based on the clinical information above, an assumption was made in the model that patients receiving Berinert® SC have similar attack frequency as patients receiving Takhzyro® 300 mg. Moreover, the attack rate frequency expects to last throughout the model time horizon of 5 years, based on sustained long-term outcomes from the COMPACT OLE trial (4).

All patients in the model assume to suffer from 40 attacks annually if left untreated (5). This corresponds to the patient characteristics in the COMPACT trial if left untreated and refers to the relevant patient population for treatment with prophylactic C1-INH in Denmark. In addition, during the run-in period in the HELP trial on Takhzyro®, the mean attack rate ranged from 3.2 to 4.0 attacks per month across the 4 treatment groups (12).

In the model, patients treated with both Berinert® SC and Takhzyro® 300 mg will have an 84% attack reduction annually. This proportion is the estimated attack rate reduction for Berinert® SC vs placebo in the meta-analysis performed by Bernstein and colleagues (26). The annual proportion of attack rate reductions will result in 6.40 attacks in total annually for Berinert® SC and Takhzyro® 300 mg.

Around 85% of the attacks are assumed to require rescue medication (on-demand treatment), based on clinical expert comments and previous DMC estimations (8). Five percent of the attacks that require rescue medication are severe attacks on neck/head with hospitalization, 2% require doctor visits and 10% outpatient visits. All remaining attacks, irrespective of its severity, are self-treated with recue medications at home.

Proportion and number of attacks that are used in the model base case are presented in Table 6 below.

Table 6 Annual reduction of attacks with prophylactic C1-INH treatments (used in model)

	C1-INH SC (Berinert®)	**Takhzyro® 300 mg**
Annual reduction of attacks	84.0%	84.0%

No. of attacks annually	6.40	6.40
No. of these attacks that are severe (on neck/head)	0.27 (5%)	0.27 (5%)
No. of these attacks that require doctor visit	0.11 (2%)	0.11 (2%)
No. of these attacks that require outpatient visit	0.54 (10%)	0.54 (10%)

2.5 Cost perspective

The cost analysis was conducted from a restricted societal perspective. This means that all relevant treatment-related costs are included, irrespective of who carries the costs.

2.6 Time horizon

The time horizon is presented per year and for 5 years, discounted 3.5% annually (22).

The annual cost (per patient per year) reflects the value that is applied to the calculation of total budget impact.

The 5-year time horizon reflects the recommendation from the Danish Medicine Council that prophylactic treatment with C1-INH should be given for several years but not for a lifetime (1). In addition, even if laryngeal attacks might be fatal, the fatal outcomes are considered minor and the mortality among these patients when they are treated are considered similar as the general population.

2.7 Model assumptions

The main assumption in the cost analysis is no difference in HAE attack reductions between Berinert® SC and Takhzyro® 300 mg. The similar attack rate reductions are further assumed constant over the 5-year time horizon.

The model also assumes that most of the patients are treated for their HAE attacks with on-demand treatment in their homes, irrespective of the severity of the attacks. There are only a few patients that are assumed to receive treatment at the hospital (doctor visit or outpatient visit with a nurse).

2.7.1 Costs not included in the analysis

Some cost parameters were not included in the cost-and budget impact analysis.

Adverse events

Adverse events were not included in the cost analysis. The current treatment with Berinert® SC is well tolerated and patients rarely experience side effects. If side effects occur, it is most often reactions at the injection site (1).

In the COMPACT trial, adverse events were reported by similar proportions of patients in the Berinert® SC groups and the placebo groups. The majority of reported adverse events were mild in 95%, 76% and 83% of the patients in the 40 IU/kg, 60 IU/kg and the combined placebo groups respectively. Most reported adverse events were injection-site reactions (ISRs). ISRs were reported in 28%, 35%, and 24% of patients treated with 40 IU/kg, 60 IU/kg and combined placebo groups, respectively (5). The long-term safety was further supported in the COMPACT OLE study with similar adverse event profiles reported in both treatment arms of the study. The most frequently observed adverse event were injection-site reactions (4).

In addition, In the HELP study, none of the patients treated with Takhzyro® 300 mg every 2 weeks withdrew from the study because of adverse events. The most common adverse events were injection-site reactions reported by 51.9% and 29.3% of the patients in the Takhzyro® 300 mg every 2 weeks and placebo groups respectively (12).

In conclusion, it is thus not possible to claim that there are differences in the tolerability of the different products. A significant difference is not expected, and the general safety profile is good.

Adverse events were therefore not considered relevant in the cost analysis of Berinert® SC.

Mortality

Mortality was not included in the cost analysis. As mentioned earlier, HAE can potentially be a life-threatening disease if airway obstruction is caused by laryngeal edema. After having current treatment options available to the patients, mortality has dropped dramatically, and today there are nearly no deaths in Denmark because of HAE (1).

Mortality is therefore not considered relevant in the cost analysis of Berinert® SC. This has also been confirmed by the Danish Medicine Council (1).

Quality of life

Published literature have shown significant improvements in quality of life in patients included in the COMPACT trial compared to placebo (27). The improved quality of life continued during the follow-up study COMPACT OLE (28). Similar outcomes have been seen in the HELP trial where patients with HAE had significantly better HRQoL compared to placebo (29). From the data available from the publications, it is thus not possible to claim that there are differences in HRQoL of the different products. A significant difference is not expected, and the quality-of-life improvements in both treatment arms are considered similar.

2.8 Resource use and unit cost

The cost inputs to the analysis are categorized as medicine costs, hospital costs and patient costs.

Medicine costs consist of medicine costs for the intervention Berinert® SC and the comparator Takhzyro® 300 mg. Medicine costs also consist of medicine costs for on-demand treatment.

Hospital costs consist of nurse and physician time spent for treatment of HAE attacks at the hospital.

Patient costs consist of patient time spent for taking the treatment medicine at home, and travel time and time spent for treatment of HAE attacks at the hospital. Patient costs also consist of transportation costs to and from the hospital for all visits that require hospital visits.

2.8.1 Medicine costs

Medicine costs consist of medicine costs for the intervention Berinert® SC, medicine costs for the comparator Takhzyro® 300 mg and medicine costs for on-demand treatment with either Cinryze® IV, Berinert® IV, Firazyr® SC or Berinert®/Cinryze® IV + Firazyr® SC.

The recommended dose for the intervention medicine Berinert® SC is 60 IU/kg twice weekly (18) and the general weight in an HAE patient is 73.12 kg (Table 5). The total IU per patient weight is 4,387 IU and the number of administrations annually are 104. The price is calculated based on DKK per IU. The DKK per IU (in PPP, excl VAT) is 11.66 and similar to DKK per IU of C1-INH Berinert® IV 1500 IU (30). This will result in 51,151 DKK per administration and 5.33 million DKK per year in medicine costs per patient. [redacted]

The recommended dose for the comparator medicine Takhzyro® is 300 mg every 2 weeks (25) and is not based on patient weight. The price per package is 99 519 DKK (in PPP, excl VAT) (30). The DKK per mg is 331.73 and it costs 2.59 million DKK per year in medicine costs per patient.

The dose recommendations and proportions receiving the different on-demand treatments have already been presented in Table 3 above. The price per package, price per IU and total medicine cost per HAE attack is presented in Table 7 below. The total medicine cost per HAE attack is further weighted by the proportion who receive the different treatment options (from Table 3) and multiplied by number of attacks annually in each treatment arm (from Table 6).

Table 7 Unit costs and calculated costs for on-demand treatment

On-demand treatment Product	Price per package (30) (in DKK, PPP excl VAT)	Dose per administration	Cost per HAE attack (in DKK)
Firazyr® 30 mg SC	13 589	30 mg	19 569**
Berinert® 1500 IU IV	17 490	1500 IU	17 490*
Cinryze® 2X500 IU IV	11 599	1000 IU	11 599*
Firazyr® SC + Berinert® IV/Cinryze® IV	N/A	30 mg Firazyr® + 1500 IU Berinert®/1000 IU Cinryze®	28 134

N/A=Not applicable; *No. of administrations are 1 dose per HAE attack; ** 44% of the patients who take Firazyr® assumed to need two doses for optimal effect (31).

