Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende lanadelumab som mulig standardbehandling til forebyggende behandling af arveligt angioødem

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om lægemidlets samlede pris er rimelig, når man sammenligner den med lægemidlets værdi for patienterne.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	22. januar 2020
Ikrafttrædelsesdato	22. januar 2020
Dokumentnummer	68167
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 22. januar 2020

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Takhzyro®
Generisk navn	Lanadelumab
Firma	Shire Pharmaceuticals Ireland Limited
ATC-kode	B06AC05
Virkningsmekanisme	Lanadelumab er et fuldt humant, monoklonalt antistof. Lanadelumab hæmmer det aktive plasmakallikreins proteolytiske aktivitet. Øget plasmakallikreinaktivitet fører til angioødemanfald hos patienter med arveligt angioødem. Lanadelumab giver vedvarende kontrol af plasmakallikreinaktiviteten og begrænser dermed genereringen af bradykinin.
Administration/dosis	Lanadelumab er beregnet til subkutan administration. Den anbefalede startdosis er 300 mg hver 2. uge. Dosisnedsættelse til 300 mg lanadelumab hver 4. uge kan overvejes hos stabile patienter uden anfald, herunder især patienter med lav kropsvægt.
EMA-indikation	Lanadelumab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** lanadelumab som mulig standardbehandling til forebyggende behandling af arveligt angioødem.

Medicinrådet finder, at der er et rimeligt forhold mellem lægemidlets værdi og omkostningerne ved lanadelumab sammenlignet med intravenøs C1-esteraseinhibitor.

Anbefalingen gælder for patienter med minimum fire anfald om måneden. For patienter med væsentligt nedsat livskvalitet, som ikke opfylder kriteriet om fire månedlige anfald, kan behandlingen først opstartes efter enkeltansøgning til den regionale lægemiddelkomite.

Den sundhedsøkonomiske analyse er behæftet med stor usikkerhed, særligt vedrørende patientantal og andel der kan behandles med reduceret dosis. 12 måneder efter anbefalingens ikrafttrædelse ønsker Medicinrådet information om, hvor mange patienter der er opstartet behandling med lanadelumab, og hvor mange af patienterne der har opnået dosisreduktion, for at vurdere om antagelserne har været retvisende. Medicinrådet anmoder derfor de behandlende læger om at opsamle disse informationer.

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

Hvad er værdien af rutinemæssig forebyggelse med lanadelumab hos voksne patienter og børn ≥ 12 år med arveligt angioødem sammenlignet med nuværende standardbehandling?

3 Formål

Formålet med baggrund for Medicinrådets anbefaling vedrørende lanadelumab som mulig standardbehandling til forebyggende behandling af arveligt angioødem er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Arveligt angioødem er en sjælden, arvelig tilstand præget af uforudsigelige anfald af hævelser i hud og slimhinder. 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.

Arveligt angioødem skyldes en genetisk defekt i det blodbaserede protein C1-esteraseinhibitor, hvilket resulterer i mangelfuld eller dysfunktionel C1-esteraseinhibitor. Aktuelt er der i Danmark registreret 109 patienter med arveligt angioødem, som jævnligt kontrolleres på det Nationale Kompetencecenter for HAE på Odense universitetshospital.

Behandlingen opdeles i akut anfaldsbehandling og forebyggende behandling. Behovet for forebyggende behandling vurderes under hensyntagen til patientens sygdomsaktivitet, anfaldsfrekvens/sværhedsgrad/ lokation, livskvalitet og eventuelt manglende sygdomskontrol med anfaldsbehandling.

Lanadelumab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af arveligt angioødem hos patienter på 12 år og derover.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den endelige ansøgning vedrørende lanadelumab den 4. oktober 2019 (bilag 5). Vurdering af klinisk merværdi blev præsenteret og godkendt på rådsmødet den 11. december 2019. Der har været udvidet clock-stop fra den 20. november til den 11. december 2019. Medicinrådet har gennemført vurderingen af lanadelumab til forebyggende behandling af arveligt angioødem på 12 uger og 5 dage.

5 Medicinrådets vurdering af samlet værdi

Medicinrådet vurderer, at lanadelumab til forebyggende behandling af arveligt angioødem giver en **merværdi af ukendt størrelse** sammenlignet med i.v. C1-esteraseinhibitor. Evidensens kvalitet vurderes at være meget lav.

6 Høring

Ansøger har den 17. december 2019 meddelt, at de ikke agter at indgive et høringssvar.

7 Resumé af økonomisk beslutningsgrundlag

Amgros vurderer, at der er et rimeligt forhold mellem meromkostningerne og lægemidlets værdi for lanadelumab til rutinemæssig forebyggelse af tilbagevendende anfald af arveligt angioødem hos patienter på 12 år og derover, idet Amgros' hovedanalyse viser en omkostningsbesparelse ved ibrugtagning af lanadelumab.

De sundhedsøkonomiske analyser er forbundet med betydelige usikkerheder. Meromkostningerne er afhængige af antagelsen om, hvor stor en andel af patienterne der dosisreduceres og antagelsen om, hvor

mange anfald patienterne i gennemsnit har om året. Samtidig er det sandsynligt, at effekten af i.v. C1-esteraseinhibitor er underestimeret i de sundhedsøkonomiske analyser. Amgros har udført følsomhedsanalyser, som belyser usikkerhederne, hvor det ses, at meromkostningerne forbundet med behandling med lanadelumab øges betydeligt, hvis det antages, at en mindre andel af patienterne dosisreduceres, hvis det gennemsnitlige antal anfald om året reduceres, eller hvis effekten af i.v. C1-esteraseinhibitor er underestimeret.

8 Overvejelser omkring alvorlighed/forsigtighed

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

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende arveligt angioødem

Formand	**Indstillet af**
Rikke Elkjær Andersen Speciallæge	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
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
Sekretariatets arbejdsgruppe: Jesper Skov Neergaard (projekt- og metodeansvarlig) Heidi Møller Johnsen (projektdeltager) Gedske Thomsen (projektdeltager) Anette Pultera Nielsen (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistiker) Annemette Anker Nielsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	22. januar 2020	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

1. Amgros' beslutningsgrundlag
2. Amgros' sundhedsøkonomiske analyse
3. Medicinrådets vurdering af lanadelumab til forebyggende behandling af arveligt angioødem
4. Ansøgers endelige ansøgning
5. Medicinrådets protokol for vurdering af lanadelumab til forebyggende behandling af arveligt angioødem

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af lanadelumab (Takhzyro) til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover. Vurderingen er baseret på en kombination af lægemidlets gennemsnitlige inkrementelle omkostninger baseret på SAIP (sygehusapotekets indkøbspris), Medicinrådets vurdering af den kliniske merværdi og eventuel inddragelse af andre overvejelser.

Dato for Medicinrådsbeslutning	22-01-2020
Firma	Takeda
Lægemiddel	Lanadelumab (Takhzyro)
Indikation	Lanadelumab (Takhzyro) er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover.

Overordnet konklusion

Medicinrådet har vurderet, at lanadelumab (Takhzyro) til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover sammenlignet med profylaktisk behandling med i.v. C1-esterase-inhibitor giver:

- Merværdi af ukendt størrelse, med meget lav evidenskvalitet

Behandling med lanadelumab (Takhzyro) til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover er forbundet med ekstreme besparelser sammenlignet med profylaktisk behandling med i.v. C1-esterase-inhibitor. Baseret på en sammenvejning af Amgros' sundhedsøkonomiske vurdering og andre overvejelser, vurderer Amgros, at lægemidlets behandlingspris står i rimeligt forhold med den kliniske merværdi.

Amgros' sundhedsøkonomiske vurdering

- Amgros vurderer, at der er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for lanadelumab (Takhzyro) til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover

Meromkostningerne er primært drevet af antagelserne om, andelen af patienter, der dosisreduceres efter 6 måneder og antal anfald om året. Amgros' følsomhedsanalyser belyser usikkerhederne ved antagelserne om disse to parametre, hvor det ses, at meromkostningerne forbundet med behandling med lanadelumab (Takhzyro) øges betydeligt, hvis andelen af patienter, der dosisreduceres, reduceres eller hvis gennemsnitlige antal anfald om året reduceres.

Andre overvejelser

Lanadelumab (Takhzyro) er den ene af to lægemidler, som behandler denne indikation til profylakse behandling. Der er indgået en aftale med lanadelumab (Takhzyro), og aftalen vil kunne forlænges indtil der bliver lavet et udbud på denne type behandling.

Igennem 2019 har flere af lægemidlerne indenfor dette område været i restordre og ved at få endnu et lægemiddel godkendt, kan vi bedre sikre forsyningen i fremtiden. Lanadelumab (Takhzyro) er et rekombinant lægemiddel, som ikke er afhængigt at plasmaforsyningen.

Sundhedsøkonomisk vurdering

Tabel 1: Overblik over Amgros' vurdering (baseret på SAIP).

Population	Komparator	Merværdi	Evidens for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover	Profylaktisk behandling med i.v. C1-esterase-inhibitor	Merværdi af ukendt størrelse	Meget lav evidenskvalitet	Rimeligt

Vurderingen er baseret på, at Medicinrådet har valgt profylaktisk behandling med i.v. C1-esterase-inhibitor som komparator for patientpopulationen, og vurderingen af meromkostninger og klinisk værdi beror på denne.

Resumé af resultaterne fra Amgros' afrapportering

Konklusion på omkostnings- og budgetkonsekvensanalyserne

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

Inkrementelle omkostninger per patient

Behandling med lanadelumab (Takhzyro) er forbundet med ekstreme besparelser sammenlignet med behandling med komparator.

I Tabel 2 ses de inkrementelle omkostninger for lanadelumab (Takhzyro) sammenlignet med i.v. C1-esterase-inhibitor (Berinert og Cinryze).

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for lanadelumab (Takhzyro) sammenlignet med C1-esterase-inhibitor (Berinert) på ca. [redacted] DKK og C1-esterase-inhibitor (Cinryze) på ca. [redacted] DKK.

Tabel 2: Resultat af Amgros' hovedanalyse for lanadelumab (Takhzyro) sammenlignet med C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze), DKK, SAIP.

Omkostningselement	Lanadelumab (Takhzyro)	C1-esterase-inhibitor (Berinert)	C1-esterase-inhibitor (Cinryze)
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Omkostninger til anfald	[redacted]	[redacted]	[redacted]
Patientomkostninger	12.301	97.145	186.231
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

Hvis analysen udføres på baggrund af AIP, bliver de inkrementelle omkostninger per patient for lanadelumab (Takhzyro) sammenlignet med C1-esterase-inhibitor (Berinert) ca. -6,3 mio. DKK og C1-esterase-inhibitor (Cinryze) ca. -7,2 mio. DKK. Lægemiddelomkostningerne for lanadelumab (Takhzyro) er ca. 33,8 mio. DKK, for C1-esterase-inhibitor (Berinert) er lægemiddelomkostningerne ca. 37,1 mio. DKK og C1-esterase-inhibitor (Cinryze) er lægemiddelomkostningerne 37,8 mio. DKK i AIP.

Følsomhedsanalyser af relevans

Amgros har udarbejdet følsomhedsanalyser, der belyser usikkerhederne forbundet med antagelserne om gennemsnitlige antal anfald om året samt antallet af patienter, der dosisreduceres efter 6 måneder uden anfald. Resultaterne viser, at meromkostningerne forbundet med behandling med lanadelumab (Takhzyro) øges betydeligt, hvis andelen af patienter, der dosisreduceres, reduceres eller hvis gennemsnitlige antal anfald om året reduceres.

Resultat af Amgros' følsomhedsanalyserne kan ses i Tabel 3.

Tabel 3: Resultatet af Amgros' følsomhedsanalyse, DKK.

Parameter	Værdi	Inkrementelle omkostninger C1-esterase-inhibitor (Berinert)	Inkrementelle omkostninger C1-esterase-inhibitor (Cinryze)
Resultatet af hovedanalysen		[redacted]	[redacted]
Antal anfald om året	24	[redacted]	[redacted]
	48	[redacted]	[redacted]
Andel af patienter, der dosisreduceres	61,0%	[redacted]	[redacted]
	92,8%	[redacted]	[redacted]

Budgetkonsekvenser

Amgros vurderer, at anbefaling af lanadelumab (Takhzyro) som mulig standardbehandling vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for den nuværende patientantal og ca. [redacted] DKK i år 5 for det potentielt øgede patientantal. Hvis analysen udføres med AIP, vil budgetkonsekvenserne være på ca. -12 mio. DKK i år 5 for det nuværende patientantal og ca. 31 mio. DKK i år 5 for det potentielt øgede patientantal.

LANADELUMAB (TAKHZYRO)

HEREDITÆRT ANGIOØDEM

AMGROS 3. januar 2020

AMGROS

OPSUMMERING

Baggrund

Lanadelumab (Takhzyro) er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover. Omkring 30-40 patienter med HAE modtager forebyggende behandling i Danmark. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Takeda.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med lanadelumab (Takhzyro) sammenlignet med profylaktisk behandling med i.v. C1-esterase-inhibitor til voksne patienter og børn ≥ 12 år med HAE.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af lanadelumab (Takhzyro) sammenlignet med C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze). De inkrementelle omkostninger er angivet i SAIP.

I scenariet, Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for lanadelumab (Takhzyro) ca. [redacted] DKK sammenlignet med C1-esterase-inhibitor (Berinert) og ca. [redacted] DKK sammenlignet med C1-esterase-inhibitor (Cinryze). Hvis analysen udføres med AIP bliver de inkrementelle omkostninger -6,3 mio. DKK sammenlignet med C1-esterase-inhibitor (Berinert) og ca. -7,2 mio. DKK sammenlignet med C1-esterase-inhibitor (Cinryze).

Amgros vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af lanadelumab (Takhzyro) som standardbehandling vil være ca. [redacted] DKK for det nuværende patientantal i år 5 og ca. [redacted] DKK for den potentielt øgede patientantal i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. -12 mio. DKK i år 5 for det nuværende patientantal, mens budgetkonsekvenserne er ca. 31 mio. DKK i år 5 for det potentielt øgede patientantal.

Konklusion

Behandling med lanadelumab (Takhzyro) er forbundet med ekstreme besparelser sammenlignet med behandling med både C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze).

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
HAE	Hereditært angioødem
I.v.	Intravenøs
PLO	Praktiserende Lægers Organisation
SAIP	Sygehusapotekernes indkøbspriser

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Takeda
Handelsnavn:	Takhzyro
Generisk navn:	Lanadelumab
Indikation:	Rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover.
ATC-kode:	B06AC05

Proces	
Ansøgning modtaget hos Amgros:	04-10-2019
Endelig rapport færdig:	03-01-2020
Sagsbehandlingstid fra endelig ansøgning:	91 dage
Arbejdsgruppe:	Camilla Nybo Holmberg Pernille Winther Johansen

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

1 BAGGRUND

Lanadelumab (Takhzyro) er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover. Takeda (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af lanadelumab (Takhzyro) og har den 04.10.2019 indsendt en ansøgning til Medicinrådet om anbefaling af lanadelumab (Takhzyro) som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af lanadelumab (Takhzyro) som standardbehandling på danske hospitaler af den nævnte indikation. I analyserne sammenlignes behandling med lanadelumab (Takhzyro) med profylaktisk behandling med intravenøs C1-esterase-inhibitor.

1.2 Patientpopulation

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. HAE viser sig ved anfaldsvise hævelser i hud og slimhinder. 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 (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-esterase-inhibitor, hvilket resulterer i mangelfuld eller dysfunktionel C1-esterase-inhibitor. Der findes to typer af HAE; type I og type II HAE. Type I HAE er karakteriseret ved lav produktion af normalt C1-esterase-inhibitor. 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-esterase-inhibitor. Ved mangel eller dysfunktionalitet af C1-esterase-inhibitor kan der opstå en kædereaktion, der kan få 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). I 2014 opgjorde professor Anette Bygum HAE-patienterne i Danmark. Her var antallet 95 danske patienter tilhørende 31 danske familier med type I og type II HAE (3). Aktuelt er der registreret 109 patienter, som jævnligt kontrolleres på det Nationale Kompetencecenter for HAE på Odense Universitetshospital. Samme opgørelse fra 2014 viste, at anfaldsfrekvensen varierede fra asymptomatiske patienter med 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 dødelige karakter af sygdommen 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 er for den enkelte patient uforudsigeligt. Det samme er sværhedsgraden. 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.

1.3 Nuværende behandling

Behandlingsmål for type I og type II HAE er at minimere anfaldshyppigheden og/eller anfaldenes sværhedsgrad. Behandlingen opdeles i akut anfaldsbehandling og forebyggende behandling.

Til anfaldsbehandling anvendes enten intravenøs substitution af manglende funktionelt C1-esterase-inhibitor eller det bradykinin-blokerende lægemiddel icatibant, som administreres subkutant. Når anfaldet først er i gang og hævelsen dannet, kan det være sværere at påvirke varigheden og sværhedsgraden af anfaldet med medicin. For at medicinen har optimal effekt, skal denne derfor helst tages tidligst muligt i anfaldets udvikling. Ved rettidig behandling reduceres varigheden til ½-3 timer, og behandlingssvigt ses sjældent; dog vil det variere, hvilken anfaldsbehandling patienten har størst gavn af. Ved anfaldsdebut kan patienten ikke selv vurdere, om anfaldet udvikler sig i mild, moderat eller svær grad. Strategien er derfor at behandle alle anfald. De fysiske rammer og det psykiske stress som patienten befinder sig i når anfaldet debuterer, kan være en udfordring i forhold til den intravenøse selvadministration.

Til forebyggende behandling anvendes de to lægemidler C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze). Begge lægemidler indeholder C1-esterase-inhibitor. Behandlingerne administreres intravenøst og oftest hver 3.-4. dag.

Den forebyggende behandling iværksættes i henhold til den gældende internationale guideline fra World Allergy Organization og European Academy Allergy and Clinical Immunology fra 2017 (2). Der eksisterer 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 med anfaldsbehandling. Da alle disse faktorer varierer over tid, vurderes behovet for forebyggende behandling ved hvert kontrolbesøg. Patientens præferencer er også en væsentlig faktor. Flere patienter ser en barriere i den nuværende forebyggende behandling, da lægemidlerne administreres i.v. Derfor er det i dag patienter med hyppige anfald, som overvejende behandles forebyggende. Ud af de 120 danske patienter anslår fagudvalget at ca. 30-40 patienter får forebyggende behandling. De fleste patienter administrerer selv deres anfaldsbehandling såvel som deres forebyggende behandling (eventuelt med hjælp fra pårørende). Patienter, der ikke selv behersker teknikken behandles på lokalt hospital.

1.4 Behandling med lanadelumab (Takhzyro)

Indikation

Lanadelumab (Takhzyro) er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover.

Virkningsmekanisme

Lanadelumab er et fuldt humant monoklonalt antistof fremstillet ved rekombinant DNA-teknologi, som hæmmer det aktive plasmakallikreins proteolytiske aktivitet, hvorved risikoen for angioødemanfald mindskes.

Dosering

Den anbefalede dosis for lanadelumab (Takhzyro) er 300 mg hver 2. uge. Lanadelumab (Takhzyro) administreres ved subkutan injektion, og patienten eller eventuelt en pårørende kan, efter oplæring, selv administrere behandlingen.

1.4.1 Komparator

Medicinrådet har defineret profylaktisk behandling med i.v. C1-esterase-inhibitor som komparator.

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af lanadelumab (Takhzyro) som rutinemæssig forebyggelse for følgende populationer:

- Hvilken klinisk merværdi tilbyder rutinemæssig forebyggelse med lanadelumab (Takhzyro) hos voksne patienter og børn ≥ 12 år med arveligt angioødem sammenlignet med nuværende standardbehandling?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af inkrementelle omkostninger per patient sammenlignes behandling med lanadelumab (Takhzyro) med behandling med i.v. C1-esterase-inhibitor. Ansøger har indsendt en analyse, der sammenligner lanadelumab (Takhzyro) med en kombination af 50% C1-esterase-inhibitor (Berinert) og 50% C1-esterase-inhibitor (Cinryze).

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøgers omkostningsanalyse har til formål at estimere de inkrementelle omkostninger ved behandling med lanadelumab (Takhzyro). Ansøger har valgt at komparator består af en kombination af 50% C1-esterase-inhibitor (Berinert) og 50% C1-esterase-inhibitor (Cinryze).
Analysen inkluderer omkostninger til lægemidler, behandling af anfald, patienttid og transport. Analysen inkluderer ikke monitorering, administrations- eller bivirkningsrelaterede omkostninger, da disse antages af ansøger at være ens på tværs af lægemidlerne.

Modellen er en partitioned survival model, hvor den gennemsnitlige patient opstartes i behandling i en alder af 41 år og derefter i gennemsnit modtager behandling i 20,4 år. Ansøger har anvendt mortalitetsraten for den generelle befolkning i Danmark i 2019 fra Danmarks Statistik til at estimere den gennemsnitlige tid patienterne behandles. Ansøger antager, at patienter, der behandles med lanadelumab (Takhzyro), opstartes i en dosis på 300 mg hver 2. uge. Hvis patienterne er anfaldsfrie efter 6 måneder, vil disse patienter nedjusteres til en dosis på 300 mg hver 4. uge, hvilket ansøger antager at være 76,9% af patienterne baseret på studiedata fra HELP-03 (5). Patienter vil herefter fortsætte i de respektive doser i resten af modellens tidshorisont.

Antal anfald om året for patienter, der er kandidater til forebyggende behandling, antages at være 50,5 anfald om året. Denne antagelse bygger på en anfaldfrekvens varierende fra 1 anfald til 84 anfald om året, hvor det gennemsnitlige antal anfald om året er 17 jf. Medicinrådets protokol (6). Ansøger antager samtidig, at patienter, der er kandidater til forebyggende behandling, vil ligge i den øvre halvdel af fordelingen over gennemsnittet (17-84 anfald). Den øvre halvdel af fordelingen antager ansøger at være uniform fordelt, hvilket resulterer i et gennemsnit på 50,5 anfald om året. Det gennemsnitlige antal anfald om året reduceres for patienter, der behandles med lanadelumab (Takhzyro) 300 mg hver 2. uge, med en faktor 0,013, mens gennemsnittet reduceres med en faktor 0,09 for patienter, der behandles med lanadelumab (Takhzyro) 300 mg hver 4. uge. Den relative risiko er 0,27 for komparator, når der laves en indirekte sammenligning med lanadelumab (Takhzyro) 300 mg hver 2. uge.

Amgros' vurdering

Ansøger benytter som komparator en kombination af 50% C1-esterase-inhibitor (Berinert) og 50% C1-esterase-inhibitor (Cinryze), hvilket ikke stemmer overens med behandlingen af HAE. Amgros vælger derfor at udarbejde egen hovedanalyse, hvor lanadelumab (Takhzyro) sammenlignes med både C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze) særskilt. Modellen er i høj grad drevet af andel af patienter, der dosisreduceres efter 6. måneder samt gennemsnitlige antal anfald om året. Amgros har derfor bedt regionerne udpege klinikere med ekspertise indenfor det relevante område, og bedt de valgte klinikere om at validere ansøgers grundlæggende antagelser og estimater. Regionerne udpegede to kliniker, der svarede på spørgsmål angående ansøgers modelstruktur og estimater. På baggrund af deres svar finder Amgros anledning til at ændre på ansøgers estimater angående gennemsnitlige antal anfald om året til 36 anfald, svarende til 3 anfald om måneden.
Den relative risiko for anfald for komparator bygger på en indirekte sammenligning, hvor C1-esterase-inhibitor 1000 IE sammenlignes med lanadelumab (Takhzyro) 300 mg hver 2. uge. I dansk klinisk praksis anvendes en dosis på 1500 IE, hvorfor der er risiko for, at den relative risiko for komparator er underestimeret, hvilket overestimerer antal anfald om året og derved overestimerer de gennemsnitlige meromkostninger til fordel for lanadelumab (Takhzyro). I mangel på bedre estimater benytter Amgros dog ansøgers estimat i Amgros' hovedanalyse.

Amgros vurderer, at ansøgers modeltilgang er acceptabel, men udarbejder egen hovedanalyse, hvor gennemsnitlige antal anfald om året ændres til 36. Samtidig ændrer Amgros komparator til både at være C1-esterase-inhibi-

tor (Berinert) og C1-esterase-inhibitor (Cinryze). Amgros vurderer samtidig, at analysens resultat er drevet af gennemsnitlige antal anfald om året og andelen af patienter, der dosisreduceres efter 6 måneder, hvilket er forbundet med store usikkerheder. Amgros udarbejder derfor følsomhedsanalyser, der belyser usikkerheden ved disse parametre.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en livslang tidshorisont. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4%, mens omkostninger fra år 36 er diskonteret med en rate på 3%.

Amgros' vurdering

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

2.1.3 Omkostninger

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

Lægemiddelomkostninger

Ansøger har inkluderet omkostninger til lægemidler. For lanadelumab (Takhzyro) anvendes en dosis på 300 mg, mens der for både C1-esterase-inhibitor (Cinryze) og C1-esterase-inhibitor (Berinert) anvendes en dosis på 1500 IE.

Alle anvendte lægemiddelpriser er i SAIP, se Tabel 1.

Tabel 1: Anvendte lægemiddelpriser, SAIP (november 2019).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Lanadelumab (Takhzyro)	300 mg	1	[redacted]	Amgros
C1-esterase-inhibitor (Berinert)	500 IE	1	[redacted]	Amgros
C1-esterase-inhibitor (Cinryze)	500 IE	2	[redacted]	Amgros

Amgros' vurdering

Ansøger har valgt at benytte en fast dosis på 1500 IE for både C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze), hvilket ikke stemmer overens med den angivet dosis i begge lægemidlers produktresuméer. Amgros har fået regionernes udpegede klinikere til at validere ansøgers estimater vedrørende dosering af de anvendte lægemidler. Regionens udpegede kliniker vurderer at en dosis på 1500 IE for både C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze) er i overensstemmelse med dansk klinisk praksis.

Ansøgers tilgang accepteres.

Omkostninger til behandling af anfald

Ansøger har i deres hovedanalyse inkluderet omkostninger til behandling af anfald, hvilket indbefatter lægemiddelomkostninger til icatibant (Firazyr), se Tabel 2. Ansøger antager, at 85% af alle anfald kræver akut behandling, hvori den medicinske behandling består af 30 mg icatibant (Firazyr). Gennem samtale med en kliniker antager ansøger, at 1/3 af patienterne kræver to behandlinger med icatibant (Firazyr).

Tabel 2: Lægemiddelpriser for anfaldsbehandling, SAIP (november 2019).

	Styrke	Pakningsstørrelse	Pris [DKK]	Pris per anfald [DKK]	Kilde
Icatiabant (Firazyr)	30 mg	3 ml	[redacted]	[redacted]	Amgros

I forbindelse med behandling af anfald inkluderer ansøger omkostninger til lægebesøg, ambulant besøg og indlæggelser. Ansøger har estimeret enhedsomkostninger for hospitalsomkostninger ved brug af DRG-takster 2019 og Praktiserende Lægers Organisation (PLO) honorartabel.

Ansøger antager, at behandlingskrævende anfald kan inddeles i tre grupper; anfald, der kræver lægebesøg, anfald, der kræver et ambulant besøg og anfald, der kræver indlæggelse. Frekvensen for behandlingskrævende anfald fordeler sig således, at 10,26% kræver lægebesøg, 17,42% kræver ambulant besøg mens 10,74% kræver indlæggelse.

De anvendte takster ses i Tabel 3.

Tabel 3: Omkostninger til behandling af anfald.

	Enhedsomkostning [DKK]	Kode	Kilde
Lægebesøg	142	Konsultation	PLO honorartabel
Ambulant besøg	3.287	16MA98: MDC16 1-dags-gruppe, pat. mindst 7 år	DRG-takster 2019
Indlæggelse	21.911	16MA10: Øvrige sygdomme i blod og bloddannende organer	DRG-takster 2019

Amgros' vurdering

Amgros har talt med regionernes udpegede klinikere og bedt dem validere ansøgers estimater vedrørende fordelingen af behandlingskrævende anfald. Klinikerne vurderer, at frekvensen for behandlingskrævende anfald fordeler sig således, at 2% kræver lægebesøg, 10% kræver ambulant besøg mens 5% kræver indlæggelse.

Ansøgers tilgang accepteres, men ændrer frekvensen for fordelingen af behandlingskrævende anfald i Amgros' hovedanalyse.

Patientomkostninger

Ansøger har valgt at inkludere omkostninger til patienttid. Dette er gjort på baggrund af administration af lægemidler og inkluderer den effektive tid på hospitalet, ventetid og transport. Ansøger anvender Amgros' enhedsomkostning for patienttid, som er 180 DKK per time, og patienttransportomkostninger på 100 DKK per besøg. Ansøgers estimerede patienttid for administration af lægemidler kan ses i Tabel 4.

Tabel 4: Ansøgers estimat af effektiv patienttid for administration af lægemidler.

	Patienttid [minutter]	Totale omkostninger [DKK]
Lanadelumab (Takhzyro)	5	15
C1-esterase-inhibitor (Berinert)	11	33
C1-esterase-inhibitor (Cinryze)	25	75

Ansøger vælger derudover at inkludere omkostninger til patienttid for anfald, hvilket indbefatter den effektive tid på hospitalet/klinik, ventetid og transport. Ansøger antager, at patienttransportomkostninger til lægebesøg

ved praktiserende læge er 50% af patienttransportomkostninger til hospitalet. Ansøgers estimerede patienttid for behandling af anfald kan ses i .
Tabel 5.

Tabel 5: Ansøgers estimat af effektiv patienttid for behandling af anfald.

	Transporttid [besøg]	Patienttid [minutter]	Totale patientomkostninger [DKK]
Icatibant (Firazyr)	-	5	20
Lægebesøg	0,5	60	230
Skadestuebesøg	1	60	280
Indlæggelse	1	480	1.540

Amgros' vurdering

Ansøgers tilgang accepteres.

2.2 Følsomhedsanalyser

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

- Tidshorisonten: 2 år, 5 år, 10 år, livstid
- Blanding af komparator: 100% C1-esterase-inhibitor (Berinert), 100% C1-esterase-inhibitor (Cinryze)
- Andel af patienter, der dosisreduceres: 61,0%, 92,8%
- Gennemsnitlig antal anfald om året: +/- 20%
- Relativ risiko lanadelumab (Takhzyro) 300 mg hver 2. uge sammenlignet med ingen forebyggende behandling: 0,07, 0,24
- Relativ risiko lanadelumab (Takhzyro) 300 mg hver 4. uge sammenlignet med ingen forebyggende behandling: 0,04, 0,19
- Relativ risiko lanadelumab (Takhzyro) sammenlignet med C1-esterase-inhibitor 1000 IE: 0,14, 0,54
- Andel af anfald, som kræver akut behandling: 82,5%, 87,5%
- Omkostninger til behandling af anfald: +/- 20 %
- Behandlinger med icatibant (Firazyr): 1 injektion, 2 injektioner

Amgros' vurdering

Ansøger har inkluderet en række følsomhedsanalyser for at undersøge analysens usikkerheder. Dette er i tråd med Amgros' metodevejledning. Det er dog kun resultatet af de analyser, som Amgros finder mest relevante, som bliver præsenteret, da dette er parametre forbundet med stor usikkerhed.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i Tabel 6.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for lanadelumab (Takhzyro) sammenlignet med komparator til at være ca. [redacted] DKK per patient.

Tabel 6: Resultatet af ansøgers hovedanalyse, DKK.

	Lanadelumab (Takhzyro)	Komparator (50% Berinert og 50% Cinryze)	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Omkostninger til anfald	[redacted]	[redacted]	[redacted]
Patientomkostninger	24.961	188.578	-163.616
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.1.1 Ansøgers følsomhedsanalyser

Ansøger undersøger i en følsomhedsanalyse andelen af patienter, der dosisreduceres efter 6. måneder uden anfald. Estimatet for andelen af patienter varieres, så der anvendes den nedre og øvre grænse indenfor estimatets 95% konfidensinterval, svarende til hhv. 61,0% og 92,8%.
I en anden følsomhedsanalyse undersøger ansøger den relative risiko for at opleve et anfald, når patienten behandles med lanadelumab (Takhzyro) 300 mg hver 4. uge sammenlignet med patienter, der ikke er i forebyggende behandling. Igen varieres estimater, så der anvendes den nede og øvre grænse indenfor estimatets 95% konfidensinterval, hvilket er hhv. 0,04 og 0,19. En tilsvarende følsomhedsanalyse undersøges den relative risiko for at opleve et anfald, når patienten behandles med lanadelumab (Takhzyro) sammenlignet med i.v. C1-esterase-inhibitor. Estimaterne hertil er 0,14 og 0,52.

Resultat af følsomhedsanalyserne kan ses i Tabel 7.

Tabel 7: Resultatet af ansøgers følsomhedsanalyse, DKK.

Parameter	Værdi	Inkrementelle omkostninger
Resultatet af hovedanalysen		[redacted]
Andel af patienter, der dosisreduceres	61,0%	[redacted]
	92,8%	[redacted]
Relativ ratio for anfald, der behandles med lanadelumab (Takhzyro) 300 mg hver 4. uge	0,04	[redacted]
	0,19	[redacted]
Relativ risiko for anfald, der behandles med lanadelumab (Takhzyro) sammenlignet med i.v. C1-esterase-inhibitor	0,14	[redacted]
	0,52	[redacted]

3.2 Amgros' hovedanalyse

Amgros' hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af:

- Lanadelumab (Takhzyro) sammenlignes med C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze) hver for sig
- Justeret gennemsnit for antal anfald om året
- Justeret frekvens for fordelingen af behandlingskrævende anfald

Resultaterne fra Amgros' hovedanalyse præsenteres i Tabel 8.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for lanadelumab (Takhzyro) sammenlignet med komparator på ca. [redacted] DKK sammenlignet med C1-esterase-inhibitor (Berinert) og ca. [redacted] DKK sammenlignet med C1-esterase-inhibitor (Cinryze).

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for lanadelumab (Takhzyro) ca. 34 mio. DKK, mens de total inkrementelle omkostninger bliver ca. -6,3 mio. DKK per patient sammenlignet med C1-esterase-inhibitor (Berinert) og ca. -7,2 mio. DKK per patient sammenlignet med C1-esterase-inhibitor (Cinryze).

Tabel 8: Resultatet af Amgros' hovedanalyse ved sammenligning med komparator, DKK.

	Lanadelumab (Takhzyro)	C1-esterase-inhibitor (Berinert)	C1-esterase-inhibitor (Cinryze)
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Omkostninger til anfald	[redacted]	[redacted]	[redacted]
Patientomkostninger	12.301	97.145	186.231
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

3.2.1 Amgros' følsomhedsanalyser

Amgros udarbejder følsomhedsanalyser, der belyser usikkerhederne forbundet med antagelserne om gennemsnitlige antal anfald om året. Estimatet varieres fra 24 anfald om året, svarende til 2 anfald om måneden, og 48

anfald om året, svarende på 4 anfald om måneden. Disse estimater er baseret på udtalelser fra regionens udpegede kliniker. Derudover udarbejder Amgros en følsomhedsanalyse, der belyser usikkerheden ved antallet af patienter, der dosisreduceres efter 6. måneder uden anfald. Ligesom i ansøgers følsomhedsanalyse, vælger Amgros at variere estimatet for andelen af patienter, så der anvendes den nedre og øvre grænse indenfor estimatets 95% konfidensinterval, svarende til hhv. 61,0% og 92,8%.

