Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende berotralstat til forebyggende behandling af arveligt angioødem

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. berotralstat, version 1.0
2. Forhandlingsnotat fra Amgros vedr. berotralstat
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedr. berotralstat til forebyggende behandling af arveligt angioødem, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. berotralstat til forebyggende behandling af arveligt angioødem, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Berotralstat

Forebyggende behandling af arveligt angioødem

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

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

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

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Indholdsfortegnelse

1. Begreber og forkortelser

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

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for behandling med berotralstat i 5 år ca. [redacted] DKK pr. patient sammenlignet med lanadelumab. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. -3,5 mio. DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af subkutan C1-esteraseinhibitor som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. -4,0 mio. DKK i år 5.

Forskellen mellem berotralstat og lanadelumab i reduktion i anfald er behæftet med stor usikkerhed, da estimatet er baseret på indirekte analyser. Samtidig har estimatet stor betydning for analysens resultat. De inkrementelle omkostninger er dog i stor udstrækning udelukkende drevet af lægemiddelpriserne.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af berotralstat som mulig standardbehandling på danske hospitaler til forebyggende behandling af arveligt angioødem (HAE). Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra BioCryst Pharmaceuticals. Medicinrådet modtog ansøgningen den 13. september 2021.

3.1 Patientpopulation

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

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af berotralstat på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har berotralstat sammenlignet med lanadelumab som forebyggende behandling for patienter med arveligt angioødem?

4. Vurdering af den sundhedsøkonomiske analyse

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

4.1 Antagelser og forudsætninger for modellen

Sammenligningen med lanadelumab er lavet på baggrund af data fra tre studier, APEX-2 [2], APEX-J [3] og HELP [4]. APEX-2 er et internationalt, dobbelt-blindet, randomiseret, placebo-kontrolleret fase III-studie, der sammenligner to doseringer af berotralstat overfor placebo. APEX- J er ligeledes et dobbelt-blindet, randomiseret, placebo-kontrolleret fase III-studie udført i Japan. HELP er et internationalt, dobbelt-blindet, randomiseret, placebo-kontrolleret fase III-studie, der sammenligner forskellige doseringer af lanadelumab overfor placebo.

Grundet manglende data, der direkte sammenligner berotralstat og lanadelumab, har ansøger udarbejdet en indirekte analyse baseret på Buchers metode, som tager udgangspunkt i data fra APEX-2, APEX-J og HELP og undersøger effekten af berotralstat i forhold til lanadelumab. Ansøger finder ikke, at der er signifikant forskel på berotralstat og lanadelumab på effekt og sikkerhedsprofil, hvorfor ansøger har udarbejdet en omkostningsminimeringsanalyse.

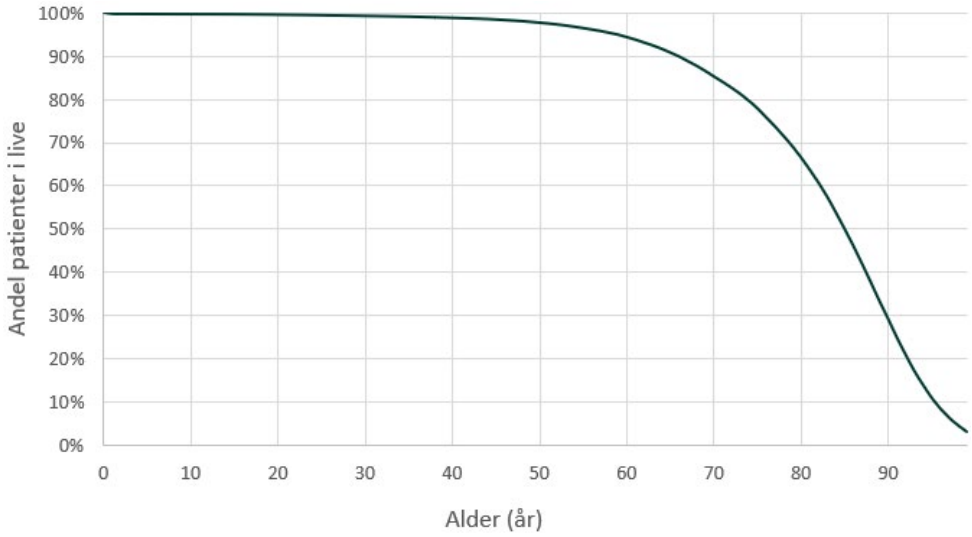
4.1.1 Modelbeskrivelse

Ansøger har indsendt en omkostningsminimeringsanalyse til at estimere omkostningerne forbundet med behandlingen med berotralstat og lanadelumab. Modellen estimerer omkostninger forbundet med behandling, hvorimod omkostninger i forbindelse med behandling af anfald ikke er inkluderet, da disse forventes at være ens.

Ansøger har dog udarbejdet en følsomhedsanalyse, hvor ansøger inkluderer omkostninger til behandling af anfald i form af lægemiddelomkostninger og hospitalsomkostninger. Ansøger antager, at ubehandlede HAE-patienter i gennemsnit har 39 anfald om året svarende til det gennemsnitlige antal anfald for patienterne inkluderet i APEX-2 og HELP. Hertil antager ansøger, at lanadelumab reducerer antallet af anfald om året med 87 %, hvilket svarer til at patienten i gennemsnit får 0,4 anfald om

måneden. Ansøgers indirekte analyse estimerer en rate ratio (RaR) på 4,18, hvilket betyder, at berotralstat medfører 4,18 gange så mange anfald som lanadelumab, svarende til 1,8 anfald om måneden.

Ansøger antager, at patienter med HAE skal have livslang behandling, og derfor inkluderer ansøger en overlevelseskurve for den generelle befolkning til at estimere en gennemsnitlig behandlingsvarighed. Overlevelseskurven for den generelle befolkning fra Danmarks Statistik kan ses i Figur 1.