Medicine unit costs and resource utilizations for the intervention Berinert® SC and the comparator Takhzyro® 300 mg are presented below.

Table 8 Medicine resource utilizations for intervention, comparator, and on-demand medicine

Medicine cost parameter	Resource Utilization	Used in model (DKK per year)
Intervention: Berinert® SC 2000/3000 IU	60 IU/kg, 73.12 kg, twice a week	5.33 million
Comparator: Takhzyro® SC 300 mg	300 mg, every 2 weeks	2.59 million
On-demand treatment		
Firazyr® 30 mg SC	17%, Int&Comp 6.40 attacks/yr,	Intervention: 119 647 Comparator: 119 647
Berinert® 1500 IU IV	75% , Int&Comp 6.40 attacks/yr	
Firazyr® SC + Berinert® IV/Cinryze® IV	8%, Int&Comp 6.40 attacks/yr	

2.8.2 Hospital costs

Hospital costs consist of nurse and physician time spent for treatment of HAE attacks at the hospital.

According to the previous DMC protocol assessment of Berinert® SC (8), the DMC estimated that around 85% of the total HAE attacks require on-demand treatment, based on answers from their clinical experts. Among the 85% who require on-demand treatment, 2% require doctor visit at the hospital and 10% outpatient visit with a nurse at the primary care. Both doctor visit and outpatient visit with a nurse expects to take 1 hour each.

In addition, 5% of the HAE attacks are assumed to be severe and affecting neck and head and these attacks require hospitalization for 24 hours, according to DMC's clinical experts (8). This corresponds to one working day and night for a physician. The total costs for these visits do not differ between the treatment arms since total number of attacks are the same in the model.

The hourly wage for a nurse has been retrieved from the Danish KRL (Kommunernes og Regionernes Løndatakontor) and the gross annual salary was 451.68 DKK. People who work 100% work for 141.83 hours a month (22) so the hourly wage is 265,39 DKK. By including overhead costs, the hourly wage is multiplied by 2 (22). This makes the hourly wage used in the model 530.77 DKK. The hourly wage for a physician is 780.00 DKK and has been estimated by the DMC in their previous protocol assessment of Berinert® SC (8).

The hospital unit costs and resource utilizations for the intervention Berinert® SC and the comparator Takhzyro® are presented below.

Table 9 Hospital unit costs for intervention and comparator medicine

Hospital cost parameter	Unit cost (in DKK)
Physician time (hourly wage)	780
Nurse time (hourly wage)	531

Table 10 Hospital resource utilizations for intervention and comparator medicine

Hospital cost parameter	Resource Utilization
Physician time spent on doctor visit for HAE attack	1h/visit, 0.11 attacks/year
Nurse time spent on outpatient visit for HAE attack	1h/visit, 0.54 attacks/year
Physician time spent on treatment of very severe HAE attacks on neck/head	24 hours per visit, 0.27 attacks/year
Total hospital costs for HAE treatment	5 513 DKK/year

2.8.3 Patient costs

Patient costs consist of patient time spent for taking the treatment medicine at home and time spent for travel and treatment of HAE attacks at the hospital. Patient costs also consist of transportation costs to and from the hospital for all hospital visits.

Patient time spent for taking the treatment medicine at home is assumed 20 minutes for both intervention and comparator. Patient time for hospital visits for treatment of HAE attacks and severe HAE attacks on neck/head are similar in both treatment arms.

The estimations of patient time for hospital visits for treatment of HAE attacks are similar as the physician and nurse time for all the hospital visits estimated above (2.8.2 Hospital costs). However, 40 minutes are assumed for travel to and from the hospital and are added to the total patient time for each hospital visit. In addition, transportation costs are included for transportation to and from the hospital. The daily driving distance is assumed to be 14 km based on DMC Guideline from 2020 (22). The cost per km is 3.52 DKK, and retrieved from statens skattefri kørselsgodtgørelse (befordringsgodtgørelse) (22).

The hourly wage for the general population is 179 DKK and has been estimated by the DMC in their previous protocol assessment of Berinert® SC (8).

The patient unit costs and resource utilizations for the intervention Berinert® SC and the comparator Takhzyro® 300 mg are presented below.

Table 11 Patient unit costs for intervention and comparator medicine

Patient cost parameter	Unit cost (in DKK)
Patient time (hourly wage for the general population)	179
Costs for transportation	3.52

Table 12 Patient resource utilizations for intervention and comparator medicine

Patient cost parameter	Resource Utilization
Patient time spent on doctor visit for HAE attack	1h/visit (+40 min travel and 14 km distance), 0.11 attacks/year
Patient time spent on outpatient visit for HAE attack	1h/visit (+40 min travel and 14 km distance), 0.54 attacks/year
Patient time spent on treatment of very severe HAE attacks on neck/head at the hospital	24 hours per visit (+40 min travel and 14 km distance), 0.27 attacks/year
Transportation costs for hospital visits for treating HAE attacks	14 km distance per hospital visit
Total patient costs annually for HAE treatment	**1 930 DKK/year**

Patient time spent on medicine treatment (prophylactic treatment)	At home, Int Berinert® SC: 20 min 2 admin/week (104 admin per year)
	At home, Comp Takhzyro®: 20 min admin every two weeks (26 admin per year)
Total patient costs annually for prophylactic treatment	**Intervention Berinert® SC: 6 222 DKK/year**
	Comparator Takhzyro®: 1 551 DKK/year

2.9 Results

The main results from the cost analysis are presented in Table 13. The results are presented from a 5-year perspective, and in average per patient per year. The costs are 3.5% discounted and presented both from a restricted societal perspective (incl patient costs) and with patient costs excluded. All cost categories (i.e., medicine costs, hospital costs and patient costs) are presented separately.

In the model base case, the average total cost per patient per year is 2,570,000 DKK more costly with Berinert® SC 60 IU/kg compared to Takhzyro® 300 mg for prophylactic treatment of HAE in patients with high/ultra-high attack frequency (Table 13). With the lower dose of Berinert® SC 40 IU/kg, the average total cost per patient per year is only 900,000 DKK more costly with Berinert® SC 40 IU/kg compared to Takhzyro® 300 mg (

Table 14).

The main cost driver is medicine costs, where prophylactic medicine costs in the base case analysis with Berinert® SC 60 IU/kg cost in average 2,567,000 DKK more per patient compared to Takhzyro® 300 mg. There is no difference in costs for on-demand medicine and hospital treatment of HAE attacks. Patient cost is also higher for Berinert® SC compared to Takhzyro® 300 mg and is due to more frequent yearly administrations of Berinert® SC.

Table 13 Base case results on Berinert® SC 60 IU/kg in average per patient per year and per patient in 5 years (in DKK, discounted)

	Berinert® SC 60 IU/kg	Takhzyro® 300 mg	Difference
In average per patient per year			
Medicine costs	***5 097 387***	***2 530 139***	***2 567 248***
Prophylactic medicine costs	*4 985 563*	*2 418 315*	*2 567 248*
On-demand medicine costs	*111 824*	*111 824*	*0*
Hospital costs	***5 152***	***5 152***	***0***
HAE attacks	*5 152*	*5 152*	*0*
Patient costs	***7 620***	***3 254***	*4 366*
Total (incl patient costs)	**5 110 159**	**2 538 545**	**2 571 614**
Total (excl patient costs)	***5 102 540***	***2 535 291***	***2 567 248***
Total 5 years			
Medicine costs	***25 486 937***	***12 650 696***	***12 836 241***
Prophylactic medicine costs	*24 927 817*	*12 091 575*	*12 836 241*
On-demand medicine costs	*559 120*	*559 120*	*0*
Hospital costs	***25 761***	***25 761***	***0***
HAE attacks	*25 761*	*25 761*	*0*
Patient costs	***38 099***	***16 270***	*21 828*
Total (incl patient costs)	**25 550 797**	**12 692 727**	**12 858 069**
Total (excl patient costs)	***25 512 698***	***12 676 457***	***12 836 241***