Resultat af Amgros' følsomhedsanalyserne kan ses i Tabel 9.

Tabel 9: Resultatet af Amgros' følsomhedsanalyse, DKK.

Parameter	Værdi	Inkrementelle omkostninger C1-esterase-inhibitor (Berinert)	Inkrementelle omkostninger C1-esterase-inhibitor (Cinryze)
Resultatet af hovedanalysen		[redacted]	[redacted]
Antal anfald om året	24	[redacted]	[redacted]
	48	[redacted]	[redacted]
Andel af patienter, der dosisreduceres	61,0%	[redacted]	[redacted]
	92,8%	[redacted]	[redacted]

4 BUDGETKONSEKVENSER

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

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

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Ansøger har estimeret antallet af patienter, som forventer at komme i behandling med lanadelumab (Takhzyro) i scenariet, hvor lanadelumab (Takhzyro) anbefales som mulig standardbehandling. Ansøger antager, at udover de 35 patienter, som på nuværende tidspunkt behandles med forebyggende behandling, vil yderligere 30 patienter opstartes i forebyggende behandling med lanadelumab (Takhzyro), hvis det bliver anbefalet som standardbehandling, grundet administrationsvejen. Disse patienter er medtaget i budgetkonsekvensanalysen i begge scenarier. Estimatet er over en 5-årig periode. Ansøger har antaget, at ingen patienter modtager lanadelumab (Takhzyro) i scenariet, hvor lanadelumab (Takhzyro) ikke bliver anbefalet som mulig standardbehandling. Tabel 10 viser ansøgers estimat af antal patienter årligt.

Tabel 10: Ansøgers estimat af antal patienter per år.

	Anbefales som standardbehandling					Anbefales ikke som standardbehandling				
	År 1	År 2	År 3	År 4	År 5	År 1	År 2	År 3	År 4	År 5
Lanadelumab (Takhzyro)	21	34	47	55	59	0	0	0	0	0
Komparator (50% Berinert og 50% Cinryze)	18	9	0	0	0	35	35	35	35	35
Ingen forebyggende behandling	27	23	18	11	6	30	30	30	30	30

Amgros' vurdering af estimeret antal patienter

Amgros accepterer ansøgers estimeret antal patienter, men udarbejder egen budgetkonsekvensanalyse gældende for både det nuværende patientantal, som får forebyggende behandling, og det potentielt øgede patientantal, som forventes at komme i forebyggende behandling jf. Medicinrådets protokol (6). Samtidig ekskluderer Amgros de 30 ubehandlede patienter, som er kandidater til forebyggende behandling i Amgros' budgetkonsekvensanalyse, men inkluderer dem derimod i en følsomhedsanalyse af budgetkonsekvensanalysen.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen, undtagen patientomkostninger. Med de indlagte antagelser estimerer ansøger, at anvendelse af lanadelumab (Takhzyro) vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5.

Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 11.

Tabel 11: Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal.

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

Amgros' vurdering

Amgros udarbejder egen budgetkonsekvensanalyse, hvor resultatet fra Amgros' hovedanalyse anvendes.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Amgros udarbejder to budgetkonsekvensanalyser for både det nuværende patientantal, som får forebyggende behandling, og det potentielt øgede patientantal, som forventes at komme i forebyggende behandling
- Amgros ekskluderer ubehandlede patienter, som er kandidater til forebyggende behandling.

Med de indlagte antagelser estimerer Amgros, at anvendelse af lanadelumab (Takhzyro) til det nuværende patientantal vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5, se Tabel 12. Ved anvendelse af lanadelumab (Takhzyro) til det potentielt øgede patientantal vil budgetkonsekvenserne resultere i ca. [redacted] DKK i år 5, se Tabel 13.

Tabel 12: Amgros' analyse af totale budgetkonsekvenser for det nuværende patientantal, 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]

Tabel 13: Amgros' analyse af totale budgetkonsekvenser for det potentielt øgede patientantal, 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]

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. -12 mio. DKK i år 5 for det nuværende patientantal, mens budgetkonsekvenserne bliver ca. 31 mio. DKK i år 5 for det potentielt øgede patientantal.

4.2.1 Amgros' følsomhedsanalyse af budgetkonsekvensanalysen

Amgros har udarbejdet en følsomhedsanalyse af budgetkonsekvenserne, der belyser konsekvenser ved inkluderingen af de 30 ubehandlede patienter, som er kandidater til forebyggende behandling.

Resultatet af Amgros' følsomhedsanalyse af budgetkonsekvenserne kan ses i Tabel 14.

Tabel 14: Amgros' følsomhedsanalyse af budgetkonsekvenserne for det potentiel øgede patientantal ved år 5, DKK.

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

5 DISKUSSION

Behandling med lanadelumab (Takhzyro) er forbundet med ekstreme besparelser sammenlignet med både C1-esterase-inhibitor (Berinert) og C1-esterase-inhibitor (Cinryze).

Meromkostningerne er primært drevet af antagelserne om andelen af patienter, der dosisreduceres efter 6 måneder, og antal anfald om året. Amgros' følsomhedsanalyser belyser usikkerhederne ved antagelserne om disse to parametre, hvor det ses, at meromkostningerne forbundet med behandling med lanadelumab (Takhzyro) øges betydeligt, hvis andelen af patienter, der dosisreduceres, reduceres eller hvis gennemsnitlige antal anfald om året reduceres.

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AMGROS

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Medicinrådet

Medicinrådets vurdering af lanadelumab til forebyggende behandling af arveligt angioødem

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om vurderingen

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

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

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	11. december 2019
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Dokumentnummer	64652
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 11. december 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Takhzyro®
Generisk navn	Lanadelumab
Firma	Shire Pharmaceuticals Ireland Limited
ATC-kode	B06AC05
Virkningsmekanisme	Lanadelumab er et fuldt humant, monoklonalt antistof. Lanadelumab hæmmer det aktive plasmakallikreins proteolytiske aktivitet. Øget plasmakallikreinaktivitet fører til angioødemanfald hos patienter med arveligt angioødem. Lanadelumab giver vedvarende kontrol af plasmakallikreinaktiviteten og begrænser dermed genereringen af bradykinin.
Administration/dosis	Lanadelumab er beregnet til subkutan administration. Den anbefalede startdosis er 300 mg hver 2. uge. Dosisnedsættelse til 300 mg lanadelumab hver 4. uge kan overvejes hos stabile patienter uden anfald, herunder især patienter med lav kropsvægt.
EMA-indikation	Takhzyro er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover.

2 Medicinrådets konklusion

Medicinrådet vurderer, at lanadelumab til forebyggende behandling af arveligt angioødem giver en **merværdi af ukendt størrelse** sammenlignet med i.v. C1-esteraseinhibitor. Evidensens kvalitet vurderes at være meget lav.

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.

• **Samlet værdi kan ikke kategoriseres:** På grund af usikkerheder omkring effektforholder det ikke muligt at kategorisere lægemidlets samlede værdi.

3 Forkortelser

CI:	Konfidensinterval
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HAE:	Arveligt angioødem
HR:	*Hazard ratio*
OR:	*Odds ratio*
RR:	Relativ risiko

4 Formål

Formålet med Medicinrådets vurdering af lanadelumab til forebyggende behandling af arveligt angioødem er at vurdere den værdi, lægemidlet har i forhold til et eller flere lægemidler til samme patientgruppe (komparator(er)).

Med udgangspunkt i vurderingen og en omkostningsanalyse udarbejdet af Amgros beslutter Medicinrådet, om lanadelumab kan anbefales som mulig standardbehandling.

5 Baggrund

Arveligt angioødem (HAE)

HAE er en sjælden, arvelig tilstand præget af uforudsigelige anfald af hævelser i hud og slimhinder. HAE debuterer oftest i de første teenageår, men for nogle allerede i barndommen. HAE viser sig ved anfaldsvise hævelser i hud og slimhinder. 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 varer i gennemsnit 3 dage uden behandling (nogle op til 7 dage).

HAE kan potentielt være livstruende, hvis hævelserne f.eks. rammer de øvre luftveje [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. Funktionen af C1-esteraseinhibitor er at regulere kallikrein og bradykinin. Kallikrein og bradykinin frigives i kroppen som svar på skade eller en infektion. De forårsager lokale hævelser og smerte. Der findes to typer af HAE. Hyppigst forekommer type I og type II HAE. 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 mangel eller dysfunktionalitet af C1-esteraseinhibitor produceres der for meget kallikrein og bradykinin, hvorved der opstår en kædereaktion, der kan få 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]. I 2014 opgjorde professor Anette Bygum HAE-patienterne i Danmark. Her var antallet 95 danske patienter tilhørende 31 danske familier med HAE type I og II [3]. Aktuelt er der registreret 109 patienter, som jævnligt kontrolleres på det Nationale Kompetencecenter for HAE på Odense universitetshospital. Samme 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 dødelige karakter af sygdommen 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 er for den enkelte patient uforudsigeligt. Det samme er sværhedsgraden. Foruden sygdomsaktivitet, frekvens og sværhedsgrad af anfald, fylder sygdomsbyrden mellem anfaldene 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 den uforudsigelige og potentielt livstruende sygdom HAE har derfor stor betydning for livskvaliteten med risiko for personlige omkostninger både i forhold til familie- og arbejdsliv. Flere patienter oplever f.eks. en stigmatisering som følge af hyppig behandling og anfald. 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.

Nuværende behandling

Behandlingsmål med den nuværende behandling er at minimere anfaldshyppigheden og/eller anfaldenes sværhedsgrad. Behandlingen opdeles i akut anfaldsbehandling og forebyggende behandling.

Til anfaldsbehandling anvendes enten intravenøs substitution af manglende funktionelt C1-esteraseinhibitor (Berinert/Cinryze/Ruconest) eller et bradykinin-blokerende præparat icatibant (Firazyr), som administreres subkutant. Berinert og Cinryze er plasmaderiverede produkter mens Ruconest indeholder rekombinant C1-esteraseinhibitor. Når anfaldet først er i gang og hævelsen dannet, kan det være sværere at påvirke varigheden og sværhedsgraden af anfaldet med medicin. For at medicinen har optimal effekt, skal denne derfor helst tages tidligst muligt i anfaldets udvikling. Ved rettidig behandling reduceres varigheden til ½-3 timer, og behandlingssvigt ses sjældent; dog vil det variere, hvilken anfaldsbehandling patienten har størst gavn af. Ved anfaldsdebut kan patienten ikke selv vurdere, om anfaldet udvikler sig i mild, moderat eller svær grad. Strategien er derfor at behandle alle anfald. De fysiske rammer og det psykiske stress, som patienten befinder sig i, når anfaldet debuterer, kan være en udfordring i forhold til den intravenøse selvadministration.

Til forebyggende behandling anvendes de to produkter Berinert og Cinryze. Begge produkter indeholder C1-esteraseinhibitor. Behandlingerne administreres intravenøst og oftest hver 3.-4. dag. Berinert doseres efter vægt, hvor standarddosis er 20 enheder/kg. En standardpatient på 75 kg behandles således med 1.500 enheder hver 3.-4. dag. I klinisk praksis optimeres behandlingen hos den enkelte patient afhængig af behandlingseffekt. Det sker typisk ved at ændre doseringsfrekvensen eller ved at øge dosis. Cinryze anvendes oftest i en fast dosis på 1.000 enheder hver 3.-4. dag.

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]. Der eksisterer 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 med anfaldsbehandling. Da alle disse faktorer varierer over tid, vurderes behovet for forebyggende behandling ved hvert kontrolbesøg. Patientens præferencer er også en væsentlig faktor. Flere patienter ser en barriere i den nuværende forebyggende behandling, da den administreres i.v. Derfor er det i dag patienter med hyppige anfald, som overvejende behandles forebyggende. Ud af de 120 danske patienter anslår fagudvalget, at ca. 30-40 patienter får forebyggende behandling. De fleste patienter administrerer selv deres anfaldsbehandling såvel som deres forebyggende behandling (eventuelt med hjælp fra pårørende). Patienter, der ikke selv behersker teknikken behandles på lokalt sygehus.

Anvendelse af det nye lægemiddel

Lanadelumab er et fuldt humant monoklonalt antistof fremstillet ved rekombinant DNA-teknologi, som hæmmer det aktive plasmakallikreins proteolytiske aktivitet, hvorved risikoen for angioødemanfald mindskes.

Lanadelumab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af HAE hos patienter på 12 år og derover. Det administreres ved subkutan injektion i modsætning til den eksisterende profylaktiske behandling. Patienten eller eventuelt en pårørende kan, efter oplæring, selv administrere behandlingen.

Den anbefalede dosis er 300 mg hver 2. uge.

6 Metode

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

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokollen som blev godkendt af Medicinrådet den 21. juni 2019.

Ansøgningen indeholder en sammenligning med C1-esteraseinhibitor, som er den komparator, som er defineret i protokollen.

For effektmålene anfaldsfrihed, anfaldsfrekvens og bivirkninger er sammenligningen foretaget ved en indirekte analyse ved brug af Buchers metode med placebo som fælles komparator. Den indirekte analyse for anfaldsfrihed er baseret på absolutte effektestimater fra studierne, idet data fra komparatorstudiet ikke tillader udregning af et relativt effektestimat. Det relative effektestimat for sammenligningen mellem lanadelumab og C1-esteraseinhibitor er beregnet ud fra en antaget hændelsesrate på 18 % som svarer til andelen af patienter som opnår en 90 % reduktion i anfaldsfrekvens ved behandling med komparator. For effektmålene anfaldsfrekvens og bivirkninger baseres den indirekte sammenligning på de relative effektestimater fra studierne. Den absolutte effektforskel for sammenligningen mellem lanadelumab og C1-esteraseinhibitor er, for effektmålet bivirkninger, beregnet ud fra en antaget hændelsesrate på 0 % som ophører med behandling på grund af en uønsket hændelse ved behandling med C1-esteraseinhibitor. For effektmålet livskvalitet er sammenligningen narrativ.

Medicinrådets sekretariat og fagudvalget er enige i ansøgers fremgangsmåde og vurderer, at kategoriseringen kan basere sig på de indsendte analyser med følgende bemærkninger:

- For effektmålet bivirkninger målt ved andelen af patienter, der ophører med behandling grundet bivirkninger, har ansøger anvendt andelen af patienter, der ophører med behandling grundet uønskede hændelser som grundlag for den indirekte sammenligning.

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

Både den relative og absolutte effekt indgår i kategoriseringen af et lægemiddel. Dette foregår i en trinvis proces. Fagudvalget kategoriserer først den relative foreløbige kategori på baggrund af væsentlighedskriterierne og den absolutte foreløbige kategori på baggrund af de præspecificerede mindste klinisk relevante forskelle. Her er der tale om en ren kvantitativ proces. Herefter fastlægger fagudvalget den aggregerede kategori for hvert effektmål ved at sammenholde de foreløbige kategorier. Her kan fagudvalget inddrage deres kliniske indsigt. Når den samlede kategori for lægemidlets værdi skal fastlægges, sammenvejer fagudvalget alle effektmål. Effektmålenes kategorier kombineres med effektmålenes vægt, og eventuelle kliniske overvejelser inddrages. Den samlede kategorisering af lægemidlets værdi er således delvis en kvantitativ og delvis en kvalitativ proces, hvor der foretages en klinisk vurdering af det foreliggende datagrundlag. Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk værdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har foretaget litteratursøgning efter publicerede, randomiserede studier med data på sammenligningen mellem lanadelumab og C1-esteraseinhibitor som angivet i protokollen. Der blev identificeret 117 referencer, som blev screenet på titel-abstract-niveau. 17 referencer blev screenet på fuldtekstniveau, og heraf blev 5 referencer fra 3 kliniske studier inkluderet. Ud over de fundne referencer blev *European Public Assessment Report* (EPAR) for lanadelumab og C1-esteraseinhibitor anvendt.

De kliniske studier, som vurderingen baseres på, er følgende:

Titel	**Forfatter og publikationsår**	**Intervention**	**Komparator**	**Studienavn**	**Fase**	**NCT-nummer**
Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial.	Banerji et al., JAMA, 2018 [6]	Lanadelumab	Placebo	HELP-03	3	NCT02586805
Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis.	Banerji et al., NEJM, 2017 [7]	Lanadelumab	Placebo	DX-2930-02	1b	NCT02093923
Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks.* *Indirect comparison of intravenous vs. subcutaneous C1-inhibitor placebo-controlled trials for routine prevention of hereditary angioedema attacks.*	Zuraw et al., NEJM, 2010 [8] Lumry et al., Allergy Asthma Proc, 2014 [9] Bernstein et al., Allergy Asthma Clin Immunol, 2019 [10]	C1-esteraseinhibitor	Placebo	CHANGE	3	NCT01005888

8 Databehandling

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

9 Lægemidlets værdi

9.1 Konklusion

Hvad er værdien af rutinemæssig forebyggelse med lanadelumab hos voksne patienter og børn ≥ 12 år med arveligt angioødem sammenlignet med nuværende standardbehandling?

Fagudvalget vurderer, at lanadelumab til forebyggende behandling af patienter med arveligt angioødem giver en **merværdi af ukendt størrelse** sammenlignet med i.v. C1-esteraseinhibitor. Evidensens kvalitet vurderes at være meget lav.

I tabellen herunder fremgår den samlede kategori for lægemidlet og kvaliteten af den samlede evidens. Man kan også se både absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 1: Kategorier og resultater

Effektmål	Måleenhed	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi pr. effektmål
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Anfaldsfrihed Retningsgivende mindste klinisk relevante forskel: 15 %-point Justeret: 7,5 %-point	Andel af patienter som oplever en 90 % reduktion i anfaldsfrekvens (symptomfrihed) fra baseline	Kritisk	44 %-point (18; 70)	Merværdi af ukendt størrelse	3,42 (1,98; 4,87)	Stor merværdi	Stor merværdi
Helbredsrelateret livskvalitet Retningsgivende mindste klinisk relevante forskel: 6 point Justeret: 3 point	Ændring fra baseline målt med AEQoL	Kritisk	Intet estimat	Kan ikke kategoriseres	Intet estimat	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel af patienter som oplever en forbedring på 6 point fra baseline		N/A*	N/A*	Intet estimat	Kan ikke kategoriseres	
Anfaldsfrekvens Retningsgivende mindste klinisk relevante forskel: 20 Justeret: 10 %	Procentvis ændring i antallet af HAE-anfald pr. måned fra baseline	Vigtig	-73 % (-87; -45)	Merværdi af ukendt størrelse	0,27 (0,13; 0,55)	Stor merværdi	Stor merværdi
Uønskede hændelser Retningsgivende mindste klinisk relevante forskel: 10 %-point Justeret: 5 %-point	Andel patienter der ophører behandling grundet uønskede hændelser	Vigtig	-0,06 %-point (- 1,00; 90,3)	Kan ikke kategoriseres	0,94 (0,01; 91,31)	Kan ikke kategoriseres	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi		Merværdi af ukendt størrelse					
Kvalitet af den samlede evidens		Meget lav					

* Der er kun efterspurgt relative effektestimater for dette effektmål.

9.1.1 Gennemgang af studier

Karakteristika

Nedenfor ses en oversigt over væsentlige studiekarakteristika

Tabel 2: Oversigt over studiekarakteristika

Studie	Studiedesign	Inklusions-kriterier	Behandlings-arme	N	Effektmål	Behandlings-varighed
HELP-03 [6]	Randomiseret Dobbeltblindet Placebo-kontrolleret **Parallelgruppe**	HAE type I eller II ≥ 12 år ≥ 1 anfald pr. måned	Lanadelumab 150 mg q4w	28	Primære Investigator bekræftede HAE-anfald fra dag 0-182 Sekundære Investigator bekræftede HAE-anfald, som kræver anfaldsbehandling fra dag 0-182 HAE-anfald af moderate til svær intensitet	26 uger
			Lanadelumab 300 mg q4w	29		
			Lanadelumab 300 mg q2w	27		
			Placebo	41		
DX-2930-02 [7]	Randomiseret Dobbeltblindet Placebo-kontrolleret **Parallelgruppe**	HAE type I eller II ≥ 18 år ≥ 2 anfald pr. måned og min. 1 anfald indenfor seneste 6 måneder	Lanadelumab 400 mg q2w	11	Primære HAE-anfald pr. uge fra dag 8-50 Sekundære HAE-anfald pr. uge fra dag 1-50 HAE-anfald pr. uge fra dag 8-64 HAE-anfald pr. uge fra dag 8-92	2 doser med 14 dages mellemrum (dag 1 og dag 15)
			Lanadelumab 300 mg q2w	5		
			Lanadelumab 100 mg q2w	4		
			Lanadelumab 30 mg q2w	4		
			Placebo	13		
CHANGE [8]	Randomiseret Dobbeltblindet Placebo-kontrolleret ***Cross-over***	HAE type I eller II ≥ 6 år ≥ 2 anfald pr. måned	C1-Inhibitor i.v. hver 3-4 dag	11	Primære HAE-anfald normaliseret til antallet af dage i studiet Sekundære Gennemsnitlig affaldssværhedsgrad Gennemsnitlig varighed af anfald Forbrug af anfaldsmedicin	24 uger: 12 uger aktiv og 12 uger placebo
			Placebo	11		

I HELP-03-studiet er den primære analyse udført på *intention to treat*-populationen, som inkluderer alle randomiserede patienter, som har modtaget minimum en dosis af aktiv behandling eller placebo. Alle sikkerhedsanalyser er udført på *safety*-populationen, som består af alle patienter, som har modtaget minimum en dosis af aktiv behandling eller placebo.

I DX-2930-02 er alle *efficacy*-analyser udført på alle patienter behandlet med lanadelumab 300 mg eller mere og placebobehandlede patienter med en baseline affaldsfrekvens på minimum 2 anfald de foregående 3 måneder. Alle sikkerhedsanalyser er baseret på *safety*-populationen, der inkluderer alle randomiserede patienter, som har modtaget mindst en dosis af forsøgsmedicinen.

I CHANGE-studiet er de statistiske analyser udført på *efficacy*-datasættet, som består af alle randomiserede patienter, som har afsluttet hele den indledende behandlingsfase og modtaget mindst en dosering i crossover-fasen. Alle sikkerhedsanalyser er udført på *safety*-datasættet, som består af alle patienter, som har modtaget en hel eller delvis infusion af behandlingen.

Der er forskelle i studiedesignet for de inkluderede studier. Komparatorstudiet, CHANGE, er et overkrydsningsstudie, mens studierne for lanadelumab er parallelgruppestudier. I overkrydsningsstudier kan der være problemer med bl.a. *carry-over*-effekter fra den ene behandlingsperiode til den anden. I CHANGE-studiet er der testet for sekvens- og periodeeffekter (i hvilken rækkefølge patienten har fået aktiv behandling og placebo, og om der er forskelle i effekt mellem periode 1 og periode 2). I studiet er der ikke signifikante sekvens- og periodeeffekter.

Der er også forskel i behandlingsvarigheden mellem de inkluderede studier, hvor effektestimaterne for lanadelumab primært er baseret på 26 ugers behandling, mens effektestimater for C1-esteraseinhibitor baseres på 12 ugers aktiv behandling. De to behandlinger har forskellig administrationsvej og farmakokinetik, og derfor er det vanskeligt at vurdere, om forskellen i behandlingsvarighed påvirker de indirekte effektestimater. Fagudvalget vurderer dog, at behandlingsvarigheden ikke påvirker estimaterne, fordi data for hvert lægemiddel er opgjort på det tidspunkt, hvor lægemidlerne forventes at have maksimal effekt, altså efter *steady state*-koncentrationen er opnået.

I CHANGE-studiet anvendes en fast dosering af C1-inhibitor på 1.000 enheder i.v. hver 3.-4. dag. Dette er i overensstemmelse med den anbefalede dosis for præparatet Cinryze og i overensstemmelse med den praksis, man anvender i Danmark, når en patient behandles forebyggende med Cinryze. I Danmark anvendes præparatet Berinert sammenlignet med Cinryze hyppigere i den profylaktiske behandling af patienter med HAE. Berinert indgives ligeledes i.v., men modsat Cinryze indgives Berinert som en vægtjusteret dosis (20 enheder/kg). Det er sandsynligt, at patienterne i CHANGE-studiet kunne opnå en bedre behandlingseffekt, hvis C1-esteraseinhibitor blev administreret i en højere dosis eller efter patienternes vægt. Et dosiseskalationsstudie med CINRYZE har vist, at nogle patienter kan opnå en bedre effekt, hvis præparatet indgives i en højere dosis [11]. Derfor er der risiko for, at effekten af C1-esteraseinhibitor er underestimeret i studiet.

Population

Indenfor studierne

Som det fremgår af tabel 2, er der tale om studier med relativt få patienter i hver af behandlingsarmene. I det største studie (HELP-03) er der under 30 patienter randomiseret i hver af de aktive behandlingsarme. I DX-2930-02 er der blot randomiseret 5 patienter til behandling med lanadelumab 300 mg hver 2. uge og 13 patienter til placebo. Komparatorstudiet (CHANGE) har 11 patienter i hver behandlingsarm, men idet der er tale om et overkrydsningsforsøg har det højere statistisk styrke, end hvis studiet var udført som et parallelgruppeforsøg med det samme patientantal.

Indenfor studierne er det lave antal af patienter medvirkende til, at der observeres lidt forskelle i baselinekarakteristika mellem behandlingsarmene. I CHANGE-studiet vurderes det ikke at have betydning, idet overkrydsningen gør, at hver patient fungerer som sin egen kontrol. I DX-2930-02 observeres der bl.a. forskelle i patienternes historiske anfaldsfrekvens, kønsfordeling og alder. Det er sandsynligvis de lave patientantal, fremfor selve randomiseringen, der er årsag til disse forskelle. I HELP-03 er der tilsyneladende lidt forskel i kønsfordelingen, særligt mellem patienter randomiseret til lanadelumab 300 mg q2w og patienter randomiseret til placebo, idet der er en højere andel af kvinder i placebogruppen. Der er dog ikke grund til at tro, at behandlingseffekten er forskellig mellem kvinder og mænd. Den historiske anfaldsfrekvens (i de foregående 12 måneder) varierer også mellem grupperne. Denne forskel er ikke i samme grad afspejlet i anfaldsfrekvensen i run-in perioden, som synes mere sammenlignelig på tværs af behandlingsarmene. Derfor vurderes forskellen i den historiske anfaldsfrekvens ikke at have betydning.

Mellem studierne

Der er vanskeligt at vurdere, om der er forskel i anfaldsfrekvensen ved baseline mellem studierne. Studiernes inklusionskriterier angiver, at patienter i CHANGE-studiet har min. 2 anfald pr. måned, mens patienter i HELP-03 og DX-2930-02 har henholdsvis min. 1 anfald pr. måned og min. 2 anfald pr. år, hvoraf et af anfaldene har været indenfor de seneste 6 måneder. Anfaldsfrekvensen ved baseline er ikke opgivet i CHANGE-studiet. I HELP-03 og DX-2930-02 er den månedlige anfaldsfrekvens ved baseline opgjort til henholdsvis 3,7 anfald pr. måned og 0,33-0,39 anfald pr. uge (svarende til ca. 1,3-1,6 anfald per måned). 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.

Fagudvalget har samlet vurderet, at studierne er tilstrækkelig ens, og at studierne kan danne grundlag for en sammenlignende kvantitativ analyse. Fagudvalget vurderer i øvrigt, at patientpopulationerne i studierne er sammenlignelige med danske HAE-patienter.

Resultater og vurdering

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

Anfaldsfrihed (kritisk)

Fagudvalget ønskede dette effektmål opgjort som en forskel i andelen af patienter, som opnår en 100 % reduktion i anfaldsfrekvens fra baseline, idet det at opnå symptomfrihed vil kunne eliminere frygten for larynxødem (hævelser i de øvre luftveje), hvilket har stor betydning for patienternes livskvalitet. Til vurdering af effektmålet anfaldsfrihed har ansøger indsendt komparative data på andelen af patienter, som opnår en 90 % reduktion i anfaldsfrekvens fra baseline. Dette er i overensstemmelse med protokollen, hvor 90 % reduktion i anfaldsfrekvens er angivet som et brugbart alternativ til en 100 % reduktion. I protokollen er der defineret en retningsgivende mindste klinisk relevant forskel på 15 %-point.

I HELP-03-studiet oplevede 44,4 % af patienterne, at de blev anfaldsfri (helt fravær af anfald under studiet) ved behandling med lanadelumab 300 mg q2w, mens kun 2,4 % af patienterne behandlet med placebo oplevede anfaldsfrihed. Der er dermed en markant højere andel, som opnår anfaldsfrihed ved behandling med lanadelumab end ved behandling med placebo. Som nævnt ovenfor er der ikke grundlag for en sammenligning af 100 % anfaldsfrihed med i.v. C1-esteraseinhibitor, men fagudvalget bemærker, baseret på deres kliniske erfaring, at andelen af patienter, som opnår anfaldsfrihed med den nuværende standardbehandling, er meget begrænset (estimeret til ca. 0,5-1,0 % i protokollen).

I HELP-03-studiet er forskellen i andelen af patienter, som opnår 90 % reduktion i deres anfaldsfrekvens fra baseline på 61,8 %-point (39,5; 78,8) sammenlignet med placebo. I CHANGE-studiet er forskellen i 90 % reduktion mellem C1-esteraseinhibitor og placebo på 18,2 %-point (6,6; 40,1). Resultatet af den indirekte sammenligning viser, at en højere andel af patienter behandlet med lanadelumab opnår 90 % reduktion i deres anfaldsfrekvens, idet effektestimatet baseret på den indirekte analyse er 44 %-point (18; 70).

Baseret på den absolutte effektforskel har lanadelumab foreløbigt en **merværdi af ukendt størrelse** vedr. anfaldsfrihed, idet den nedre grænse i konfidensintervallet for det indirekte effektestimat er højere end den justerede mindste klinisk relevante forskel på 7,5 %-point.

Den relative effektforskel er afledt af den absolutte effektforskel, som var udgangspunktet for den indirekte analyse. Det relative estimat på 3,42 (1,98; 4,87) er beregnet ved brug af en antaget hændelsesrate på 18 % som svarer til andelen af patienter som opnår 90 % reduktion i deres anfaldsfrekvens fra baseline ved behandling med C1-esteraseinhibitor. Baseret på den relative effektforskel har lanadelumab foreløbigt en **stor merværdi** vedr. anfaldsfrihed, idet den nedre grænse for konfidensintervallet på 1,98 er større end 1,33.

På aggregeret niveau vurderer fagudvalget, at lanadelumab har en **stor merværdi** vedr. anfaldsfrihed (meget lav evidenskvalitet), idet den relative effektforskel viste en stor merværdi og den absolutte effektforskel understøtter denne effekt, da andelen af patienter, som opnår en 90 % reduktion i anfaldsfrekvens ligger betydeligt højere end den mindste klinisk relevante forskel.

Helbredsrelateret livskvalitet (kritisk)

Fagudvalget har ønsket 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. Scoren går fra 0-100, hvor en højere score indikerer en dårligere livskvalitet. Den mindste klinisk relevante forskel er sat til 6 point, da denne forskel er fundet at være klinisk betydende ved anvendelse af AE-QoL. Der foreligger kun data med AEQoL fra HELP-03-studiet med lanadelumab, og derfor har det ikke været muligt at lave en indirekte sammenligning for dette effektmål.

I HELP-03-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, idet forskellen mellem lanadelumab og placebo på 16,57 point (4,62; 28,53) er højere end den mindste klinisk relevante forskel på 6 point. Resultaterne fra HELP-03-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 CHANGE-studiet er livskvalitet målt ved det generiske livskvalitetsværktøj SF-36. SF-36 er et generisk instrument, som bygger på 36 spørgsmål udarbejdet til at vurdere livskvalitet. Spørgeskemaet er inddelt i 8 helbredsrelaterede domæner: fysisk funktion, fysisk betingede begrænsninger, psykisk betingede begrænsninger, social funktion, fysisk smerte, psykisk helbred, energi samt alment helbred. Scoren måles på en skala fra 0-100, hvor højere score repræsenterer bedre livskvalitet [12]. Resultaterne er opgjort som gennemsnitlige ændringer i domænespecifikke og overordnede score [9]. De to globale score *Physical Component Summary* og *Mental Component Summary* viser statistisk signifikante forbedringer i patienternes livskvalitet ved behandling med C1-esteraseinhibitor sammenlignet med placebo, det samme gør de enkelte domænespecifikke scorer. Fagudvalget har ikke kendskab til publicerede mindste klinisk relevante forskelle på SF-36 for patienter med HAE, og derfor er der ikke grundlag for at vurdere, om de statistisk signifikante forskelle også er klinisk relevante.

Idet der ikke foreligger komparativ evidens for livskvalitet mellem lanadelumab og C1-esteraseinhibitor, har fagudvalget ikke noget grundlag for at kategorisere lanadelumabs værdi. Derfor fastsættes den foreløbige kategori for livskvalitet til **kan ikke kategoriseres**. Fagudvalget noterer sig, at begge behandlinger påvirker patienternes livskvalitet i positiv retning.

Anfaldsfrekvens (vigtig)

Fagudvalget vil vurdere anfaldsfrekvens ved at se på forskellen i den gennemsnitlige procentvise ændring i antallet af HAE-anfald pr. måned. Anfaldsfrekvens er et effektmål, som traditionelt rapporteres i studier på forebyggende behandling af arveligt angioødem. Den procentvise ændring er valgt, fordi der er stor individuel variation i anfaldsfrekvens fra patient til patient. Fagudvalget anser en reduktion på 20 % som den mindste klinisk relevante forskel.

De relative effektestimater danner grundlag for den indirekte analyse. Baseret på den relative effektforskel på 0,27 (0,13; 0,55) har lanadelumab foreløbigt en **stor merværdi** vedr. anfaldsfrekvens, idet den øvre grænse for konfidensintervallet på 0,55 er mindre end 0,75.

Den absolutte effektforskel er beregnet med udgangspunkt i det relative effektestimat. Beregningen er uafhængig at hændelsesraten for komparator, da de absolutte effektforskelle er opgjort som en procentvis forskel. Baseret på den absolutte effektforskel på -73 % (-87; -45) har lanadelumab foreløbigt en **merværdi af ukendt størrelse** vedr. anfaldsfrekvens, idet den øvre grænse for konfidensintervallet på -45 % er lavere end den justerede mindste klinisk relevante forskel på -10 %.

På aggregeret niveau vurderer fagudvalget, at lanadelumab har en **stor merværdi** vedr. anfaldsfrekvens (meget lav evidenskvalitet) idet både den relative og den absolutte effekt viste en gevinst ved lanadelumab sammenlignet med C1-esteraseinhibitor. På den absolutte skala lå effektestimatet noget højere end den mindste klinisk relevante forskel.