Figur 1. Den generelle befolknings overlevelse

Medicinrådets vurdering af ansøgers model

Jf. vurderingsrapporten vurderer fagudvalget, at berotralstat er et dårligere behandlingsalternativ end lanadelumab, fordi det samlet set vurderes mindre effektivt til at forebygge angioødemanfald. Derfor vælger Medicinrådet at udarbejde en omkostningsanalyse, som tager højde for forskel i effekt på anfald mellem berotralstat og lanadelumab og på den måde inddrager forskel i omkostningerne til behandling af anfald i den sundhedsøkonomiske analyse. Forholdet mellem berotralstat og lanadelumab i reduktion i anfald er dog behæftet med stor usikkerhed, da det er baseret på indirekte analyser og et lille patientantal i de kliniske studier. Medicinrådet vælger derfor at udarbejde to følsomhedsanalyser for at undersøge betydningen af effektforskellen i anfaldsfrekvens mellem berotralstat og lanadelumab. Dette undersøges ved, at RaR varieres til øvre og nedre grænse indenfor estimatets 95 % konfidensinterval, hhv. RaR = 8,25 og RaR = 2,12.

Medicinrådet vurderer ikke, at en omkostningsminimeringsanalyse er den rette tilgang, når lægemidlerne ikke vurderes lige gode. Medicinrådet vælger derfor at inkludere omkostninger til behandling af anfald i Medicinrådets hovedanalyse samt udarbejde følsomhedsanalyser, der undersøger betydningen af effektforskellen i anfaldsfrekvens.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 58 år, svarende til livstid, da patienterne i gennemsnit er 42 år i modellen.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år. Omkostninger, der ligger efter år 35, bliver diskonteret med en rate på 2,5 % pr. år

Medicinrådets vurdering af ansøgers analyseperspektiv
Fagudvalget forklarer, at det kan være svært at give et bud på en gennemsnitlig behandlingsvarighed. Dette skyldes, at nogle patienter vil have behov for livslang behandling, men andre patienter stopper undervejs, da sygdommens sværhedsgrad vil variere over tid. Fagudvalget vurderer dog, at 5 år er en mere rimelig tidshorisont, som også er anvendt i andre sager indenfor HAE. Denne ændring vurderes at have stor betydning for analysens resultat, da de inkrementelle omkostninger akkumuleres hvert år. Derfor vil en reducering i tidshorisonten reducere forskellene i omkostningerne mellem berotralstat og lanadelumab.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv, men ændrer tidshorisonten til 5 år i Medicinrådets hovedanalyse.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af berotralstat sammenlignet med lanadelumab. Ansøger har inkluderet lægemiddelomkostninger, omkostninger til administration og patientomkostninger. Ansøger har ikke inkluderet omkostninger til monitorering, udlevering af lægemidlerne, bivirkningsrelaterede omkostninger eller omkostninger til behandling af anfald, da disse ikke vurderes at være forskellige mellem berotralstat og lanadelumab.

4.2.1 Lægemiddelomkostninger

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

Den anbefalede dosis af berotralstat er 150 mg peroralt én gang dagligt.

Den anbefalede dosis af lanadelumab er 300 mg subkutan hver 2. uge.

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

Tabel 1. Anvendte lægemiddelpriser, SAIP (marts 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Berotralstat	150 mg	28 stk.	[redacted]	Amgros
Lanadelumab	300 mg	1 stk.	[redacted]	Amgros

Ifølge produktresuméet for lanadelumab kan dosisreduktion til 300 mg hver 4. uge overvejes hos patienter, der er stabilt anfaldsfrie, især hos patienter med lav vægt. På nuværende tidspunkt er ca. 50 % af patienterne behandlet med lanadelumab i Danmark i gang med trinvis dosisreduktion fra 300 mg hver 2. uge til 300 mg hver 4. uge. Medicinrådet vælger at udarbejde en følsomhedsanalyse, hvor 50 % af patienterne behandlet med lanadelumab dosisreduceres efter 2 år i behandling. Dette er valgt grundet gradvis dosisreduktion på lanadelumab i klinisk praksis i Danmark.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger for lanadelumab i form af timeomkostninger for sundhedspersonale. Ansøger antager, at ca. 6 % (2 patienter ud af 35 i forebyggende behandling) af patienter, der modtager behandling med lanadelumab, vil have behov for at modtage hjælp til administrering af lanadelumab på hospitalet. Hertil antager ansøger, at administrationen varetages af en sygeplejerske og tager 20 min.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger

Fagudvalget kender ikke til patienter, der modtager hjælp til administrering af lanadelumab på hospitalet. Fagudvalget kender til [redacted], som har behov for hjælp til selvadministration, hvilket varetages i forbindelse med hjemmehjælp. Medicinrådet vælger derfor at ændre andelen af patienter, der modtager hjælp til administrering af lanadelumab på hospitalet til 0 patienter i Medicinrådets hovedanalyse. Denne ændring har minimal betydning for analysens resultat.

Medicinrådet ændrer andelen af patienter, der modtager hjælp til administrering af lanadelumab på hospitalet til 0 patienter i Medicinrådets hovedanalyse.

4.2.3 Omkostninger til behandling af anfald

I ansøgers hovedanalyse antager ansøger, at der ikke er forskel i frekvensen af anfald mellem berotralstat og lanadelumab, da ansøger ikke finder, at der er signifikant forskel i effekt på berotralstat og lanadelumab.

I ansøgers følsomhedsanalyse, som antager en forskel i reduktion af anfald mellem berotralstat og lanadelumab med en RaR på 4,18, inkluderer ansøger omkostninger til behandling af anfald i form af lægemiddelomkostninger og hospitalsomkostninger.