Table 14 Scenario analysis results on Berinert® SC 40 IU/kg in average per patient per year and per patient in 5 years (in DKK, discounted)

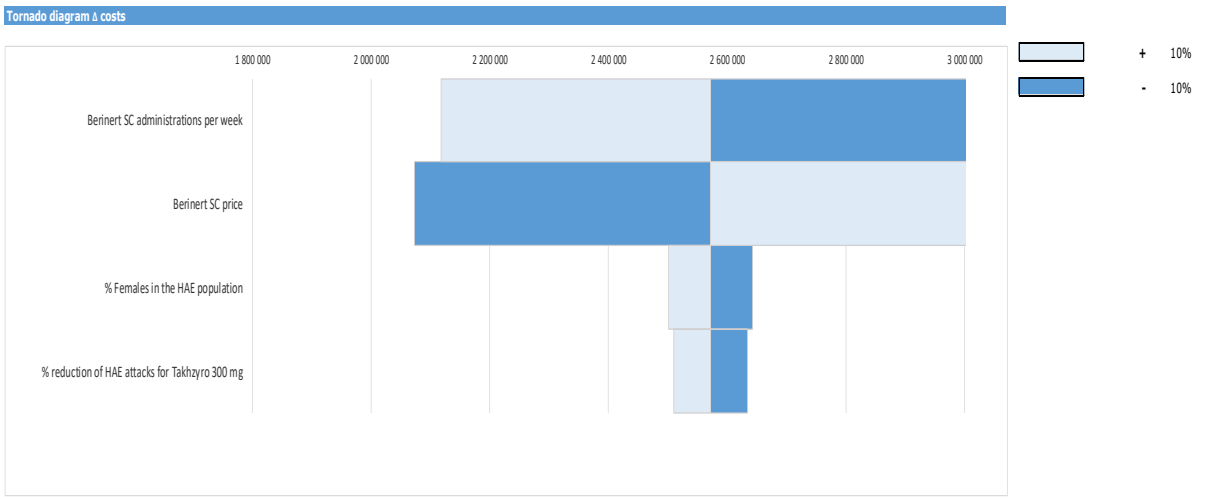
	Berinert® SC 40 IU/kg	Takhzyro® 300 mg	Difference
In average per patient per year			
Medicine costs	***3 435 533***	***2 530 139***	***905 394***
Prophylactic medicine costs	*3 323 709*	*2 418 315*	*905 394*

On-demand medicine costs	*111 824*	*111 824*	*0*
Hospital costs	***5 152***	***5 152***	***0***
HAE attacks	*5 152*	*5 152*	*0*
Patient costs	***7 620***	***3 254***	*4 366*
Total (incl patient costs)	**3 448 305**	**2 538 545**	**909 759**
Total (excl patient costs)	***3 440 685***	***2 535 291***	***905 394***
Total 5 years			
Medicine costs	***17 177 665***	***12 650 696***	***4 526 969***
Prophylactic medicine costs	*16 618 544*	*12 091 575*	*4 526 969*
On-demand medicine costs	*559 120*	*559 120*	*0*
Hospital costs	***25 761***	***25 761***	***0***
HAE attacks	*25 761*	*25 761*	*0*
Patient costs	***38 099***	***16 270***	*21 828*
Total (incl patient costs)	**17 241 525**	**12 692 727**	**4 548 797**
Total (excl patient costs)	***17 203 426***	***12 676 457***	***4 526 969***

2.10 Sensitivity analysis

The uncertainty in the underlying cost parameters was assessed using one-way sensitivity analysis. Some cost parameters were varied independently over an interval of ±10-20%. The parameters that were varied were Berinert® SC price (DKK/IU), number of administrations per week with Berinert® SC, percentage reduction in HAE attacks for Takhzyro® 300 mg and percentage females in the HAE population. The results are presented in a tornado diagram with ±10% variations (Figure 1).

Figure 1 Tornado diagram with ±10% variation



As seen in Figure 1, the cost analysis is most sensitive to the price and number of administrations per week for Berinert® SC. For instance, by vary the Berinert® SC price with ±10% (from 10.49 to 12.83 DKK/IU, base case 11.66 DKK/IU) the difference in average cost per patient for Berinert® SC is between 2.07 million to 3.07 million DKK more costly compared to Takhzyro® 300 mg (Base Case 2.57 million DKK more costly). The model is not sensitive to ±10% percentage females in the HAE population and ±10% reduction in percentage HAE attacks for Takhzyro® 300 mg.

Other independent variations were also performed in a separate one-way sensitivity analysis table and the rationale for these variations were explained (Table 15). The results presented in Table 15 can additionally confirm that dosage and price of Berinert® SC are the two most sensitive parameters in the model. For instance, by reducing the Berinert® SC dose to 40 IU/kg instead of base case 60 IU/kg, the average difference in cost moves from 2.57 million DKK more costly to only 900,000 DKK more costly per patient per year for Berinert® SC 40 IU/kg compared to Takhzyro® 300 mg.

[redacted]

Table 15 One-way sensitivity analysis

				Average cost per patient per year		
Parameter	Base Case value	Changed to value	Rationale	C1-INH SC Berinert®	Takhzyro® 300 mg	Incremental
Base Case results (restricted societal, average cost per patient per year, discounted)				**5 110 159**	**2 538 545**	**2 571 614**
Proportion females in the HAE population	67%	50%	Clinical expert comment*	5 289 835	2 538 545	2 751 289
Dose IU/kg of Berinert® SC	60	40	Clinical trial protocol (5), SmPC section 5.1, German data, and Spanish recommendation**	3 448 305	2 538 545	909 759
Annual reduction of HAE attacks	Berinert® SC 84.00%	Berinert® SC 84.00%	Check sensitiveness	5 110 159	2 663 168	2 446 991
	Takhzyro® 300 mg 84.00%	Takhzyro® 300 mg 67.20% (-20%)				
Takhzyro® administration	Every 2nd week	Every 4th week	DMC assessment of Takhzyro®***	5 110 159	1 328 663	3 781 496
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3,5%	0%	Check sensitiveness	5 467 658	2 716 138	2 751 520
Cost perspective	Patient costs included	Patient costs excluded	Check sensitiveness	5 102 540	2 538 545	2 563 994
[redacted]						

Spanish clinical recommendation for introduction of Berinert® SC [4](32)(32); ***DMC assessment of Takhzyro® , Dec 2019 (11))

[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

3. Budget impact

The total patient population is estimated to be 31 the initial year if the reimbursement of Berinert® SC is granted in Denmark. The number is based on current HAE patient population subject for treatment with Berinert® SC in Denmark (i.e., HAE adults with high/ultra-high attack frequency of ≥40 attacks annually, if left untreated). [redacted]

If Berinert® SC is not reimbursed, the population receiving Berinert® SC is estimated to be 1 patient from year 1 and onwards. Based on company information, there is currently one patient who would prefer to continue with Berinert® SC irrespective of clinical recommendation in Denmark.

There are currently five different prophylactic treatment options available for Danish patients, i.e., Takhzyro® 300 mg, Berinert® SC, C1-INH IV (Berinert® IV and Cinryze® IV), Danol® (danazol) and Cyklokapron® (tranexamic acid) (1). Out of these treatment options, only Berinert® SC, Takhzyro® 300 mg and C1-INH IV are recommended for prophylactic treatment among patients with high/ultra-high attack frequency.

Most of the patients are currently receiving Takhzyro® and many patients switch their treatment from C1-INH IV to Takhzyro® 300 mg, based on the latest clinical treatment recommendations for prophylactic HAE in Denmark. [redacted] There are several reasons to this increase. For instance, it is based on individual preferences, the availability of more treatment options for patients, and an increased demand for prophylactic treatment among patients with HAE.

[redacted] However, despite the availability of prophylactic treatments, such as intravenously administered C1-INH therapy, oral attenuated androgens and monoclonal antibodies, there is a medical need for additional prophylactic treatment as standard recommendation in patients that do not have an effect or cannot use available treatments because of safety and tolerability issues.