Uønskede hændelser (vigtig)

Fagudvalget 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 anvendt andelen af patienter, som ophører med behandling på grund af uønskede hændelser som grundlag for den indirekte sammenligning. Fagudvalget anser uønskede hændelser som et brugbart alternativ, idet bivirkninger udgør en delmængde af den samlede mængde uønskede hændelser og vurderer, at den mindste klinisk relevante forskel på 10 %-point fortsat er gældende.

Den nuværende standardbehandling er veltolereret, og patienterne oplever sjældent bivirkninger. Dette er afspejlet i data fra studierne, hvor kun meget få patienter ophører med behandling på grund af uønskede hændelser. I CHANGE-studiet med C1-esteraseinhibitor er der ingen patienter, som ophører med behandling på grund af uønskede hændelser. Det samme gør sig gældende i DX-2930-02-studiet, mens kun en patient i placebogruppen ophørte med behandling på grund af en uønsket hændelse i HELP-03-studiet. Ingen af patienterne behandlet med lanadelumab 300 mg q2w ophørte med behandling på grund af uønskede hændelser.

Baseret på den absolutte og den relative effektforskel kan værdien af lanadelumab foreløbigt **ikke kategoriseres**, idet de få events medfører et meget bredt konfidensinterval for det indirekte effektestimat.

På aggregeret niveau kan fagudvalget, på grund af usikkerheder, **ikke kategorisere** lanadelumabs værdi. vedr. uønskede hændelser, der medfører behandlingsophør (meget lav evidenskvalitet). De få hændelser antyder, at begge behandlinger er veltolererede. Fagudvalget finder det derfor også rimeligt at antage, at der ikke er forskel på de to behandlinger, hvad angår andelen af patienter, som ophører med behandling på grund af uønskede hændelser.

Gennemgang af bivirkninger

Den mest almindeligt (52,4 %) observerede bivirkning forbundet med lanadelumab var reaktioner på injektionsstedet, herunder smerter på injektionsstedet, erytem på injektionsstedet og blå mærker på injektionsstedet. Af disse reaktioner var 97 % af mild sværhedsgrad, og 90 % forsvundet inden for 1 dag, efter de indtrådte og med en gennemsnitsvarighed på 6 minutter.

De mest almindelige observerede bivirkninger forbundet med C1-esteraseinhibitor er hovedpine og kvalme.

Generelt vurderes både lanadelumab og C1-esteraseinhibitor at være veltolererede behandlinger.

9.1.2 Evidensens kvalitet

Evidensens kvalitet er samlet set vurderet som værende **meget lav**.

GRADE-vurderingen er udført separat for de direkte sammenligner, der bruges som grundlag for den indirekte sammenligning. Evidensens kvalitet for sammenligningen mellem lanadelumab og placebo er vurderet som værende **lav**. Evidensens kvalitet for sammenligningen mellem C1-esteraseinhibitor og placebo er vurderet som værende **meget lav**. Evidensens kvalitet for sammenligningen mellem lanadelumab og C1-esteraseinhibitor er nedgraderet et niveau for *indirectness*, idet der er tale om en indirekte sammenligning. Den samlede kvalitet ender dermed på meget lav. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

10 Andre overvejelser

Akkumuleret effekt over tid

Da behandlingsvarigheden i henholdsvis lanadelumab-studierne og C1-esteraseinhibitor studiet er forskellig, bad fagudvalget ansøger om at diskutere, hvor hurtigt effekten for de enkelte præparater indtræder og samtidig hvornår *steady state*-koncentrationen forventes at være opnået. Ansøger har i diskussionen taget udgangspunkt i præparaternes plasmahalveringstid og tid til *steady state*. C1-esteraseinhibitor har en kort halveringstid og behandlingen indgives ofte (hver 3.-4. dag). *Steady state*-koncentrationen opnås, i kraft af administrationsvejen, indenfor relativ kort tid. For lanadelumab opnås *steady state*-koncentrationen først efter 70 dage. Effekten af lægemidlerne vurderes på denne baggrund at være opgjort på et tidspunkt, hvor lægemidlerne hver især må forventes at have maksimal effekt.

Vedrørende dosisreduktion

I protokollen bad fagudvalget ansøger om at bidrage med information om, hvor mange patienter som forventes at blive reduceret til 300 mg hver 4. uge. Fagudvalget kan med det begrænsede kendskab til lanadelumab ikke vurdere, om det vil være muligt at reducere doseringsfrekvensen til hver 4. uge og har heller ikke noget grundlag for at vurdere, hvor mange patienter der vil have tilstrækkelig gavn af behandling hver 4. uge. Ifølge lanadelumabs produktresumé kan dosisreduktion overvejes hos patienter, der er stabilt anfaldsfrie, især hos patienter med lav vægt. Derfor må det forventes, at dosis hos en andel af patienterne kan reduceres og ikke alle patienter forventes at skulle behandles med fuld dosis hver 2. uge.

Kriterier for forebyggende behandling

Behovet for forebyggende behandling vurderes under hensyntagen til patientens sygdomsaktivitet, anfaldsfrekvens/sværhedsgrad/lokation, livskvalitet og eventuelt manglende sygdomskontrol med anfaldsbehandling.

Fagudvalget forslår følgende kriterier for opstart af forebyggende behandling:

- Min. 4 anfald om måneden
- Væsentlig nedsat livskvalitet uagtet antallet af anfald.

Da ovenstående faktorer varierer over tid, bør behovet for forebyggende behandling vurderes ved hvert kontrolbesøg.

11 Fagudvalgets vurdering af samlet værdi og samlet evidensniveau

Fagudvalget vurderer, at lanadelumab til forebyggende behandling af patienter med HAE giver en **merværdi af ukendt størrelse** sammenlignet med i.v. C1-esteraseinhibitor. Evidensens kvalitet vurderes at være meget lav.

Fagudvalget har i den samlede vurdering lagt vægt på, at en betydeligt større andel af patienterne opnår 90 % reduktion i anfaldsfrekvensen med lanadelumab sammenlignet med C1-esteraseinhibitor, udtrykt ved en stor merværdi på det kritiske effektmål anfaldsfrihed. Der fandtes ikke komparative data for 100 % reduktion i anfaldsfrekvens. På det vigtige effektmål anfaldsfrekvens er der ligeledes påvist en stor merværdi af lanadelumab sammenlignet med C1-esteraseinhibitor. Fagudvalget har lagt vægt på, at lanadelumab er veltolereret på lige fod med C1-esteraseinhibitorer, og at der ikke er set væsentlige bivirkninger i studierne. På det kritiske effektmål livskvalitet er data ikke sammenlignelige, fordi der i studierne er anvendt forskellige måleredskaber. Derfor er det ikke muligt at fastslå, om, og i givet fald hvor meget, lanadelumab forbedrer livskvaliteten sammenlignet med C1-esteraseinhibitor. Dog bemærker fagudvalget, at der er påvist en betydelig effekt af lanadelumab på livskvalitet sammenlignet med placebo, hvor en stor andel af patienter opnår en klinisk relevant forbedring af livskvalitet. I den samlede vurdering har fagudvalget også inddraget usikkerheden vedrørende komparator fra den indirekte sammenligning. I CHANGE-studiet administreres C1-esteraseinhibitor som en fast dosis på 1.000 enheder. I dansk klinisk praksis gives C1-esteraseinhibitor i en gennemsnitlig dosis på 1.500 enheder, som kan øges til op mod 2.500 enheder, hvis effekten ikke er tilfredsstillende. Dette er medvirkende til, at effekten af komparator i studiet sandsynligvis er underestimeret i forhold til den behandling, som gives i dansk klinisk praksis.

Fagudvalget forventer desuden, at den stigmatisering, som mange patienter oplever som følge af hyppig behandling og anfald, vil blive reduceret ved behandling med lanadelumab for en stor andel af patienterne.

12 Rådets vurdering af samlet værdi og samlet evidensniveau

Medicinrådet vurderer, at lanadelumab til forebyggende behandling af arveligt angioødem giver en **merværdi af ukendt størrelse** sammenlignet med i.v. C1-esteraseinhibitor. Evidensens kvalitet vurderes at være meget lav.

13 Relation til eksisterende behandlingsvejledning

Der findes ingen tidligere behandlingsvejledning fra RADS eller Medicinrådet på området.

14 Referencer

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende arveligt angioødem

Formand	**Indstillet af**
Rikke Elkjær Andersen Speciallæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke udpege en kandidat	Region Nordjylland
Afventer udpegning	Region Midtjylland
Shailajah Kamaleswaran Speciallæge	Region Syddanmark
Kan ikke udpege en kandidat	Region Sjælland
Kan ikke udpege en kandidat	Region Hovedstaden
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
Sekretariatets arbejdsgruppe: Jesper Skov Neergaard (projekt- og metodeansvarlig) Heidi Møller Johnsen (projektdeltager) Gedske Thomsen (projektdeltager) Anette Pultera Nielsen (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistiker) Annemette Anker Nielsen (teamleder)

16 Versionslog

Version	Dato	Ændring
1.0	11. december 2019	Godkendt af Medicinrådet

17 Bilag 1: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

Banerji et al., 2018. HELP-03. NCT02586805

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Some concerns**	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. De er tendens til forskelle i visse baselinekarakteristika, f.eks. den historiske anfaldsfrekvens, kønsfordeling og anvendelse af forebyggende behandling op til studiets start.
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Low**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får.
Effect of adhering to intervention	**Low**	
Missing outcome data	**Low**	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.
Risk of bias in measurement of the outcome	**Low**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får.
Risk of bias in selection of the reported result	**Low**	Analyser udført efter den statistiske analyse plan.
Overall risk of bias	**Low**	Den samlede risiko for bias vurderes som *low*, selvom ubalance i visse baselinekarakteristika medfører *some concerns* i forhold til randomiseringen.

Fagudvalget bemærker at:

- Dyax Corp (nu Shire Human Genetic Therapies) var involveret i designet og gennemførelsen af studiet, herunder indsamling, håndtering, analyse og fortolkning af data og i gennemgangen af manuskriptet.
- En stor del af forfatterne har økonomiske interessekonflikter.

Banerji et al., 2017. DX-2930-02. NCT02093923

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Some concerns**	Patienterne er randomiseret 2:1 til enten placebo eller lanadelumab. Behandlingsallokering foregik via et *Interactive Web-based Randomization System (IWRS).* De er tendens til forskelle i visse baselinekarakteristika, f.eks. den historiske anfaldsfrekvens og kønsfordeling. Der er tale om meget små grupper, så det skyldes sandsynligvis tilfældigheder.
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Low**	Dobbeltblindet studie. Hverken personale, patienter eller sponsor har kendskab til, hvilken behandling patienterne får.
Effect of adhering to intervention	**Low**	
Missing outcome data	**Low**	Der blev udført en post hoc-modificeret intention to treat-effektivitetsanalyse, der udelukkede to patienter. Sikkerhedsanalyser blev udført på sikkerhedspopulationen, som omfattede alle patienter, der modtog en eller flere doser af studiemedicin Manglende data blev ikke forsøgt imputeret.
Risk of bias in measurement of the outcome	**Low**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får.
Risk of bias in selection of the reported result	**Low**	Analyser udført efter den offentliggjorte protokol.
Overall risk of bias	**Low**	Den samlede risiko for bias vurderes som *low*, selvom ubalance i visse baseline karakteristika medfører *some concerns* i forhold til randomiseringen.

Fagudvalget bemærker at:

- Dyax Corp (nu Shire Human Genetic Therapies) var involveret i designet og gennemførelsen af studiet, herunder indsamling, håndtering, analyse og fortolkning af data.
- En stor del af forfatterne har økonomiske interessekonflikter.

Zuraw et al., 2010; Lumry et al., 2014. CHANGE. NCT01005888

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Some concerns**	Randomiseringsproceduren er stort set ikke beskrevet. Der er ikke umiddelbart forskelle i baselinekarakteristika. Der er tale om små behandlingsgrupper. Randomiseringskoderne blev opbevaret af undersøgelsesstedets farmaceut. Lægemidlerne (C1INH-nf eller placebo) blev rekonstitueret på undersøgelsesstedets apotek i henhold til randomiseringsprocedurerne og blev herefter leveret til investigator for at opretholde studiets blinding.
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Low**	Dobbeltblindet studie. Hverken personale (med undtagelse af en ublindet farmaceut) og patienter har kendskab til, hvilken behandling patienterne får.
Effect of adhering to intervention	**Low**	
Missing outcome data	**Low**	Effektivitetsdatasættet bestod af alle forsøgspersoner, der blev randomiseret i en af to behandlingssekvenser, og som afsluttede hele den indledende behandlingsfase og desuden modtog mindst en behandling i crossover-fasen. Sikkerhedsdatasættet bestod af alle forsøgspersoner, der modtog en fuldstændig eller delvis infusion af terapeutisk behandling. Manglende data blev ikke forsøgt imputeret.
Risk of bias in measurement of the outcome	**Low**	Dobbeltblindet studie. Hverken personale (med undtagelse af en ublindet farmaceut) og patienter har kendskab til, hvilken behandling patienterne får.
Risk of bias in selection of the reported result	**Low**	Analyser udført efter den offentliggjorte protokol.
Overall risk of bias	**Low**	Den samlede risiko for bias vurderes som *low*, selvom randomiseringen ikke er beskrevet i tilstrækkelige detaljer (*some concerns*), vurderes det ikke at have betydning for studiets validitet.

Fagudvalget bemærker at:

- En stor del af forfatterne har økonomiske interessekonflikter.

17.2 GRADE-evaluering af evidenskvaliteten

Lanadelumab vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lanadelumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Anfaldsfrihed (follow up: 26 weeks; assessed with: Andel af patienter som oplever en 100 % reduktion i anfaldsfrekvens (symptomfrihed) fra baseline)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	12/27 (44.4%)	1/41 (2.4%)	**RR 18.2** (2.5 to 132.2)	**42 more per 100** (from 18 more to 62 more)	⊕⊕◯◯ LOW	CRITICAL
Anfaldsfrihed (follow up: 26 weeks; assessed with: Andel af patienter som oplever en 90 % reduktion i anfaldsfrekvens (symptomfrihed) fra baseline)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	18/27 (66.7%)	2/41 (4.9%)	**RR 13.8** (3.5 to 54.9)	**62 more per 100** (from 40 more to 79 more)	⊕⊕◯◯ LOW	CRITICAL
Helbredsrelateret livskvalitet (follow up: 26 weeks; assessed with: Ændring fra baseline målt med AEQoL)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	27	41	-	MD **16.57 points lower** (28.53 lower to 4.62 lower)	⊕⊕◯◯ LOW	CRITICAL
Helbredsrelateret livskvalitet (follow up: 26 weeks; assessed with: Andel af patienter som oplever en forbedring på 6 point fra baseline)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	21/26 (80.8%)	14/38 (36.8%)	**RR 2.2** (1.4 to 3.5)	**44 more per 100** (from 22 more to 66 more)	⊕⊕◯◯ LOW	CRITICAL
Anfaldsfrekvens (assessed with: Procentvis ændring i antallet af HAE-anfald pr. måned fra baseline)												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	-/27	1/41	**Rate ratio 0.13** (0.07 to 0.24)		⊕⊕⊕◯ MODERATE	IMPORTANT
Uønskede hændelser (assessed with: Andel patienter der ophører behandling grundet uønskede hændelser)												
2	randomised trials	not serious	not serious	not serious	serious [c]	none	0/32 (0.0%)	1/54 (1.9%)	**RR 0.50** (0.02 to 11.84)	**2 fewer per 100** (from 3 fewer to 7 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Det er ikke muligt at vurdere inkonsistens, idet der kun foreligger ét studie; b. Der er nedgraderet på optimal information size; c. Der er tale om meget få hændelser, som gør estimatet usikkert.

C1-esterase inhibitor vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	C1-esterase-inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
Anfaldsfrihed (follow up: 12 weeks; assessed with: Andel af patienter som oplever en 90 % reduktion i anfaldsfrekvens (symptomfrihed) fra baseline)												
1	randomised trials	not serious	serious [a]	serious [b]	serious [c]	none	22	22	-	MD **18.2 %-point lower** (40.1 lower to 6.6 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Helbredsrelateret livskvalitet (assessed with: AE-QoL)												
0							Der foreligger ikke data på AE-QoL i dette studie				-	CRITICAL
Anfaldsfrekvens (follow up: 12 weeks; assessed with: Procentvis ændring i antallet af HAE-anfald pr. måned fra baseline)												
1	randomised trials	not serious	serious [a]	serious [b]	serious [c]	none	-/22	-/22	**Rate ratio 0.48** (0.39 to 0.59)		⨁◯◯◯ VERY LOW	IMPORTANT
Uønskede hændelser (follow up: 12 weeks; assessed with: Andel patienter der ophører behandling grundet uønskede hændelser)												
1	randomised trials	not serious	serious [a]	serious [b]	serious [d]	none	0/22 (0.0%)	0/22 (0.0%)	**RR 1.00** (0.02 to 48.28)	**0 fewer per 100** (from 3 fewer to 3 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Det er ikke muligt at vurdere inkonsistens, idet der kun foreligger ét studie; b. Dosis i studiet afviger fra standardbehandling i Danmark, hvor C1-esteraseinhibitor gives som en vægtjusteret dosis; c. Der er nedgraderet på optimal information size; d. Der er tale om meget få hændelser, som gør estimatet usikkert.

Application for the assessment of clinically added value of Takhzyro (lanadelumab) for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

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1 Basic information

Table 1 Contact information

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Area of responsibility	
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Table 2 Overview of the pharmaceutical

Proprietary name	Takhzyro®
Generic name	Lanadelumab
Marketing authorization holder in Denmark	Shire Pharmaceuticals Ireland Limited Blocks 2 & 3 Miesian Plaza 50-58 Baggot Street Lower Dublin 2 Ireland
ATC code	B06AC05
Pharmacotherapeutic group	Other haematological agents, drugs used in hereditary angioedema
Active substance(s)	Lanadelumab
Pharmaceutical form(s)	Solution for subcutaneous injection
Mechanism of action	Lanadelumab is a fully human, monoclonal antibody (IgG1/ κ-light chain). Lanadelumab inhibits active plasma kallikrein proteolytic activity. Increased plasma kallikrein activity leads to angioedema attacks in patients with HAE through the proteolysis of high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin. Lanadelumab provides sustained control of plasma kallikrein activity and thereby limits bradykinin generation in patients with HAE.
Dosage regimen	The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.
Therapeutic indication relevant for assessment (as	TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

defined by the European Medicines Agency, EMA)	
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes (BEGR)
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	300 mg lanadelumab in 2 ml of solution in a single use vial (type I glass) with a coated butyl rubber stopper and an aluminium seal with violet flip-off cap. Pack size of 1 vial. Each pack also contains the following items: Empty 3 ml syringe 18G vial access needle 27G x ½ inch (0.4 x 13 mm) injection needle
Orphan drug designation	Yes.

2 Abbreviations

AE	Adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
ALAT	Alanine transaminase
ARR	Absolute Risk Reduction
ASAT	Aspartate aminotransferase
C1-INH	C1-esterase inhibitor
CI	Confidence interval
DMC	Danish Medicines Council
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HAE	Hereditary Angioedema
HRQoL	Health Related Quality of Life
ITC	Indirect Treatment Comparison
IU	International Units

IV	Intravenous
MCS	Mental Component Score
NMA	Network Meta-Analysis
PCS	Physical Component Score
Q2w	Every 2 weeks
Q4w	Every 4 weeks
RaR	Rate Ratio
RR	Risk Ratio
SC	Subcutaneous
SD	Standard deviation
SF-36	Short Form 36
SLR	Systematic Literature Review
TEAE	Treatment Emergent Adverse Event

3 Summary

This application concerns Takhzyro (lanadelumab), indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

HAE is a rare, hereditary condition characterized by unpredictable attacks of swelling of the skin and mucous membranes called angioedema. HAE can potentially be life-threatening if the swelling, e.g. affects the upper airways.

Lanadelumab is a fully human, monoclonal antibody which inhibits active plasma kallikrein proteolytic activity. Increased plasma kallikrein activity leads to angioedema attacks in patients with HAE. Lanadelumab provides sustained control of plasma kallikrein activity and thereby limits bradykinin generation in patients with HAE.

The Systematic Literature Review following the methodology defined by the Medicines Council identified three clinical studies concerning two medicinal products. Routine prevention of HAE was investigated in two clinical studies (a phase Ib study and the pivotal phase III study HELP-03) of subcutaneous lanadelumab, and one clinical study (CHANGE-B) of intravenously administered C1-INH (Cinryze®). A total of 5 publications have been included in the present application.

No head to head studies comparing lanadelumab and C1-INH were identified. However, as the three identified clinical studies had a common comparator (placebo), an Indirect Treatment Comparison a.m. Bucher was conducted for the outcomes attack rate per month (all data normalized for one month to be 28 days), responder rate ≥90% and discontinuations due to TEAEs. An ITC was not possible neither for the outcome Quality of Life due to use of different QoL tools (AE-QoL vs. SF-36) nor for the outcome Attack Freedom due to lack of reported data for C1-INH. Data for the general adverse event profile has been provided.

The ITC was conducted even though the HELP-03 study was a randomized parallel group study, while the CHANGE-B study was a cross-over study. In addition, reporting of several of the outcomes differed, but a feasibility review of the studies led to the conclusion that an ITC was possible.

The ITC showed that lanadelumab statistically significantly reduced the attack rate per month as compared to C1-INH and had a significantly higher proportion of patients with ≥90% response, while there was no difference in the proportion of patients discontinuing treatment due to TEAEs.

While a comparison between the intervention and the comparator of quality of life was not possible due to use of different tools, lanadelumab improved the QoL as compared to placebo with almost twice the minimal clinically important difference of 6 points.

A review of the general adverse event profile show that both lanadelumab and C1-INH are well-tolerated.

Overall the data indicate that lanadelumab is superior to C1-INH IV for routine prevention of HAE attacks.

The number of patients expected to be treated with lanadelumab, either shifting from intravenous or acute treatment is difficult to estimate due to the multiplicity of factors influencing the clinician’s and the patient’s preference.

4 Literature search

The systematic literature review was executed according to the guidance provided by the Danish Medicine Council in the protocol.

4.1.1 Eligibility criteria

Study eligibility criteria as applied to abstract and full-text screening were defined in terms of the population, interventions, comparisons, outcomes, and study design (PICOS) structure as outlined in the appendix (Table 14, page 38).

4.1.2 Literature review

Relevant studies were identified by searching MEDLINE and CENTRAL.

In the DMC protocol, the literature search was prepared for MEDLINE (via PubMed) and CENTRAL (via Cochrane Library). Due to the account accessibility at the third-party vendor for the SLR, searches were run using the Ovid SP® platform from database inception to 26 July 2019 in the following electronic databases:

- MEDLINE and MEDLINE in-Process and E-pubs ahead of print
- EDM Reviews - Cochrane Central Registers of Controlled Trials

Comprehensive search strategies were developed by the DMC to identify all relevant publications that included terms relating to HAE regarding interventions of interest (lanadelumab, C1-INH, and study designs of interest [randomised controlled trials]).

Full search strategies conducted in the electronic databases are provided in the appendix (Table 15, page 39 and Table 16, page 40).

4.1.3 Study identification and selection

Electronic searches were conducted on 26 July 2019 using the search strategies developed and provided by the DMC (presented in appendix 8.1, p. 38).

All abstracts were reviewed according to the eligibility criteria, fully described in the protocol, by two systematic reviewers independently. Any studies that were queried were referred to a third reviewer and agreement reached.

Two systematic reviewers screened full papers retrieved from the initial searches in duplicate, and a decision was made about any studies that were queried after discussion with a third reviewer.

After removing duplications, 120 citations (incl. 3 EPARs) were screened. After abstract screening, 20 citations were eligible for full-text screening.

Twelve full-text publications were excluded due to inappropriate interventions (mostly due to the dose provided) (n=8), population (n=2), and study design (n=2), leaving five articles that were included in the SLR. The excluded studies are listed in Table 17 (p. 42).

In addition to the electronic search, three EPARs were identified and included through a search of the EMA website.

Three studies (reported in five articles and three EPARs) were identified for inclusion in this review. The studies are presented in section 4.1.5 (p. 9).

The PRISMA flow chart is presented in the appendix (Figure 7, p. 41).

4.1.4 Data extraction

Two investigators independently extracted data for the final list of selected eligible studies. Any discrepancies observed between the data extracted by the two data extractors was resolved by involving a third reviewer and coming to a consensus. Data was stored and managed in Microsoft Excel Workbooks.

Data on study characteristics, interventions, patient characteristics, and outcomes were extracted where available in accordance with the definitions in the DMC protocol.

4.1.5 Included trials

Table 3 Relevant studies included in the assessment

Reference (title, author, journal, year)	**Trial name**	**NCT number**	**Dates of study (start and expected completion date)**	**Relevant for clinical question <x>***
Banerji A, et al. HELP Investigators. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121. [Banerji 2018]	*HELP-03*	*NCT02586805*	*MAR 2016-APR 2017*	*1*
Banerji A, et al. Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis. N Engl J Med. 2017 Feb 23;376(8):717-728. [Banerji 2017]	In this application referred to as DX-2930-02 Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema (HAE) Subjects (phase Ib study)	*NCT02093923*	*APR 2014-MAY 2015*	*1*
Zuraw BL, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010 Aug 5;363(6):513-22. *Lumry WR, et al. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy Asthma Proc. 2014 Sep-Oct;35(5):371-6.* *Bernstein JA, et al. Indirect comparison of intravenous vs.*	*CHANGE B*	*NCT01005888*	*SEP 2005-AUG 2007*	*1*

subcutaneous C1-inhibitor placebo-controlled trials for routine prevention of hereditary angioedema attacks. Allergy Asthma Clin Immunol. 2019 Mar 7;15:13.				
**when multiple clinical questions are defined in the protocol*				

In addition, the following European Public Assessment Reports were consulted for data.

Study	Source	Year	Report
HELP-03 and DX-2930-02	EMA	2018	Assessment report: Takhzyro, international non-proprietary name: lanadelumab (Procedure No. EMEA/H/C/004806/0000)[1]
CHANGE B	EMA	2011	Assessment report: Cinryze, International non-proprietary name: C1-esterase inhibitor, human (Procedure No. EMEA/H/C/001207)[2]
	EMA	2016	Assessment report: Cinryze, International non-proprietary name: C1-esterase inhibitor, human (Procedure No. EMEA/H/C/001207/II/0045)[3]

4.2 Main characteristics of included studies

The main characteristics of each of the studies above are presented in Table 18 Study characteristics - HELP-03study (lanadelumab) on page 43, Table 19 Study characteristics - Lanadelumab phase IB study (DX-2920-02) on page 46, and Table 20 Study characteristics - CHANGE B (C1-inhibitor) on page 49, respectively.

Main differences between studies

Differences in study design

The CHANGE study was a crossover study, whereas HELP-03 and DX-2930-02 were parallel-arm studies. The 12-week treatment duration in each of the 2 crossover periods in the CHANGE study is not easily comparable to the 26-week treatment period in the parallel group in the HELP-03 study. Different study duration is assumed to be a consequence of the different pharmacokinetic characteristics of the 2 interventions and the differing half-lives

In the HELP-03 study, patients entered a run-in period of 4 weeks before start of treatment. In the CHANGE study, there was no run-in period. This could have an impact on the detection of treatment effects, especially if previous treatment in the CHANGE study had long-term effects that could carry over into the study period.

The steady state of reduction in HAE attacks was expected to be reached for patients after 70 days on lanadelumab treatment. However, no such data for C1-INH exist. Therefore, evidence supporting the adequacy of the 12-week treatment period to show any relevant treatment effects with C1-INH is lacking

Differences in baseline demographics and disease characteristics

Patients in the CHANGE, DX-2930-02, and HELP-03 studies exhibited a similar age distribution, but the age inclusion criteria differed (≥6, ≥18, and ≥12 years, respectively). The youngest patients in the CHANGE study were aged 9 years, whereas the youngest patients in the HELP-03 and DX-2930-02 studies were aged 12 and 18 years, respectively. The CHANGE study also featured a higher proportion of female patients. Race was deemed comparable between the studies; in all 3 studies, most patients were white. Body weight was

comparatively higher in patients in the HELP-03 study, which was assumed to be related to the differences in sex distribution.

The sample size in the CHANGE study (N=22) was considerably smaller than that in the HELP-03 study (N=125).

Patients included in the CHANGE study experienced ≥2 HAE attacks per month (EMEA/H/C/001207), whereas patients included in the HELP-03 study experienced ≥1 attack per month, and patients included in the DX-2930-02 study experienced ≥2 attacks per year and ≥1 attack in the past 6 months. The mean baseline monthly attack rates were 1.56 and 3.9 in the DX-2930-02 and HELP-03 studies, respectively. The baseline attack rate was not reported in the CHANGE study.

Table 4 shows a summary on disease characteristics. Although all studies recruited patients with HAE-1 and HAE-2, a greater proportion of patients with HAE-1 were enrolled in the HELP-03 study than in the CHANGE study (90.4% vs 81.8%, respectively). These proportions are deemed to be comparable.

The proportion of patients in the HELP-03 study with a history of prophylaxis therapy was lower than that in the CHANGE study (56.8% vs 100%). From a clinical perspective, this could not be seen as an indicator of the severity of disease. HAE activity was variable over time, and the severity of disease was therefore difficult to measure.

Table 4 Disease characteristics of patients with HAE in the HELP-03, DX-2930-02 and CHANGE-B studies

	Regimen	N	HAE Type, n (%)		Disease Duration, mo		Attacks per Month Before Treatment,* n				History of Laryngeal Attacks, n (%)	Prior Use of Prophylaxis, n (%)
			Type 1	Type 2	Mean	SD	Mean	SD	Min	Max		
HELP-03 (Banerji 2018, EMEA/H/C/004806/0000)	Lanadelumab 300 mg q2w	27	23 (85.2)	4 (14.8)	—	—	2.96	2.794	0	12	20 (74.1)	14 (51.8)
	Lanadelumab 300 mg q4w	29	27 (93.1)	2 (6.9)	—	—	3.76	3.512	0	14	17 (58.6)	20 (68.9)
	Placebo	41	38 (92.7)	3 (7.3)	—	—	4.15	3.978	0	15	27 (65.9)	25 (58.5)
DX-2930-02 (Banerji 2017)	Lanadelumab 300 mg q2w	5	—	—	—	—	1.32†	—	—	—	2 (40.0)	—
	Placebo	13	—	—	—	—	1.56†	—	—	—	6 (46.0)	—
CHANGE (Zuraw 2010)	C1-INH IV 1000 IU first	11	9 (81.8)	2 (18.2)	19.3	14.4	—	—	—	—	—	11 (100.0)
	Placebo first	11	9 (81.8)	2 (18.2)	16.8	7.9	—	—	—	—	—	11 (100.0)

SD, standard deviation.

*CHANGE: no run-in period; HELP-03: run-in period.

†Converted to attack rate per month (i.e., 28 d) based on the reported values of per-week attack rate (mean [SD] in the European Public Assessment Report: lanadelumab 400 mg q2w, 0.55 [0.174]; lanadelumab 300 mg q2w, 0.33 [0.246]; placebo, 0.39 [0.177])

Difference in outcomes

The three studies differed markedly in the outcomes assessed. This is tabulated in Table 5 below.

The outcomes of interest in the HELP-03, DX-2930-02, and CHANGE studies are summarized in Table 5. Two outcomes (attack rate and discontinuations due to adverse events) were reported in all 3 studies. The proportion of patients with ≥90% reduction in attacks in comparison to baseline has been reported in the HELP-03 study, and was estimated through a mixed logistic regression model in the ITC by Bernstein et al[4] for the CHANGE study data. However, Bernstein et al only report this outcome in terms of absolute effects (difference between C1-INH IV 1000 IU and placebo); the estimated proportions under placebo and C1-INH IV 1000 IU treatment are not reported. The authors do not provide details about whether baseline values have been accounted for in their statistical model. However, because of the crossover study design, this may have been deemed irrelevant.

In addition to availability of outcome data, we have assessed the definitions of all outcomes of interest as summarized in Table 25ff p.59ff in the ITC section. In summary, the main differences in attack rate data between the studies were deduced through reporting of attacks: attack rates in the HELP-03 study were reported by patients and confirmed by investigators. In the DX-2930-02 study, attacks were reported exclusively by patients and never confirmed by investigators. In the CHANGE study, investigators assessed HAE attacks reported by patients. HAE attack rates were measured per week over a period of 26 weeks in the HELP-03 study and over a period of 50 days in the DX-2930-02 study. In the CHANGE study, there were 2 observation periods of 12 weeks' duration each during which patients received either placebo or C1-INH IV treatment.

Table 5 Outcomes of interest assessed in HELP, DX-2930-02 and CHANGE-B

Endpoint	HELP-03	DX-2930-02	CHANGE	Notes
Attacks, n (or attack rate/attacks/mo)	√	√	√	Differences in duration of follow-up will be accounted for through normalization of all attack rates reported to 28 days.
≥90% reductions in the number of HAE attacks/mo	√	×	√	In the HELP-03 study, percentages of patients with ≥90% reductions **from baseline** in the number of monthly HAE attacks are reported. In the CHANGE study, percentages of patients with ≥90% reductions in the number of monthly HAE attacks on active treatment **relative to placebo** were reported. These are the outcomes of a mixed logistic regression model that accounts for the crossover design. However, Bernstein et al do not mention whether baseline values were accounted for in these models – these might have been deemed irrelevant because of the crossover design with identical baseline values in the 2 treatment sequences.
Patients attack-free, %	√	√	×	
Change in total score AE-QoL	√	×	×	
Responders, % (judged by AE-QoL score)	√	×	×	In the HELP-03 study, responders are defined as patients experiencing an improvement of ≥6 points from baseline.
Change in total score SF-36 PCS	×	×	√	SF-36 PCS was not reported in HELP-03 study.

Endpoint	HELP-03	DX-2930-02	CHANGE	Notes
Change in total score SF-36 MCS	×	×	√	SF-36 MCS was not reported in HELP-03 study.
Withdrawals due to AE	√	√	√	

The detailed definitions of the outcomes are listed in Table 25ff p.59ff in the ITC section.

In summary there are several differences in the study design, baseline demographics and disease characteristics that should be taken into consideration when comparing the safety and efficacy of lanadelumab and C1-INH IV.

Further considerations will be described in the section on results of the comparative analysis (see section 5.1.3, p. 22).

5 Clinical questions

5.1 *What is the value of routine lanadelumab prevention in adult patients and children ≥12 years of age hereditary angioedema compared to current standard treatment?*

Population

- Children ≥12 years and adults with HAE type I or II.

Intervention

- Lanadelumab 300 mg every 2 weeks.

Comparator

Prophylactic treatment with iv C1-esterase inhibitor.

- Adults: C1-esterase inhibitor 1,500 units iv every 3-4 days.
- Children ≥ 12 years: C1-esterase inhibitor approx. 1,000 units iv every 3-4 days.