Ansøger antager hertil, at 85 % af alle anfald kræver medicinsk behandling. Ansøger antager, at patienter, der oplever et anfald, behandles med 30 mg icatibant, hvoraf 33 % af patienterne, som modtager icatibant som anfaldsbehandling, antages at skulle have to behandlinger. I forbindelse med behandling af anfald vil 2 % kræve besøg ved praktiserende læge, 10 % kræver ambulant besøg, mens 5 % kræver indlæggelse. Enhedsomkostningerne brugt i forbindelse med de forskellige behandlingskrævende anfald har ansøger baseret på 2021 DRG-takster.

Medicinrådets vurdering af ansøgers antagelser vedr. omkostninger til behandling af anfald

Da fagudvalget vurderer, at berotralstat er et dårligere behandlingsalternativ end lanadelumab, vælger Medicinrådet at inkludere omkostninger til behandling af anfald.

I forbindelse med tidligere sager indenfor HAE har fagudvalget vurderet ressourceforbruget i forbindelse med behandling af anfald. Fagudvalget vurderede, at 25 % af anfaldene er milde, 50 % er moderate, og 25 % er svære, hvoraf 5 % af disse er svære anfald på hoved og hals. Patienterne, der oplevede et anfald, behandles med enten i.v. C1-esteraseinhibitor (Berinert), i.v. C1-esteraseinhibitor (Cinryze), icatibant eller en kombination af icatibant og i.v. C1-esteraseinhibitor (Berinert) eller i.v. C1-esteraseinhibitor (Cinryze). I.v. C1-esteraseinhibitor (Berinert) doseres som 20 IE/kg, i.v. C1-esteraseinhibitor (Cinryze) doseres som 1000 IE, mens icatibant doseres som 30 mg. Anvendte lægemiddelpriser til anfaldsbehandling, som ikke allerede er præsenteret i Tabel 1, kan ses i Tabel 2. Fordelingen og samlede omkostninger pr. anfald kan ses i Tabel 3. Enhedsomkostningerne for besøg ved egen læge eller hospitalet kan ses i Tabel 4.

Tabel 2. Lægemiddelpriser for anfaldsbehandling, SAIP (marts 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
C1-esteraseinhibitor (Berinert)	1500 IE	1 stk.	[redacted]	Amgros
C1-esteraseinhibitor (Cinryze)	500 IE	2 stk.	[redacted]	Amgros
Icatibant	30 mg	3 ml.	[redacted]	Amgros

Tabel 3. Fordeling af medicinsk behandling samt omkostning pr. anfald, DKK

	Fordeling	Omkostning pr. anfald [DKK]
I.v. C1-esteraseinhibitor (Berinert)	70 %	[redacted]
I.v. C1-esteraseinhibitor (Cinryze)	5 %	[redacted]
Icatibant	17 %	[redacted]
Icatibant + i.v. C1-esteraseinhibitor (Berinert)/i.v. C1-esteraseinhibitor (Cinryze)	8 %	[redacted]

Tabel 4. Estimater for ressourceforbruget forbundet med behandling af anfald

	Enhedsomkostning [DKK]	Reference
Besøg ved praktiserende læge	147	PLO honorartabel, 2021
Ambulant besøg	3.114	2021 DRG-takst: 16MA98
Indlæggelse	22.545	2021 DRG-takst: 16MA10

Medicinrådet vælger at anvende ansøgers følsomhedsanalyse, som inkluderer omkostninger til behandling af anfald i Medicinrådets hovedanalyse. Derudover ændrer Medicinrådet anfaldsbehandlingen, så den inkluderer både icatibant og i.v. C1-esteraseinhibitor.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrationsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid. Derudover har ansøger inkluderet patientomkostninger i forbindelse med selvadministration af lanadelumab i eget hjem, hvilket antages at vare 5 min.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

I ansøgers følsomhedsanalyse, hvor de modellerer en forskel i effekt mellem berotralstat og lanadelumab, inkluderer ansøger også patientomkostninger i forbindelse med behandling af anfald. Hertil antager ansøger, at besøg ved praktiserende læge og ambulant besøg på hospitalet varer 1 time, mens indlæggelse varer 8 timer.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet vælger at inkludere omkostninger til behandling af anfald i Medicinrådets hovedanalyse, og derfor vælger Medicinrådet også at inkludere patient- og transportomkostninger dertil. I forbindelse med en tidligere ansøgning indenfor HAE har fagudvalget vurderet ressourceforbruget i forbindelse med behandling af anfald, hvor svære anfald på hoved og hals vil kræve en indlæggelse på 24 timer.

Fagudvalgets estimerede patienttid i forbindelse med administration af lanadelumab og behandling af anfald kan ses i Tabel 5.

Tabel 5. Estimat af effektiv patienttid og transport pr. administration og behandling af anfald

	Patienttid [minutter]	Transport [antal gange]
Administration		
Selvadministration af lanadelumab	15	-
Anfaldsbehandling		
Lægebesøg	60	1
Ambulant besøg	60	1
Indlæggelse	1.440 (24 timer)	1
Administration af icatibant eller i.v. C1-esteraseinhibitor	15	-

Medicinrådet vælger at anvende ansøgers følsomhedsanalyse, som inkluderer patientomkostninger til behandling af anfald i Medicinrådets hovedanalyse. Derudover ændrer Medicinrådet tiden til selvadministration af lanadelumab til 15 min og varighed af indlæggelse til 24 timer.

4.3 Følsomhedsanalyser

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

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i behandlingsvarigheden og hjælp til administration med lanadelumab undersøges. Følgende følsomhedsanalyser er udført:

Tabel 6. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Behandlingsvarighed – 1 år	Behandlingsvarigheden med berotralstat og lanadelumab sættes til 1 år
Behandlingsvarighed – 3 år	Behandlingsvarigheden med berotralstat og lanadelumab sættes til 3 år
Behandlingsvarighed – 10 år	Behandlingsvarigheden med berotralstat og lanadelumab sættes til 10 år
Hjælp til administration af lanadelumab – 0 %	Andelen af patienter, der har behov for hjælp til administration af lanadelumab, sættes til 0 %
Hjælp til administration af lanadelumab – 10 %	Andelen af patienter, der har behov for hjælp til administration af lanadelumab, sættes til 10 %

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Tidshorisonten svarer i denne analyse til den gennemsnitlige behandlingsvarighed. I Medicinrådets hovedanalyse antages den gennemsnitlige behandlingsvarighed at være 5 år, men da dette estimat er meget usikkert, præsenterer Medicinraadet en følsomhedsanalyse, hvor tidshorisonten ændres til 10 år.