In addition, there are patient groups in which some of the available treatments are not indicated, e.g., Takhzyro® for pregnant and lactating women. Since women are often having more frequent and severe attacks it is therefore of extra importance to have effective and safe treatments available for this patient group. Moreover, limitations of intravenously (IV) administered C1-INH prophylaxis include the frequency of breakthrough attacks and the burden of venous access (13).

Cyklokapron® and Danol® have not been included in the budget impact calculation of Berinert® SC since these treatments are assumed to be provided to a similar number of patients over time. This was also agreed by DMC in their previous assessment of Berinert® SC (8).

3.1 Annual treatment costs in budget impact model

Three different treatment options have been used in the budget impact calculation for Berinert® SC, i.e., annual treatment costs for Takhzyro®, annual treatment costs for C1-INH IV Cinryze® and annual treatment costs for Berinert® SC.

The average annual treatment cost for Berinert® SC in the budget impact calculations has been derived from the model calculations on the average annual treatment costs for Berinert® SC, undiscounted and with patient costs excluded. Intervention medicine costs, costs for on-demand treatment and hospital costs for treatment of HAE attacks are all included in the final budget impact calculations. The annual treatment cost for Berinert® SC is 5,459,505 DKK.

The average annual treatment cost for Takhzyro® in the budget impact calculations has also been derived from the model calculations on the average annual treatment costs for Takhzyro®, undiscounted and with patient costs excluded. Comparator medicine costs, costs for on-demand treatment and hospital costs for treatment of HAE attacks are all included in the final budget impact calculations. The annual treatment cost for Takhzyro® SC is 2,712,656 DKK.

The annual treatment cost for C1-INH IV Cinryze® is 1,814,410 DKK. The price for Cinryze IV 2X500 IU (PPP excl VAT) is 11,598.97 DKK and was retrieved from medicinpriser.dk, accessed in Feb 2021. The price per IU is 11.60 DKK (11,598.97/(500*2)).

The recommended dose for each administration is 1500 IU and is the same recommended dose that was stated in the Danish Medicine Council protocol for Berinert® SC from June 2019. The recommended dose interval is every 3-4 days (every 3.5 days) and was also recommended from the same DMC protocol from 2019. With a dose of 1500 IU every 3.5 days and a cost of 11.60 DKK per IU, makes the total annual treatment cost for C1-INH IV Cinryze® to 1,814,410 DKK, undiscounted.

On-demand treatment costs, hospital costs for treatment of HAE attacks and patient costs were not included in the final budget impact calculations since potential differences in HAE attack rates for C1-INH IV Cinryze® was not validated and assessed in this application of Berinert® SC. If these costs would be included in the final budget impact calculations, the annual costs for C1-INH IV Cinryze® would be higher and the total budget impact for Berinert® SC somewhat lower. The total impact of including these costs would however be negligible since patients treated with C1-INH IV Cinryze® are so few.

Each annual cost for each treatment option has been multiplied by number of patients per year 1-5 if Berinert® SC gets recommended vs. not recommended as standard treatment in Denmark.

The expected number of patients receiving each treatment option is presented in Table 16 below. The total number of patients on prophylactic treatment expect to increase from year 1-5 irrespective of whether Berinert® SC is granted or not. There are several reasons to this increase. For instance, it is based on individual preferences, the availability of more treatment options for patients, and an increased demand for prophylactic treatment among patients with HAE.

Table 16 Number of patients per year

	Year 1	Year 2	Year 3	Year 4	Year 5
If Berinert® SC is granted					
Berinert® SC	3	3	3	4	5
C1-INH IV	1	1	1	1	1
Takhzyro® 300 mg	27	27	28	29	30
Total	**31**	**31**	**32**	**34**	**36**
If Berinert® SC is NOT granted					
Berinert® SC	1	1	1	1	1
C1-INH IV	3	2	2	3	4

Takhzyro® 300 mg	27	28	29	30	31
Total	**31**	**31**	**32**	**34**	**36**

The total budget impact if Berinert® SC is granted is 88.95 million DKK at year 1. The total budget impact if Berinert® SC is not granted is 83.46 million DKK during the same year. That gives a total difference of 5.49 million DKK.

The results of the budget impact analysis are presented in Table 17 below.

Table 17 Base case budget impact results (undiscounted, excl patient costs, in DKK)

	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Total if Berinert® SC is granted	91 434 640	91 434 640	94 147 297	102 319 457	110 491 618
Total if Berinert® SC is not granted	84 144 451	85 042 697	87 755 353	92 282 420	96 809 486
Difference (total budget impact)	7 290 189	6 391 943	6 391 943	10 037 038	13 682 132

If number of patients increase, the total budget impact of Berinert® SC will also increase.

Sensitivity analyses show that if number of patients on Berinert® SC increase by 20% (i.e., from 3 to 3.6 patients on Berinert® SC year 1, if recommended), the budget impact will increase from 5.5 to 8.8 million DKK at the same year. In addition, several patients who are currently receiving on-demand treatment expect to switch to prophylactic treatment due to the more user-friendly subcutaneous administration form, and according to DMC the relevant patient population for prophylactic treatment expects to increase (8). If number of patients are doubled (i.e., added by additional 30 patients), the Danish professional committee expects that 75% of the additional patients will be treated with Takhzyro®, and 25% will be treated with Berinert® SC if Berinert® SC is recommended. If Berinert® SC is not recommended, 100% of the additional 30 patients will switch to prophylactic treatment with Takhzyro® (8). This will result in a total budget impact of 27.03 million DKK during year 1.

The different budget impact sensitivity analyses have been presented in Table 18 below.

Table 18 Budget impact sensitivity analyses (undiscounted, excl patient costs, in DKK)

Difference (total budget impact)	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
+20% Berinert® SC patients	8 769 400	8 894 560	8 894 560	12 733 310	16 572 060
No of patients doubled (+30 patients in total yr 1-5)	27 033 761	27 158 921	27 158 921	29 905 770	32 652 619

In real clinical practice the lower dose of Berinert® SC 40 IU/kg is expected to be used in a larger number of patients than the higher dose of 60 IU/kg. If the lower dose of Berinert SC 40 IU/kg is tested in a budget impact scenario analysis, with the same estimated number of patients as in Table 16, the total budget impact of Berinert® SC 40 IU/kg would decrease to only 3.73 million DKK at year

1 [redacted]

[redacted]

Difference (total budget impact)	Year 1	Year 2	Year 3	Year 4	Year 5
Berinert® SC 40 IU/kg	3 733 959	2 835 713	2 835 713	4 702 693	6 569 672
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4. Discussion

In the model base case, the average total cost per patient per year is 2,570 000 DKK more costly with Berinert® SC 60 IU/kg compared to Takhzyro® 300 mg for prophylactic treatment of HAE in patients with high/ultra-high attack frequency. The main cost driver is the medicine costs, where prophylactic medicine with Berinert® SC cost in average 2,567,000 DKK more per patient compared to Takhzyro® 300 mg. Other cost differences are patient time for prophylactic treatment where Takhzyro® 300 mg has less administrations annually. Hospital costs for HAE attack treatment and medicine costs for on-demand treatment are similar in both treatment arms. With the lower dose of Berinert® SC, the average total cost per patient per year is only 900,000 DKK more costly with Berinert® SC 40 IU/kg compared to Takhzyro® 300 mg.

[redacted] (2) [redacted].

Other assumptions are that on-demand treatments and hospital visits for treating HAE attacks are similar in both treatment arms. Hospital costs annually for on-demand treatment that require hospital visits are 5,513 DKK in both treatment arms.