Comments for the PICO

The three studies identified in the SLR met the PICO in most aspects. However, the following should be taken into consideration when assessing the data:

- No studies reported data C1-inh using the dose of 1,500 units iv every 3-4 days. Therefore, data for the dose of 1,000 units iv every 3-4 days has been included in the application as agreed with the Medicines Council during a teleconference 28th June 2019.
- Data reported separately for the age ≥12 years and ≤18 years was very limited and do not allow for a formal comparison. To the extent available data have been shown in the relevant sections and tables as agreed with the Medicines Council during a teleconference 28th June 2019.
- Outcomes reported differed between the studies as described on p. 13.

5.1.1 Presentation of relevant studies

HELP

The HELP-03 study (Banerji 2018[5]) was a phase 3 randomized, double-blind, placebo-controlled trial (N=125) with a parallel-group design and a study treatment duration of 26 weeks. Patients aged ≥12 years who experienced ≥1 attack per month were included. The mean age was 40.7 years. Female patients were 70.4% of the study sample; 90.4% of patients were white. The mean weight was 80.7 kg (median, 77.3 kg; EMEA/H/C/004806/0000 [2]. The proportion of patients with a history of prophylaxis therapy was 72%. On average, the baseline attack rate was 3.9 attacks per 4 weeks. Data on HAE attacks were reported by patients and confirmed by investigators.[6] The majority of patients had HAE-1 (90.4%); 9.6% had HAE-2.

The primary outcome was the total number of investigator-confirmed HAE attacks.[6] Patients treated with lanadelumab 300 mg q2w or 300 mg q4w experienced significant reductions in the mean monthly total HAE attack rate (defined as attacks per 28-day period): 0.26 and 0.53 attacks per month, respectively, compared with 1.97 attacks per month in the placebo arm (each comparison, $P<0.001$).

Exploratory endpoints included the proportion of attack-free patients and the proportion of patients with reductions of ≥90% in the attack rate compared with the run-in period. Health-related QoL was assessed through the Angioedema Quality of Life Questionnaire (AE-QoL) scores. AE-QoL responders were defined as those who had an improvement of ≥6 points in AE-QoL score. Discontinuations due to adverse events were reported as a safety outcome of interest.

For further details, see Table 18.

Lanadelumab phase Ib study

The DX-2930-02 study (Banerji 2017[7]) was a phase 1b multicentre, double-blind, placebo-controlled, multiple-ascending-dose trial (N=37). Patients with hereditary angioedema with C1 inhibitor deficiency were randomly assigned in a 2:1 ratio to receive either lanadelumab (n=24) or placebo (n=13) in 2 administrations 14 days apart.

Patients aged ≥18 years were included. The mean age was 39.9 years. Women were 62.2% of the total sample; 100% of patients were white. The mean weight was not reported. At baseline, a mean of 6.1 angioedema attacks were reported by patients in the previous 3 months. The distribution of HAE-1 and HAE-2 was not reported.

The primary outcome was the total number of patient-reported HAE attacks over 6 weeks (days 8–50). Patients treated with lanadelumab 300 mg q2w experienced significant reductions in the mean monthly total HAE attack rate: 0 attacks per week compared with 0.37 attacks per week for the placebo arm (*P*<0.01). Secondary outcomes of interest were proportion of attack-free patients and discontinuations due to adverse events.

Further details can be found in Table 19, p. 46.

CHANGE B

The CHANGE study (Zuraw 2010,[8] Lumry 2014,[9] EMEA/H/C/001207,[2] Bernstein 2019[4]; N=22) was a phase 3 double-blind, placebo-controlled crossover study consisting of two 12-week periods spanning a total study treatment duration of 24 weeks. Each patient acted as his or her own control in the study. Patients aged ≥6 years were included.

This was a phase III, double-blinded, randomized, placebo-controlled cross-over study consisting of two 12-weeks periods spanning a total study duration of 24 weeks to determine the safety and efficacy of C1-INH (CINRYZE®) for the prevention of acute HAE attacks in patients 6 years and older with HAE type I or II. [Zuraw 2010] Due to the cross-over design each patient served as his/her own control.

The intervention was 1,000 Units (U) of C1-INH administered intravenously (IV) every 3 to 4 days (approximately twice weekly) for 12 weeks, followed by matching placebo (saline) administered IV every 3 to 4 days for 12 weeks. (N=22)

The primary outcome was the number of HAE attacks during each prophylactic therapy period. Secondary outcomes included number of subject withdrawals during each prophylactic therapy period, average severity of HAE attacks during each prophylactic therapy period, average duration of HAE attacks during each prophylactic therapy period, number of open-label C1-INH infusions required during each prophylactic therapy

period, antigenic C1-INH) serum levels, and functional C1-INH serum levels. [Zuraw 2010]. Further detail can be found in Table 20.

5.1.2 Results per study

HELP-03

The results per outcome from the HELP-03study are tabulated in Table 34 on p. 74. In addition to data for the ITT-population, the limited available data for the age group 12 to ≤18 years has been shown in the table.

In the table, some data that are not directly related to the predefined outcomes and dosing is also included for the steady state period (day 70-182) as the data are used as the basis for the response to the Medicines Council questions in the protocol section "other considerations".

Attack freedom

In the lanadelumab 300 mg q2w arm 44.4% of all patients were attack free over the 26-week study period as compared to 31.0% in the 300 q4w arm and 2.4% in the placebo arm. [6]

During the steady state period (days 70-182) the proportion of attack free patients was 76.6% (62.3% — 85.9%) as compared to 2.7% (0.4% - 12.6%) in the placebo group. [6] The steady state period can be considered a more appropriate measure for the long-term efficacy of lanadelumab due to the 14 day half-life of the compound (cf. section 6.2, 32).

The absolute risk reduction was -42.0% (-61.8% to – 18.1%) for lanadelumab 300 mg q2w compared to placebo with a p-value of <0.001. Banerji, Riedl (6)

Responder rate ≥90%

In the lanadelumab 300mg q2w arm 66.7% of all patients had a reduction in number of attacks of ≥90%, as compared to 55.2% in the lanadelumab q4w group and 4.9% in the placebo group. A difference between lanadelumab 300 mg q2w and placebo of -61.8% (-78.8% to 3-9.5%) as compared to placebo with a p-value of <0.001. [6]

Health Related Quality of Life

Change from baseline assessed by the Quality of Life questionnaire (AE-QoL)

In the lanadelumab 300 mg q2w group the mean improvement from baseline in AE-QoL (21.29 [-28.21 to – 14.37] was significantly (p=0.003) better compared to the change of -4.72 (-10.46 to 1.02) in the placebo group, Similarly in the lanadelumab 300 q4w the mean improvement of -17.38 (-24.17 to – 10.58) was statistically significantly (p=0.03) better than placebo. [6]

The difference of 11.83 points clearly exceed the minimal clinically important difference of 6 points defined by the Medicines Council.

Percentage of patients experiencing an improvement of 6 points from baseline in AE-QoL.

In the lanadelumab 300mg q2w group 80.77% (69.9%-91.6%) of patients experienced an improvement ≥6 points from baseline as compared to 36.84% (25.9%-47.8%) in the placebo group, a difference of 43.9% in favour of lanadelumab 300 mg q2w as compared to placebo with a p-value <0.001. [6]

Attack rate

In the lanadelumab 300 mg q2w group the mean attack rate (normalized per 28 days) for days 0-182 (mean 0.26 [0.14-0.46]) was significantly (p<0.001) lower than the mean attack rate (1.97 [1.64-2.36]) in the placebo

group, an absolute difference of 1.71 attacks per month with a relative risk of 0.13 in favour of lanadelumab. [6]

In the lanadelumab 300 mg q2w group the mean attack rate (normalized per 28 days) for the steady state period (days 70-182) (mean 0.16 [0.07-0.35]) was significantly ($p<0.001$) lower than the mean attack rate (1.88 [1.54-2.30]) in the placebo group, an absolute difference of 1.72 attacks per month with a relative risk of 0.09 in favour of lanadelumab. [6]

Similar results were seen in the lanadelumab 300 mg q4w group with a mean attack rate of 0.53 compared to the mean attack rate for placebo of 1.97 ($p<0.001$). [6]

Adverse events -discontinuations

In the lanadelumab 300 mg q2w group no patients discontinued treatment due to TEAEs as compared to one patient in the placebo group. [6]

Adverse events - Qualitative assessment of safety profile

An overview of the adverse events reported in the clinical trials is provided on p.29.

DX-2930-02 [Banerji 2017]

The results per outcome from the lanadelumab phase Ib study are tabulated in Table 36 on p.81.

Attack freedom

In the lanadelumab 300 mg q2w group all 4 patients were attack free, while only 3 of 11 patients in the placebo group were attack free during the study period from day 8 to day 50.[7]

Responder rate ≥90%

Data for the responder rate ≥90% of patients was not reported. [7]

Health Related Quality of Life

Data for HRQoL was not collected. [7]

Attack rate

In the lanadelumab 300 mg q2w group the mean normalized 28-day attack rate was 0 (zero) as compared to 1.48 (0.41, 2.55) in the placebo group. [7]

Adverse events -discontinuations

There were no discontinuations due to TEAEs in either group.[1, 7]

Adverse events - Qualitative assessment of safety profile

An overview of the adverse events reported in the clinical trials is provided on p.29

CHANGE-B

The results per outcome from the CHANGE B study are tabulated in Table 37 on p.84.

There were discrepancies in the data reported among the publications of the CHANGE study (detailed below). However, we will focus primarily on the data reported in the EMEA/H/C/001207[2] publication in the ITC

because these data are deemed the most relevant and accurate. The Lumry 2014 publication focuses on patients where health related QoL data were available, whereas the Bernstein 2019 publication reports the findings of an ITC.

The mean age was 38.1 years according to Zuraw 2010 and Bernstein 2019 and 41.69 years according to Lumry 2014. The median age was 37.5 years according to EMEA/H/C/001207; in contrast to the other publications, the EMEA/HC/C/001207 report focused on the median rather than the mean age. Female patients were 90.9% (Zuraw 2010) or 87.5% (Lumry 2014) of the total sample; 95.5% (Zuraw 2010, Bernstein 2019) of the patients were white. The mean weight was 73.4 kg (Zuraw 2010, Bernstein 2019); the median weight was 69.3 kg (Bernstein 2019) and 67.4 kg (EMEA/H/C/001207). HAE-1 was present in 81.8% of patients and HAE-2 in 18.2% of patients (Zuraw 2010). All patients had a history of prophylaxis therapy. The baseline attack rate was not reported. Data on HAE attacks were reported by patients; independent experts were not consulted.

The primary outcomes were the absolute and percentage reductions in number of attacks of angioedema per 28-day period. Patients treated with C1-INH IV 1000 IU twice weekly experienced 6.2 attacks per 12-week period; those who received placebo experienced 12.73 attacks (P<0.001, as reported in Zuraw 2010). In Lumry 2014, the mean numbers of attacks reported per 28-day period were 2.24 with C1-INH IV 1000 IU twice weekly and 4.2 with placebo. Differences in outcome data were noted may be because only data on patients with health related QoL were provided in the Lumry 2014 publication. In the EMEA/H/C/001207 publication, a mean of 6.1 attacks over a 12-week period with C1-INH 1000 IU IV twice weekly versus 12.7 with placebo were noted. These results differed by 1 decimal point from those in Zuraw 2010. Only the EMEA/H/C/001207 data will be considered in the ITC. AE-QoL score data were not obtained in the CHANGE study; however, Short Form 36 (SF-36) physical and mental component scores (PCS and MCS) were given in the Lumry 2014 study. The mean SF-36 PCS was 40.49, whereas the MCS was 49.49. The proportion of attack-free patients was not reported in any of the publications. Bernstein 2019 reported the proportion of patients with a ≥90% reduction in attacks in comparison to placebo. AE-QoL responders were not reported. Discontinuations due to adverse events were reported in the EMEA/H/C/001207 publication; there were no discontinuations in any of the treatment arms.

Table 6 gives an overview on the discrepancies in data reported in the Lumry 2014, Zuraw 2010 and EMA/HC/C/001207 publications as described above. Data reported on age and weight was relevant for the feasibility assessment, yet was not considered in the Bucher ITC, described in section 8.4. Data on HAE attacks per 12 weeks was normalized to 28 days; as mentioned above, exclusively data from the EMA/HC/C/001207 publication was considered in the ITC.

Table 6 Discrepancies in reporting of baseline characteristics and the outcome HAE attacks per 12 weeks in the Lumry 2014, Zuraw 2010 and EMA/HC/001207 publications

	Regimen		Age (years)		Body weight (kg)		HAE attacks per 12 weeks	
		N	Mean	Std	Mean	Std	Mean	Std
CHANGE (Lumr	C1-INH 1,000 IU first	5	33.2	10	—	—	6.72	5.88

	Placebo first	13	41.2	13.7	—	—	12.6	4.20
CHANGE (Zuraw 2010)[8]	C1-INH 1,000 IU first	11	41.7	19.3	70.5	9.3	6.26	—
	Placebo first	11	34.5	14.8	76.3	25.7	12.73	—
CHANGE (EMA/H/C/ 001207)[2]	C1-INH 1,000 IU first	11	Median: 40	—	Median: 70.5	—	6.1	5.43
	Placebo first	11	Median: 35	—	Median: 64.3	—	12.7	4.80

Attack freedom

The rate of attack freedom was not reported for the CHANGE-B study.

Responder rate ≥90%

The responder rate was not reported in the main publication [8], but can be sourced from *Bernstein et al* who performed an indirect treatment comparison on individual patient data.[4]

In the C1-INH IV 1000 IU every 3-4 days group, the proportion of patients achieving a ≥90% reduction in attack rate as compared to placebo was 18.2% (-40.1% to -6.6%; p<0.001). [4]

Health Related Quality of Life

Data for HRQoL was reported using the generic SF-36 QoL tool. Data are shown in Table 37 (p. 84).

SF-36 is a generic HRQoL tool without any predefined MCID for HAE. While the results in the CHANGE B study show a statistically significant difference between C1-INH and placebo, it is not possible to assess if this statistical difference also translates into a relevant clinical difference as no predefined MCID for HAE exists for the SF-36 tool.

Attack rate

The attack rate for the CHANGE study has been reported in several different publications as described above. Takeda has chosen to base the presentation and analysis of data in this application on the data reported in the EPAR.

The mean attack rate per 12 weeks in the CHANGE-B study was 6.1 (3.83-8.37) in the C1-INH IV 1000 IU every 3-4 days group compared to a mean attack rate of 12.7 (10.69-14.71) in the placebo group. [2]

The above data can be normalized to meet the requirements of attack rate per month (=28 days) in the Medicines Council protocol.

The mean attack rate per 28 days in the CHANGE-B study was 2.09 in the C1-INH IV 1000 IU every 3-4 days group compared to a mean attack rate of 4.24 (10.69-14.71) in the placebo group, a difference of -2.16 attacks per 28 days in favour of C1-INH IV. [2]

Data from other sources (*Zuraw 2010, Lumry 2014, Bernstein 2019*) are provided in the data table for the CHANGE-B study (Table 37 on p. 84).

Adverse events -discontinuations

There were no discontinuations in either group. [2]

Adverse events - Qualitative assessment of safety profile

An overview of the adverse events reported in the clinical trials is provided on p. 29

5.1.3 Comparative analyses

After having conducted a feasibility analysis it was concluded that an Indirect Treatment Comparison was feasible for the outcomes HAE attack rate per 28 days, ≥90% reductions in number of HAE attacks as well as withdrawals due to adverse events. Insufficient data were available for the outcomes Attack Freedom and AE-QoL.

Table 5 on p. 13 shows data availability for all outcomes of interest.

A full description of the ITC methodology is available in section 8.3 on p. 51.

Attack freedom

Data for attack freedom was not reported for C1-INH IV. No comparison can therefore be made.

Data for lanadelumab show that in the lanadelumab 300 mg q2w arm 44.4% of all patients were attack free over the 26-week study period as compared to 31.0% in the 300 q4w arm and 2.4% in the placebo arm. [6]

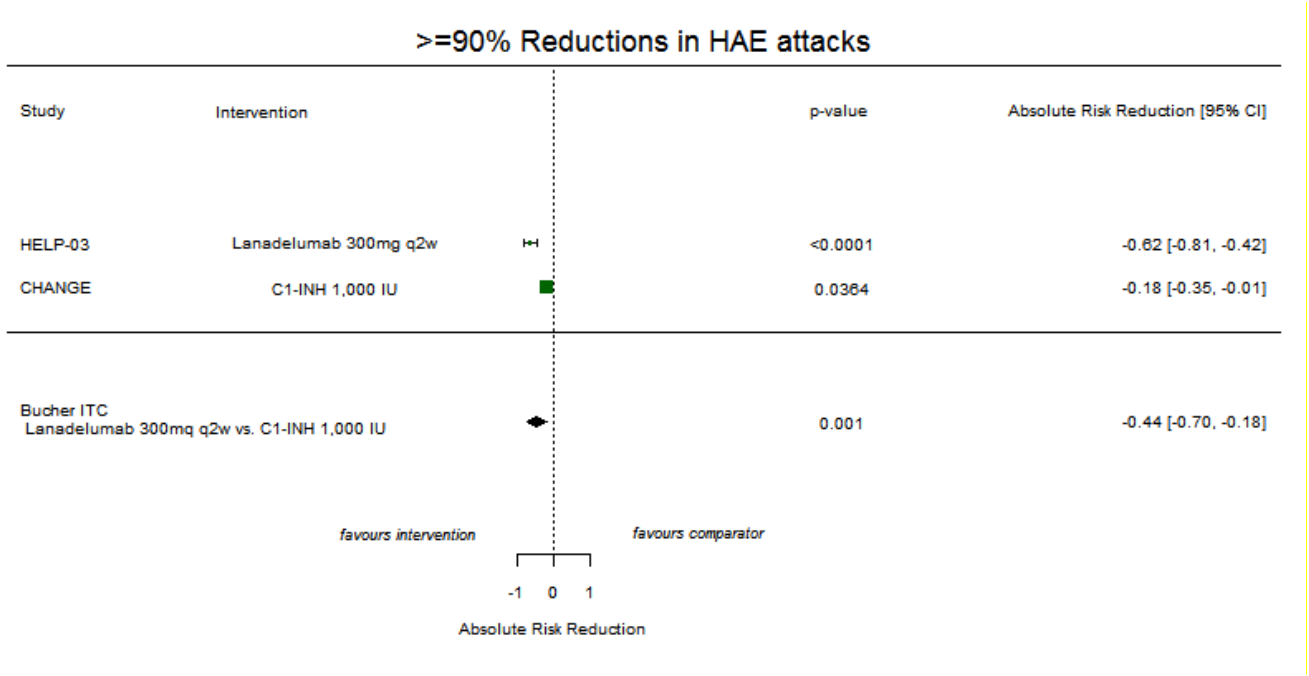
During the steady state period (days 70-182) the proportion of attack free patients was 76.6% (62.3% — 85.9%) as compared to 2.7% (0.4% - 12.6%) in the placebo group. [6] The steady state period can be considered a more appropriate measure for the long-term efficacy of lanadelumab.

≥90 reductions in the number of HAE attacks per 28 days

Due to limited data availability, the outcome of ≥90% reductions in the number of monthly HAE attacks could only be assessed in terms of ARR. No data were available in the DX-2930-02 study; therefore, no pairwise meta-analysis was conducted to pool the HELP-03 and DX-2930-02 study data. Figure 1 shows the corresponding findings for this outcome.

Both the HELP-03 and CHANGE studies show that active treatment was statistically significantly more effective than placebo in reducing the number of monthly HAE attacks by more than 90%; the corresponding 95% CIs of ARR did not include 0. The result of the Bucher ITC also indicated that lanadelumab 300 mg q2w was statistically significantly more effective than C1-INH 1000 IU in reducing monthly HAE attacks by more than 90% (ARR=–0.44, 95% CI [–0.70, –0.18]). Treatment with lanadelumab 300 mg q2w resulted in 44 additional cases with more than 90% reductions in monthly HAE attacks compared to C1-INH 1000 IU. The corresponding 95% CI did not include 0.

Figure 1 ≥90% reductions in # of monthly HAE attacks (Absolute Risk Reduction)



Risk ratio

Results in terms of RR are estimated through ARR, resulting in RR of 3.42 with corresponding 95%CI of [1.98, 4.87], P=0.0332. On average, the risk of ≥90% reductions in the number of monthly HAE attacks is increased by factor 3.42 under lanadelumab 300mg q2w treatment when compared to C1-INH 1000 IU. This corresponds to a 242% increase under lanadelumab 300mg q2w treatment. As for ARR, this result indicates a statistically significant difference in favour of lanadelumab 300 mg q2w since 1 is not covered by the corresponding CI. To obtain this result, we follow Bernstein et al. who estimate that approximately 18% of individuals achieve a 90% reduction in the number of monthly HAE attacks with the current standard treatment, which corresponds to the risk in the comparator arm r_c. Health related quality of life

A formal comparison of HRQoL results from the HELP-03 and CHANGE studies is not possible, primarily due to use of different QoL tools and different reporting of results. First and foremost, the two studies used different tools to measure HRQoL: the disease-specific Angioedema Quality of Life (AE-QoL) instrument was used in HELP-03, whereas the generic quality of life instrument, the SF-36 was used in CHANGE-B.

The SF-36 is a generic tool designed to measure HRQoL and to capture a full range of health states with no focus on a particular disease[10, 11].

Generic instruments, such as the SF-36, have been shown to be less sensitive than disease-specific HRQoL instruments [9, 12-14] (e.g. Patrick et al, 1989; Ren et al, 1998; Boyle, 2001). Furthermore, no Minimal Clinically Important Difference (MCID) has been estimated for the use of SF-36 in patients with HAE.

Finally, the CHANGE study used SF-36 Version 1 which captures a smaller range of potential levels of functioning in the role functioning scales compared with the SF-36 Version 2 and thus may be less sensitive to changes on these HRQoL domains. [9].

As a generic tool, the SF-36 may not adequately characterize the disease-specific HRQoL impact and burden associated with HAE.

In contrast, the AE-QoL is a content-valid, angioedema-specific HRQoL tool, developed per FDA guidelines with input from AE experts and patients [15, 16]. Moreover, unpublished evidence from concept elicitation and cognitive interviews as well as psychometric validation provides robust support for the content and psychometric validity of the AE-QoL specifically in the HAE patient population.

Given the use of different HRQoL instrument, accurate comparison of the HRQoL results from the HELP-03 and CHANGE-B studies would require a cross-walk algorithm between the SF-36 and AE-QoL scores, which is not available.

Additional differences between the two studies relevant for the assessment of QoL are summarized in Table 7

Table 7 Differences between HELP-03and CHANGE-B studies

Study Characteristic	**HELP-03**	**CHANGE-B**
HRQoL tool	AE-QoL (disease-specific)	SF-36 (generic)
Trial design	Parallel design	Crossover design
Treatment durations	26 weeks in the parallel group	12 weeks in each of the two crossover periods
Run-in period	4 weeks	No run-in period
Sample size	N=125	N=22
Outcome definition	Proportion of responders reported (improvement of ≥6 points in AE-QoL score) and change in AE-QoL scores from baseline	Change in SF-36 PCS and SF-36 MCS scores only

The HRQoL results reported for HELP-03and CHANGE-B are summarized in Table 8.

Table 8 QoL outcomes in HELP-03and CHANGE-B

Trial ID	**Treatment**	**N**	**Responders: AE-QoL, n (%)***	**AE-QoL mean change from baseline**	**SF-36 PCS: mean (SD) change from baseline**	**SF-36 MCS: mean (SD) change from baseline**
CHANGE	C1-INH: 1000 units	16	--	--	7.51 (7.71)	4.12 (10.04)
	Placebo	16	--	--	0.65 (8.05)	–4.87 (9.47)
HELP	Lanadelumab: 300 mg q4w	27	17 (63.0)	–17.38 (95% CI, –24.17, –10.58)	--	--
	Lanadelumab: 300 mg q2w	26	21 (80.8)	–21.29 (95% CI, –28.10, –14.37)	--	--
	Placebo	38	14 (36.8)	–4.72 (95% CI, –10.46, –1.02)	--	--

* Patients who were considered to have responded (responders) to the therapy were defined as achieving an improvement greater than or equal to the minimal clinically important difference of –6 for total scores from days 0 through 182. The questionnaire consisted of 4 domains (functioning, fatigue and mood, fears and shame, and nutrition) and 17 questions that were taken together for a total score. Total raw scores were transformed to a linear scale of 0 to 100, with lower scores indicating lower impairment or higher health–related quality of life

In the HELP-03study 80.8% of the patients in the lanadelumab 300 mg q2w group experienced an improvement in quality of life exceeding the MCID by the Medicines Council of 6 points. [6]

In the CHANGE-B study the difference between C1-INH and placebo was also statistically significantly different. However, as no MCID is defined for the use of the generic SF-36 HRQoL tool in HAE, it cannot be concluded that the difference is also clinically relevant.

Attack rate per 28 days

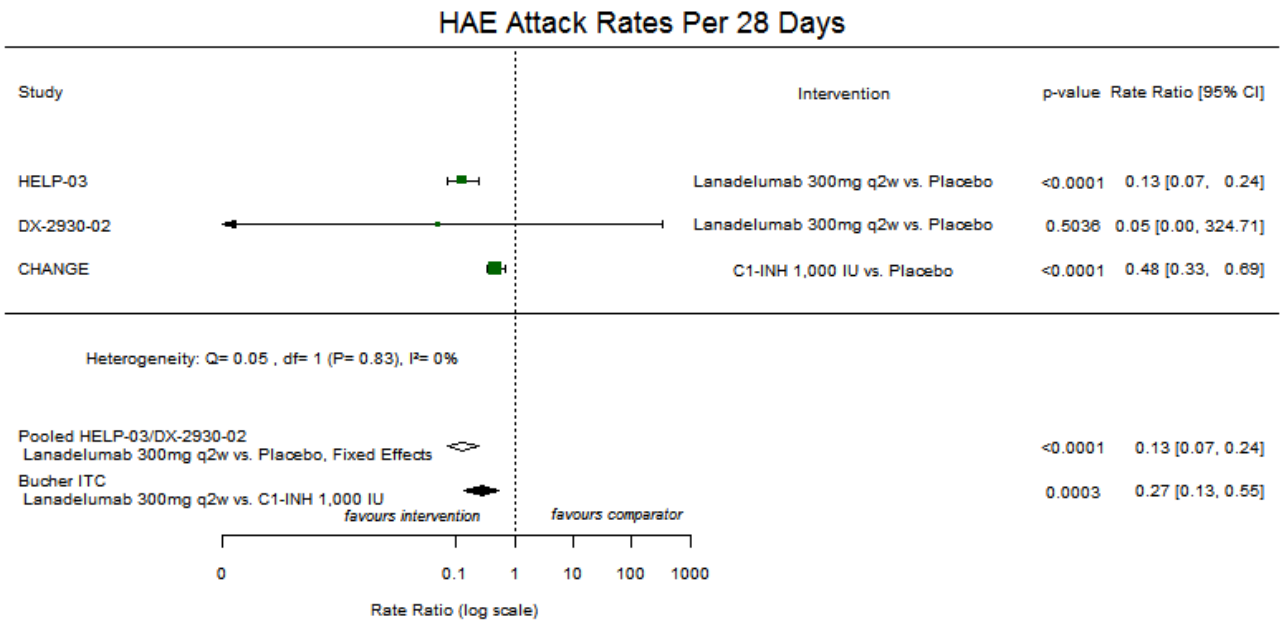
The attack rate has been calculated both for the period of days 0-182, and as a sensitivity analysis for the steady state period (day 70-182).

Figure 2 shows the base case results for HAE attack rate per 28 days assessed in terms of RaR. The individual study results of the HELP-03 and CHANGE studies indicate that there was a statistically significant difference between lanadelumab 300 mg q2w versus placebo as well as between C1-INH 1000 IU versus placebo. In the DX-2930-02 study, there was a large amount of uncertainty because SE was not reported and had to be estimated through a continuity correction of 0.05 added to 0 events, resulting in a wide 95% CI.

There were no issues with heterogeneity when pooling the HELP-03 and DX-2930-02 studies; I^2 was 0%, and the *P*-value of the Q statistic was clearly greater than 0.2 (*P*=0.83). Therefore, a fixed-effect model could be used to pool the two studies. The pooled result corresponds to the individual study estimate of RaR of the HELP-03 study; the weight of the HELP-03 study was considerably higher than that of the DX-2930-02 study due to the high variance in the latter study.

The indirect comparison of lanadelumab 300 mg q2w and C1-INH 1000 IU via the Bucher method resulted in an RaR of 0.27 with corresponding 95% CI of 0.13 to 0.55, indicating that lanadelumab 300 mg q2w was statistically significantly more effective than C1-INH 1000 IU in reducing HAE attack rates per 28 days. Treatment with lanadelumab 300 mg q2w reduced the rate of HAE attacks per 28 days by a factor of 0.27. The value of 1 was not covered by the 95% CI, and the *P*-value of <0.0003 indicated statistical significance.

Figure 2: HAE Attack Rates Per 28 Days Assessed in terms of Rate Ratio



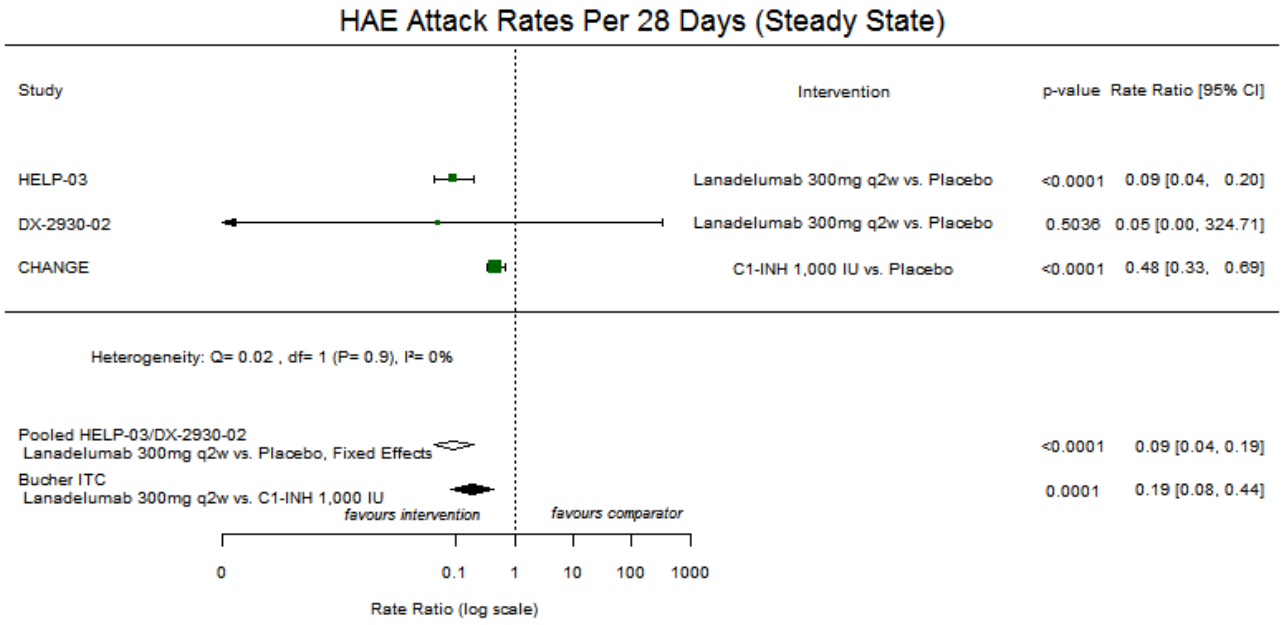
Absolute difference in attack rate

Results in terms of absolute difference in attack rate are estimated through RaR, resulting in -3.09 with corresponding 95%CI of [-3.68, -1.90], *P* =0.0297. On average, the HAE rate per 28 days is reduced by 3.09 attacks under lanadelumab 300 mg q2w treatment when compared to C1-INH 1,000 IU. As for RaR, this result indicates a statistically significant difference in favour of lanadelumab 300 mg q2w since 0 is not covered by the corresponding CI. To obtain this estimate, a HAE rate of 4.23 per 28 days was assumed for C1-INH, corresponding to the CHANGE study data.

Sensitivity analysis HELP-03 data in steady state

The findings of the sensitivity analysis considering steady-state data obtained in days 70 to 182 of treatment in the HELP-03 study (Figure 3) were similar to the base case. The individual study result of the HELP-03 study differed, and as expected, RaR was slightly lower compared to the base case. As reported with the base case analysis, the pooled estimate of the HELP-03 and DX-2930-02 studies was very similar to the individual study result of the HELP-03 study. The Bucher ITC resulted in a pooled RaR of 0.19 (95% CI [0.08, 0.44]), indicating that lanadelumab 300 mg q2w was statistically significantly more effective than C1-INH 1000 IU. Treatment with lanadelumab 300 mg q2w reduced the rates of HAE attacks per 28 days by a factor of 0.19.

Figure 3 HAE Attack Rates Per 28 Days (Rate Ratio) – Sensitivity Analysis at Steady State



Absolute difference in attack rate

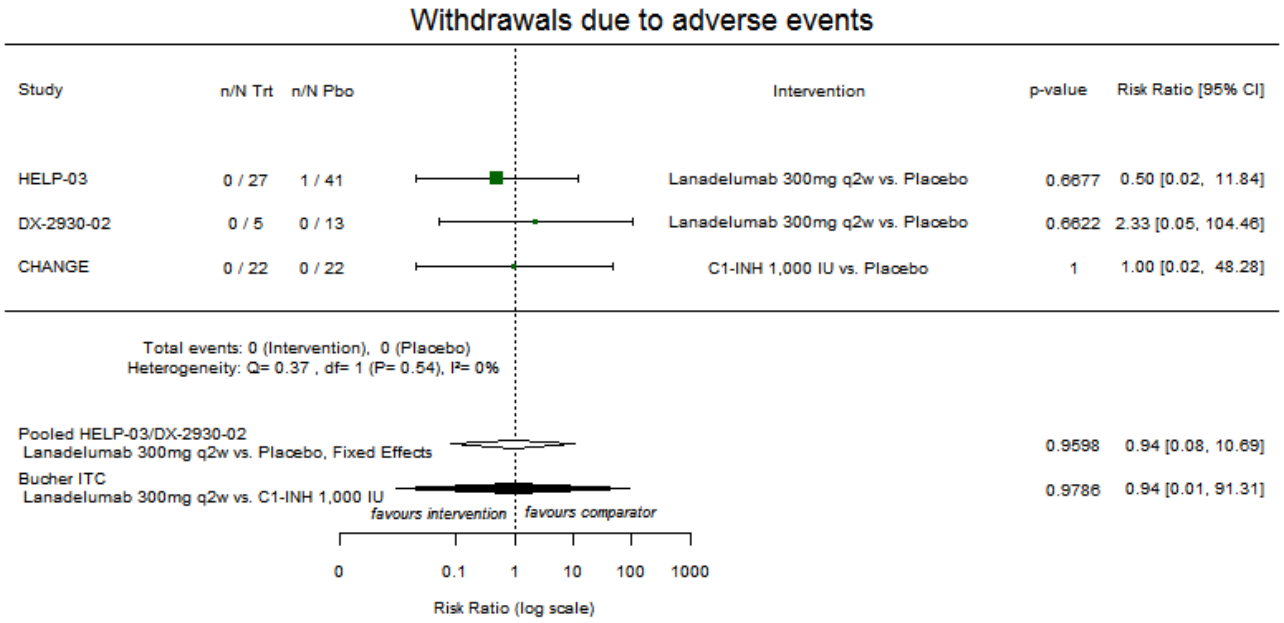
Results in terms of absolute difference in attack rate are estimated through RaR, resulting in -3.44 with corresponding 95%CI of [-3.90, -2.37], P=0.0313. On average, the HAE rate per 28 days is reduced by 3.44 attacks under lanadelumab 300 mg q2w treatment when compared to C1-INH 1000 IU. As for RaR, this result indicates a statistically significant difference in favour of lanadelumab 300 mg q2w since 0 is not covered by the corresponding CI. To obtain this estimate, a HAE rate of 4.23 per 28 days was assumed for C1-INH, corresponding to the CHANGE study data.