Medicinrådet vælger at præsentere en følsomhedsanalyse, hvor tidshorisonten ændres til 10 år. Medicinrådet vælger at udarbejde egne følsomhedsanalyser, der undersøger 50 % dosisreduktion på lanadelumab og forskellen i effekt i anfaldsreduktion mellem berotralstat og lanadelumab.

4.4 Opsummering af basisantagelser

I Tabel 7 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 7. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	58 år	5 år
Diskonteringsrate	1-35 år: 3,5 % 36-70 år: 2,5 %	3,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patient- og transportomkostninger	Lægemiddelomkostninger Omkostninger til anfaldsbehandling Patient- og transportomkostninger
Dosering:		
Berotralstat	150 mg peroralt dagligt	150 mg peroralt dagligt
Lanadelumab	300 mg s.c. hver 2. uge	300 mg s.c. hver 2. uge
Dosisjustering	Nej	Nej
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyser bygger på samme antagelser som ansøgers hovedanalyser med undtagelse af de væsentligste ændringer, der fremgår af Tabel 7.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. -3,5 mio. DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 8.

Tabel 8. Resultatet af Medicinrådets hovedanalyse ved sammenligning med lanadelumab, DKK, diskonterede tal

	Berotralstat	Lanadelumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Omkostninger til anfaldsbehandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	22.203	11.676	10.526
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 9.

Tabel 9. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Tidshorisont på 10 år	[redacted]
50 % dosisreduktion på lanadelumab efter to års behandling	[redacted]
Forskellen i anfaldsfrekvens mellem berotralstat og lanadelumab, RaR = 8,25	[redacted]
Forskellen i anfaldsfrekvens mellem berotralstat og lanadelumab, RaR = 2,12	[redacted]

6. Budgetkonsekvenser

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

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

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

6.1 Estimat af patientantal og markedsandel

Ansøger antager, at der vil være ca. 35 patienter i Danmark, som modtager lanadelumab og derved vil være kandidater til behandling med berotralstat ved anbefaling af berotralstat. Ansøger antager, at berotralstat vil have et markedsoptag på 100 % allerede fra år 1, svarende til at alle nuværende patienter vil skifte fra lanadelumab til berotralstat.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis berotralstat anbefales som mulig standardbehandling og hvis ikke berotralstat anbefales. Fagudvalget estimerer ligeledes, at 35 patienter forventes at være kandidater til behandling med berotralstat til den pågældende indikation, se Tabel 10. Dog vurderer fagudvalget, at berotralstat vil være relevant for patienter, der ikke har tilstrækkelig effekt af lanadelumab, eller patienter, der har væsentlige gener ved den subkutane administrationsvej. Fagudvalget vurderer, at det vil gælde 15 % af patienter, der på nuværende tidspunkt modtager lanadelumab.

Tabel 10. Medicinrådets estimat af antal patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Berotralstat	5	5	5	5	5
Lanadelumab	30	30	30	30	30
			Anbefales ikke		
Berotralstat	0	0	0	0	0
Lanadelumab	35	35	35	35	35

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor markedsoptaget for berotralstat er ændret til 15 %.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- 15 % markedsoptag for berotralstat.

Medicinrådet estimerer, at anvendelse af berotralstat vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 11. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. -4,0 mio. DKK i år 5.

Tabel 11. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med berotralstat er forbundet med inkrementelle omkostninger på [redacted] DKK sammenlignet med behandling med lanadelumab. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelpriserne.

Forholdet mellem berotralstat og lanadelumab i reduktion i anfald er behæftet med stor usikkerhed, da estimatet er baseret på indirekte analyser samt et lille antal patienter i de kliniske studier. Hvis RaR øges til øvre grænse indenfor estimatets 95 % konfidensinterval (RaR = 8,25), stiger de inkrementelle omkostninger til [redacted] DKK pr. patient. Hvis RaR derimod reduceres til nedre grænse indenfor estimatets 95 % konfidensinterval (RaR = 2,12), falder de inkrementelle omkostninger til [redacted] DKK pr. patient. At forskellen mellem berotralstat og lanadelumab i reduktion i anfald er behæftet med stor usikkerhed har således stor betydning for analysens resultat.

Der er usikkerhed vedr. behandlingsvarigheden for patienter med HAE, da fagudvalget har svært at give et bud på en gennemsnitlig behandlingsvarighed. Dette skyldes, at nogle patienter vil have behov for livslang behandling, mens andre patienter stopper undervejs, da sygdommens sværhedsgrad vil variere over tid. Analysens tidshorisont har ligeledes stor betydning for analysens resultat, da de inkrementelle omkostninger blot akkumuleres hvert år. Hvis tidshorisonten øges til 10 år, [redacted] de inkrementelle omkostninger til [redacted] DKK pr. patient.

Dosisreduktion på lanadelumab kan overvejes hos patienter, der er stabilt anfaldsfrie, især hos patienter med lav vægt. På nuværende tidspunkt er ca. 50 % af patienterne på lanadelumab i Danmark i gang med trinvis dosisreduktion fra 300 mg hver 2. uge til 300 mg hver 4. uge. I Medicinrådets følsomhedsanalyse, hvor 50 % af patienter, der behandles med lanadelumab, dosisreduceres efter 2 år i behandling, falder de inkrementelle omkostninger til [redacted] DKK pr. patient.