The cost analysis is most sensitive to the Berinert® SC price (DKK/IU), the Berinert® SC dosage (IU/kg) and number of administrations with Takhzyro® 300 mg. If the dose of Berinert® SC is varied from the model base case of 60 IU/kg to [redacted] Spanish data and recommendations of a lower dose corresponding to around 40 IU/kg (as also is mentioned in the SmPC section 5.1), Berinert® SC costs only 900,000 DKK more per patient compared to Takhzyro® 300 mg. Lower doses of Berinert® SC will result in similar costs in both treatment arms and lower total budget impact of implementing Berinert® SC to the Danish market

[redacted]

[redacted]

[redacted]

4.1 Relevance of the analysis

The patient *population* subject for treatment with Berinert® SC is children ≥ 12 years and adults with HAE type I or II and who suffer from high/ultrahigh attack frequency of ≥ 40 attacks annually if left untreated, and/or in patients who do not tolerate existing treatment (Table 2). The definition of patient population in the cost analysis is in line with the definition defined by the Danish Medicines Council (1).

The *intervention* is Berinert® 2000 IU and 3000 IU that is given subcutaneously at home. The *comparator* is Takhzyro® (Takhzyro®) 300 mg that is also given subcutaneously at home. Both intervention and comparator are in line with the PICO format stated in the Danish Medicines Council protocol of Berinert® SC (1).

The *outcomes* in the model are differences in medicine costs and administration costs, and similar attack rate reduction, and on-demand treatment in both treatment arms. There is no difference in adverse events, mortality, and Health Related Quality of Life (HRQoL) between treatment arms. Attack frequency, HRQoL and adverse events have been identified as important clinical outcomes from the Danish Medicines Council protocol (1).

4.2 Model structure

The model costs are calculated by multiplying unit costs with estimated resource utilizations for each cost parameter. The costs are further presented for 5 years and in average per year.

The rationale for a 5-year time horizon is based on the recommendation from the Danish Medicines Council that prophylactic treatment with C1-INH should be given for several years but not for a lifetime (1).

Two cost parameters were not included in the cost analysis, i.e., adverse events and mortality.

The current treatment with Berinert® SC is well tolerated and patients rarely experience side effects (4, 5). In addition, none of the patients treated with Takhzyro® 300 mg every 2 weeks withdrew from the study because of adverse events (12). It is thus not possible to claim that there are differences in the tolerability of the different products. A significant difference is not expected, and the general safety profile is good.

As mentioned earlier, HAE can potentially be a life-threatening disease if airway obstruction is caused by laryngeal edema. After having current treatment options available to the patients, mortality has dropped dramatically, and today there are nearly no deaths in Denmark as a result of HAE (1). Mortality is therefore not considered relevant in the cost analysis of Berinert® SC and Takhzyro® 300 mg.

4.3 Cost data

Danish unit costs and resource utilizations were used. Costs were reported in Danish krone (DKK) discounted at 3,5% annually. The cost analysis was conducted from a restricted societal perspective in Denmark, including both health care costs and potential costs for patient time and transportation. For the medicine costs, medicine prices were retrieved from medicinpriser.dk (30). Resource utilizations were mainly retrieved from clinical experts. For the hospital costs, most costs for hospital visits were based on the hourly wage for a physician multiplied by 2 to include overhead and local costs. Patient costs and transportation costs were retrieved from DMC Guideline recommendations (22).

There are some uncertainties in the cost estimations. For instance, several assumptions were made regarding time spent for travel and hospital visits. In addition, some cost parameters were not included in the cost analysis. For example, adverse events and one-time cost for educating the patient for self-administration at home were not included in the analysis. One-time costs have a minor impact on the total costs and both treatment arms require education for self-administration. Costs for educating the patient for self-administration at home were therefore not considered relevant to include in the cost analysis.

5 Conclusion

Despite the availability of intravenously administered C1-INH therapy and oral attenuated androgens, HAE remains a serious clinical condition with a high, unmet medical need for better prophylactic treatment. In addition, limitations of C1-INH prophylactic IV include the frequency of breakthrough attacks and the burden of venous access.

Moreover, there are patient groups in which some of the available treatments are not indicated, e.g., Takhzyro® for pregnant and lactating women. Since women are often having more frequent and severe attacks it is therefore of extra importance to have effective and safe treatments available for this patient group.

As the first and only low-volume, subcutaneously administered C1-INH replacement therapy, Berinert® SC represents a major advance in the prophylactic treatment of HAE attacks by virtue of its favourable efficacy, preferred route of administration and safety profile (6).

Berinert® SC is most appreciated for its physiological mode of action and long history of safe use, allowing use in patients with comorbidities and for HAE patients intending to conceive or already pregnant.

References

1. Medicinrådet. Medicinrådets protokol for vurdering vedrørende C1-esterase-inhibitor til forebyggende behandling af arveligt angioødem. Medicinrådet: Medicinrådet, Medicinrådet; 2021. Contract No.: Dokumentnummer 97666.
2. Moshe Fridman DS, Subhransu Prusty, John-Philip Lawo. Indirect comparison between human C1-inhibitor (C1-INH) subcutaneous treatment and lanadelumab for routine prevention of hereditary angioedema (HAE) attacks. Presented at the ISPOR US annual meeting May 18–20, 2020. 2020;Poster Number: PRO65.
[redacted]
4. Craig T, Zuraw B, Longhurst H, Cicardi M, Bork K, Gattan C. Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks. J Allergy Clin Immunol Pract. 2019;7(8):1793-802.
5. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. New England Journal of Medicine. 2017;376(12).
6. Behring MC. Foreløbig ansøgning til Medicinrådet om vurdering af Berinert for subkutan brug til patienter med HAE. 2020.
7. Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol. 2004;114(3 Suppl):S51-131.
8. Medicinrådet. Baggrund for Medicinrådets anbefaling af subkutan C1- esteraseinhibitor til forebyggende behandling af arveligt angioødem. 2020.
9. Maurer M, Magerl M, Ansotegui I, Aygoren-Pursun E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73(8):1575-96.
10. Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hebert J, Kanani A, et al. The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol. 2019;15:72.
11. Medicinrådet. Medicinrådets vurdering af lanadelumab til forebyggende behandling af arveligt angioødem. 2019.
12. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108-21.
13. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010;363(6):513-22.
14. Riedl MA, Bernstein JA, Craig T, Banerji A, Magerl M, Cicardi M, et al. An open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention of attacks in hereditary angioedema: design of the HELP study extension. Clin Transl Allergy. 2017;7:36.
15. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6(1):24.
16. Gower RG, Busse PJ, Aygoren-Pursun E, Barakat AJ, Caballero T, Davis-Lorton M, et al. Hereditary angioedema caused by c1-esterase inhibitor deficiency: a literature-based analysis and clinical commentary on prophylaxis treatment strategies. World Allergy Organ J. 2011;4(2 Suppl):S9-S21.
17. Craig T, Aygoren-Pursun E, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 2012;5(12):182-99.
18. Laegemiddelstyrelsen. PRODUKTRESUMÉ for Berinert, pulver og solvens til injektionsvæske, opløsning 2000 IE og 3000 IE. 2021.

[redacted]

22. Medicinrådet. Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren. 2020.
23. Folkesundhed SIf. Vægtøgning i den danske befolkning 1994-2013. Denmark: Statens Institut for Folkesundhed; 2019.
24. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med. 2017;376(12):1131-40.
25. EMA. EPAR Takhzyro product information - ANNEX I - SUMMARY OF PRODUCT CHARACTERISTICS. 2018.
26. Bernstein JA, Li HH, Craig TJ, Manning ME, Lawo JP, Machnig T, et al. Indirect comparison of intravenous vs. subcutaneous C1-inhibitor placebo-controlled trials for routine prevention of hereditary angioedema attacks. Allergy Asthma Clin Immunol. 2019;15:13.
27. Lumry WR, Craig T, Zuraw B, Longhurst H, Baker J, Li HH, et al. Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2018;6(5):1733-41 e3.
28. Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet J Rare Dis. 2021;16(1):86.
29. Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. Allergy. 2020.
30. Laegemiddelstyrelsen. Medicinpriser.dk 2021 [Available from: https://www.medicinpriser.dk/default.aspx.
31. Newswire CP. 44% of the patients who take Firazyr need two doses for optimal effect. 2019 [Available from: https://www.prnewswire.co.uk/.
32. Caballero Molina GQT, Lleonart Bellfill, Baeza Ochoa de Ocariz,, Almero Ves GC. Propuesta del GEAB para el inicio de concentrado plasmático de C1-Inhibidor (cpC1INH) (Berinert®) subcutáneo como profilaxis a largo plazo en AEH-C1-INH. Investigational Allergology and Clinical Immunology. 2020;30.