Discontinuations due to adverse events

Figure 4: Withdrawal due to AEs assessed in terms of Absolute Risk Reduction

Figure 5 shows the results for withdrawals due to AEs in terms of RR. None of the individual studies result in a statistically significant difference in interventions. When pooling the results of the HELP-03 and DX-2930-02 studies, there was no issue of between-study heterogeneity (*P*=0.54). As noted in section 4.1.1, the HELP-03 study had a larger weight than the DX-2930-02 study; therefore, the pooled estimate tends toward the HELP-03 study. The indirect comparison of lanadelumab 300 mg q2w and C1-INH 1000 IU results in a RR of 0.94 (95% CI [0.01, 91.31]). In line with the result obtained through ARR, there was no statistically significant difference in withdrawals due to AEs; however, the point estimate indicates that the risk of withdrawals due to AEs was decreased by a factor of 0.94 under lanadelumab 300 mg q2w treatment compared to C1-INH 1000 IU.

Figure 5: Withdrawal due to AEs assessed in terms of risk ratio



Absolute risk reduction

Results in terms of ARR are estimated through RR, resulting in ARR of -0.0006 with corresponding 95%CI of [-0.010, 0.9032], *P* =0.9979. On average, the risk of withdrawals due to adverse events is decreased by 0.06% under lanadelumab 300mg q2w treatment when compared to C1-INH 1,000 IU. As for RR, this result does not indicate a statistically significant difference in interventions since 0 is covered by the corresponding CI. To obtain this result, we assume a risk of 0 withdrawals due to AEs under C1-INH 1,000 IU treatment and we add a continuity correction of 0.01 to avoid zero counts.

Qualitative assessment of adverse events

Information on adverse events in the SmPC has been provided in the tables below.

Overall both lanadelumab and C1-INH seem to be well-tolerated.

As both medicinal products are injected (SC. and IV. respectively) local injection site reactions occur. However due the intravenous administration of C1-INH there is a risk of thrombophlebitis and venous thrombosis and the increased risk of an indwelling catheter related to the IV access, which is not present with lanadelumab.

In addition, it seems as if the incidence of headache (very common) as well as gastrointestinal adverse events, in particular nausea, is higher with C1-INH than with lanadelumab.

Table 9 Lanadelumab adverse event profile

TAKHZYRO adverse events[17]		
System organ class	**Adverse drug reaction**	**Frequency**
Immune system disorders	Hypersensitivity*	Common
Nervous system disorders	Dizziness	Common
Skin and subcutaneous tissue disorders	Rash maculo-papular	Common
Musculoskeletal and connective tissue disorders	Myalgia	Common
General disorders and administration site conditions	Injection site reactions**	Very common
Investigations	ALAT increased	Common
	ASAT increased	Common
*Hypersensitivity includes pruritus, discomfort and tingling of tongue. **Injection site reactions include pain, erythema, bruising, discomfort, haematoma, haemorrhage, pruritus, swelling, induration, paraesthesia, reaction, warmth, oedema and rash.		

Table 10 C1-INH adverse event profile

CINRYZE Adverse events [18]		
System Organ Class	**Adverse reaction**	**Frequency**
Immune system disorders	Hypersensitivity	Common
Metabolism and nutrition disorders	Hyperglycaemia	Uncommon
Nervous system disorders	Headache	Very common
	Dizziness	Common
Vascular disorders	Venous thrombosis, phlebitis, venous burning, hot flush	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon
Gastrointestinal disorders	Nausea	Very common
	vomiting	Common
	Diarrhoea, abdominal pain	Uncommon
Skin and subcutaneous tissue disorders	Rash, erythema, pruritus	Common
	Contact dermatitis,	Uncommon
Musculoskeletal and connective tissue disorders	Joint swelling, arthralgia, myalgia	Uncommon
General disorders and administration site conditions	Injection site rash/erythema, infusion site pain, pyrexia	Common
	Chest discomfort	Uncommon

In the context of potential adverse reactions, it should be noted that lanadelumab is manufactured through a recombinant process, which eliminates the risk of infectious agents in the product. This in contrast to plasma derived products, like C1-INH, where the source of the product is human plasma.

This issue has been addressed by the Medicines Council in several previous processes in the area of haemophilia as reflected in the background material for the Medicines Council treatment guideline for medicinal products for the treatment of haemophilia A.[19]

The conclusion by the Medicines Council is that “On this basis plasma products are as a starting point considered less safe, and recombinant products should be preferred”. [19]

6 Other considerations

The Medicines Council has asked the applicant to address the topics listed in the sections below.

6.1 Route of administration

[Choice of preventive treatment has until recently been partly driven by the patient preferences, as there may be a barrier to intravenous self-administration and the relatively frequent dosage of C1 esterase inhibitor. By virtue of the subcutaneous administration, the specialist committee expects a part of the patients who today have opted out of preventive treatment will want preventive treatment. It is the committee's assessment that it is primarily those patients who today are unable to administer themselves treatment, who will want the new subcutaneous treatment option. The specialist committee estimates that it will, overall be approx. 50% of HAE patients who will eventually receive prophylactic treatment (those 30-40 as of today receives preventive treatment and approx. 30 that will want to switch from attack treatment alone for preventive treatment). Therefore, it is crucial to highlight the financial consequences of one extension of the current patient population.]

According to the Danish Medicines Council protocol, the current population with HAE is estimated to be 120 patients of whom approximately 30-40 patients are estimated to currently receiving prophylaxis with intravenous C1-INH. [20]

Due to the recent regulatory approval of two subcutaneously administered medicines (Takhzyro and Berinert 2000/3000 SC), the current treatment pattern for this group of patients is expected to change.

The Medicines Council expects that approximately 30 patients currently receiving attack treatment will shift to prophylactic treatment with subcutaneous administration.

Takeda has assessed the current and potential future situation, and identified a multitude of parameters that will influence the stakeholders in the decision-making process

The patient is an important stakeholder in the decision-making process, but the preference of the patient and the attitude of the health care professional will be highly individualized as many parameters influence the decision. For example

- Some patients are very reluctant to or can simply not manage the intravenous administration process, which can be cumbersome and stress not only the patients but also relatives/caretakes
- The frequency of administration (as needed, every 3-4 days, every second week or every four weeks) may impact the patient preference as well as the clinician’s assessment of the patient compliance
- Some patients have a high level of anxiety due to the uncertainty of not knowing when and where the next attack will occur. The patient may in this case prefer a prophylactic treatment with low risk of breakthrough of the disease
- The frequency, severity and location of the attacks are very different from patient to patient. Patients with frequent and/or severe laryngeal attacks and their clinician may be more prone to preferring prophylactic treatment with subcutaneous administration than patients with less frequent and/or less severe and peripherally located attacks.
- In contrast to current plasma derived treatment options, lanadelumab is manufactured through a recombinant process. This means that the risk of lack of supply is close to none as compared to

plasma-derived products that are dependent on continuous availability of plasma as well as an unproblematic manufacturing process.

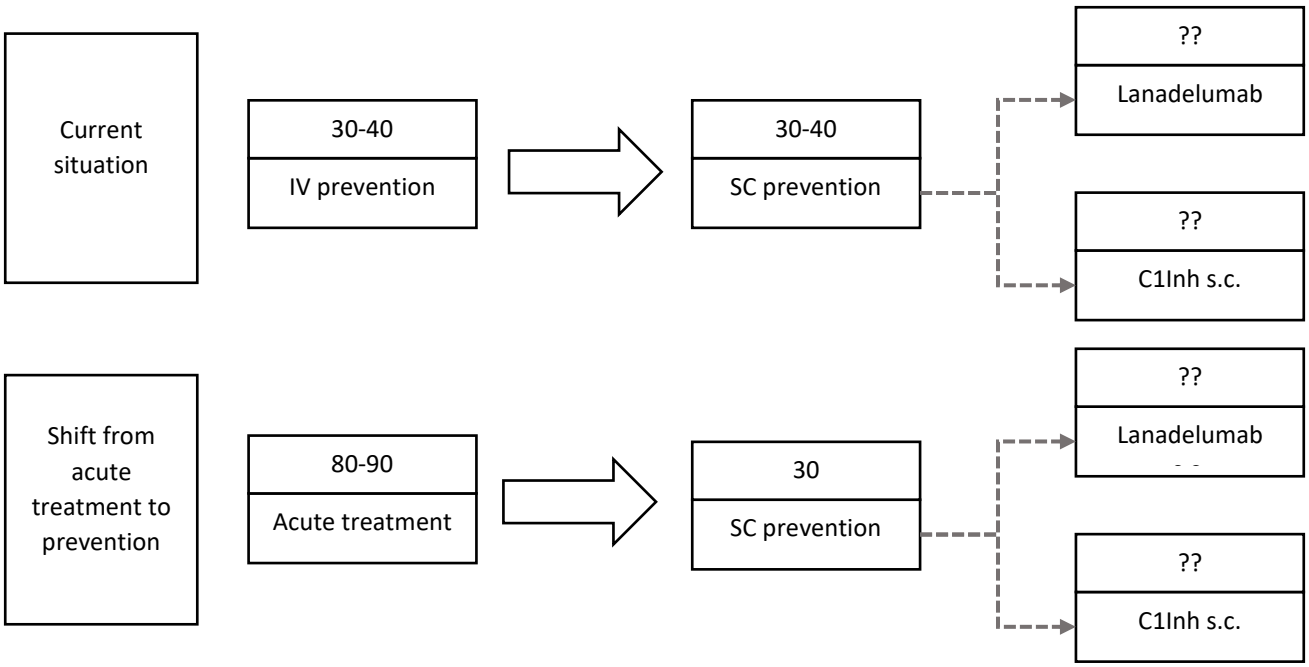
- The overall clinical and social situation for the patient will be taken into consideration by the clinician when choosing the relevant treatment option

Based on the uncertainties of the impact of the above parameters Takeda has concluded that a prediction of the actual number of patients shifting from acute attack treatment to prophylactic treatment is very difficult.

However, when assessing the financial consequences (budget impact) of extending the current patient population, this should be evaluated based on the added clinical value of Takhzyro for routine prevention vs acute treatment with C1-INH and not vs prevention treatment with C1-INH.

Current and expected future patient distribution is shown in the flow chart below

Figure 6 Current and expected future patient distribution



The estimated financial consequences (budget impact) of extending the current patient population are presented in the health economic application to Amgros.

6.2 Accumulated effect over time

[The subject committee wants applicants to discuss how quickly the effect occurs and when steady state occurs for both intervention and comparator.]

Time to onset of action and steady state is dependent on the pharmacokinetics and pharmacodynamics of the medicines, especially time to maximum concentration and time to reach steady state. The values for lanadelumab and intravenous C1-INH IV are tabulated below.

Due to the very short T½ for C1-INH IV, the ongoing treatment every 3-4 days should be considered the steady state, whilst steady state for lanadelumab does not occur until after 70 days.

Table 11 Pharmacokinetics of lanadelumab and C1-inhibitors

	Lanadelumab[17]	C1-INH (Cinryze)[18]	C1-INH (Berinert) [21]
C_{max}	5 days	1.2 (0.3-26) hours	0.8 hours
Time to steady state	70 days	Not reported*	Not reported
$T_{½}$	14 days	56 hours	36.1 hours
		* time to reach steady state has not been reported for Cinryze as the relevance is limited due to the short halftime and high frequency of infusions.	

No data for the early effect for lanadelumab was collected separately as part of the HELP-03study. Post-hoc statistical analyses were performed both for the period of Day 0-182 and the steady state period from Day 70-182. The analysis shows that the proportion of attack free patients was 44.4% during the Day 0-182 period, and even higher during the steady state period (Day 70-182) for lanadelumab 300 mg q2w as compared to placebo as shown in the table below. [6]

Table 12 Attack free patients at day 0-182 and at steady state (day 70-182)

Attack free patients [6]	Lanadelumab 300 q2w	Placebo
Day 0-182	44.4%	2.4%
Day 70-182	76.9%	2.7%

The effect of lanadelumab is thus high already from initiation of treatment and increases to an even higher level when steady state concentrations is reached for lanadelumab.

6.3 Dose reduction

[The Summary of Product Characteristics states that dose reduction to 300 mg lanadelumab every 4 weeks may be considered in stable patients without attacks, especially those with low body weight. It is unclear how many patients there are practice will get the dose down. The applicant should therefore provide information on how many people is expected to be reduced to 300 mg every 4 weeks.]

In the phase III pivotal trial (HELP) dosing of 300 mg every 4 weeks was investigated as one of the arms of the study. Data show that the efficacy of q4w dosing was significantly higher than placebo, but not fully at the same level as for the 300 mg q2w dosing as described in section0. It should also be noted that there are no statistical significance in efficacy between 300 mg qw2 dosing and qw4 dosing. (see Table 34, p. 74)

The proportion of patients expected to shift from 300 mg every second week to 300mg every four weeks has not been formally investigated. Such data are expected to become available through clinical experience by the treating physicians and post-marketing experience. Lanadelumab has been available in a clinical setting for a very short period of time, no such data are yet available. However estimates have been provided below based on the data from the clinical program.

The EMA recommended the use of the q4w dosing directly for patients with low weight. The reason for this recommendation is the fact that pharmacokinetic analyses show a lower exposure for lanadelumab in subject

with higher weight, identifying that higher body weight was correlated to higher risk of experiencing an attack. Detailed data are available in the EPAR (table 9, p. 52). However not only patients with low weight are expected to be able to be managed with lanadelumab 300 mg q4w.

It follows from the lanadelumab SPC "The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight".[17]

It is expected in real world clinical practice that clinicians will initiate patients on lanadelumab q2w dosing and down titrate to a q4w treatment regimen based on treatment success, i.e. when patients are stably attack free [Interviews with clinical experts 2019].

The time to first attack data from the HELP-03 study, conducted from day 70 to day 182 (corresponding to the achievement of steady state of lanadelumab plasma concentration), demonstrated that 76.9% of patients treated with a dosing regimen of 300 mg q2w were attack free during this period (see Table 34, p. 74).

The assumption that a proportion of patients would receive the lower dose in clinical practice was supported by the opinion of several clinical experts (including clinical experts from Denmark, Sweden, Finland, Norway and UK), who stated that they would reduce the frequency of dosing for patients who they considered to be well-controlled on treatment.

In clinical practice, if patients are switched onto the dosing regimen of 300 mg q4w but their condition is then deemed not to be adequately controlled, they may be switched back to the 300 mg q2w dosing regimen. However, it may also be the case that patients who remain on the 300 mg q2w dosing regimen will experience a period where they are attack free and are, as a result, switched to the 300 mg q4w dosing regimen. Therefore, although the proportion of patients assumed to be on each dosing regimen may vary over time, in the absence of long-term data it is assumed that on average 76.9% of patients will be treated with 300 mg q4w after 6 months. Additionally, data from the HELP-04 extension study, as presented below, demonstrate that a patient's attack rate remains stable over time, indicating that any switching of dosing regimens would be limited in the longer term.

Rollover patients who had received Takhzyro in the HELP-03 study maintained low HAE attack rates over 6 months (182 days) of the long-term extension study HELP-04, demonstrating the persistent efficacy of Takhzyro (Table 13). Baseline attack rates for patients who received Takhzyro during the HELP-03 ranged from 3.18 to 3.54, which reduced to 0.26–0.54 by the end of the 26-week HELP-03 study. These same patients had a mean attack rate of 0.19–0.47 attacks per month at interim data readout for the long-term extension study HELP-04, which amounts to a total 83.9–90.5% reduction from baseline in attacks per month (Table 13). Furthermore, patients who had received placebo in the HELP-03 study also showed a substantial reduction in mean attack rate of 90.7% at the interim data readout from the long-term extension study HELP-04 compared to their baseline attack rate as measured during the run-in period of the HELP-03 Study (EPAR table 19, p. 65). *[1]*

Table 13 Mean HAE attack rates reduction in roll-over patients

	Rollover patients **Study 03 treatment to Study 04 treatment**	

	Placebo → 300 mg q2w (n=33)	300 mg q2w → 300 mg q2w (n=25)	300 mg q4w → 300 mg q2w (n=25)	150 mg q4w → 300 mg q2w (n=26)	All rollover patients (n=109)
Mean HAE attack rate in attacks per month (SD)					
Baseline	3.81 (2.997)	3.47 (2.392)	3.54 (2.580)	3.18 (1.739)	3.52 (2.48)
HELP-03	2.39 (1.935)	0.26 (0.451)	0.54 (0.785)	0.44 (0.569)	1.01 (1.49)
HELP-04	0.39 (0.897)	0.19 (0.303)	0.47 (0.648)	0.19 (0.292)	0.31 (0.62)

Note: q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation. Sources: EPAR table 19, p. 65[1]

7 References

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8 Appendices

8.1 Literature search

8.1.1 SLR - Eligibility criteria

Inclusion and exclusion criteria applied during the SLR are listed below.

Table 14 SLR – Inclusion/exclusion criteria

Category	Inclusion criteria listed in DMC protocol 51017	Inclusion criteria used in SLR
Patients	Children ≥12 years old and adults with hereditary angioedema type 1 and type 2 (HAE-1/2)	Children ≥12 years old and adults with HAE-1/2*
Interventions	- Lanadelumab 300 mg every 2 weeks	- Lanadelumab 300 mg every 2 weeks - C1 esterase inhibitor (C1-INH) 1000 or 1500 units IV every 3–4 days for patients ≥12 years old
Comparators	- Prophylactic treatment with IV C1-INH o Adults: C1-INH 1500 units IV every 3–4 days o Children ≥12 years old: C1-INH approx. 1000 unit IV every 3–4 days	- Placebo/no intervention - Any other treatment that would facilitate an indirect comparison
Outcomes	- Total attack freedom (percentage of patients with a 100% reduction in attack frequency) - 90% attack freedom (percentage of patients with a 90% reduction in attack frequency – depending on data availability) - Health-related quality of life (change from baseline and percentage of patients experiencing improvement of 6 points from baseline) o Measured through Angioedema Quality-of-Life Questionnaire score - Attack rate (percentage change in number of HAE attacks per month) - Adverse events (percentage of patients discontinuing treatment due to adverse events)	No change from DMC protocol
Study design	- Randomised, controlled, prospective clinical trials - Data from the European Medicines Agency's European public assessment reports - Indirect treatment comparison incorporating relevant randomised controlled trials	No change from DMC protocol
Other	English and Danish (Non-English articles with an English abstract will be identified in the searches, but the full-text article will not be reviewed if published in a language other than English or Danish)	No change from DMC protocol
Jurisdictions of interest	- No limits in peer-reviewed journals	No change from DMC protocol

* Studies focusing on children of all ages will be included in full-text screening to ensure there is no subgroup data on children aged 12–17 years; if the data are not reported at this stage, they will be excluded.

C1-INH, C1 esterase inhibitor; DMC, Danish Medicines Council; IV, intravenous; SLR, systematic literature review.

8.1.2 MedLine Search Strategy

The MedLine search was performed using the search strategy provided by the DMC.

Table 15 Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions 1946 to 25 July 2019 (Date ran: Friday, 26 July 2019)

#	Searches	Results
1	exp Angioedemas, Hereditary/	999
2	((C1 and Inhibitor* and Deficienc*) or (hereditary and (edema* or oedema* or angioedema* or angiooedema*))).ti,ab.	1,116
3	1 or 2	1,751
4	(prophyl* or prevent*).ti,ab.	1,436,752
5	3 and 4	409
6	lanadelumab.nm. or (DX-2930 or Takhzyro or lanadelumab).ti,ab.	18
7	exp Complement C1 Inhibitor Protein/	1,031
8	((C1* and Inhibitor*) or (Cinryze or Berinert or C1NH or C1lN)).ti,ab.	10,697
9	7 or 8	10,898
10	6 or 9	10,908
11	((randomized controlled trial or controlled clinical trial).pt. or (randomised or randomized or placebo).ti,ab. or exp Clinical Trials as topic/ or randomly.ti,ab. or trial.ti.) not (animals/ not humans/)	1,231,249
12	and 10 and 11	61

8.1.3 Cochrane Search Strategy

The COCHRANE CENTRAL search was performed using the search strategy provided by the DMC.

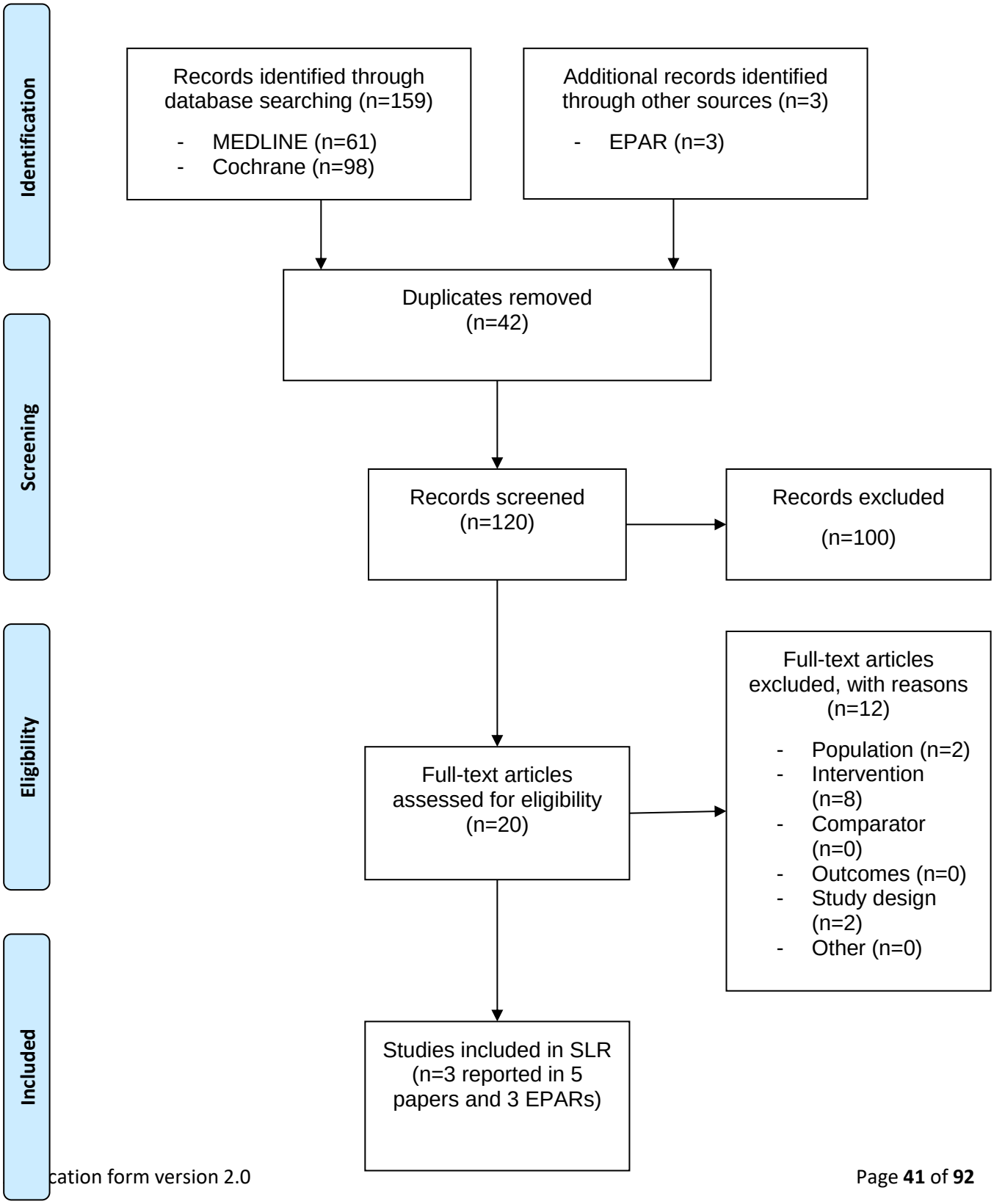
Table 16 EBM Reviews - Cochrane Central Register of Controlled Trials June 2019 (Date ran: Friday, 26 July 2019)

#	Searches	Results
1	exp Angioedemas, Hereditary/	76
2	(C1 and Inhibitor* and Deficienc*).ti,ab,kw.	75
3	(hereditary and (edema* or angioedema* or angioedema*)).ti,ab,kw.	304
4	or/1-3	317
5	(prophyl* or prevent*).ti,ab. or prophylaxis.kw.	154,178
6	4 and 5	153
7	(DX-2930 or Takhzyro or lanadelumab).ti,ab,kw.	38
8	exp Complement C1 Inhibitor Protein/	59
9	((C1* and Inhibitor*) or Cinryze or Berinert or C1NH or C1IN).ti,ab,kw.	854
10	8 or 9	856
11	7 or 10	885
12	6 and 11	122
13	("conference abstract" or review).pt. or NCT*.au.	159,407
14	12 not 13	98

8.1.4 PRISMA flow chart

A total of 159 publications were identified by the database search. After abstract screening and subsequent full text assessment, a total of three studies reported in 5 papers and 3 EPARs were identified.

Figure 7 PRISMA flow chart



8.1.5 List of excluded studies

Twelve full text articles were excluded after full text review.

Table 17 List of excluded studies

Author	Year	Title	Reason for exclusion
Lumry W, et al	2018	Health-related quality of life with subcutaneous C1-inhibitor for prevention of attacks of hereditary angioedema	Intervention
Aygoren-Pursun E, et al	2017	Preventing hereditary angioedema attacks in children using Cinryze: interim efficacy and safety phase 3 findings	Population
Greve J & Hahn J	2017	Recombinant human C1 esterase inhibitor for hereditary angio-oedema	Other; review/editorial
Li HH, et al	2018	Subcutaneous C1-esterase inhibitor to prevent hereditary angioedema attacks: safety findings from the COMPACT trial	Intervention
Longhurst H, et al	2017	Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor	Intervention
Lumry W, et al	2013	Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children	Population
Riedl MA, et al	2017	Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial	Intervention
Riedl MA, et al	2016	Subcutaneous administration of human C1 inhibitor with recombinant human hyaluronidase in patients with hereditary angioedema	Intervention
Riedl MA, et al	2015	Subcutaneous human C1-inhibitor with recombinant human hyaluronidase for the prevention of angioedema attacks in patients with hereditary angioedema: results of a randomized, double-blind, dose-ranging, crossover study	Other; conference abstract
Waytes AT, et al	1996	Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate	Intervention
Weller K, et al	2017	Health-related quality of life with hereditary angioedema following prophylaxis with subcutaneous C1-inhibitor with recombinant hyaluronidase	Intervention
Zuraw BL, et al	2015	Phase II study results of a replacement therapy for hereditary angioedema with subcutaneous C1-inhibitor concentrate	Intervention

8.2 Main characteristics of included studies

8.2.1 Study characteristics

Table 18 Study characteristics - HELP-03study (lanadelumab)

Trial name [Banerji 2018]	HELP
NCT number	NCT02586805
Objective [Banerji 2018]	A study to evaluate the Efficacy and Safety of lanadelumab for Long Term Prophylaxis against Acute Attacks of Hereditary Angioedema (HAE)
Publications – title, author, journal, year	Banerji A, et al.; HELP Investigators. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121.
Study type and design [Banerji 2018]	Phase 3 interventional randomized parallel, quadruple blinded, placebo-controlled study. Patients were enrolled and assigned to interventions using an interactive web-based randomization system (Rho Inc) by blinded study staff in the order of enrolment. Eligible patients were randomized 2:1 to receive subcutaneously injected lanadelumab or placebo. Randomization was stratified by normalized number of attacks during the run-inperiod:1 to less than 2, 2 to less than 3, or 3 or more attacks within 4 weeks using a within-stratum block size of 9.
Follow-up time [Banerji 2018]	The prespecified study period on active drug was 26 weeks.
Population (inclusion and exclusion criteria) www.ct.gov)	Inclusion Criteria: • Males and females 12 years of age or older at time of screening • Documented diagnosis of HAE, Type I or II • Baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks • Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver provides informed consent, are willing and able to read, understand and sign an assent form. • Males and females who are fertile and sexually active must adhere to contraception requirements. Exclusion Criteria: • Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema, idiopathic angioedema, or recurrent angioedema associated with urticaria. • Participation in a prior DX-2930 study • Treatment with any other investigational drug or exposure to an investigational device within 4 weeks prior screening • Exposure to angiotensin-converting enzyme (ACE) inhibitors or any oestrogen-containing medications within 4 weeks prior to screening. • Exposure to androgens within 2 weeks prior to entering the run-in period. • Use of long-term prophylactic therapy for HAE within 2 weeks prior to entering the run-in period. • Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. • Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome). • Pregnancy or breastfeeding.

Intervention	Lanadelumab 150 mg every 4 weeks (n=28) Lanadelumab 300 mg every 4 weeks (n=29) Lanadelumab 300 mg every 2 weeks (n=27) Placebo (n=41) All patient received injections every two weeks with those in the every 4 weeks groups receiving placebo every second week.				
Baseline characteristics		**150 mg/4 weeks** (n = 28)	**300 mg/4 weeks** (n = 29)	**300 mg/2 Weeks** (n = 27)	**Placebo** (n = 41)
	No. (%) of patients				
	Age, mean (SD), y	43.4 (14.9)	39.5 (12.8)	40.3 (13.3)	40.1 (16.8)
	<18	1 (3.6)	3 (10.3)	2 (7.4)	4 (9.8)
	18 to <65	24 (85.7)	26 (89.7)	25 (92.6)	35 (85.4)
	≥65	3 (10.7)	0	0	2 (4.9)
	Females	20 (71.4)	19 (65.5)	15 (55.6)	34 (82.9)
	Males	8 (28.6)	10 (34.5)	12 (44.4)	7 (17.1)
	Race				
	White	25 (89.3)	23 (79.3)	26 (96.3)	39 (95.1)
	Black	1 (3.6)	6 (20.7)	1 (3.7)	2 (4.9)
	Asian	2 (7.1)	0	0	0
	BMI, mean (SD)	26.9 (4.7)	28.1 (5.1)	31.0 (7.8)	27.5 (7.7)
	Hereditary angioedema type				
	Type I	25 (89.3)	27 (93.1)	23 (85.2)	38 (92.7)
	Type II	3 (10.7)	2 (6.9)	4 (14.8)	3 (7.3)
	Age at symptom onset, mean (SD)	12.0 (8.8)	14.6 (11.2)	15.0 (8.7)	11.2 (8.2)
	History of laryngeal attacks	17 (60.7)	17 (58.6)	20 (74.1)	27 (65.9)
	No. of attacks in 12 mo before screening, median (IQR)	34 (12-55)	24 (12-50)	20 (8-36)	30 (17-59)
	Use of long-term prophylaxis in 3 mo before screening				
	Plasma-derived C1 inhibitor	9 (32.1)	18 (62.1)	11 (40.7)	22 (53.7)
	Oral therapy	2 (7.1)	1 (3.4)	0	1 (2.4)
	Combination therapy	1 (3.6)	1 (3.4)	3 (11.1)	1 (2.4)
	No prophylaxis	16 (57.1)	9 (31.0)	13 (48.1)	17 (41.5)
	Run-in hereditary angioedema attack rate, mean (SD) attacks per mo	3.2 (1.8)	3.7 (2.5)	3.5 (2.3)	4.0 (3.3)
	Normalized run-in attack rate category, attacks per mo				
	1-<2	10 (35.7)	9 (31.0)	7 (25.9)	12 (29.3)
	2-<3	3 (10.7)	5 (17.2)	6 (22.2)	8 (19.5)
	≥3	15 (53.6)	15 (51.7)	14 (51.9)	21 (51.2)
Primary and secondary endpoints	<u>Primary outcomes:</u> • Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attacks During Treatment Period <u>Secondary outcomes</u> • Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attack Requiring Acute Treatment • Rate of Moderate or Severe Investigator Confirmed Hereditary Angioedema (HAE) Attacks				

	• Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attacks During Day 14 Through Day 182 <u>Exploratory outcomes</u> • the percentage of patients who were attack-free, • number of attack-free days • responders • number of high morbidity attacks • time to first HAE attack after Day 14 • Health–related quality of life using the Angioedema Quality of Life Questionnaire <u>Other outcomes</u> Adverse events and antidrug antibodies.
Method of analysis	This study was powered to compare effects of lanadelumab vs placebo but was neither designed nor powered to compare the effects of the 3 lanadelumab groups. All efficacy analyses were conducted using the intent-to treat population, defined as all randomized patients exposed to study treatment; analyses were performed according to patients'randomized treatment assignment. Adverse event analyses were conducted using the safety population, which included all patients who received 1 or more dose of study treatment; analyses were performed according to the actual treatment received. The primary and secondary efficacy endpoints for each active treatment group were compared with the placebo group using a Poisson regression model including a covariate for the normalized run-in period attack rate and accounting for potential overdispersion, with the overall type I error controlled at .05. To adjust for the potential of an inflated overall type I error rate due to multiple comparisons, the primary end point and rank-ordered secondary end points were tested in a fixed sequence for each lanadelumab treatment group vs the placebo group comparison at a 1.67%significance level ($\alpha/3$; 2-sided).
Subgroup analyses	No subgroup analysis of relevance for the Medicines Council protocol has been performed. Data for patients below 18 years are very limited, but have been provided in the results section of the application.

Table 19 Study characteristics - Lanadelumab phase IB study

Trial name	A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects. Note! In this application this study will be referred as the ” DX-2930-02”
NCT number	NCT02093923
Objective	The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetic profile of multiple subcutaneous administrations of DX-2930 across a range of doses in Hereditary Angioedema subjects.
Publications – title, author, journal, year	Banerji A, et al. Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis. N Engl J Med. 2017 Feb 23;376(8):717-728. [Banerji 2017]
Study type and design	Phase 1b, multicenter, double-blind, placebo-controlled, multiple-ascending-dose trial. Patients were randomly assigned in a 2:1 ratio to receive either lanadelumab (24 patients) or placebo (13 patients).
Follow-up time	50 days
Population (inclusion and exclusion criteria)	Inclusion Criteria: • At least 18 years of age at the time of screening. • Documented diagnosis of HAE (Type I or II) • Experiencing ≥2 HAE attacks per year, with at least 1 attack in the past 6 months reported by the subject. • Willing and able to read, understand, and sign an informed consent form. • Females of childbearing potential must agree to be abstinent or else use acceptable forms of contraception throughout study • Males with female partners of childbearing potential must agree to be abstinent or use a medically acceptable form of contraception throughout study. Exclusion Criteria: • Exposure to an investigational drug or device within 90 days prior to study. • History of exposure within the past 5 years to a monoclonal antibody or recombinant protein bearing an Fc domain. • Concomitant diagnosis of another form of chronic angioedema • Use of long-term prophylaxis for HAE within 90 days prior to study. • Use of C1-INH that exceeds a total of 30 days within the past 90 days prior to study; any use of C1-INH within 7 days prior to study. • Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption within 90 days prior to study. • Exposure to androgens within 90 days prior to study. • Presence of an indwelling catheter. • Diagnosis of HIV. • Active liver disease or liver function test abnormalities • History of substance abuse or dependence. • Pregnancy or breastfeeding. • Any condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results
Intervention	Study drug was administered in two administrations 14 days apart. Patients assigned to lanadelumab were enrolled in sequential dose groups: total dose of 30 mg (4 patients), 100 mg (4 patients), 300 mg (5 patients), or 400 mg (11 patients).