8. Referencer

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

2. Zuraw B, Lumry WR, Johnston DT, Aygören-Pürsün E, Banerji A, Bernstein JA, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. J Allergy Clin Immunol. 2020;

3. Ohsawa I, Honda D, Suzuki Y, Fukuda T, Kohga K, Morita E, et al. Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: A phase 3 randomized trial. Allergy Eur J Allergy Clin Immunol. 2020;(November):1–11.

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

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. marts 2022	Godkendt af Medicinrådet

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 58 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 12.

Tabel 12. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Berotralstat	Lanadelumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	0	5.998	-5.998
Patientomkostninger	0	15.620	-15.620
Totale omkostninger	[redacted]	[redacted]	[redacted]

*Resultaterne i afsnittet er ansøgers estimat af de inkrementelle omkostninger pr. patient. Dog har der været en mindre fejl i den indsendte ansøgning, som Medicinrådet har rettet. Derfor stemmer resultaterne ikke overens med resultaterne præsenteret i ansøgers tekniske dokument.

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af berotralstat vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 13.

Tabel 13. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.03.2022
Leverandør	Biocryst
Lægemiddel	Orladeyo (berotralstat)
Ansøgt indikation	Arveligt angioødem HAE

Forhandlingsresultat

Amgros har opnået følgende pris på berotralstat:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Berotralstat	150 mg/tablet	28 stk.	114.086,00	[redacted]	[redacted]

Prisen er betinget af en anbefaling af Medicinrådet.

Anbefales berotralstat ikke af Medicinrådet indkøbes berotralstat til AIP indtil 1. september 2022[redacted]

[redacted]

Konkurrencesituationen

Berinert og lanadelumab er begge anbefalet af Medicinrådet. Nedenstående tabel viser den årlige lægemiddelpris for de forebyggende behandlinger af arveligt angioødem berinert, lanadelumab og berotralstat.

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Dosering	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Berotralstat	150 mg/dag	150 mg, 28 stk.	[redacted]	[redacted]	[redacted]
Lanadelumab	300 mg hver 4. uge	300 mg, 1 stk.	[redacted]	[redacted]	[redacted]
Lanadelumab	300 mg hver 2. uge	300 mg, 1 stk.	[redacted]	[redacted]	[redacted]
Berinert	40 IE/kg/3,5 dag**	3000 IE	[redacted]	[redacted]	[redacted]
Berinert	60 IE/kg/ 3,5 dag**	3000 IE	[redacted]	[redacted]	[redacted]

*Betinget af godkendelse i Medicinrådet
** Berinert kan gives hver 3. eller 4. dag. Derfor er den årlige lægemiddelpris ovenfor udregnet for behandling hver 3,5 dag.
***Vægt brugt i den sundhedsøkonomiske afrapportering på Berinert: 73,12 kg.

Status fra andre lande

Norge: Anbefalet[1]
Sverige: Anbefalet[2]
England: Anbefalet[3]

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/berotralstat-orladeyo

[2] https://www.tlv.se/beslut/beslut-lakemedel/begransad-subvention/arkiv/2021-12-17-orladeyo-ingar-i-hogkostnadsskyddet-med-begransning.html

[3] https://www.nice.org.uk/guidance/ta738/informationforpublic

BioCryst Ireland ltd
Block 4, Harcourt Centre,
Harcourt road,
Dublin 2, D02HW77

Medicinrådet,
Dampfærgevej 27-29, 2,
100 København,
Denmark

Object: observations on the draft assessment report, economic report and additional information available

21st of January 2022,

Dear secretary of Danish Medicine Council,

Thank you for the draft assessment report and draft economic report for berotraltat (Orladeyo®) from the Expert Committee.

We would like to take this opportunity to bring a few important facts to the Council's attention which we believe to be relevant for the Council's consideration of berotralstat (Orladeyo®).

1) <u>WAO/EAACI Guideline update and position of Orladeyo® in the therapeutic strategy</u>

On 10th of January 2022, WAO/EAACI have published new guidelines on the management of HAE which we attached for the Council's attention.

In these guidelines, WAO/EAACI recommend the use of berotralstat (Orladeyo®) as first line long-term prophylaxis, alongside lanadelumab (Takhzyro®) and plasma-derived C1-INH, with level A evidence (Mauer et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update; attached for your attention):

- *"Taken together, this guideline recommends any of the three medications for the first-line long-term prophylactic treatment of patients with HAE-1/2, i.e., plasma-derived C1-INH, lanadelumab, berotralstat, based on the results of randomized controlled clinical trials. Where all three first-line LTP medications are available, the choice of which one to use should be made by shared decision making." (quote from updated WAO/EACCI guideline)*
- *"Currently, there is not enough evidence to recommend any of these three over each other." (quote from updated WAO/EACCI guideline)*

This recommendation reflects the consensus view of 50 international HAE experts and is based on all available clinical evidence.

Based on the available evidence, both WAO/EACCI guideline HAE expert group as well as the Norwegian decision forum reached the conclusion that berotralstat (Orladeyo®) should be used as a first-line prophylactic treatment, therefore positioning it alongside lanadelumab and plasma-derived C1-INHs in the therapeutic strategy.

The same-line positioning of beroltralstat, alongside lanadelumab and C1-INHs, is also reflected in recent HTA decisions for Orladeyo® in Germany[1], France[2] and Norway[3].

2) <u>Comparative efficacy of Orladeyo®</u>

We would like to reiterate the significant methodological limitations associated with an indirect comparison of berotralstat and lanadelumab due to the heterogeneity across HAE trials in terms of study designs, study setting, treatment duration, minimum baseline attack frequency, HAE attack measurement and analysis, baseline HAE attacks rates, prior long-term prophylaxis use, concomitant therapy in the trials etc. These limitations render such an indirect comparison inappropriate and, in the absence of a head-to-head trial of both treatments, preclude a robust conclude on the relative efficacy of berotralstat and lanadelumab.