Medicinrådet

Medicinrådets protokol for vurdering vedrørende C1-esterase-inhibitor til forebyggende behandling af arveligt angioødem

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden *Metoder*, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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 den ansøgende virksomhed få besked.

Dokumentoplysninger	
Godkendelsesdato	11-01-2021
Dokumentnummer	97666
Versionsnummer	1.0

Indholdsfortegnelse

1. Begreber og forkortelser ... 3

2. Introduktion ... 4

2.1 Arveligt angioødem ... 4

2.2 Subkutan C1-esteraseinhibitor ... 5

2.3 Nuværende behandling ... 5

3. Kliniske spørgsmål ... 6

3.1 Klinisk spørgsmål 1 ... 6

3.2 Effektmål ... 7

3.2.1 Kritiske effektmål ... 7

3.2.2 Vigtige effektmål ... 8

4. Litteratursøgning ... 9

5. Den endelige ansøgning ... 10

6. Evidensens kvalitet ... 13

7. Andre overvejelser ... 13

8. Relation til behandlingsvejledning ... 14

9. Referencer ... 15

10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet ... 16

11. Versionslog ... 17

12. Bilag 1: Søgestrenge ... 18

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 11. januar 2021

1. Begreber og forkortelser

AE-QoL:	*Angioedema Quality of Life Questionnaire*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EQ-5D:	*EuroQol five dimension scale*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HAE:	Arveligt angioødem (*hereditary angioedema*)
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention to treat*
MKRF:	Mindste klinisk relevante forskel
NICE:	*The National Institute for Health and Care Excellence*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PP:	*Per Protocol*
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra CSL Behring AB, som ønsker, at Medicinrådet vurderer subkutan C1-esteraseinhibitor (handelsnavn: Berinert®) som forebyggende behandling til patienter med arveligt angioødem (HAE). Medicinrådet modtog den foreløbige ansøgning den 13. november 2020.

Subkutan C1-esteraseinhibitor er tidligere blevet vurderet af Medicinrådet og sammenlignet med intravenøs C1-esteraseinhibitor. Medicinrådet besluttede den 26. august 2020 ikke at anbefale subkutan C1-esteraseinhibitor. Ansøger har siden anmodet om en revurdering, hvor subkutan C1-esteraseinhibitor sammenlignes med lanadelumab, der i mellemtiden er blevet anbefalet af Medicinrådet som mulig standardbehandling. Ansøger har tilkendegivet, at subkutan C1-esteraseinhibitor efter deres vurdering hverken er bedre eller dårligere end lanadelumab til hele den godkendte indikation og dermed kan indgå i Medicinrådets hurtigere proces på syv uger, hvilket ansøger derfor har anmodet Medicinrådet om. Medicinrådet har accepteret, at subkutan C1-esteraseinhibitor på den baggrund kan vurderes i Medicinrådets hurtigere proces.

2.1 Arveligt angioødem

HAE er en sjælden, arvelig tilstand præget af uforudsigelige anfald af hævelser i hud og slimhinde, kaldet angioødem. HAE debuterer oftest i de første teenageår, men for nogle allerede i barndommen. Hævelserne er meget smertefulde og funktionsbegrænsende og rammer forskellige steder på kroppen. Oftest rammes ekstremiteterne, ansigtet, kønsorganerne, mave-tarm-kanalen og de øvre luftveje. Anfald, der rammer mave-tarm-kanalen, kan medføre voldsomme smerter, opkast og diarré. Et anfald kan vare op til 7 dage (gennemsnitlig 3 dage) uden behandling.

HAE kan potentielt være livstruende, hvis hævelserne f.eks. rammer de øvre luftveje, hvor et larynxødem (hævelse omkring strubehovedet og stemmelæberne) kan forårsage luftvejsobstruktion [1]. Efter tilkomsten af de nuværende behandlingsmuligheder er mortaliteten faldet drastisk, og i dag forekommer der stort set ikke dødsfald i Danmark som følge af HAE.

HAE skyldes en genetisk defekt i det blodbaserede protein C1-esteraseinhibitor, hvilket resulterer i mangelfuld eller dysfunktionel C1-esteraseinhibitor. Der findes flere typer af HAE. Hyppigst forekommer type I og type II. Type I HAE er karakteriseret ved lav produktion af normalt C1-esteraseinhibitor. Op til 90 % af patienterne har type I HAE. De resterende ca. 10 % har type II HAE, som er karakteriseret ved normal produktion, men manglende funktionalitet af C1-esteraseinhibitor. Ved begge typer af HAE kan mangel eller dysfunktionalitet af C1-esteraseinhibitor medføre en kædereaktion, der får de små blodkar til at lække væske ud i det tilstødende væv. Dette er årsagen til, at et ødem opstår. [2]

Den nøjagtige forekomst af HAE er ukendt, men det anslås, at HAE påvirker ca. 1 ud af 10.000-50.000 personer verden over [1,2]. Aktuelt er der i Danmark registreret 109 patienter, som jævnligt kontrolleres på det Nationale Kompetencecenter for HAE på Odense Universitetshospital. En opgørelse fra 2014 viste, at anfaldsfrekvensen varierede fra asymptomatiske patienter/1 anfald om året og op til 84 anfald om året. Den gennemsnitlige frekvens lå på 17 anfald om året [3].

Den uforudsigelige og potentielt livstruende sygdom påvirker patienternes livskvalitet. Selv mellem anfald, hvor patienterne ellers er symptomfri, oplever mange patienter stadig angst og begrænsninger i de daglige aktiviteter [4]. Mønstret i anfaldende og sværhedsgraden heraf er for den enkelte patient uforudsigeligt. Sygdomsbyrden mellem anfaldene fylder således rigtig meget for HAE-patienterne. Hvornår kommer det næste anfald, hvor er jeg, har jeg anfaldsmedicin i nærheden og er jeg overhovedet i stand til at administrere medicinen selv? At leve med HAE har derfor stor betydning for livskvaliteten med risiko for personlige omkostninger i forhold til familie- og arbejdsliv. Netop på grund af den store sygdomsbyrde, er det ønskeligt for HAE-patienter, at fremtidige HAE-behandlinger ikke blot holder anfaldshyppigheden nede, men at behandlingen sigter mod at gøre HAE-patienter anfaldsfrie.

2.2 Subkutan C1-esteraseinhibitor

Berinert® indeholdende C1-esteraseinhibitor er oprenset og koncentreret fra humant plasma. Subkutan administration af C1-esteraseinhibitor erstatter manglende eller dysfunktionelt C1-esteraseinhibitor hos patienten, hvorved genereringen af bradykinin bliver begrænset og risikoen for angioødemanfald mindsket.

Berinert® til subkutan injektion er indiceret til profylakse af tilbagevendende anfald af HAE hos unge og voksne med mangel på C1-esteraseinhibitor. Den anbefalede dosis ved subkutan indgift er 60 IU/kg to gange om ugen (hver 3.-4. dag).

2.3 Nuværende behandling

Behandlingsmål for HAE type I og II er at minimere anfaldshyppigheden og/eller anfaldenes sværhedsgrad. Behandlingen af HAE er opdelt i behandling af akutte anfald og forebyggende behandling.

Til behandling af akutte anfald anvendes enten intravenøs substitution af manglende funktionelt C1-esteraseinhibitor (produkterne Berinert®/Cinryze/Ruconest) eller et bradykininblokerende præparat icatibant (Firazyr), som administreres subkutant.