<table>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristic</th><th>Lanadelumab Dose Group</th><th></th><th>Total Lanadelumab (N = 24)</th><th>Placebo (N = 13)</th><th>All patients (N = 37)</th><th></th><th></th></tr>
<tr><td></td><td>30 mg (N = 4)</td><td>100 mg (N = 4)</td><td>300 mg (N=5)</td><td>400 mg (N = 11)</td><td></td><td></td><td></td></tr>
<tr><td>Male, no (%)</td><td>1 (25)</td><td>1 (25)</td><td>4 (80)</td><td>2 (18)</td><td>8 (33)</td><td>6 (46)</td><td>14 (38)</td></tr>
<tr><td>Female, no (%)</td><td>3 (75)</td><td>3 (75)</td><td>1(20)</td><td>9 (82)</td><td>16 (67)</td><td>7 (54)</td><td>23 (62)</td></tr>
<tr><td>Age — yr</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>46.3±15.5</td><td>36.3±18.0</td><td>33.2±10.0</td><td>40.5±14.3</td><td>39.3±14.1</td><td>41.2±13.7</td><td>39.9±13.8</td></tr>
<tr><td>Range</td><td>23–55</td><td>25–63</td><td>22-46</td><td>20–68</td><td>20–68</td><td>18–71</td><td>18–71</td></tr>
<tr><td>Attacks of angioedema in the previous 12 months</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>7.0±4.2</td><td>10.5±6.7</td><td>14.8±12.4</td><td>35.2±38.8</td><td>22.1±29.1</td><td>22.7±35.9</td><td>22.3±31.2</td></tr>
<tr><td>Range</td><td>3–12</td><td>5–20</td><td>6-36</td><td>11–144</td><td>3–144</td><td>3–140</td><td>3–144</td></tr>
<tr><td>Attacks of angioedema in the previous 3 months</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>2.0±0.8</td><td>3.5±1.7</td><td>3.6±3.1</td><td>9.5±9.0</td><td>6.0±7.0</td><td>6.3±8.9</td><td>6.1±7.6</td></tr>
<tr><td>Range</td><td>1–3</td><td>2–5</td><td>1-9</td><td>3–36</td><td>1–36</td><td>0–35</td><td>0–36</td></tr>
<tr><td>History of laryngeal attack — no. (%)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>0</td><td>1 (25)</td><td>2 (40)</td><td>8 (73)</td><td>11 (46)</td><td>6 (46)</td><td>17 (46)</td></tr>
<tr><td>No</td><td>4 (100)</td><td>3 (75)</td><td>3 (60)</td><td>3 (27)</td><td>13 (54)</td><td>7 (54)</td><td>20 (54)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary safety outcomes were:
Number of Patients with Treatment-Emergent Adverse Events (TEAE)
Proportion of Patients with Treatment-Emergent Adverse Events (TEAE)
Number of Patients with Serious Adverse Events (SAEs)
Proportion of Patients with Serious Adverse Events
The primary efficacy end point was the number of attacks of angioedema per week from day 8 to day 50.</td></tr>
<tr><td>Method of analysis</td><td>Statistical analysis and programming of tables and listings were conducted using SAS® Release 9.3 or higher (SAS Institute Inc., Cary, NC, USA). Continuous data were summarized with descriptive statistics and categorical data were summarized with frequencies (number of patients in category) and percentages. Percentages were computed using the number of patients with available data. Missing data were not imputed.
The primary efficacy endpoint was the number of HAE attacks per week from days 8 to 50. The endpoint was a repeated measure of the number of distinct HAE attacks reported in a 7-day period (168 hours) for each patient. All reports of HAE attacks during the study and for the historical baseline rate were patient provided. Last observation carried forward and imputation of missing data were not used in this analysis.
The generalized estimating equation (GEE) approach with Poisson distribution assumption was applied to the repeated-measures mixed model with independence working correlation structure. The baseline attack rate was used as a covariate. To avoid any possible undue influence of a baseline attack rate outlier, any potential outliers were tested using the Dixon gap test (with $\alpha = 0.05$) before performing any efficacy analyses. If an outlier was present by the Dixon gap test, it was given the value of mean ± 2 SD, where mean and SD were computed without the presence of the Dixon outlier. The least-squares (LS) mean (log of the mean event rate) for each dose level and its corresponding SE was directly estimated from the GEE model. The mean event rate was estimated by transforming the LS means by</td></tr>
</table>

	the exponential function. The ratio of the mean event rate per week for each dose level versus placebo and its 95% confidence intervals (CIs) were estimated by transforming the LS mean difference and its 95% CI by the exponential function. The percentage change in mean attack rate of each active treatment group from the attack rate of placebo, defined as 100% × (treatment attack rate – placebo attack rate) / placebo attack rate, also was displayed. For cases in which there were no HAE attacks, an arbitrarily small value (0.000001) was imputed for the HAE occurrence variable to enable the GEE analyses to converge.
Subgroup analyses	NA

Table 20 Study characteristics - CHANGE B (C1-inhibitor)

Trial name	CHANGE-B
NCT number	NCT01005888
Objective	The study objective was to determine the safety and efficacy of C1-INH-nanofiltered (CINRYZE®) for the prevention of acute HAE attacks.
Publications – title, author, journal, year	Zuraw BL, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010 Aug 5;363(6):513-22. [Efficacy and safety data] Lumry WR, et al. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy Asthma Proc. 2014 Sep-Oct;35(5):371-6. [Quality of Life data] Lumry W, et al. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children. J Pediatr. 2013 May;162(5):1017-22.e1-2. [Adolescent subgroup]
Study type and design	This was a phase III, double-blinded, randomized, placebo-controlled cross-over study consisting of two 12-week treatment periods.
Follow-up time	Two fixed treatment periods of 12 weeks each.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Documented HAE • Normal C1q level • Relatively frequent angioedema attacks (at least 2 per month on average) • Both genders • Age ≥6 years of age Exclusion Criteria: • Low C1q level • B-cell malignancy • Presence of anti-C1-INH autoantibody • History of allergic reaction to C1-INH or other blood products • Narcotic addiction • Current participation in any other investigational drug study or within the past 30 days • Participation in a C1 esterase inhibitor trial, or received blood or a blood product in the past 90 days • Pregnancy or lactation • Any clinically significant medical condition, such as renal failure, that in the opinion of the investigator would interfere with the subject's ability to participate in the study
Intervention	1,000 Units (U) of C1INH-nf administered intravenously (IV) every 3 to 4 days (approximately twice weekly) for 12 weeks, followed by matching placebo (saline) administered IV every 3 to 4 days for 12 weeks. (N=22)
Baseline characteristics	Placebo with Crossover to C1 Inhibitor C1 Inhibitor with Crossover to Placebo

		(N = 11)	(N=11)
	General		
	Age — yr	34.5±14.8	41.7±19.3
	Female sex — no. (%)	11 (100)	9 (81.8)
	Weight — kg	76.3±25.7	70.5±9.3
	Height — cm	163.2±8.8	166.2±6.9
	Years since diagnosis	16.8±7.9	19.3±14.4
	Type II hereditary angioedema — no. (%)	2 (18.2)	2 (18.2)
	Race or ethnic group — no. (%)†		
	White	11 (100)	10 (90.9)
	Black	0	1 (9.1)
	Hispanic	0	0
	Androgen therapy at baseline — no. (%)‡	1 (9.1)	2 (18.2)
Primary and secondary endpoints	*Primary endpoint* • Number of Hereditary Angioedema (HAE) Attacks During Each Prophylactic Therapy Period (An HAE attack was defined as the subject-reported indication of swelling at any location following a report of no swelling on the previous day. Analyses include observed attack counts and normalized attack counts (i.e., the number of attacks observed during each therapy period, normalized for the number of days the subject participated in that period)). Secondary endpoints: • Number of Subject Withdrawals During Each Prophylactic Therapy Period • Average Severity of HAE Attacks During Each Prophylactic Therapy Period • Average Duration of HAE Attacks During Each Prophylactic Therapy Period • Number of Open-label C1INH-nf Infusions Required During Each Prophylactic Therapy Period • Antigenic C1 Inhibitor (C1INH) Serum Levels • Functional C1INH Serum Levels		
Method of analysis	For the prophylaxis study, the primary end point was the attack rate (normalized to 12 weeks) during the administration of C1 inhibitor minus the attack rate during the administration of placebo. A generalized-estimating-equation analysis of variance for the crossover study design was performed on the basis of a Poisson assumption, with effects for treatment sequence, treatment period, and subjects within sequence; each subject served as his or her own control. All subjects who completed the entire initial study period and who received at least one study injection during the crossover period were included in the analysis. Secondary end points were analyzed by means of the Wilcoxon signed-rank test. All significance tests for both studies were two-sided, with a P value of less than 0.05 considered to indicate statistical significance.		
Subgroup analyses	No subgroup analysis of relevance for the Medicines Council protocol has been performed. Data for patients below 18 years are very limited, but have been provided in the results section of the application.		

8.3 Methodology for the Indirect Treatment Comparison

The methodology for assessing feasibility of and conducting the indirect comparison is described in the following sections.

8.3.1 Studies identified

HELP-03

The HELP-03 study (Banerji 2018[6]) was a phase 3 randomised, double-blind, placebo-controlled trial (N=125) with a parallel-group design and a study treatment duration of 26 weeks. Patients aged ≥12 years who experienced ≥1 attack per month were included. The mean age was 40.7 years. Female patients were 70.4% of the study sample; 90.4% of patients were white. The mean weight was 80.7 kg (median, 77.3 kg; EMEA/H/C/004806/0000[2]. The proportion of patients with a history of prophylaxis therapy was 72%. On average, the baseline attack rate was 3.9 attacks per 4 weeks. Data on HAE attacks were reported by patients and confirmed by investigators.[6] The majority of patients had HAE-1 (90.4%); 9.6% had HAE-2.

The primary outcome was the total number of investigator-confirmed HAE attacks.[6] Patients treated with lanadelumab 300 mg q2w or 300 mg q4w experienced significant reductions in the mean monthly total HAE attack rate (defined as attacks per 28-day period): 0.26 and 0.53 attacks per month, respectively, compared with 1.97 attacks per month in the placebo arm (each comparison, $P<0.001$).

Exploratory endpoints included the proportion of attack-free patients and the proportion of patients with reductions of ≥90% in the attack rate compared with the run-in period. Health-related QoL was assessed through the Angioedema Quality of Life Questionnaire (AE-QoL) scores. AE-QoL responders were defined as those who had an improvement of ≥6 points in AE-QoL score. Discontinuations due to adverse events (AEs) were reported as a safety outcome of interest.

DX-2930-02

The DX-2930-02 study (Banerji 2017[7]) was a phase 1b multicentre, double-blind, placebo-controlled, multiple-ascending-dose trial (N=37). Patients with hereditary angioedema with C1 inhibitor deficiency were randomly assigned in a 2:1 ratio to receive either lanadelumab (n=24) or placebo (n=13) in 2 administrations 14 days apart.

Patients aged ≥18 years were included. The mean age was 39.9 years. Women were 62.2% of the total sample; 100% of patients were white. The mean weight was not reported. At baseline, a mean of 6.1 angioedema attacks were reported by patients in the previous 3 months. The distribution of HAE-1 and HAE-2 was not reported.

The primary outcome was the total number of patient-reported HAE attacks over 6 weeks (days 8–50). Patients treated with lanadelumab 300 mg q2w experienced significant reductions in the mean monthly total HAE attack rate: 0 attacks per week compared with 0.37 attacks per week for the placebo arm ($P<0.01$). Secondary outcomes of interest were proportion of attack-free patients and discontinuations due to AEs.

CHANGE

The CHANGE study (Zuraw 2010,[8] Lumry 2014,[9] EMEA/H/C/001207, [2] Bernstein 2019[22]; N=22) was a phase 3 double-blind, placebo-controlled crossover study consisting of two 12-week periods spanning a total study treatment duration of 24 weeks. Each patient acted as his or her own control in the study. Patients aged

≥6 years were included. There were discrepancies in the data reported among the publications of the CHANGE study (detailed below). However, we will focus primarily on the data reported in the EMEA/H/C/001207[2] publication in the ITC because these data are deemed the most relevant and accurate. The Lumry 2014 publication focuses on patients where health-related QoL data were available, whereas the Bernstein 2019 publication reports the findings of an ITC.

The mean age was 38.1 years according to Zuraw 2010 and Bernstein 2019 and 41.69 years according to Lumry 2014. The median age was 37.5 years according to EMEA/H/C/001207; in contrast to the other publications, the EMEA/HC/C/001207 report focused on the median rather than the mean age. Female patients were 90.9% (Zuraw 2010) or 87.5% (Lumry 2014) of the total sample; 95.5% (Zuraw 2010, Bernstein 2019) of the patients were white. The mean weight was 73.4 kg (Zuraw 2010, Bernstein 2019); the median weight was 69.3 kg (Bernstein 2019) and 67.4 kg (EMEA/H/C/001207). HAE-1 was present in 81.8% of patients and HAE-2 in 18.2% of patients (Zuraw 2010). All patients had a history of prophylaxis therapy. The baseline attack rate was not reported. Data on HAE attacks were reported by patients; independent experts were not consulted.

The primary outcomes were the absolute and percentage reductions in number of attacks of angioedema per 28-day period. Patients treated with C1-INH 1000 IU IV bw experienced 6.2 attacks per 12-week period; those who received placebo experienced 12.73 attacks (P<0.001, as reported in Zuraw 2010). In Lumry 2014, the mean numbers of attacks reported per 28-day period were 2.24 with C1-INH 1000 IU IV bw and 4.2 with placebo. Differences in outcome data were noted may be because only data on patients with health-related QoL were provided in the Lumry 2014 publication. In the EMEA/H/C/001207 publication, a mean of 6.1 attacks over a 12-week period with C1-INH 1000 IU IV bw versus 12.7 with placebo were noted. These results differed by 1 decimal point from those in Zuraw 2010. Only the EMEA/H/C/001207 data will be considered in the ITC. AE-QoL score data were not obtained in the CHANGE study; however, Short Form 36 (SF-36) physical and mental component scores (PCS and MCS) were given in the Lumry 2014 study. The mean SF-36 PCS was 40.49, whereas the MCS was 49.49. The proportion of attack-free patients was not reported in any of the publications. Bernstein 2019 reported the proportion of patients with a ≥90% reduction in attacks in comparison to placebo. AE-QoL responders were not reported. Discontinuations due to AEs were reported in the EMEA/H/C/001207 publication; there were no discontinuations in any of the treatment arms.

Table 21 gives an overview on the discrepancies in data reported in the Lumry 2014, Zuraw 2010 and EMEA/HC/C/001207 publications as described above. Data reported on age and weight was relevant for the feasibility assessment, yet was not considered in the Bucher ITC. Data on HAE attacks per 12 weeks was normalised to 28 days; as mentioned above, exclusively data from the EMEA/HC/C/001207 publication was considered in the ITC.

Table 21: Discrepancies in reporting of baseline characteristics and the outcome HAE attacks per 12 weeks in the Lumry 2014, Zuraw 2010 and EMA/HC/001207 publications

	Regimen		Age (years)		Body weight (kg)		HAE attacks per 12 weeks	
		N	Mean	Std	Mean	Std	Mean	Std
CHANGE (Lumry 2014)	C1-INH 1000 IU first	5	33.2	10	—	—	6.72	5.88

	Placebo first	13	41.2	13.7	—	—	12.6	4.20
CHANGE (Zuraw 2010)	C1-INH 1000 IU first	11	41.7	19.3	70.5	9.3	6.26	—
	Placebo first	11	34.5	14.8	76.3	25.7	12.73	—
CHANGE (EMA/H/C/ 001207)	C1-INH 1000 IU first	11	Median: 40	—	**Median:** 70.5	—	6.1	5.43
	Placebo first	11	Median: 35	—	**Median:** 64.3	—	12.7	4.80

8.3.2 Comparability of studies

Study design

The different study designs posed a primary challenge in pooling the 3 studies. The CHANGE study was a crossover study, whereas HELP-03 and DX-2930-02 were parallel-arm studies. Crossover studies harbour the theoretical risk that the effects of the first treatment might carry over into the second treatment period, and may therefore confound the detection of treatment effects. Random-effects models can account for between-study heterogeneity by assigning a suitable distribution to the treatment effect. Bayesian hierarchical models may also account for a combined trial design in meta-analysis; at present, this is exclusively published for pairwise meta-analysis by Curtin et al,[23] and to our knowledge, no methodology is readily available for ITC.[23]

Suitable methodology to account for the crossover design of the CHANGE study was used for the majority of outcomes of interest reported in the 4 publications of the CHANGE study. For the ITC, we will focus on the EMEA/H/C/001207 data, in which the crossover study design has been accounted for through mixed models. Lumry 2014 found that the carryover effect was not statistically significant and therefore removed it from their statistical model, resulting in least squares mean differences between active intervention and placebo on the "attack rate per month" outcome. Bernstein 2019 reports the mean difference in attack rate per month as the output of a mixed model, including fixed factors for treatment, period, sequence, and random effect of patient in the study. Zuraw 2010 and EMEA/H/C/001207 use a generalised-estimating-equation analysis of variance for the crossover study design based on a Poisson assumption with effects for treatment sequence, treatment period, and patients within sequence to estimate attack rate per 12 weeks. Discontinuations due to AEs were reported in a descriptive way and not as the output of a statistical model. Because of the reporting of attack rate in multiple ways and discrepancies in the actual numbers, a decision was made to use only data from the EMEA/H/C/001207 report in the ITC. The EMEA/H/C/001207 data seem most relevant and have also accounted for the crossover study design (in contrast to Lumry 2014, in which no mixed model was used).

In addition to the differences in study design, the 12-week treatment duration in each of the 2 crossover periods in the CHANGE study is not easily comparable to the 26-week treatment period in the parallel group in the HELP-03 study. Different study duration is assumed to be a consequence of the different pharmacokinetic characteristics of the 2 interventions and the differing half-lives. Differences in study duration could have been addressed by using data from a 12-week interim analysis of HELP-03; however, an interim analysis at 12 weeks

was not performed. According to Banerji 2018,[6] the steady state of reduction in HAE attacks was expected to be reached for patients after 70 days on lanadelumab treatment. However, no such data for C1-INH IV exist. Therefore, evidence supporting the adequacy of the 12-week treatment period to show any relevant treatment effects with C1-INH IV is lacking. The corresponding limitations will have to be described.

In the HELP-03 study, patients entered a run-in period of 4 weeks before start of treatment. In the CHANGE study, there was no run-in period. This could have an impact on the detection of treatment effects, especially if previous treatment in the CHANGE study had long-term effects that could carry over into the study period.

Table 22 shows an overview of the trial design for the HELP-03 and CHANGE studies; detailed information on interventions, treatment duration as well as duration of follow-up is provided.

Table 22. Overview of trial design for the HELP-03 (Banerji 2018,[6] DX-2930-02, Banerji 2017,[7] and EMEA/H/C/004806/0000[2] and CHANGE (Zuraw 2010,[8] Lumry 2014,[9] and EMEA/H/C/001207[2]) studies

Study	Randomised Population	N	Study Design	Treatment	Treatment Duration	Duration of Follow-Up
Banerji 2018 (HELP-03)	HAE-1 or -2 Age: ≥12 years History of HAE attack: ≥1 attack/4 wk during the run-in period	125	Phase 3, multicentre, randomised, double-blind, placebo-controlled; parallel design	Lanadelumab • 150 mg q4w (n=28) • 300 mg q4w (n=29) • 300 mg q2w (n=27) Placebo (n=41)	6 mo (13 doses over 26 wk)	26 wk
Banerji 2017 (DX-2930-02)	HAE-1 or -2 Age: ≥18 years History of HAE attack: ≥2 attacks/y, ≥1 in the past 6 months	37	Phase 1b, randomised, double-blind, placebo-controlled, multiple ascending dose; parallel design	Lanadelumab • 400 mg q2w (n =11) • 300 mg q2w (n=5) • 100 mg q2w (n=4) • 30 mg q2w (n=4) Placebo (n=13)	2 doses, 14 d apart	4 mo (~17.38 wk, 121.67 d)
Zuraw 2010 **Lumry 2014 (CHANGE)**	HAE-1 or -2 Age: ≥6 years History of HAE attack: ≥2 attacks/mo	22 (16 in Lumry 2014)	Phase 3, multicentre, randomised, double-blind, placebo-controlled; crossover design	C1-INH IV 1000 IU first (n=11) Placebo first (n=11)	12 wk each on C1-INH IV 1000 IU, and placebo C1-INH IV IU treated every 3–4 d	24 wk

Covariates and sample size

Table 23 shows a summary on baseline characteristics in the three studies of interest. Patients in the CHANGE, DX-2930-02, and HELP-03 studies exhibited a similar age distribution, but the age inclusion criteria differed (≥6, ≥18, and ≥12 years, respectively). The youngest patients in the CHANGE study were aged 9 years, whereas the youngest patients in the HELP-03 and DX-2930-02 studies were aged 12 and 18 years, respectively. The CHANGE study also featured a higher proportion of female patients. Race was deemed comparable between the studies; in all 3 studies, most patients were white. Body weight was comparatively higher in patients in the

HELP-03 study, which was assumed to be related to the differences in sex distribution. The sample size in the CHANGE study (N=22) was considerably smaller than that in the HELP-03 study (N=125). Differences in sample size could also result in different precision of estimates of HAE attack rates at baseline and other covariates of interest, which induces difficulties in comparability.

Inclusion criteria in the CHANGE were ≥2 HAE attacks per month (EMEA/H/C/001207), whereas in the HELP-03 study it was ≥1 attack per month, and in the DX-2930-02 study it was ≥2 attacks per year and ≥1 attack in the past 6 months. Consequently, the mean baseline monthly attack rates were 1.56 and 3.9 in the DX-2930-02 and HELP-03 studies, respectively. The baseline attack rate was not reported in the CHANGE study.

Table 24 shows a summary on disease characteristics. Although all studies recruited patients with HAE-1 and HAE-2, a greater proportion of patients with HAE-1 were enrolled in the HELP-03 study than in the CHANGE study (90.4% vs 81.8%, respectively). These proportions are deemed to be comparable.

The proportion of patients in the HELP-03 study with a history of prophylaxis therapy was lower than that in the CHANGE study (56.8% vs 100%). In theory, prophylaxis therapy could be seen as an indicator for disease severity. However, this is not a valid assumption from a clinical perspective. HAE angioedema attacks occur naturally in unpredictable cycles; months during which a large number of attacks occur may be followed by months with lower disease activity. Consequently, HAE activity is variable over time, and the disease activity is difficult to measure.

Table 23. Baseline demographics of patients with HAE in the HELP-03,[6] [2] DX-2930-02,[7] and CHANGE[8] [2] studies

			Age, y					Body weight, kg					Sex		Race		
	Regimen	N	Mean	Median	SD	Min	Max	Mean	Median	SD	Min	Max	Female, n (%)	Male, n (%)	White, n (%)	Black, n (%)	Asian, n (%)
HELP-03 (Banerji 2018, EMEA/H/C/004806/0000)	Lanadelumab 300 mg q2w	27	40.3	—	13.3	15	62	90.55	—	25.150	55.2	150.0	15 (55.6)	12 (44.4)	26 (96.3)	1 (3.7)	0 (0)
	Lanadelumab 300 mg q4w	29	39.5	—	12.8	12	59	78.50	—	16.575	46.8	121.1	19 (65.5)	10 (34.5)	23 (79.3)	6 (20.7)	0 (0)
	Placebo	41	40.1	—	16.8	12	70	76.33	—	22.669	36.7	146.0	34 (82.9)	7 (17.1)	39 (95.1)	2 (4.9)	0 (0)
DX-2930-02	Lanadelumab 300 mg q2w	5	33.2	—	10	22	46	—	—	—	—	—	1 (20)	4 (80)	5 (100.0)	0 (0)	0 (0)
	Placebo	13	41.2	—	13.7	18	71	—	—	—	—	—	7 (54)	6 (46)	13 (100.0)	0 (0)	0 (0)
CHANGE (Zuraw 2010)	C1-INH 1000 IU first	11	41.7	—	19.3	—	—	70.5	—	9.3	—	—	9 (81.8)	2 (18.2)	10 (90.9)	1 (9.1)	0 (0)
	Placebo first	11	34.5	—	14.8	—	—	76.3	—	25.7	—	—	11 (100)	0 (0)	11 (100.0)	0 (0)	0 (0)
CHANGE (EMEA/H/C/001207)	C1-INH 1000 IU first	11	—	40	—	14	73	—	70.5	—	58.1	87.1	—	—	—	—	—
	Placebo first	11	—	35	—	9	64	—	64.3	—	37.6	113.9	—	—	—	—	—

SD, standard deviation.

Table 24. Disease characteristics of patients with HAE in the HELP-03,[6] [2] DX-2930-02[7] and CHANGE[8] studies

	Regimen	N	HAE Type, n (%)		Disease Duration, mo		Attacks per Month Before Treatment,* n				History of Laryngeal Attacks, n (%)	Prior Use of Prophylaxis, n (%)
			Type 1	Type 2	Mean	SD	Mean	SD	Min	Max		
HELP-03 (Banerji 2018, EMEA/H/C/004806/0000)	Lanadelumab 300 mg q2w	27	23 (85.2)	4 (14.8)	—	—	2.96	2.794	0	12	20 (74.1)	14 (51.8)
	Lanadelumab 300 mg q4w	29	27 (93.1)	2 (6.9)	—	—	3.76	3.512	0	14	17 (58.6)	20 (68.9)
	Placebo	41	38 (92.7)	3 (7.3)	—	—	4.15	3.978	0	15	27 (65.9)	25 (58.5)
DX-2930-02 (Banerji 2017)	Lanadelumab 300 mg q2w	5	—	—	—	—	1.32†	—	—	—	2 (40.0)	—
	Placebo	13	—	—	—	—	1.56†	—	—	—	6 (46.0)	—
CHANGE (Zuraw 2010)	C1-INH 1000 IU first	11	9 (81.8)	2 (18.2)	19.3	14.4	—	—	—	—	—	11 (100.0)
	Placebo first	11	9 (81.8)	2 (18.2)	16.8	7.9	—	—	—	—	—	11 (100.0)

SD, standard deviation.

*CHANGE: no run-in period; HELP-03: run-in period.

†Converted to attack rate per month (ie, 28 d) based on the reported values of per-week attack rate (mean [SD] in the European Public Assessment Report: lanadelumab 400 mg q2w, 0.55 [0.174]; lanadelumab 300 mg q2w, 0.33 [0.246]; placebo, 0.39 [0.177]).

Outcomes of interest

The outcomes of interest in the HELP-03, DX-2930-02, and CHANGE studies are summarised in Table 25. Two outcomes (attack rate and discontinuations due to AEs) were reported in all 3 studies. The proportion of patients with ≥90% reduction in attacks in comparison to baseline has been reported in the HELP-03 study, and was estimated through a mixed logistic regression model in the ITC by Bernstein et al[22] for the CHANGE study data. However, Bernstein et al only report this outcome in terms of absolute effects (difference between C1-INH IV 1000 IU and placebo); the estimated proportions under placebo and C1-INH IV 1000 IU treatment are not reported. The authors do not provide details about whether baseline values have been accounted for in their statistical model. However, because of the crossover study design, this may have been deemed irrelevant.

In addition to availability of outcome data, we have assessed the definitions of all outcomes of interest as summarised in Table 26 -Table 28. In summary, the main differences in attack rate data between the studies were deduced through reporting of attacks: attack rates in the HELP-03 study were reported by patients and confirmed by investigators. In the DX-2930-02 study, attacks were reported exclusively by patients and never confirmed by investigators. In the CHANGE study, investigators assessed HAE attacks reported by patients. HAE attack rates were reported normalised to 28 days in the HELP-03 study and per week in the DX-2930-02 study. In the CHANGE study, these were reported per 12 weeks. For comparability, attack rates in the 3 studies were normalised to a duration of 28 days. The corresponding uncertainty estimates (standard errors and confidence interval [CI] bounds) are invariant to transformation; therefore, these adjustments are deemed feasible.

Table 25. Outcomes considered in the HELP-03,[6] [2] DX-2930-02, [7] and CHANGE[8] [2] studies

Endpoint	HELP-03	DX-2930-02	CHANGE	Notes
Attacks, n (or attack rate/attacks/mo)	√	√	√	Differences in duration of follow-up will be accounted for through normalisation of all attack rates reported to 28 days.
≥90% reductions in the number of HAE attacks/mo	√	×	√	In the HELP-03 study, percentages of patients with ≥90% reductions **from baseline** in the number of monthly HAE attacks are reported. In the CHANGE study, percentages of patients with ≥90% reductions in the number of monthly HAE attacks on active treatment **relative to placebo** were reported. These are the outcomes of a mixed logistic regression model that accounts for the crossover design. However, Bernstein et al do not mention whether baseline values were accounted for in these models – these might have been deemed irrelevant because of the crossover design with identical baseline values in the 2 treatment sequences.
Patients attack-free, %	√	√	×	No definition or analysis of attack-free in CHANGE.
Change in total score AE-QoL	√	×	×	AE-QoL only collected in HELP-03 study.
Responders, % (judged by AE-QoL score)	√	×	×	In the HELP-03 study, responders are defined as patients experiencing an improvement of ≥6 points from baseline.
Change in total score SF-36 PCS	×	×	√	SF-36 PCS was not reported in HELP-03 study.
Change in total score SF-36 MCS	×	×	√	SF-36 MCS was not reported in HELP-03 study.
Withdrawals due to AE	√	√	√	

Table 26. Outcome definition, number of attacks (or attack rate)

	HELP-03	DX-2930-02	CHANGE
Primary endpoint (Y/N)	Yes	Yes	Yes
Time frame, wk	26 (from days 0–182)	6 (from days 8–50)	12
Definition	Investigator-confirmed HAE attacks	Patient-reported HAE attacks	Investigator-confirmed HAE attacks*
Outcome measure	Attacks/28 d	Attacks/wk	Attacks/12 wk
Absolute effects	Difference in change from baseline	Difference in change from baseline	Mean difference between C1-INH 1000 IU and placebo
Relative effects	Rate ratio	Rate ratio Relative decrease vs placebo in rate of attacks, %	—
Frequency of observation	On an individual basis	On an individual basis	Per day*
Statistical methods	Difference was estimated from a nonlinear function of the model parameters. Results of rate ratio are from a Poisson regression model accounting for overdispersion; treatment group and normalised baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable.	Analysed rates of attacks using a mixed model of repeated measures with the assumption of a Poisson distribution and using the baseline attack rate as a covariate	A generalised-estimating-equation analysis of variance for the crossover study design was performed on the basis of a Poisson assumption, with effects for treatment sequence, treatment period, and patients within sequence; each patient served as his or her own control.
Accounted for baseline attack rate	Yes	Yes	No
Accounted for the crossover design	Not relevant	Not relevant	Yes
Accounted for multiplicity	Yes because of different lanadelumab dosing regimens	No	Not relevant because there was only 1 comparison
Imputation of missing data?	No	No	No

*Patients were instructed to document all attacks daily and were evaluated at least weekly by study personnel to determine whether patients had any attacks during the previous week.

Table 27. Outcome definition, ≥90% reductions in the number of monthly HAE attacks

	HELP-03	DX-2930-02	CHANGE
Primary endpoint (Y/N)	No	—	No
Time frame, wk	26 (from days 0–182)	—	12
Definition	Reduction in attack rate from the run-in period of ≥90%	—	Investigator-confirmed HAE attacks*
Outcome measure	≥90% reductions in the number of HAE attacks/28 d	—	Attacks/12 wk
Absolute effects	Mean difference vs placebo	—	Mean difference vs placebo
Relative effects	RR can be estimated from data provided.	—	Insufficient data to estimate RR
Statistical methods	Each lanadelumab treatment group was compared with placebo without adjustment for multiplicity using a Fisher exact test.	—	Percentage of patients experiencing a 90% reduction rate vs placebo was derived from mixed logistic regression models. Treatment and sequence within treatment were considered as fixed effects. Model output reported included the percentage of patients with corresponding 95% CI.
Accounted for the crossover design	Not relevant	—	Yes
Accounted for multiplicity	No; this was an exploratory outcome.	—	Not relevant because there was only 1 comparison
Imputation of missing data?	No	—	No

*Patients were instructed to document all attacks daily and were evaluated at least weekly by study personnel to determine whether patients had any attacks during the previous week.

Table 28. Outcome definition, withdrawals due to adverse events

	HELP-03	DX-2930-02	CHANGE
Time frame, wk	26 (from days 0–182)	6 (from days 8–50)	12
Definition	Any adverse event leading to discontinuation	Discontinuations due to adverse events	Discontinuations due to adverse events
Outcome measure	Number (proportion) of patients	Number of patients	Number of patients who discontinued owing to adverse events
Statistical analysis	Only descriptive statistics reported	Only descriptive statistics reported	Only descriptive statistics reported
Accounted for the crossover design	Not relevant	Not relevant	No
Accounted for multiplicity	No	No	Not relevant

Conclusion

As described in Section 8.3.2., the similarity assumption was deemed to hold among the 3 studies with respect to the covariates age and race. Sex distributions over the studies were different, with a higher proportion of female patients in the CHANGE study. We assume that mean weight was also lower in the CHANGE study owing to differences in sex distributions. The number of attacks at baseline was not reported in the CHANGE study, and therefore the similarity assumption could not be assessed for this covariate. This is deemed to be a consequence of the crossover design; because of repeated measurements in the same patients, it is not necessary to account for differences in baseline values. Per inclusion criteria, there may be differences in number of baseline attacks, given that the CHANGE study required ≥2 HAE attacks per month (EMEA/H/C/001207), whereas the HELP-03 study required ≥1 attack per month, and the DX-2930-02 study required ≥2 attacks per year and ≥1 attack in the past 6 months. Furthermore, a lower proportion of patients in the HELP-03 study had a history of prophylaxis therapy compared with patients in the CHANGE study (56.8% vs 100%, respectively). Taken together, this could in theory indicate different disease severity. However, due to the natural heterogeneity of the condition (as described in Section 8.3.2.2), baseline values can differ widely, even in patients with overall similar disease severity. However, because HAE angioedema attacks have inherent natural variability, with months during which a large number of attacks occur followed by potentially some time with lower disease activity, baseline values can differ widely, even in patients with overall similar disease severity. The proportion of patients with HAE-1 and HAE-2 was deemed comparable over the studies, and the proportion of patients with a history of prophylaxis use was considerably lower in the HELP-03 study than in the CHANGE study.