In their assessment report, Expert Committee acknowledged that uncertainty exists in the different methods of measuring and confirming the rate of HAE attacks across trials and that it is therefore unclear how this may impact the comparative efficacy estimate. The Expert Committee concluded that available date is sparse, further emphasizing the uncertainty in the comparison and recognizing that conclusions from the available comparative data should be drawn with caution.

We recognize the Expert Committee's conclusion that the indirect treatment comparison is insufficient to support an added clinical value compared to lanadelumab. However, the lack of demonstrating added clinical value is not equivalent to the demonstration of a *lower* clinical value compared to lanadelumab, which is implicit in the decision of the Expert Committee to position berotralstat as second-line (rather than parallel) to lanadelumab.

[1] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, *Berotralstat (hereditäres Angioödem) – Nutzenbewertung gemäß § 35a SGB V.* 2021. https://www.iqwig.de/projekte/a21-80.html
[2] Avis de la Commission de la Transparence – Orladeyo 2021. https://www.has-sante.fr/jcms/p_3298588/fr/orladeyo-150-mg-berotralstat
[3] ID2021_048 Berotralstat (Orladeyo) for rutinemessig forebygging av tilbakevendende anfall av hereditært angioødem (HAE) hos voksne og ungdom i alderen 12 år og eldre. https://nyemetoder.no/Documents/Beslutninger/Beslutningsforum%2025102021_Protokoll%20.pdf

We respectfully would like to draw the Council's attention to the fact that several other Health Technology Assessment agencies, including IQWiG[1], CADTH[4], INESSS[5], ICER[6] have also recognized significant methodological limitations in the indirect comparison of available long-term prophylactic treatments for HAE and have conclude that such indirect comparisons are not a feasible or appropriate approach to draw robust conclusions for comparative efficacy.

As mentioned in 1) above, the parallel first-line positioning of berotralstat, lanadelumab and plasma-derived C1-INHs for HAE long-term prophylaxis in the updated WAO/ EACCI guideline also reflects the fact that all indirect comparisons of these treatments were considered to be inappropriate to support conclusions that any of these treatments is more efficacious than another.

Based on these two points above, we struggle to understand on what basis the DMC expert committee has concluded that berotralstat should be used second-line to lanadelumab and C1-INHs, particularly in light of the conflicting, evidence-based view of international clinical experts and other HTA agencies that have positioned all three treatments as same-line interventions.

Finally, we have no comments on the economic report. There is a several factual errors in the description of the berotralstat clinical studies in the draft clinical assessment report, which we have highlighted in the document using the Word commenting functions (see attachment).

BioCryst remains available to answer any questions you might have.

Yours sincerely

Luke Robinson

[4] CADTH Common Drug Review, *Clinical Review Report for Lanadelumab (Takhzyro) (Indication for routine prevention of attacks of hereditary angioedema in adolescents and adults).* 2020. https://cadth.ca/sites/default/files/cdr/clinical/sr0618-takhzyro-clinical-review-report.pdf

[5] Institut national d'excellence en santé et en services sociaux (INESSS). *Réévaluation de TakhzyroMC (lanadélumab injectable) : angioedème héréditaire*. Qc : INESSS; 2020. https://numerique.banq.qc.ca/patrimoine/details/52327/4143839

[6] Institute for Clinical and Economic Review (ICER). *Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value – Final Evidence Report.* 2018. https://icer.org/wp-content/uploads/2020/10/ICER_HAE_Final_Evidence_Report_111518-1.pdf

Medicinrådet

Medicinrådets vurdering vedr. berotralstat til forebyggende behandling af arveligt angioødem

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

Dokumentoplysninger	
Godkendelsesdato	26. januar 2022
Dokumentnummer	133094
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 27. januar 2022

1. Medicinrådets konklusion

Medicinrådet vurderer, at den samlede værdi af berotralstat, sammenlignet med lanadelumab til rutinemæssig forebyggelse af tilbagevendende anfald af arveligt angioødem, ikke kan kategoriseres på det nuværende datagrundlag.

Medicinrådet vurderer, at berotralstat er et dårligere behandlingsalternativ end lanadelumab, fordi det samlet set vurderes mindre effektivt til at forebygge angioødemanfald og har lavere effekt på helbredsrelateret livskvalitet.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

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

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

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

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

2. Begreber og forkortelser

AE-QoL: *Angioedema Quality of Life Questionnaire*

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

EPAR: *European Public Assessment Report*

EQ-5D: *EuroQol five dimension scale*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

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

HAE: Arveligt angioødem (*hereditary angioedema*)

HTA: Medicinsk teknologivurdering *(Health Technology Assessment)*

IQWIG: *The Institute for Quality and Efficiency in Healthcare*

ITT: *Intention to treat*

MKRF: Mindste klinisk relevante forskel

NICE: *The National Institute for Health and Care Excellence*

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

PP: *Per protocol*

RR: Relativ risiko

SMD: *Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af berotralstat til rutinemæssig forebyggelse af tilbagevendende anfald af arveligt angioødem er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra BioCryst Ireland Limited. Medicinrådet modtog ansøgningen den 13. september 2021.

Det kliniske spørgsmål er:

Hvilken værdi har berotralstat sammenlignet med lanadelumab som forebyggende behandling for patienter med arveligt angioødem?

3.1 Arveligt angioødem

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

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

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

Den nøjagtige forekomst af HAE er ukendt, men det anslås, at HAE påvirker ca. 1 ud af 10.000-50.000 personer verden over [1,2]. Aktuelt er der i Danmark registreret 110 patienter, som jævnligt kontrolleres på det Nationale Kompetencecenter for HAE på Odense Universitetshospital. En opgørelse fra 2014 viste, at anfaldsfrekvensen varierede fra asymptomatiske patienter/ 1 anfald om året og op til 84 anfald om året. Den gennemsnitlige frekvens lå på 17 anfald om året [3].