Den forebyggende behandling iværksættes i henhold til den gældende internationale guideline fra World Allergy Organization og European Academy Allergy and Clinical Immunology fra 2017 [5]. Jævnfør denne guideline eksisterer der ikke faste kriterier for, hvilke patienter der tilbydes forebyggende behandling. Behovet for forebyggende behandling vurderes under hensyntagen til patientens sygdomsaktivitet, anfaldsfrekvens/sværhedsgrad/lokation, livskvalitet og eventuelt manglende sygdomskontrol

ved behandling af akutte anfald. Da alle disse faktorer varierer over tid, bliver behovet for forebyggende behandling vurderet ved hvert kontrolbesøg. Patientens præferencer er også en væsentlig faktor, f.eks. i forhold til administrationsvej.

Til forebyggende behandling anvendes to behandlingsprincipper i Danmark. Det ene princip består i substitution af manglende funktionelt C1-esteraseinhibitor, og her anvendes et af de to produkter Berinert® eller Cinryze®. Behandlingerne administreres intravenøst og oftest hver 3.-4. dag. Det andet behandlingsprincip består i at hæmme det aktive plasmakallikreins proteolytiske aktivitet, hvorved risikoen for angioødemanfald mindskes. Her anvendes lanadelumab (Takhzyro®), som er et humant monoklonalt antistof. Lanadelumab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af HAE hos patienter på ≥ 12 år og er anbefalet som mulig standardbehandling af Medicinrådet hos patienter med minimum fire anfald om måneden. Den anbefalede dosis er 300 mg subkutant hver 2. uge.

De fleste patienter administrerer selv deres forebyggende behandling (eventuelt med hjælp fra pårørende). Patienter, der ikke selv behersker teknikken, behandles på lokalt sygehus. Ud af de ca. 120 danske patienter anslår fagudvalget, at ca. 30-40 patienter får forebyggende behandling, heraf er hovedparten i behandling med lanadelumab.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)) og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har subkutan C1-esteraseinhibitor sammenlignet med lanadelumab som forebyggende behandling for patienter med arveligt angioødem?

Population
Børn ≥ 12 år og voksne med HAE type I eller II.

Intervention
Berinert® (C1-esteraseinhibitor) s.c. 60 enheder/kg hver 3.-4. dag.

Komparator
Lanadelumab 300 mg hver 2. uge.

Effektmål
De valgte effektmål fremgår af Tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i Tabel 1. For hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1 Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Retningsgivende mindste klinisk relevante forskel
Anfaldsfrihed	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel af patienter som oplever en 100 % reduktion i anfaldsfrekvens (symptomfrihed) fra baseline	10 %-point
Helbredsrelateret livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Ændring fra baseline målt med Angioedema Quality of life Questionnaire (AE-QoL)	6 point
			Andel af patienter som oplever en forbedring på 6 point fra baseline	Anvendes til bestemmelse af den relative effektforskel. Der er derfor ikke fastsat en MKRF
Anfaldsfrekvens	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Procentvis reduktion i antallet HAE-anfald pr. måned	15 %-point
			Gennemgang af sværhedsgraden af de tilbageværende anfald (gennembruds-anfald) ved de to behandlinger†.	-
Bivirkninger	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter der ophører behandling grundet bivirkninger	10 %-point
			Kvalitativ gennemgang af lægemidlernes bivirkningsprofil	-

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
† Foruden opgørelsen af den gennemsnitlige reduktion i anfaldsfrekvens ønsker fagudvalget også en gennemgang af sværhedsgraden af de tilbageværende anfald (gennembrudsanfald) ved de to behandlinger. Se mere under beskrivelsen af effektmålet.

3.2.1 Kritiske effektmål

Anfaldsfrihed

Det vigtigste for patienterne er at blive anfaldsfrie. Dette vil fjerne den uforudsigelighed, som patienterne lever med, herunder også frygten for larynxødem, som har stor betydning for patienternes livskvalitet. Medicinrådet vil derfor vurdere subkutan C1-esteraseinhibitors effekt på andelen af patienter, som er anfaldsfrie og anser det som et kritisk effektmål. Medicinrådet ønsker effektmålet opgjort som en forskel i andelen af patienter, som opnår en 100 % reduktion i anfaldsfrekvens fra baseline. I DX-2930-03

studiet med lanadelumab opnår ca. 44 % symptomfrihed [6], men data fra *open label extension*-studiet såvel som national og international klinisk erfaring tyder på, at der er betydeligt flere, som bliver symptomfrie [7,8]. Fagudvalget anslår, på baggrund af disse erfaringer, at ca. 70 % af patienterne opnår symptomfrihed ved behandling med lanadelumab i Danmark. Fagudvalget vurderer på denne baggrund, at en forskel på 10 %-point i andelen, som opnår anfaldsfrihed, er klinisk relevant.

Helbredsrelateret livskvalitet
Helbredsrelateret livskvalitet er et kritisk effektmål i vurderingen af subkutan C1-esteraseinhibitor, da HAE under anfald såvel som mellem anfald påvirker patientens livskvalitet.

Medicinrådet ønsker livskvalitet belyst ved det validerede spørgeskema Angioedema Quality of Life Questionnaire (AE-QoL). Værktøjet inkluderer sygdomsrelevante domænescorer (funktion, træthed/humør, angst/skam og ernæring) samt en samlet score [9]. Scoren går fra 0-100, hvor en højere score indikerer en dårligere livskvalitet. Medicinrådet ønsker, at vurderingen bliver baseret på den samlede score, og den mindste klinisk relevante forskel er sat til 6 point, da denne forskel er fundet at være klinisk betydende ved anvendelse af AE-QoL [10]. Medicinrådet ønsker den relative effektforskel for AE-QoL totalscore opgjort som andelen af patienter, der opnår en reduktion på 6,0 point fra baseline. Der er ikke fastsat en mindste klinisk relevant forskel for denne måleenhed, da det udelukkende vedrører den relative effektforskel.

Hvis der findes alternative livskvalitetsværktøjer, f.eks. EQ-5D, som kan muliggøre en indirekte sammenligning, kan ansøger inkludere data herfra i den endelige ansøgning. Hvis data ikke muliggør en indirekte sammenligning, skal ansøger inkludere og diskutere livskvalitetsdata separat for både intervention og komparator.

3.2.2 Vigtige effektmål

Anfaldsfrekvens
Det primære behandlingsmål med rutinemæssig forebyggelse er at reducere frekvensen af HAE-anfald, og anfaldsfrekvens er derfor et vigtigt effektmål. Medicinrådet vil belyse anfaldsfrekvens ved at se på forskellen i det gennemsnitlige antal af HAE-anfald pr. måned. Hvad angår anfaldsfrekvens, er lanadelumab en effektiv behandling. Et tidligere studie har vist en gennemsnitlig reduktion i anfaldsfrekvens på 87 % hos patienter behandlet med 300 mg hver 2. uge. Den gennemsnitlige anfaldsfrekvens reduceres fra ca. 3,5 anfald/måned før opstart af behandling til gennemsnitlig 0,26 anfald/måned efter 26 ugers behandling. I studiet sås også en betydelig effekt i placebo-armen, hvor anfaldsfrekvensen blev halveret fra ca. 4 anfalds/måned før opstart af behandling til gennemsnitlig 1,97 anfald/måned efter 26 ugers opfølgning [6]. Fagudvalget har valgt en gennemsnitlig procentvis ændring som mindste klinisk relevante forskel for at tage højde for, at der er stor variation i anfaldsfrekvens fra patient til patient. Fagudvalget anser en forskel på 15 %-point i den gennemsnitlige anfaldsfrekvens som den mindste klinisk relevante forskel.

Foruden opgørelsen af den gennemsnitlige reduktion i anfaldsfrekvens ønsker fagudvalget også en gennemgang af sværhedsgraden af de tilbageværende anfald (gennembrudsanfald) ved de to behandlinger. Konkret ønskes en opgørelse af andelen af anfald karakteriseret ved henholdsvis mild, moderat og svær sværhedsgrad.

Bivirkninger
Bivirkninger kan have betydning for den enkelte patients livskvalitet og kan føre til ophør af behandling. Da behandlingen forventes at skulle gives kontinuerligt gennem mange år, ønsker Medicinrådet, at bivirkninger inkluderes som et vigtigt effektmål. Den nuværende behandling med lanadelumab er veltolereret, og patienterne oplever sjældent bivirkninger. Opstår der bivirkninger, er det oftest reaktioner ved injektionsstedet.