Data were presented for HAE attack rate, ≥90% reductions in the number of monthly HAE attacks, and discontinuations due to AEs in the HELP-03 and in the CHANGE studies. The HELP-03 study is a parallel-arm study, whereas the CHANGE study is a crossover study. However, crossover study design has been accounted for in the statistical methods used to analyse HAE attack rate as well as ≥90% reductions in the number of monthly HAE attacks.

HAE attack rate was normalised to 28 days in the HELP-03 study and will be transformed from different durations of follow-up (12 weeks in the CHANGE study and 1 week in the DX-2930-02 study) to ensure that the data are comparable. The corresponding uncertainty estimates (standard error and 95% CI bounds) are invariant to transformation; therefore, this approach is feasible. However, the mean differences reported comparing C1-INH 1000 IU and placebo do not account for differences at baseline; this might be a

consequence of the crossover study design. This could induce limitations of incomparability of data, especially the absolute difference data, and will have to be discussed.

Reductions of ≥90% in the number of monthly HAE attacks is reported as a mean difference from baseline in the HELP-03 study and as a mean difference in comparison to placebo in the CHANGE study. This results in the same issue as described for HAE attack rates per 28 days. In addition, for the CHANGE study, the proportions of individuals with ≥90% reductions in monthly HAE attacks is not reported directly, limiting the options of the ITC to an estimation of absolute risk reduction (ARR) only; risk ratio (RR) can then however be estimated through ARR since the corresponding CI bounds are invariant to transformation, given that the risk in the comparator arm, r_c, is a constant.

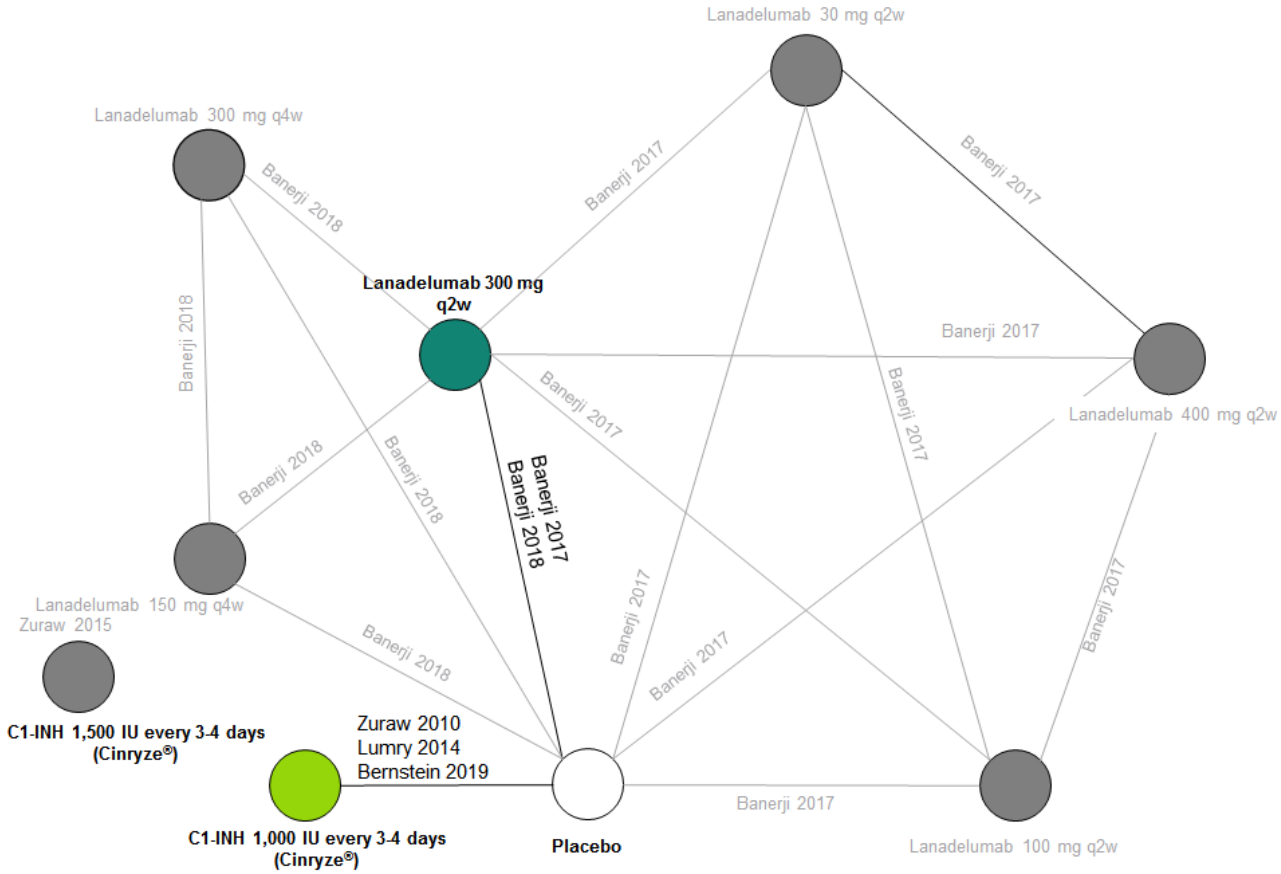
Discontinuations due to AEs have only been reported in a descriptive way in the 3 studies. The corresponding numbers of events are low; therefore, a continuity correction will have to be conducted to estimate the corresponding RRs.

For the proportion of attack-free patients, change in total AE-QoL score, proportion of responders with improvement of ≥6 points in AE-QoL score, and change in total SF-36 PCS and SF-36 MCS, data were not available in both the HELP-03 or the CHANGE study; therefore, no indirect comparison can be conducted.

Common comparator

As shown in the evidence network in Figure 8, the common comparator for C1-INH IV 1000 IU and lanadelumab 300 mg q2w is placebo. The HELP-03 study is a 4-arm study comparing 3 different dosing schemes (300 mg q2w, 300 mg q4w, and 150 mg q4w) of lanadelumab to placebo. In the DX-2930-02 study, 4 different dosing regimens (30, 100, 300, and 400 mg in 2 doses 2 weeks apart) of lanadelumab were compared with placebo. According to the European Public Assessment Report EMEA/H/C/004806/0000, the recommended starting dose is 300 mg q2w. Dose reduction to 300 mg q4w should be considered in patients who remain stably attack free on treatment. The DMC protocol stipulates that the lanadelumab 300-mg q2w dose is of interest; therefore, the network of evidence will exclusively include this dosing regimen. All other dosing regimens of lanadelumab are greyed out in the figure and therefore excluded from the network. Comparisons among the different dosing schedules of lanadelumab are not of interest per the DMC protocol.

Figure 8: Network of evidence



8.4 Indirect treatment comparison

Statistical approaches to evidence synthesis can be characterised primarily as either frequentist or Bayesian. Frequentist methods, such as adjusted indirect comparisons (eg, Bucher method, matched-adjusted indirect comparison, simulated treatment comparison), allow the indirect comparison of 2 interventions in a single step. The term *network meta-analysis* (NMA) refers to the simultaneous comparison of a larger network of interventions. A frequentist approach to NMA that is based on weighted regression was introduced by Rücker et al.[24] In a Bayesian framework, NMA is also conducted based on generalised linear models. Minimally informative priors are usually assigned to the treatment effects [25] to enable the data to speak for themselves.

For the purpose of this ITC, a frequentist approach was preferred over a Bayesian approach because of the limited evidence base (N=3 studies) and the low number of interventions of interest (lanadelumab 300 mg q2w and C1-INH 1000 IU bw). Further, the limited data available to update the minimally informative priors in a Bayesian NMA into the corresponding posteriors could lead to convergence issues. Sparse data also introduce an excessive degree of uncertainty, resulting in wide credible intervals. Although informative priors may be assigned, prior elicitation is not always straightforward. Alternatively, expert clinicians may provide estimates of expected treatment effects; these estimates should ideally be independent of the corresponding literature.[26] However, this approach was not feasible given the planned timeline for the analysis.

Two frequentist approaches to evidence synthesis are currently available. In a frequentist regression-based approach to NMA following Rücker et al,[24] several interventions can be compared to each other simultaneously in a large network of evidence. The corresponding point estimates are expected to be very similar to those obtained through a Bayesian analysis; however, the 95% CIs are usually not as wide as the credible intervals of a Bayesian analysis if the evidence base is sparse.[27]

In the Bucher method,[28] indirect comparisons are conducted via simple equations; by doing so, 2 interventions of interest can be compared to each other at once. If multiple comparisons are of interest, multiple analyses have to be conducted. In our network, only 2 interventions will be compared indirectly (lanadelumab 300 mg q2w and C1-INH IV 1000 IU bw); therefore, the Bucher method is deemed the most appropriate approach. The Bucher method is also well known to and well established with health authorities such as the DMC. The DMC protocol did not provide any detailed instructions about a specific methodology of interest. The following subsections provide further details of the ITC methods.

8.4.1 HAE attack rate per 28 days

The mean rate of HAE attacks was reported for lanadelumab 300 mg q2w, C1-INH IV 1000 IU bw and placebo in the 3 studies identified via SLR (HELP-03, DX-2930-02, and CHANGE). In the HELP-03 study, the difference in HAE attack rates comparing lanadelumab to placebo was estimated from a nonlinear function of the model parameters (Table 26). RRs were obtained through a Poisson regression model accounting for overdispersion; treatment group and normalised baseline attack rate were included as fixed effects. The logarithm of time in days each patient was observed during the treatment period was included as an offset variable. In the DX-2930-02 study, a mixed model with the assumption of a Poisson distribution was used to account for the correlation of repeated measurements of attack rates. The baseline attack rate, as a potential treatment effect modifier, was also included as a covariate in the model. In the CHANGE study, a generalised-estimating-equation analysis of variance for the crossover study design was performed on the basis of a Poisson assumption, with effects for treatment sequence, treatment period, and patients within sequence; each patient served as his or her own control. By doing so, accountability of repeated measurements, as induced through the crossover study design, was possible.

Data obtained through parallel-arm studies such as the HELP-03 study cannot be pooled directly with data obtained through crossover studies such as the CHANGE study; the crossover study design has to be accounted for in the endpoints of interest by suitable statistical methodology. For HAE attack rate, this was conducted as described above. Therefore, we can conclude that despite different study designs, data on HAE attack rate can be pooled in terms of an ITC.

In the HELP-03 and DX-2930-02 studies, baseline attack rate was considered as a covariate in the Poisson regression models estimating HAE attack rates. In the CHANGE study, however, baseline attack rate was not considered in the analysis of variance, and potential baseline differences between the 2 studies therefore could not be accounted for when data of the 3 studies were pooled. This could pose problems for data comparability (eg, if individuals receiving 1 of the treatment regimens were affected more severely at baseline than other individuals). As described above, per inclusion criteria, patients in the CHANGE study were affected more severely than patients in the HELP-03 study. The mean baseline monthly attack rates were 1.56 in the DX-2930-02 study and 3.9 in the HELP-03 study. The baseline attack rate in the CHANGE study are not available. Another consideration is that the attack rates were reported for different time frames. In the HELP-03 study, the attack rates were reported per 28 days, whereas in the DX-2930-02 study, the attack rates were reported weekly. In the CHANGE study, the attack rates were reported over a 12-week period. To ensure comparability of time frame, the HAE attack rates will be normalised to 28 days in the DX-2930-02 and CHANGE studies. The mean can be converted directly by multiplying by 4 in the DX-

2930-02 study and dividing by 3 in the CHANGE study. The corresponding standard deviation, standard error, and 95% CI bounds are invariant to transformation and therefore can be adjusted in the same way as the mean.

The relative treatment effects were estimated in terms of rate ratio (RR) of HAE attack rate per 28 days versus placebo. For lanadelumab 300 mg q2w, this represents the ratio of the rate of attacks per 28 days relative to placebo. These data were reported in the HELP-03 study; however, the CHANGE and DX-2930-02 studies did not provide these data. These effects can be estimated from the individual rates that were normalised to 28 days as described in Section 0. The pooled effect size for lanadelumab 300 mg q2w versus placebo will then be estimated as a weighted average of the individual effect measures observed in the HELP-03 and DX-2930-02 studies. A pairwise meta-analysis will be conducted for pooling the data of the 2 studies (more details are noted in Section 0.). For C1-INH IV 1000 IU bw, the RR indicates the ratio of the rate of attacks per 28 days during treatment with C1-INH IV relative to placebo. The 2 RR estimates are then used as input for an indirect comparison via the Bucher method, indirectly comparing lanadelumab 300 mg q2w and C1-INH.

In addition to relative effects in terms of rate ratio, absolute effects in terms of mean differences can be estimated. These were reported directly in the HELP-03 study for 28 days and were normalised to 28 days in the DX-2930-02 and CHANGE studies. The HELP-03 and DX-2930-02 study data were pooled via pairwise meta-analysis. The pooled estimate and the mean difference reported in the CHANGE study will then be used as an input into the Bucher method. The resulting estimate will be the mean difference and not the mean difference in change from baseline because baseline values are not accounted for in the CHANGE study data. However, as requested by the DMC, results in terms of absolute effects will have to be derived from results obtained through relative effects, and no separate analyses for absolute and relative effects are to be conducted, despite data availability.

Data preparation

The DX-2930-02 and CHANGE studies report the mean number of HAE attacks per patient, μ_i and μ_c, in the intervention i and control c. As an input to the ITC, the RR with corresponding standard error is required on the log scale. The point estimate can simply be estimated as a ratio of the rates reported and transformed to the log scale. The standard error of the RR on the log scale is estimated as[29]

$$SE(\ln(RaR)) = \sqrt{\frac{1}{a} + \frac{1}{b}},$$

where a and b refer to the number of events in intervention i and control c, respectively. The number of events are not reported but can be estimated through the mean number of HAE attacks μ_i and μ_c and the total person-days at risk per arm P_i and P_c as

$$a = \mu_i P_i$$

and

$$b = \mu_c P_{c.}$$

The person-days at risk P_i and P_c over the 28-day period are estimated as averages of the sample sizes in the intent-to-treat (ITT) population N_i and the number of patients completing the study (difference in sample size of ITT population and number of withdrawals W_i) as

$$P_i = \frac{N_i + (N_i - W_i)}{2};$$

the estimation of the person-days at risk in the control arm P_c is conducted accordingly. This equation considers the definition of person-days at risk as a cohort of people followed up from study entry until loss to follow-up. Because we do not have individual-level data, we approximate this through an average of ITT population and those completing the study.

In the HELP-03 study, the RRs with corresponding 95% CIs are reported, and the corresponding standard error is estimated from the CI as

$$SE(\ln(RaR)) = (\ln(Upper) - \ln(Lower))/3.92,$$

where *Upper* and *Lower* refer to the upper and lower bounds of the corresponding 95% CI.

% Change in number of HAE attacks per month

The % change in the number of HAE attacks per month is estimated from the results obtained in terms of RaR as:

$$\%change = (100 * RaR) - 100.$$

The bounds of the corresponding 95% CI are estimated accordingly.

8.4.2 ≥90% Reductions in the number of monthly HAE attacks

The proportion of ≥90% reductions in the number of monthly HAE attacks was reported for lanadelumab 300 mg q2w, C1-INH IV 1000 IU bw, and placebo in the HELP-03 and CHANGE studies. In, in the HELP-03 study, each lanadelumab arm was compared with placebo without adjustment for multiplicity using a Fisher exact test (Table 26). Absolute effects in terms of mean change from baseline (corresponding to the run-in period) were reported directly. For the CHANGE study, the Bernstein et al publication reported the proportion of patients experiencing a ≥90% HAE attack reduction rate over placebo as the output of a mixed logistic regression model that accounted for the crossover study design. This output corresponds to the mean difference between C1-INH 1000 IU bw and placebo, which can also be expressed as ARR. Because baseline values were not accounted for, the same limitations as described for HAE attack rate apply if these data are pooled in terms of an ITC.

Relative treatment effects are estimated through absolute effects because of limited information available in the CHANGE study; the actual proportion of ≥90% reductions in the number of monthly HAE attacks is not reported for C1-INH 1000 IU bw and placebo arms individually. However, information on the risk in the comparator arm, r_c, is provided. Estimating RR from ARR is therefore straightforward because the corresponding CI bounds are deemed invariant to transformation, and information on r_c is available.

Absolute effects in terms of ARR can be pooled. These were reported directly in the HELP-03 and CHANGE studies. These estimates will then be used as an input into the Bucher method. The resulting estimate will be the mean difference and not the mean difference in change from baseline because baseline values were not accounted for in the CHANGE study data.

In the HELP-03 and CHANGE study, the ARR with corresponding 95% CI is reported, and the corresponding standard error is estimated from the CI as:

$$SE((ARR)) = (Upper - Lower)/3.92,$$

where *Upper* and *Lower* refer to the upper and lower bounds of the corresponding 95% CI.

8.4.3 Withdrawal due to AEs

Another outcome with data availability in the 3 studies identified in the SLR is the proportion of patients discontinuing treatment because of AEs. As requested by the DMC, relative effects will be expressed as RR. In addition, absolute effects will be estimated in terms of ARR to assess the magnitude of the effect size. Withdrawals due to AEs are reported descriptively in the 3 studies; no estimates for RR are provided. Therefore, we estimate these from the number of events and sample size as shown in an example of a standard contingency table (Table 29). The number of events is small; a continuity correction will be applied, adding 0.5 to every cell of the contingency table to estimate RR.

RR will be estimated as

$$RR = \frac{\mathrm{a}/(\mathrm{a}+\mathrm{b})}{\mathrm{c}/(\mathrm{c}+\mathrm{d})}.$$

The corresponding standard error is estimated for RR on the log scale as

$$SE(\ln RR) = \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}.$$

As described above, absolute effects are estimated in terms of relative effects as required by the DMC; the corresponding details are described on p. 70.

Table 29. Contingency table for estimation of RR and ARR

	Event	**No Event**	**Σ**
Intervention	a	b	a + b
Comparator	c	d	c + d
Σ	a + c	b + d	a + b + c + d

8.4.4 Bucher method

We suggest conducting the ITC using the Bucher method, given the small network of evidence and the acceptance by health authorities. Bucher et al (1997) introduced an approach of ITC based on simple equations.[28] Binary outcomes will be assessed in terms of RR and ARR. Count outcome will be assessed in terms of RR; the estimation is conducted in the same way as for RR, and just the estimation of the standard errors is different for count data when compared with binary data as described in Sections 0. and 8.4.3. Continuous outcomes will be assessed in terms of mean difference; baseline values have only been accounted for in the HELP-03 study; therefore, these results will have to be interpreted with care.

For binary outcomes, in terms of RR, the treatment effect of the indirect comparison of active treatments A and B via common comparator baseline treatment C will be estimated as the difference of the treatment effects of the direct comparisons on the log scale as

$$ln(RR_{AB}) = ln(RR_{AC}) - ln(RR_{BC}),$$

where treatments A, B, and C correspond to lanadelumab 300 mg q2w, C1-INH IV 1000 IU bw, and placebo, respectively.

The corresponding variance is the sum of the variance of the treatment effects of the direct comparisons, estimated as

$$Var(lnRR_{AB}) = Var(lnRR_{AC}) + Var(lnRR_{BC}),$$

with standard error

$$SE(lnRR_{AB}) = \sqrt{SE(lnRR_{AC})^2 + SE(lnRR_{BC})^2}.$$

The equations in terms of RR are equivalent. To estimate absolute effects in terms of ARR, a log transformation is not necessary. Pooled ARR is estimated as the difference of the treatment effects of the direct comparisons corresponding to

$$ARR_{AB} = ARR_{AC} - ARR_{BC},$$

with variance

$$Var(ARR_{AB}) = Var(ARR_{AC}) + Var(ARR_{BC}),$$

and standard error

$$SE(ARR_{AB}) = \sqrt{SE(ARR_{AC})^2 + SE(ARR_{BC})^2}.$$

The equations for ARR, however, are only relevant if ARR cannot be estimated from RR through a transformation due to limited data availability.Pooling multiple studies that form evidence for one comparator

If more than one study is available to inform a direct comparison (as is the case for the comparison between lanadelumab 300 mg q2w and placebo), the corresponding treatment effect and variance considered in the equations of the Bucher method is a pooled estimator obtained through pairwise meta-analysis using the Mantel-Haenszel method. Pooling is conducted by assigning weights w_i to the individual studies i, either estimated through the inverse variance method, which corresponds to a fixed-effects model, or a variation of the inverse variance method following DerSimonian and Laird, which corresponds to a random-effects model. The inverse variance refers to the relative effect of each individual study that is considered in the pooling.[30]

We will assess the extent of statistical heterogeneity between the studies on each direct treatment comparison through the I^2 statistic and the *P* value of the Q-statistic. If no between-study heterogeneity (*P*>0.2) is identified, a fixed-effects model will be used to obtain the pooled estimator of the corresponding treatment effect. In that case, w_i is the inverse of the within-studies variance (v_i); thus, in the fixed-effects model, the weights are estimated as $w_{\mathrm{i}} = 1/v_i$.[30] However, in the absence of heterogeneity, the results of fixed- and random-effects models are expected to be identical.

In contrast, if between-study heterogeneity is identified (*P*<0.2), this is usually accounted for through the use of a random-effects model, which is then used to estimate the pooled effect. In that case, using the DerSimonian and Laird method, the weights $w_i^* = \frac{1}{v_i + \tau^2}$ are the inverse of the sum of the within-study variance v_i and the between-studies variance $\tau^{2,}$ where

$$\tau^2 = \begin{cases} \dfrac{Q - df}{C} & if\ Q > df \\ 0 & if\ Q \leq df. \end{cases}$$

The degrees of freedom (*df*) are the overall number of studies – 1. *C* represents a scaling factor that ensures that τ^2 is in the same metric as v_i and is calculated as

$$C = \sum_{i=1}^{k} w_i - \frac{\sum_{i=1}^{k} w_i^2}{\sum_{i=1}^{k} w_i}.$$

The Q-statistic represents the total variance and is defined as

$$Q = \sum_{i=1}^{k} w_i (y_i - \mu)^2,$$

where *k* is the number of studies, y_i is the treatment effect estimated in each study, and μ is the combined treatment effect.[31]

By inverse variance weighting, larger studies that have smaller standard errors are given more weight than the smaller studies. This choice of weight minimises the imprecision of the pooled effect estimate. Therefore, the pooled estimator always tends towards the estimator of the largest study. Using the pooled relative effects for each pairwise comparison (eg, RR_{AB}, $Var(RR_{\mathrm{AB}})$ for A versus B, and RR_{AC}, $Var(RR_{\mathrm{AC}})$ for A versus C or ARR_{AB}, $Var(\mathrm{A}RR_{\mathrm{AB}})$ for A versus B, and ARR_{AC}, $Var(\mathrm{A}RR_{\mathrm{AC}})$ for A versus C), the relative and absolute effects of B versus C are estimated indirectly as per the Bucher method described above.

8.4.5 Relative and absolute effects

As requested by the DMC, we will present relative effects in terms of RR, which is the most consistent estimate on relative effects and, therefore, preferable over OR when there are variations in event rates between trials. In contrast to OR, RR can be interpreted intuitively. Misinterpreting a treatment effect expressed as a relative reduction in odds as relative reduction in risk always overestimates treatment effects.[32]

The DMC also requests reporting of absolute effects in terms of ARR in addition to relative effects, which helps quantify the magnitude of the effect size. For example, an RR of 0.5 could mean that the risk of disease has been reduced from 80% in the control group to 40% in the experimental group (ARR = 40%), but could also mean that it only reduced from 0.8% in the control group to 0.4% in the experimental group (ARR = 0.4%). For very large or very small numbers of events, weights estimated for RR or ARR can differ considerably, resulting in different conclusions.[33, 34]

However, the DMC protocol requires estimating ARR through RR whenever feasible (in case data are available to estimate RR directly).

The DMC protocol states that

$$ARR = r_c RR - r_c,$$

where r_c represents the risk in the comparator group. Solving for RR, this results in:

$$RR = \frac{ARR - r_c}{-r_c}.$$

The DMC states that an estimate for r_c had to reflect the expectations in a Danish context; if no reliable numbers existed, the observed rates in the included studies could be used. Whenever available, we have therefore considered $\mathrm{r_c}$ as reported in the publications of the CHANGE study. As stated in the DMC protocol on page 10, the Bernstein 2019 publication provides information on r_c for the outcome of ≥90%

reductions in the number of monthly HAE attacks. This refers to the estimation of mean RR and corresponding CI through ARR.

The corresponding 95% CI bounds are considered invariant to transformation, given that r_c is a constant. The upper and lower CI bounds, UCL and LCL, are therefore transformed as shown for the mean in the equations above.

For ARR, the corresponding p-value is estimated from the transformed CI bounds as

$$P = 2(1 - F(z)),$$

where

$$z = \left|\frac{ARR}{SE}\right|, and\ SE = \frac{[UCL - (-LCL)]}{2 \cdot 1.96}.$$

8.5 F represents the cumulative distribution function of the normally distributed test statistic z. To estimate the p-value for RR, a log transformation of RR, LCL and UCL are necessary. SE and z are then estimated as shown for ARR, considering the estimates for RR on the log scale. The equation for the p-value is equivalent to ARR, and no back-transformation is necessary.ITC data input

The data inputs were reported in different formats in the literature and therefore had to be transformed to ensure consistent data input into the Bucher ITC. Details corresponding to the three outcomes of interest, including transformation, where an ITC was deemed feasible, are given below.

8.5.1 HAE attack rate per 28 days

HAE attack rates were reported per 28 days in the HELP-03 study, per week in the DX-2930-02 study, and per 12 weeks in the CHANGE study. All data were normalised to 28 days to ensure comparability. For the mean HAE attack rates, this was straightforward. The corresponding standard errors and confidence interval bounds were invariant to transformation; therefore, these could be multiplied by four in DX-2930-02 and divided by three in the CHANGE study.

The HELP-03 and DX-2930-02 study data were pooled through pairwise meta-analysis, using the R package *metafor v2.0.0* and the predefined *rma* function. The outcome was assessed in terms of rate ratios, defining HAE attack rates as count data. In the base case, HELP-03 data obtained during days 0 to 182 of treatment were considered. In addition, a sensitivity analysis (SA) was conducted on steady-state data of the HELP-03 study, which were obtained during days 70 to 182 of treatment. The rationale for doing so was to make the HELP-03 and CHANGE studies more comparable in terms of duration of follow-up. Steady-state data in the HELP-03 study corresponded to a 16-week observation time horizon, in contrast to the base case, where study participants in the HELP-03 study were observed for 26 weeks. In the CHANGE study, observation time horizon was as short as 12 weeks. Another reason for considering data on shorter follow-up in the HELP-03 study was the fact that the data of the first 2 weeks of treatment were not considered in the CHANGE study to account for the carryover effect in the crossover design and to achieve steady state.

Table 30 depicts the data input for the base case, assessing HAE attack rates in terms of rate ratio. The *rma* function required data input of RaR and corresponding variance on the log scale. In the HELP-03 study, RaR with corresponding 95% CI was reported directly. Variance of ln(RaR) was estimated through normal

approximation from the 95% CI. In the DX-2930-02 study, mean attack rates in lanadelumab 300 mg q2w and placebo arms were reported; the corresponding ratio was the RaR of interest. However, because no patients in the lanadelumab 300 mg q2w arm experienced an attack, a continuity correction adding 0.05 was applied to enable a calculation of ln(RaR) and corresponding variance (Var(ln(RaR)). No uncertainty estimate was provided for a ratio; therefore, this was estimated through the number of events and the person-days at risk in the two arms, as described in Section 0. Because there were no premature discontinuations, the person-days at risk corresponded to the sample size in the two arms. In the CHANGE study, RaR and corresponding variance was estimated in a similar way as for the DX-2930-02 study; the rates in the two arms were reported directly, and corresponding variance was estimated through the number of events and person-days at risk. Two patients discontinued the study prematurely; therefore, person-days at risk were lower than the actual sample size in the arms.

Table 30: Data input HAE attack rate per 28 days (Base Case)

Study	ln(RaR)	Var(ln(RaR)	RaR	95%LCL RaR	95%UCL RaR	Events i	Events c	PD at risk i	PD at risk c
HELP-03 Lanadelumab 300mg q2w	–2.0402	0.0988	0.13	0.07	0.24	-	-	-	-
DX-2930-02	–2.9957	20.0614	0.05	-	-	0.05	16.28	4	11
CHANGE	–0.7333	0.0347	0.4803	-	-	42.70	88.90	21	21

c=control; i=intervention; LCL=lower confidence limit; PD=person-days; UCL=upper confidence limit.

The data input for the corresponding sensitivity analysis is shown in Table 31. Estimates for the HELP-03 study differed slightly; the RaR was slightly lower, and the corresponding variance was slightly higher.

Table 31: Data input HAE attack rate per 28 days (SA Steady State in HELP-03 study)

Study	ln(RaR)	Var(ln(RaR)	RaR	95%LCL RaR	95%UCL RaR	Events i	Events c	PY at risk i	PY at risk c
HELP-03 Lanadelumab 300mg q2w	–2.4080	0.1580	0.09	0.04	0.19	-	-	-	-
DX-2930-02	–2.9957	20.0614	0.05	-	-	0.05	16.28	4	11
CHANGE	–0.7333	0.0347	0.4803	-	-	42.70	88.90	21	21

c=control; i=intervention; LCL=lower confidence limit; PY=person-years; UCL=upper confidence limit.

8.5.2 ≥90% Reductions in the number of HAE attacks

As shown in Table 32, data availability for the outcome of ≥90% reductions in the number of HAE attacks was limited. In the HELP-03 study, the mean difference in proportions experiencing the event was reported with corresponding 95% CI; this information was then used to derive ARR by multiplying mean and CI bounds by –1 and exchanging upper and lower CI bounds. This estimate accounted for baseline values. In the DX-2930-02 study, no data were provided. In the CHANGE study, the Bernstein 2019 publication was the only available data source reporting mean difference in arms. This information was used to derive ARR. The corresponding 95% CI was displayed graphically and extracted through WebPlotDigitizer 4.2 (https://apps.automeris.io/wpd/). Variance of ARR was estimated through Normal approximation from the 95% CIs as described in Section 8.4.2.

Table 32: Data input ≥90% reductions in the number of HAE attacks

Study	ARR	Var(ARR)	95% LCL ARR	95% UCL ARR
HELP-03	–0.618	0.0101	–0.788	–0.395
CHANGE	–0.182	0.0076	–0.401	–0.06

8.5.3 Withdrawals due to AEs

For the safety outcome of interest of withdrawals due to AEs, the number of events in intervention (lanadelumab 300 mg q2w) and control (placebo) arms were reported in the HELP-03, DX-2930-02, and CHANGE studies. These were used as input to the *rma* function as shown in Table 33 to pool the HELP-03 and DX-2930-02 study data. A continuity correction of 0.05 was applied to provide estimates in terms of RR. The same data were considered as input for estimation of ARR.