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

3.2 Berotralstat

Berotralstat (Orladeyo) er et oralt lægemiddel, som hæmmer det aktive plasmakallikreins proteolytiske aktivitet og herved mindsker risikoen for angioødemanfald. Hos patienter med HAE-type I og II er den normale regulering af kallikreinaktiviteten nedsat. Dette fører til en ukontrolleret stigning i plasmakallikreinaktiviteten, som, gennem en frigivelse af bradykinin, resulterer i HAE-anfald [5].

Indikationen for berotralstat (Orladeyo) er rutinemæssig forebyggelse af tilbagevendende anfald af arveligt angioødem hos voksne og unge fra 12 år. Patienten indtager lægemidlet oralt én gang daglig. En kapsel indeholder 150 mg berotralstat. Lægemidlet betragtes som et *orphan drug*. Berotralstat vil blive givet kontinuerligt gennem flere år. Behovet for forebyggende behandling vurderes løbende, da patienternes sygdomsaktivitet varierer over tid [5].

3.3 Nuværende behandling

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

Den forebyggende behandling iværksættes i henhold til den gældende internationale guideline fra World Allergy Organization og European Academy Allergy and Clinical Immunology fra 2017 [6]. Jævnfør denne guideline eksisterer der ikke faste kriterier for, hvilke patienter der tilbydes forebyggende behandling. Behovet for forebyggende behandling vurderes under hensyntagen til patientens sygdomsaktivitet, anfaldsfrekvens/sværhedsgrad/lokation, livskvalitet og eventuelt manglende sygdomskontrol ved behandling af akutte anfald. Da alle disse faktorer varierer over tid, bliver behovet for forebyggende behandling vurderet ved hvert kontrolbesøg. Patientens præferencer er også en væsentlig faktor, f.eks. i forhold til administrationsvej.

Til forebyggende behandling bliver to behandlingsprincipper anvendt i Danmark. Det ene princip består i substitution af manglende funktionelt C1-esteraseinhibitor ved et af de to produkter Berinert® eller Cinryze®. Cinryze® administreres intravenøst og oftest hver 3.-4. dag. For Berinert® findes både en intravenøs og en subkutan formulering, hvoraf

sidstnævnte blev anbefalet af Medicinrådet til forebyggende behandling den 24. august 2021. Anbefalingen gælder hos patienter med væsentlig nedsat livskvalitet, der som udgangspunkt har minimum fire anfald om måneden.

Det andet behandlingsprincip består i at hæmme det aktive plasmakallikreins proteolytiske aktivitet, hvorved risikoen for angioødemanfald mindskes. Her anvendes lanadelumab (Takhzyro®), som er et humant monoklonalt antistof. Lanadelumab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af HAE hos patienter på ≥ 12 år og er anbefalet som mulig standardbehandling af Medicinrådet hos patienter med minimum fire anfald om måneden. Den anbefalede dosis er 300 mg subkutant hver 2. uge [7].

De fleste patienter administrerer selv deres forebyggende behandling (eventuelt med hjælp fra pårørende). Patienter, der ikke selv behersker teknikken (i.v./s.c.), behandles på lokalt sygehus. Ud af de ca. 110 danske patienter med HAE anslår fagudvalget, at ca. 30-40 patienter får forebyggende behandling, hvoraf hovedparten er i behandling med lanadelumab.

4. Metode

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

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 3 fuldtekstartikler, som rapporterer data fra 3 kliniske studier. Herudover er der efter ansøgers litteratursøgning publiceret opfølgende data for lanadelumab i form af et *open-label extension*-studie (HELP OLE; NCT02741596) samt 24 måneders opfølgning fra APEX-2.

Tabel 1 - Oversigt over studier anvendt i Medicinrådets vurdering

Publikationer	Klinisk forsøg	Intervention	Kompara-tor	Population	Behandlings-tid
Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial [8] NCT03485911	**APeX-2**	Berotralstat 110 mg eller 150 mg én gang dagligt	Placebo	Patienter ≥ 12 år med HAE-type I og II.	24 uger
Randomized Trial of the Efficacy and Safety of Berotralstat (BCX7353) as an Oral Prophylactic Therapy for Hereditary Angioedema: Results of APeX-2 Through 48 Weeks (Part 2) [9]	**APEX-2 part 2** (*extension* af APeX-2*)*	Berotralstat 110 mg eller 150 mg én gang dagligt	-	Patienter ≥ 12 år med HAE-type I og II.	24 uger (sammenlagt med APeX-2 er total opfølgnings-tid 48 uger)
Poster presented at the July 2021 EACCI conference by Kiani et al. [10] NCT03485911	**APEX-2 part 3** (yderligere *extension* af APeX-2*)*				96 uger
Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: A phase 3 randomized trial [11] NCT03873116	**APeX-J**	Berotralstat 110 mg eller 150 mg én gang dagligt	Placebo	Patienter ≥ 12 år med HAE-type I og II.	24 uger
Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks A Randomized Clinical Trial [12] NCT02586805	**HELP-03**	Lanadelumab 150 mg Q4W, 300 mg Q4W eller 300 mg Q2W	Placebo	Patienter ≥ 12 år med HAE-type I og II.	26 uger

Publikationer	Klinisk forsøg	Intervention	Kompara-tor	Population	Behandlings-tid
Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study [13] NCT02741596	**HELP OLE**	Lanadeluma b 300 mg Q2W	-	Patienter ≥12 år med HAE-type I og II.	33 måneder

APeX-2 er et internationalt, multicenter, dobbelt-blindet, randomiseret, placebo-kontrolleret fase 3-studie. Studiet er et parallelgruppestudie, der inkluderede 121 patienter med HAE-type I eller II fra Europa (≥ 18 år) eller USA og Canada (≥ 12 år). Patienterne blev randomiseret 1:1:1 til berotralstat p.o. 110 mg (n = 41), berotralstat p.o. 150 mg (n = 40) eller placebo (n = 39) én gang dagligt. Randomiseringen blev stratificeret ift. anfaldsfrekvensen ved baseline (≥ 2 vs. < 2 anfald per måned).