Medicinrådet ønsker bivirkninger opgjort som andel af patienter, der ophører behandlingen på grund af bivirkninger, og en forskel mellem grupperne på 10 %-point anses som klinisk relevant. Dette begrundes med, at der i dag stort set ikke ses behandlingsophør på grund af bivirkninger ved lanadelumab, og derfor ønsker fagudvalget heller ikke, at nye behandlinger er forbundet med bivirkninger af en sådan karakter, at patienterne ophører med behandlingen.

Medicinrådet vil desuden foretage en kvalitativ gennemgang af bivirkningstyperne for subkutan C1-esteraseinhibitor og lanadelumab med henblik på at belyse bivirkningsprofilerne mht. alvorlighed, håndterbarhed og hyppighed af bivirkningerne. Ansøger bedes derfor bidrage med godkendt produktresumé for subkutan C1-esteraseinhibitor og komparator.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (fx NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor subkutan C1 esteraseinhibitor er sammenlignet direkte med lanadelumab. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

[1] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

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

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.

- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.

- Beskriv den anvendte metode detaljeret.
- Narrative analyser
- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, f.eks. behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser hvilke parametre i modellen der har størst indflydelse på resultatet.

- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Studiedesign og opfølgningstid

Der er visse forskelle i studierne med subkutan C1-esteraseinhibitor og lanadelumab, som betragtes som faktorer, som kan udfordre studiernes sammenlignelighed. Det er f.eks. selve designet, hvor studiet med subkutan C1-esteraseinhibitor er et overkrydsningsforsøg modsat studiet med lanadelumab, som er et parallelgruppeforsøg. Studiernes varighed er også forskellig. Ansøger bedes diskutere om og hvordan disse og eventuelt andre forskelle påvirker sammenligningen af subkutan C1-esteraseinhibitor og lanadelumab.

Mulighed for dosisreduktion

Produktresuméet for lanadelumab omtaler en mulighed for at reducere doseringsfrekvensen fra 300 mg hver 2. uge til 300 mg hver 4. uge. For subkutan C1-esteraseinhibitor hævder ansøger også, at mange patienter kan behandles med en reduceret dosis på 40 IU/kg. Produktresumé for subkutan C1-esteraseinhibitor omtaler ingen retningslinjer for dosisreduktion. For begge behandlinger er det dog uklart, hvor mange patienter som vil opnå tilstrækkelig effekt ved en reduceret dosis. Denne uklarhed medfører betydelige usikkerheder i de sundhedsøkonomiske analyser, og derfor bedes ansøger undersøge, og redegøre for, om der findes evidens (gerne publiceret), som kan anvendes til at understøtte antagelserne om, hvor mange af patienterne som kan behandles med en reduceret dosis. Dette gælder for både intervention og komparator. Evidensen skal ikke være begrænset af søgestrengene i bilag 1, men kan også omfatte andre publikationstyper som f.eks. observationelle studier.

Ansøger bedes redegøre for *exposure*-respons forhold for de to dosisregimer:

- 60 IU/kg hver 3.-4. dag
- 40 IU/kg hver 3.-4. dag

Foretrukken metode er populations PK/PD-modellering. Desuden, ses også gerne en redegørelse over exposure-safety forhold. På baggrund heraf bør ansøger vurdere, hvor mange patienter, der forventes at kunne reduceres til en dosis på 40 IU/kg.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

9. Referencer

1. Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008;359(10):1027–36.
2. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73(8):1575–96.
3. Bygum A. Hereditary angioedema - consequences of a new treatment paradigm in Denmark. Acta Derm Venereol. 2014;94(4):436–41.
4. Caballero T, Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. Allergy asthma Proc. 2014;35(1):47–53.
5. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. World Allergy Organ J. 2018;11:5.
6. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108–21.
7. Riedl M, Johnston D, Lumry W, Bernstein J, Nurse C, Yu M, et al. P157 ATTACK-FREE STATUS DURING EXTENDED TREATMENT WITH LANADELUMAB FOR HEREDITARY ANGIOEDEMA: HELP OLE STUDY FINAL RESULTS. Ann Allergy, Asthma Immunol. 2020;125(5):S23.
8. Banerji A, Hao J, Yu M, Bernstein J, Johnston D, Riedl M. P150 LONG-TERM EFFICACY AND SAFETY OF LANADELUMAB: FINAL RESULTS FROM THE HELP OPEN-LABEL EXTENSION STUDY. Ann Allergy, Asthma Immunol. 2020;125(5):S21.
9. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. Allergy Eur J Allergy Clin Immunol. 2012;67(10):1289–98.
10. Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M. The Angioedema Quality of Life Questionnaire (AE-QoL) – assessment of sensitivity to change and minimal clinically important difference. Allergy Eur J Allergy Clin Immunol. 2016;71(8):1203–9.

10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende arveligt angioødem

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Carsten Bindslev-Jensen *Professor*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke udpege en kandidat	Region Nordjylland
Kan ikke udpege en kandidat	Region Midtjylland
Shailajah Kamaleswaran *Speciallæge*	Region Syddanmark
Kan ikke udpege en kandidat	Region Sjælland
Kan ikke udpege en kandidat	Region Hovedstaden
Christina Gade *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Helle Houlbjerg Carlsen *Funktionsleder, farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Henrik Balle Boysen	Danske Patienter
Jørn Schultz-Boysen	Danske Patienter

Medicinrådets sekretariat

Medicinrådet

Dampfærgevej 27-29, 3.th.

2100 København Ø

+45 70 10 36 00

medicinraadet@medicinraadet.dk

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	11. januar 2021	Godkendt af Medicinrådet

12. Bilag 1: Søgestrenge

Søgestreng til PubMed:

#	Søgestreng	Kommentar
#1	"Angioedemas, Hereditary"[Mesh]	
#2	(C1[tiab] AND Inhibitor*[tiab] AND Deficienc*[tiab]) or (hereditary[tiab] AND (edema*[tiab] or oedema*[tiab] or angioedema*[tiab] or angiooedema*[tiab]))	
#3	#1 OR #2	
#4	prophyl*[tiab] OR prevent*[tiab]	Fokus på forebyggende behandling
#5	#3 AND #4	Samlet søgning for populationen
#6	lanadelumab[nm] OR DX-2930[tiab] OR Takhzyro[tiab] OR lanadelumab[tiab]	Søgetermer for interventionen
#7	“Complement C1 Inhibitor Protein”[Mesh]	Søgetermer for komparator
#8	(C1*[tiab] AND Inhibitor*[tiab]) OR Cinryze[tiab] OR Berinert[tiab] OR C1NH[tiab] OR C1IN[tiab]	
#9	#7 OR #8	
#10	#6 OR #9	Intervention + komparator
#11	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans [mh])	Cochrane RCT-filter
#12	#5 and #10 and #11	Samlet søgning

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	[mh "Angioedemas, Hereditary"]	
#2	(C1 AND Inhibitor* AND Deficienc*):ti,ab,kw	
#3	(hereditary AND (edema* or oedema* or angioedema* or angiooedema*)):ti,ab,kw	
#4	{or #1-#3}	
#5	(prophyl* or prevent*):ti,ab or prophylaxis:kw	Fokus på forebyggende behandling
#6	#4 AND #5	Samlet søgning for populationen
#7	(DX-2930 OR Takhzyro OR lanadelumab):ti,ab,kw	Søgetermer for interventionen
#8	[mh “Complement C1 Inhibitor Protein”]	Søgetermer for komparator
#9	((C1* AND Inhibitor*) OR Cinryze OR Berinert OR C1NH OR C1IN):ti,ab,kw	
#10	#8 OR #9	
#11	#7 OR #10	Intervention + komparator
#12	#6 AND #11	
#13	("conference abstract" or review):pt OR NCT*:au	
#14	#12 not #13	Samlet søgning