Table 33: Data input, withdrawals due to AEs

Study	n_i	Events i	n_c	Events c
HELP-03	27	0	41	1
DX-2930-02	5	0	13	0
CHANGE	22	0	22	0

Results per study

Table 34 Results - HELP-03study

Trial name:	HELP										
NCT number:	NCT02586805										
Outcome	Study arm	N	Results: Proportion or Mean/Median (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				ARR/DCFB	95% CI	P value	Risk/rate ratio	95% CI	P value		
Attack-free patients at 26 weeks	Lanadelumab 300 mg q4wks	29	31.0% (19.0% — 43.1%)	-28.6%	-50.0% — -5.0%	0.001	12.7	1.7 — 95.0	0.0132	Each lanadelumab treatment group was compared with placebo without adjustment for multiplicity, using a Fisher's exact test. Confidence intervals for proportions were estimated through Normal approximation. In case of small number of events in the placebo arm, these were estimated following Paterson et al. Absolute effects were reported directly. Confidence intervals for relative effects (ratio of proportions) were estimated through log-transformation.	Banerji 2018, Table 3 and Figure 2b
	Lanadelumab 300 mg q2wks	27	44.4% (31.1% — 57.8%)	-42.0%	-61.8% — -18.1%	<0.001	18.2	2.5 — 132.2	0.0041		
	Placebo	41	2.4% (0.4% — 12.6%)	—	—	—	—	—	—		
Attack-free patients steady state (days 70-182)	Lanadelumab 300 mg q4wks	29	44.8% (31.9% — 57.8%)	-42.1%	-62.2% — -18.6%	<0.001	18.4	2.5 — 132.8	0.0039	Conducted in a post hoc analysis that included region (US vs non-US) as a categorical covariate; each lanadelumab treatment group was compared with placebo without adjustment for multiplicity, using a Fisher's exact test. Confidence intervals for proportions were estimated through Normal approximation.	Banerji 2018, Table 4
	Lanadelumab 300 mg q2wks	27	76.9% (62.3% — 85.9%)	-74.2%	- 88.6% — -53.6%	<0.001	30.4	4.3 — 213.2	<0.0006		
	Placebo	41	2.7% (0.4% — 12.6%)	—	—	—	—	—	—		

Trial name:	HELP										
NCT number:	NCT02586805										
Outcome	Study arm	N	Results: Proportion or Mean/Median (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				ARR/DCFB	95% CI	P value	Risk/rate ratio	95% CI	P value	In case of small number of events in the placebo arm, these were estimated following Paterson et al. Absolute effects were reported directly.	
Patients with ≥90% reduction in attacks	Lanadelumab 300 mg q4wks	29	55.2% (42.2% — 68.1%)	-50.3%	- 68.8% — -27.7%	<0.001	11.3	2.8 — 45.5	0.0006	Each lanadelumab treatment group was compared with placebo without adjustment for multiplicity, using a Fisher's exact test. Confidence intervals for proportions were estimated through Normal approximation. Absolute effects were reported directly. Confidence intervals for relative effects (ratio of proportions) were estimated through log-transformation. Individual study results displayed in forest plots of Bucher ITC for absolute effects differ slightly from those reported in the literature since SE in data input to R package *metafor* is estimated through Normal approximation (ARR of 62%, 95%CI [-81%, -42%])	Banerji 2018, page 2113, prespecified exploratory end points section, end of first paragraph
	Lanadelumab 300 mg q2wks	27	66.7% (54.0% — 79.3%)	-61.8%	- 78.8% — - 39.5%	<0.001	13.8	3.5 — 54.9	0.0002		
	Placebo	41	4.9% (0.2% — 9.6%)	—	—	—	—	—	—		

Trial name:	HELP										
NCT number:	NCT02586805										
Outcome	Study arm	N	Results: Proportion or Mean/Median (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				ARR/DCFB	95% CI	P value	Risk/rate ratio	95% CI	P value		
Attack rate (normalized per 28 days) days 0-182	Lanadelumab 300 mg q4wks	29	Mean: 0.53 (0.36 — 0.77)	-1.44	-1.84 — -1.04	<0.001	0.27	0.18 — 0.41	<0.001	Difference was estimated from a nonlinear function of the model parameters. Results of RR are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable.	Banerji 2018, Figure 2a, Table 2
	Lanadelumab 300 mg q2wks	27	Mean: 0.26 (0.14 — 0.46)	-1.71	-2.09 — -1.33	<0.001	0.13	0.07 — 0.24	<0.001		
	Placebo	41	Mean: 1.97 (1.64 — 2.36)	—	—	—	—	—	—		
Attack rate (normalized per 28 days) days 70-182	Lanadelumab 300 mg q4wks	29	Mean: 0.37 (0.22 — 0.60)	-1.52	-1.93 — -1.11	<0.001	0.19	0.12 — 0.33	<0.001	Difference was estimated from a nonlinear function of the model parameters. Results of RR are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. Individual study results displayed in forest plots of Bucher ITC for absolute effects differ slightly from those reported in the literature since SE in data input to R package *metafor* is	Banerji 2018, Table 4
	Lanadelumab 300 mg q2wks	26	Mean: 0.16 (0.07 — 0.35)	-1.72	-2.12 — -1.33	<0.001	0.09	0.04 — 0.19	<0.001		
	Placebo	37	Mean: 1.88 (1.54 — 2.30)	—	—	—	—	—	—		

Trial name:	HELP										
NCT number:	NCT02586805										
Outcome	Study arm	N	Results: Proportion or Mean/Median (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				ARR/DCFB	95% CI	P value	Risk/rate ratio	95% CI	P value		
										estimated through Normal approximation (RR of 0.09, 95%CI [0.04, 0.20])	
Proportion of responders using the AE-QoL	Lanadelumab 300 mg q4wks	29	62.96% (50.0% — 76.0%)	-26.1%	-49.9% — -2.3%	0.0316	1.7[a]	1.0 — 2.8[a]	0.0383[a]	Chi-squared test were used to assess the difference in proportion of patients achieving a responder definition. Logistic regression models were fit to estimate treatment effects of responder definition, adjusting for other relevant covariates. Patients who were considered to have responded to the therapy were defined as achieving an improvement greater than or equal to the minimal clinically important difference of –6 for total scores from days 0 through 182. The questionnaire consisted of 4 domains (functioning, fatigue and mood, fears and shame, and nutrition) and 17 questions that were used for deriving a total score. Total raw scores were transformed to a linear scale of 0 to 100, with lower scores indicating lower impairment or	Banerji 2018, Table 4
	Lanadelumab 300 mg q2wks	27	80.77% (69.9% — 91.6%)	-43.9%	-65.5% — -22.4%	0.0001	2.2[b]	1.4 — 3.5[b]	<0.001[b]		
	Placebo	41	36.84% (25.9% — 47.8%)	—	—	—	—	—	—		

Trial name:	HELP										
NCT number:	NCT02586805										
Outcome	Study arm	N	Results: Proportion or Mean/Median (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				ARR/DCFB	95% CI	P value	Risk/rate ratio	95% CI	P value		
										higher health–related quality of life. Odds ratios represent times the odds (vs not) to achieve a responder definition compared with placebo. Confidence intervals for proportions were estimated through Normal approximation. Absolute effects were estimated in terms of absolute risk reduction. The corresponding confidence interval for a difference in proportions was estimated through Normal approximation. Relative effects were reported in terms of OR and estimated for RR; the corresponding confidence interval estimates were estimated through log-transformation.	
Change in AE-QoL	Lanadelumab 300 mg q4wks	27	Mean: -17.38 (-24.17 — -10.58)	-12.66	-24.51 — -0.80	0.03	—	—	—	Change from baseline were compared using analysis of covariance adjusting for baseline scores with pairwise t test using the Tukey-Kramer approximation.	Banerji 2018, Table 4
	Lanadelumab 300 mg q2wks	26	Mean: -21.29 (-28.21 — -14.37)	-16.57	-28.53 — -4.62	0.003	—	—	—		
	Placebo	38	Mean: -4.72 (-10.46 — 1.02)	—	—	—	—	—	—		
	Lanadelumab 300 mg q4wks	—	—	—	—	—	—	—	—	—	—

Trial name:	HELP										
NCT number:	NCT02586805										
Outcome	Study arm	N	Results: Proportion or Mean/Median (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				ARR/DCFB	95% CI	P value	Risk/rate ratio	95% CI	P value		
SF-36 Physical component scale	Lanadelumab 300 mg q2wks	—	—	—	—	—	—	—	—		
	Placebo	—	—	—	—	—	—	—	—		
SF-36 Physical component scale	Lanadelumab 300 mg q4wks	—	—	—	—	—	—	—	—	—	—
	Lanadelumab 300 mg q2wks	—	—	—	—	—	—	—	—		
	Placebo	—	—	—	—	—	—	—	—		
Discontinuations due to adverse events	Lanadelumab 300 mg q4wks	29	3.4% (0.6% — 17.2%)	-1%	-9% — 7%	0.8082	1.41	0.09 – 21.69	0.8037	Proportions of discontinuations were reported over the arms. The corresponding confidence intervals were estimated through Normal approximation. Confidence intervals for absolute and relative effects (absolute risk reductions and risk ratios) were estimated through Normal approximation including a continuity correction to account for the small number of events per arm.	Banerji 2018, Table 5
	Lanadelumab 300 mg q2wks	27	0% (0% — 12.5%)	2%	-3% — 7%	0.3611	0.50	0.02 – 11.84	0.6677		
	Placebo	41	2.4% (0.4% — 12.6%)	—	—	—	—	—	—		

Table 35 Results of the HELP-03 trial - patients < 18 years of age

Trial name:	HELP-03– patients < 18 years										
NCT number:	NCT02586805										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				ARR/DCFB	95% CI	P value	Risk ratio	95% CI	P value		
Attack rate per month	Lanadelumab 300 mg q4wks	3	Mean: 0.30 (0.002 — 0.6)	-0.62	-2.59 — 1.35	0.5383	—	—	—	The primary efficacy endpoint was compared for each active treatment group (lanadelumab) to the placebo group using a Poisson regression model. The results were adjusted for baseline attack rate by including the normalized baseline attack rate as a fixed effect in the model. The logarithm of time in days each subject was observed during the treatment period was used as an offset variable, and a Pearson chi-square scaling of standard errors was used to account for potential over-dispersion. Confidence intervals for absolute effects were estimated through Normal approximation.	EMA EPAR /H/C/004806/0000 2018, page 49
	Lanadelumab 300 mg q2wks	2	Mean: 0.31 (-0.29 — 0.91)	-0.61	-2.65 — 1.43	0.5583	—	—	—		
	Placebo	4	Mean: 0.92 (-0.05 – 1.89)	—	—	—	—	—	—		

Table 36 Results – Lanadelumab phase Ib study

Trial name:	DX-2930-02										
NCT number:	NCT02093923										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk/ rate ratio	95% CI	P value		
Attack-free patients day 8 to day 50	Lanadelumab 300 mg q2wks	4	100.0% (51.0% — 100.0%)	-72.7%	-99.0% —-46.4%	<0.001	3.67	1.40 – 9.62	0.0083	Analysis of rates of attacks using a mixed model of repeated measurements with the assumption of a Poisson distribution and using the baseline attack rate as a covariate. Confidence intervals for proportions were estimated through Normal approximation. Due to small number of events, these were estimated following Paterson et al. Confidence intervals for absolute effects were estimated through Normal approximation. Confidence intervals for relative effects were estimated through log transformation.	Banerji 2017, page 722, right column, 4th paragraph
	Placebo	11	27% (9.7% – 56.6%)	—	—	—	—	—	—		
Patients with ≥90% reduction in attacks	Lanadelumab 300 mg q2wks		—	—	—	—	—	—	—	—	—
	Placebo		—	—	—	—	—	—	—	—	—
Attack rate (per week)	Lanadelumab 300 mg q2wks	4	Mean: 0	-0.37	-0.6 - 0.1	0.0066	—	—	—	Analyzed rates of attacks using a mixed model of repeated measurements with the assumption of a Poisson distribution and using the baseline	Banerji 2017, Table 3
	Placebo	11	Mean: 0.37 (0.10 — 0.64)	—	—	—	—	—	—		

Trial name:	DX-2930-02										
NCT number:	NCT02093923										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk/ rate ratio	95% CI	P value		
										attack rate as a covariate. Confidence intervals for absolute effects were estimated through Normal approximation.	
Attack rate (normalized to 28 days)	Lanadelumab 300 mg q2wks	4	Mean: 0	-1.48	-2.55 — - 0.41	0.0066	—	—	—	Analyzed rates of attacks using a mixed model of repeated measurements with the assumption of a Poisson distribution and using the baseline attack rate as a covariate. Confidence intervals for absolute effects were estimated through Normal approximation.	Banerji 2017, normalized from weekly rates reported in Table 3
	Placebo	11	Mean: 1.48 (0.41, 2.55)	—	—	—	—	—	—		
Proportion of responders using the AE-QoL	Lanadelumab 300 mg q2wks	—	—	—	—	—	—	—	—	—	—
	Placebo	—	—	—	—	—	—	—	—		
Change in AE-QoL	Lanadelumab 300 mg q2wks	—	—	—	—	—	—	—	—	—	—
	Placebo	—	—	—	—	—	—	—	—		
SF-36 Physical component scale	Lanadelumab 300 mg q2wks	—	—	—	—	—	—	—	—	—	—
	Placebo	—	—	—	—	—	—	—	—		
SF-36 Mental component scale	Lanadelumab 300 mg q2wks	—	—	—	—	—	—	—	—	—	—
	Placebo	—	—	—	—	—	—	—	—	—	

Trial name:	DX-2930-02										
NCT number:	NCT02093923										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk/ rate ratio	95% CI	P value		
Discontinuations due to adverse events	Lanadelumab 300 mg q2wks	5	0% (0% — 13.8%)	—	—	—	—	—	—	Proportion of discontinuations in lanadelumab arm were reported. Corresponding confidence intervals were estimated following Paterson et al. for small number of events.	EMA EPAR H/C/004806/0000, page 99 study flow chart, Banerji 2017 page 5
	Placebo	13	0% (0% — 13.8%)	—	—	—	—	—	—		

Table 37 Results – CHANGE B study

Trial name:	CHANGE B										
NCT number:	NCT01005888										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk ratio	95% CI	P value		
Attack-free patients	C1 inhibitor 1000 units	—	—	—	—	—	—	—	—	—	—
	Placebo	—	—	—	—	—	—	—	—		
Patients with ≥90% reduction in attacks in comparison to placebo	C1 inhibitor 1000 units	22	NR	-18.2%	-40.1% — -6.6%	<0.001	—	—	—	Percentage of subjects experiencing a 90% reduction rate over placebo was derived from mixed logistic regression models. Individual study results displayed in forest plot of Bucher ITC for absolute effects differ slightly from those reported in the literature since SE in data input to R package *metafor* is estimated through Normal approximation (ARR of -18%, 95%CI [-35%, -1%]); the CI bounds are centered around the mean estimate in contrast to the results reported in Bernstein 2019.	Bernstein 2019, Figure 2
	Placebo	22	NR	—	—	—	—	—	—		
Attack rate per month (adults who filled out SF-36 questionnaire)	C1 inhibitor 1000 units	16	Mean: 2.24 (1.3 — 3.2)	-2.0	-3.1 — -0.8	0.001	—	—	—	Statistical analysis of the least square mean differences between C1 INH-nf and placebo at the end of each	Lumry 2014, Table 1

Trial name:	CHANGE B										
NCT number:	NCT01005888										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk ratio	95% CI	P value		
	Placebo	16	Mean: 4.20 (3.5 — 4.9)	—	—	—	—	—	—	treatment was conducted. The carryover effect was not statistically significant and therefore removed from the model. Confidence intervals were estimated through Normal approximation.	
Attack rate per month	C1 inhibitor 1000 units	22	NR	-2.3	-3.3 — -1.4	—	—	—	—	To account for study designs, mixed models were used including fixed factors for treatment, period, sequence (as indicator for placebo in the first period) and random effect of subject in the study where possible.	Bernstein 2019, Table 3
	Placebo	22	NR	—	—	—	—	—	—		
Attack rate per 12 weeks	C1 inhibitor 1000 units	22	Mean: 6.1 (3.83 — 8.37)	-6.6	-9.63 — -3.57	<0.0001	—	—	—	A generalized-estimating-equation analysis of variance for the crossover study design was performed on the basis of a Poisson assumption, with effects for treatment sequence, treatment period, and subjects within sequence; each subject served as his or her own control. CI for mean rates and absolute difference were estimated through Normal approximation.	EPAR EMA HC001207, page 41, Table 18
	Placebo	22	Mean: 12.7 (10.69 — 14.71)	—	—	—	—	—	—		

Trial name:	CHANGE B										
NCT number:	NCT01005888										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk ratio	95% CI	P value		
Attack rate per 28 days calculated from EPAR EMA HC001207, page 41, Table 18	C1 inhibitor 1000 units	22	Mean: 2.03 (1.28 — 2.79)	-2.2	-3.21 — -1.19	<0.001	—	—	—	A generalized-estimating-equation analysis of variance for the crossover study design was performed on the basis of a Poisson assumption, with effects for treatment sequence, treatment period, and subjects within sequence; each subject served as his or her own control.	EPAR EMA HC001207, page 41, Table 18, recalculated
	Placebo	22	Mean: 4.23 (3.56—4.90)	—	—	—	—	—	—		
Attack rate per 12 weeks	C1 inhibitor 1000 units	22	Mean: 6.26	-6.47	-8.73 — -4.21	<0.001	—	—	—	A generalized-estimating-equation analysis of variance for the crossover study design was performed on the basis of a Poisson assumption, with effects for treatment sequence, treatment period, and subjects within sequence; each subject served as his or her own control.	Zuraw 2010, Abstract (results)
	Placebo	22	Mean: 12.73	—	—	—	—	—	—		
Attack rate per 28 days	C1 inhibitor 1000 units	22	Mean: 2.09	-2.16	—	—	—	—	—	Mean is derived from estimates provided for 12 weeks; no uncertainty estimate is given for absolute effects since there is not enough information to estimate the corresponding SE (only SE of difference yet not individual SEs known).	Zuraw 2010, Figure 2 recalculated per 28 days
	Placebo	22	Mean: 4.24	—	—	—	—	—	—		

Trial name:	CHANGE B										
NCT number:	NCT01005888										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk ratio	95% CI	P value		
Proportion of responders using the AE-QoL	C1 inhibitor 1000 units	—	—	—	—	—	—	—	—	Outcome of interest not reported in any of the publications corresponding to the CHANGE-B study (Lumry 2014, Zuraw 2010, EMA EPAR)	—
	Placebo	—	—	—	—	—	—	—	—		
Change in AE-QoL	C1 inhibitor 1000 units	—	—	—	—	—	—	—	—	—	—
	Placebo	—	—	—	—	—	—	—	—		

Trial name:	CHANGE B										
NCT number:	NCT01005888										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk ratio	95% CI	P value		
SF-36 Physical component scale	C1 inhibitor 1000 units	16	Mean: 43.92 (37.63 – 50.21)	6.86	- 1.62 — 15.34	0.1128	—	—	—	A mixed-model ANOVA with a period effect, treatment effect, and adjustment for the baseline was used. A repeated measures approach, accounting for within-patient correlation, was used. Each patient contributed two follow-up observations, so no assumptions about the within-patient correlation structure was required, beyond assuming that the correlation was nonzero. Confidence intervals for mean estimates and absolute effects were estimated through Normal approximation.	Lumry 2014, page 373, right column, lines 1 and 2
	Placebo	16	Mean: 37.06 (31.4 – 42.7)	—	—	—	—	—	—		
SF-36 Mental component scale	C1 inhibitor 1000 units	16	Mean: 54.00 (50.2 – 57.8)	9.0	0.3 — 17.8	0.0435	—	—	—	A mixed-model ANOVA with a period effect, treatment effect, and adjustment for the baseline was used. A repeated measures approach, accounting for within-patient correlation, was used.	Lumry 2014, page 373, right text column, lines 3 and 4.

Trial name:	CHANGE B										
NCT number:	NCT01005888										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Risk ratio	95% CI	P value		
	Placebo	16	Mean: 44.98 (37.1 – 52.9)	—	—	—	—	—	—	Each patient contributed two follow-up observations, so no assumptions about the within-patient correlation structure was required, beyond assuming that the correlation was nonzero. Confidence intervals for mean estimates and absolute effects were estimated through Normal approximation.	
Discontinuations due to AEs	C1 inhibitor 1000 units	22	Mean: 0% (0% - 14.9%)	0%	-3% — 3%	1	1	0.02 — 48.28	1	Mean number of discontinuations were reported. Confidence intervals for mean estimates were estimated following Paterson et al for small number of events. Zero cell counts were accounted for through continuity correction. Confidence intervals for absolute effects were estimated through Normal approximation RR was estimated applying a continuity correction. The corresponding CI was estimated through log transformation.	EMA EPAR 001207 Cinryze Epar Public Assessment Report, page 55, line 2
	Placebo	22	Mean: 0% (0%-14.9%)	—	—	—	—	—	—		

Table 38 Results of the CHANGE trials, patients <18 years of age

Trial name:	CHANGE										
NCT number:	NCT01005888										
Outcome	Study arm	N	Results (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Discontinuations due to adverse events	C1 inhibitor 1000 units	4	0% (0%-49.0%)	0%	-0.37% - 0.37%	1.00	1.00	0.02 – 41.22	1.00	Mean number of discontinuations were reported. Confidence intervals for proportions were estimated for small number of events following Paterson et al. Confidence intervals for absolute effects were estimated through Normal approximation, applying a continuity correction. Relative effects were estimated applying a continuity correction. Corresponding confidence intervals were estimated through log transformation.	EMA EPAR H/C/001207/II/0045, page 56, Section "Discontinuation due to adverse events"
	Placebo	4	0% (0%-49.0%)	—	—	—	—	—	—		

Results per PICO (clinical question)

Table 39 Results per PICO - Comparative analysis (ITC)

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		ARR/AD	95% CI	P value	Risk/Rate ratio or %change	95% CI	P value	
≥90% reductions in HAE attacks	HELP-03 CHANGE	-44%	- 70% — -18%	<0.001	3.42	1.98 — 4.87	0.0332	≥90% reductions in HAE attacks for the included studies were synthesized through absolute risk reduction (ARR) via the Bucher method since insufficient data were available to estimate relative effects directly. Relative effects were thus estimated through absolute effects, assuming the CI bounds of ARR were invariant to transformation. The risk in the comparator group was reported for the CHANGE study in the Bernstein 2019 publication. The p-value for RR was estimated through Normal approximation of CI bounds, resulting in a normally distributed z statistic. No data were available in the DX-2930-02 study.
Attack rate (normalized per 28 days) days 0-182 – base case	HELP-03 DX-2930-02 CHANGE	-3.09	-3.68 — -1.90	0.0297	0.27	0.13-0.55	<0.0003	Attack rate results per 28 days for the included studies were synthesized in terms of relative effects (rate ratio, RaR) via the Bucher method. The HELP-03 and DX-2930-02 study results were pooled through pairwise fixed effects meta-analysis. There were no issues of between-study heterogeneity (p-value of Q statistic = 0.83). For HAE attack rate per 28 days, results in terms of absolute difference (AD) were estimated through a transformation of relative effects, obtaining information for the rate in the comparator group through the CHANGE study data. The corresponding p-value was estimated through Normal approximation of CI bounds, resulting in a normally distributed z statistic.
Attack rate (normalized per 28 days) days 70-182 in HELP-03 (SA)	HELP-03 DX-2930-02 CHANGE	-3.44	-3.90 — -2.37	0.0313	0.19	0.08 — 0.44	<0.0001	Attack rate results per 28 days for the included studies were synthesized in terms of relative effects (rate ratio, RaR) via the Bucher method. Data at days 70-182 of follow-up (at steady state) were considered in the HELP-03 study. The HELP-03 and DX-2930-02 study results were pooled through pairwise fixed effects meta-analysis. There were no issues of between-study heterogeneity (p-value of Q statistic = 0.90). Results in terms of absolute difference (AD) were estimated through a transformation of relative effects, assuming that the CI bounds were invariant to transformation. The rate in the comparator group was estimated through the CHANGE study data. The corresponding p-value was estimated through Normal approximation of the CI bounds, resulting in a normally distributed z statistic.

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		ARR/AD	95% CI	P value	Risk/Rate ratio or %change	95% CI	P value	
Discontinuations due to adverse events	HELP-03 DX-2930-02 CHANGE	-0.0006	-0.0100-0.9032	0.9979	0.94	0.01 — 91.31	0.9786	Relative effects were synthesized through risk ratio (RR) via the Bucher method. The HELP-03 and DX-2930-02 study results were pooled through pairwise fixed effects meta-analysis. There were no issues of between-study heterogeneity (p-value of Q statistic =0.54). Absolute effects were estimated through a transformation of relative effects, assuming that the corresponding CI bounds were invariant to transformation. The risk in the comparator group was estimated through the CHANGE study data. The corresponding p-value was estimated through Normal approximation of the CI bounds, resulting in a normally distributed z statistic

Medicinrådet

Medicinrådets protokol for vurdering af lanadelumab til forebyggende behandling af arveligt angioødem

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om protokollen

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

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	21.06.2019
Ikrafttrædelsesdato	21.06.2019
Dokumentnummer	51017
Versionsnummer	1.0

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

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 21.06.2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Takhzyro®
Generisk navn	Lanadelumab
Firma	Shire (Takeda pr. 1. januar 2019)
ATC-kode	B06AC05
Virkningsmekanisme	Lanadelumab er et fuldt humant, monoklonalt antistof. Lanadelumab hæmmer det aktive plasmakallikreins proteolytiske aktivitet. Øget plasmakallikreinaktivitet fører til angioødemanfald hos patienter med arveligt angioødem. Lanadelumab giver vedvarende kontrol af plasmakallikreinaktiviteten og begrænser dermed genereringen af bradykinin.
Administration/dosis	Lanadelumab er beregnet til subkutan administration. Den anbefalede startdosis er 300 mg hver 2. uge. Dosisnedsættelse til 300 mg lanadelumab hver 4. uge kan overvejes hos stabile patienter uden anfald, herunder især patienter med lav kropsvægt.
EMA-indikation	Takhzyro er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos patienter på 12 år og derover.

2 Forkortelser

CI:	Konfidensinterval
EMA:	*European Medicines Agency*
HAE:	Arveligt angioødem *(hereditary angioedema)*
HR:	*Hazard ratio*
OR:	*Odds ratio*
RR:	Relativ risiko

3 Formål

Protokollen har til formål at definere de(t) kliniske spørgsmål, der ønskes belyst i vurderingen af lanadelumab som mulig standardbehandling af patienter med arveligt angioødem (HAE). I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende lanadelumab modtaget den 7. december 2018.

Protokollen danner grundlag for den endelige ansøgning for vurdering af lanadelumab sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem lanadelumab og C1-esterase-inhibitor af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

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. HAE viser sig ved anfaldsvise hævelser i hud og slimhinder. 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 [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-esterase-inhibitor, hvilket resulterer i mangelfuld eller dysfunktionel C1-esterase-inhibitor. Der findes to typer af HAE. Hyppigst forekommer type I og type II HAE. Type I HAE er karakteriseret ved lav produktion af normalt C1-esterase-inhibitor. 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-esterase-inhibitor. Ved mangel eller dysfunktionalitet af C1-esterase inhibitor kan der opstå en kædereaktion, der kan få 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]. I 2014 opgjorde professor Anette Bygum HAE-patienterne i Danmark. Her var antallet 95 danske patienter tilhørende 31 danske familier med HAE type I og II [3]. Aktuelt er der registreret 109 patienter, som jævnligt kontrolleres på det Nationale Kompetencecenter for HAE på Odense universitetshospital. Samme 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 dødelige karakter af sygdommen 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 er for den enkelte patient uforudsigeligt. Det samme er sværhedsgraden. Foruden sygdomsaktivitet, frekvens og sværhedsgrad af anfald, fylder sygdomsbyrden mellem anfaldene 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 den uforudsigelige og potentielt livstruende sygdom HAE har derfor stor betydning for livskvaliteten med risiko for personlige omkostninger både 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.

4.1 Nuværende behandling

Behandlingsmål for HAE type I og II er at minimere anfaldshyppigheden og/eller anfaldenes sværhedsgrad. Behandlingen opdeles i akut anfaldsbehandling og forebyggende behandling.

Til anfaldsbehandling anvendes enten intravenøs substitution af manglende funktionelt C1-esterase-inhibitor (Berinert®/Cinryze/Ruconest) eller et bradykinin-blokerende præparat icatibant (Firazyr), som administreres subkutant. Når anfaldet først er i gang og hævelsen dannet, kan det være sværere at påvirke varigheden og sværhedsgraden af anfaldet med medicin. For at medicinen har optimal effekt, skal denne derfor helst tages tidligst muligt i anfaldets udvikling. Ved rettidig behandling reduceres varigheden til ½-3 timer, og behandlingssvigt ses sjældent; dog vil det variere, hvilken anfaldsbehandling patienten har størst gavn af. Ved anfaldsdebut kan patienten ikke selv vurdere, om anfaldet udvikler sig i mild, moderat eller svær grad. Strategien er derfor at behandle alle anfald. De fysiske rammer og det psykiske stress som patienten befinder sig i når anfaldet debuterer, kan være en udfordring i forhold til den intravenøse selvadministration.

Til forebyggende behandling anvendes de to produkter Berinert® og Cinryze. Begge produkter indeholder C1-esterase-inhibitor. Behandlingerne administreres intravenøst og oftest hver 3.-4. dag. Berinert® doseres efter vægt, hvor standarddosis er 20 enheder/kg. En standardpatient på 75 kg behandles således med 1.500 enheder hver 3.-4. dag. Cinryze anvendes oftest i en fast dosis på 1.000 enheder hver 3.-4. dag.

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]. Der eksisterer 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 med anfaldsbehandling. Da alle disse faktorer varierer over tid, vurderes behovet for forebyggende behandling ved hvert kontrolbesøg. Patientens præferencer er også en væsentlig faktor. Flere patienter ser en barriere i den nuværende forebyggende behandling, da den administreres i.v. Derfor er det i dag patienter med hyppige anfald, som overvejende behandles forebyggende. Ud af de 120 danske patienter anslår fagudvalget at ca. 30-40 patienter får forebyggende behandling. De fleste patienter administrerer selv deres anfaldsbehandling såvel som deres forebyggende behandling (eventuelt med hjælp fra pårørende). Patienter, der ikke selv behersker teknikken behandles på lokalt sygehus.

4.2 Lanadelumab

Lanadelumab er et fuldt humant monoklonalt antistof fremstillet ved rekombinant DNA-teknologi, som hæmmer det aktive plasmakallikreins proteolytiske aktivitet, hvorved risikoen for angioødemanfald mindskes.

Lanadelumab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af HAE hos patienter på 12 år og derover. Det administreres ved subkutan injektion i modsætning til den eksisterende profylaktiske behandling. Patienten eller eventuelt en pårørende kan, efter oplæring, selv administrere behandlingen.

Den anbefalede dosis er 300 mg hver 2. uge.

5 Kliniske spørgsmål

5.1 Klinisk spørgsmål 1

Hvad er værdien af rutinemæssig forebyggelse med lanadelumab hos voksne patienter og børn ≥ 12 år med arveligt angioødem sammenlignet med nuværende standardbehandling?

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

Intervention
Lanadelumab 300 mg hver 2. uge.

Komparator
Profylaktisk behandling med i.v. C1-esterase-inhibitor.

Voksne: C1-esterase-inhibitor 1.500 enheder i.v. hver 3.-4. dag.
Børn ≥ 12 år: C1-esterase inhibitor ca. 1.000 enheder i.v. hver 3.-4. dag.

Effektmål
Se tabel 1.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og kategori.

I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den retningsgivende mindste klinisk relevante forskel er fremkommet på samme måde som under den gamle metode og afspejler den mindste forskel, som fagudvalget vurderer, er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den justerede mindste klinisk relevante forskel. Den justerede værdi, vil være det halve af den retningsgivende værdi, i de tilfælde hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den retningsgivende MKRF end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

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

Effektmål*	Vigtighed	Kategori	Måleenhed	Retningsgivende mindste klinisk relevante forskel	Justeret 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 %-points forskel mellem grupperne	5 %-point
Helbredsrelateret livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Ændring fra baseline målt med Angioedema Quality of life Questionnaire (AE-QoL)	6 point	3 point
			Andel af patienter som oplever en forbedring på 6 point fra baseline	Der er ikke fastsat en mindste klinisk relevant forskel. Anvendes til bestemmelse af den relative effektforskel.	
Anfaldsfrekvens	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Procentvis ændring i antallet af HAE-anfald pr. måned	Gennemsnitlig procentuel reduktion på 20 %	10 %
Bivirkninger	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter der ophører behandling grundet bivirkninger	10 %-points forskel mellem grupperne	5 %-point
			Kvalitativ gennemgang af bivirkningsprofilerne for lanadelumab og standardbehandlingen	-	-

* For alle effektmål ønskes data med længst mulig opfølgningstid.

For alle effektmål ønskes som minimum en opfølgningstid på 12 uger. De komparative analyser skal baseres på sammenlignelige tidshorisonter. Alle antagelser og eventuelle forbehold som har betydning for tolkningen af analyseresultaterne skal tydeligt fremgå i den endelige ansøgning.

Kritiske effektmål

Anfaldsfrihed

Det ultimative ønske fra patienter er at blive symptomfrie. Ved at opnå symptomfrihed kan frygten for larynxødem elimineres, hvilket har stor betydning for patienternes livskvalitet. Fagudvalget vil vurdere lanadelumabs effekt på andelen af patienter, som oplever symptomfrihed og anser det som et kritisk effektmål. Med den nuværende forebyggende behandling er det ganske få patienter, som opnår symptomfrihed. Fagudvalget ønsker effektmålet opgjort som en forskel i andelen af patienter, som opnår en 100 % reduktion i anfaldsfrekvens fra baseline. Fagudvalget anslår, at kun ca. 0,5-1,0 % opnår symptomfrihed med den nuværende forebyggende behandling, og den mindste klinisk relevante forskel er derfor sat til 10 %-point. Dette er baseret på fagudvalgets kliniske erfaring. Såfremt denne analyse ikke kan leveres, ønsker fagudvalget alternativt en analyse af andelen af patienter, som opnår en 90 % reduktion i anfaldsfrekvens fra baseline. Andelen af patienter, som i dag opnår 90 % reduktion i anfaldsfrekvens er også begrænset. Ud fra den tilgængelige evidens anslår fagudvalget, at ca. 18 % opnår en 90 % reduktion med den nuværende standardbehandling [6]. Derfor sættes den mindste klinisk relevante forskel til 15 %-point.

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

Livskvalitet ønskes 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 [7]. Scoren går fra 0-100, hvor en højere score indikerer en dårligere livskvalitet. Fagudvalget ønsker, at vurderingen baseres 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 [8]. Den relative effektforskel for AE-QoL totalscore opgøres 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.

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

Vigtige effektmål

Anfaldsfrekvens
Det primære behandlingsmål med rutinemæssig forebyggelse er at reducere frekvensen af angioødemanfald. Fagudvalget vil vurdere anfaldsfrekvens ved at se på forskellen i den gennemsnitlige procentvise ændring i antallet af HAE-anfald pr. måned. Anfaldsfrekvens er et effektmål som traditionelt rapporteres i studier på forebyggende behandling af arveligt angioødem. Den procentvise ændring er valgt, fordi der er stor individuel variation i anfaldsfrekvens fra patient til patient. Fagudvalget anser en reduktion på 20 % som den mindste klinisk relevante forskel. Anfaldsfrekvens er et vigtigt effektmål.

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

Fagudvalget 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. I dag ses stort set ingen behandlingsophør på grund af bivirkninger ved den valgte komparator.

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

Mindre vigtige effektmål

Mortalitet
Som tidligere nævnt kan HAE potentielt være en livsfarlig sygdom, hvis der opstår luftvejsobstruktion som følge af larynxødem. 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. Mange patienter lever dog fortsat med frygten om det næste mulige alvorlige anfald af larynxødem. Ved at opnå symptomfrihed ved nye forebyggende behandlinger kan denne frygt elimineres. Mortalitet vurderes derfor ikke relevant i forbindelse med vurderingen af lanadelumab.

6 Litteratursøgning

Vurderingen af klinisk merværdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor lanadelumab er sammenlignet direkte med human C1-esterase-inhibitor.

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af lanadelumab og human C1-esterase-inhibitor. Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af lanadelumab og human C1-esterase-inhibitor. Det betyder, at der både skal søges efter primærstudier af lanadelumabs effekt og efter primærstudier af effekten af human C1-esterase-inhibitor. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes nedenfor. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng MEDLINE (via 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 CENTRAL (via Cochrane Library)

#	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

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

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

7 Databehandling og analyse

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

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

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

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

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

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

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

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

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

8 Andre overvejelser

Administrationsvej
Tilvalg eller fravalg af forebyggende behandling har indtil i dag delvist været drevet af patientens præferencer, da der kan være en barriere overfor intravenøs selvadministration og den relativt hyppige dosering af C1-esterase-inhibitor. I kraft af den subkutane administration forventer fagudvalget, at en del af de patienter, som i dag har fravalgt forebyggende behandling, vil ønske en forebyggende behandling. Det er fagudvalgets vurdering, at det primært er de patienter, som i dag ikke er i stand til selv at administrere i.v.-behandling, som vil ønske det nye subkutane behandlingsalternativ. Fagudvalget estimerer, at det samlet vil være ca. 50 % af HAE-patienterne, som på sigt vil modtage forebyggende behandling (de 30-40 som i dag modtager forebyggende behandling og ca. 30 yderligere, som vil ønske at skifte fra anfaldsbehandling alene til forebyggende behandling). Derfor er det afgørende at få belyst de økonomiske konsekvenser ved en udvidelse af den nuværende patientpopulation.

Akkumuleret effekt over tid
Fagudvalget ønsker, at ansøger diskuterer, hvor hurtigt effekten indtræder, og hvornår steady state indtræder for både intervention og komparator.

Dosisreduktion
Produktresuméet angiver at dosisnedsættelse til 300 mg lanadelumab hver 4. uge kan overvejes hos stabile patienter uden anfald, herunder især patienter med lav kropsvægt. Det er uklart hvor mange patienter der i praksis vil få nedjusteret dosis. Ansøger bedes derfor bidrage med information om, hvor mange som forventes at blive reduceret til 300 mg hver 4. uge.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende arveligt angioødem

Formand	**Indstillet af**
Rikke Elkjær Andersen Reservelæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke udpege en kandidat	Region Nordjylland
Runa Hyldgaard Poulsen Speciallæge	Region Midtjylland
Shailajah Kamaleswaran Speciallæge	Region Syddanmark
Kan ikke udpege en kandidat	Region Sjælland
Kan ikke udpege en kandidat	Region Hovedstaden
2 patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Jesper Skov Neergaard (projekt- og metodeansvarlig) Gedske Thomsen (projektdeltager) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder)

11 Versionslog

Version	Dato	Ændring
1.0	21.06.2019	Godkendt af Medicinrådet.