Baseline anfaldsraten blev bestemt i en såkaldt run-in periode på op til 70 dage. Patienter, som indenfor denne periode oplevede 2 eller flere HAE-anfald (bekræftet af en investigator), som var behandlingskrævende eller forårsagede funktionsnedsættelse indenfor de første 56 dage af run-in perioden, blev inkluderet.

Studiets primære effektmål var anfaldsfrekvens. Studiets sekundære effektmål var bl.a. livskvalitet (AE-QoL), antal og andel af dage patienterne oplevede HAE-symptomer, andel af patienter med respons (defineret som ≥ 50 % reduktion i antallet af anfald sammenlignet med placebo) og uønskede hændelser.

APeX-J er et dobbelt-blindet, randomiseret, placebo-kontrolleret fase 3-studie. Studiet er et parallelgruppestudie udført i Japan, der inkluderede 19 patienter på 12 år eller derover med HAE-type I eller II. Patienterne blev randomiseret 1:1:1 til berotralstat p.o. 110 mg (n = 6), berotralstat p.o. 150 mg (n = 7) eller placebo (n = 6) én gang dagligt. Randomiseringen blev stratificeret ift. baseline anfaldsfrekvens (≥ 2 vs. < 2 anfald per måned). Baseline anfaldsfrekvensen blev bestemt i en run-in periode på op til 56 dage, og patienter med 2 eller flere anfald (bekræftet af investigator) kunne indgå i studiet.

Studiets primære effektmål var anfaldsfrekvens. Studiets sekundære effektmål var bl.a. antal og andel af dage patienterne oplevede HAE-symptomer, livskvalitet (AE-QoL), andel af patienter med respons (defineret som ≥ 50 % reduktion i antallet af anfald sammenlignet med placebo) og uønskede hændelser.

HELP-03 er et internationalt, multicenter, dobbeltblindet, randomiseret placebokontrolleret fase 3-studie. Studiet er et parallelgruppestudie, der inkluderer 125 patienter på 12 år eller derover med HAE-type I eller II. Patienterne blev randomiseret 2:1 til lanadelumab-behandling (n = 84) eller placebo (n = 41). Patienter i lanadelumab-armen blev randomiseret yderligere 1:1:1 til ét af følgende tre dosisregimer: 150 mg s.c. hver 4. uge (n = 29), 300 mg s.c. hver 4. uge (n = 29) eller 300 mg s.c. hver 2. uge (n = 27).

Randomiseringen blev stratificeret ift. baseline anfaldsfrekvens (1 - < 2, 2 - < 3 og ≥ 3 anfald per måned). Baseline anfaldsfrekvensen blev bestemt i en *run-in* periode på 4 uger, patienter med 1 eller flere anfald kunne indgå i studiet. Patienter, som ikke oplevede anfald indenfor de 4 uger, kunne få run-in perioden forlænget med yderligere 4 uger, indenfor hvilke de skulle have 2 eller flere anfald for at kunne indgå i studiet.

Det primære effektmål var anfaldsfrekvens. De sekundære effektmål var bl.a. antal anfald, der krævede akut behandling, andel af symptomfri dage og livskvalitet (AE-QoL).

Det vurderes, at de tre studier indsendt af ansøger kan anvendes til at vurdere korttidseffekten af berotralstat vs. lanadelumab.

For at vurdere den langvarige kliniske effekt og sikkerhed af berotralstat og lanadelumab til forebyggende behandling af HAE har Medicinrådet i tillæg til disse studier valgt at inkludere to *open-label extension*-studier (APeX-2 part 2 og 3 samt HELP OLE):

APeX-2 part 2 og 2 er *open-label extension*-studier til APeX-2-studiet, som forventes afsluttet i 2023 [9]. APeX-2 part 2 og 3 er designet til primært at vurdere sikkerhed af berotralstat ved langvarig forebyggende behandling. Patienterne behandles med enten 110 mg eller 150 mg berotralstat, og første analyse er baseret på 48 ugers opfølgning, hvoraf de første 24 ugers data stammer fra APeX-2-studiet. APEX-2 part 2 og 3 inddrages i den samlede konklusion med henblik på at belyse sikkerhed samt den vedvarende effekt udover opfølgningstiden i de randomiserede studier.

HELP OLE: For lanadelumab vurderes effekt og sikkerhed af den langvarige forebyggende behandling i et *open-label extension*-studie (HELP OLE), som løber over 33 måneder [13]. Extensionstudiet inddrages i den samlede konklusion med henblik på at belyse den vedvarende effekt udover opfølgningstiden i det randomiserede studie.

Baseline karakteristika
Udvalgte baselinekarakteristika for de relevante behandlingsarme i studierne APeX-2, APeX-J og HELP er vist i Tabel 2.

Tabel 2 – Udvalgte baselinekarakteristika for de behandlingsarme i APeX-2, APeX-J og HELP, som anvendes i vurderingen

		APeX-2 [8]		ApeX-J [11]		HELP [12]	
		Berotral-stat 150 mg QD (n = 40)	Placebo (n = 40)	Berotral-stat 150 mg QD (n = 7)	Placebo (n = 6)	Lanadelumab 300 mg Q2W (n = 27)	Placebo (n = 41)
Alder (år),		40 (14)	44,5 (14,1)	37 (9)	42 (14)	40,3 (13,3)	40,1 (16,8)
Kvinder, n (%)		23 (58)	27 (68)	6 (86)	5 (83)	15 (55,6)	34 (82,9)
Etnicitet, n (%)	Kaukasisk	38 (95)	37 (93)	N/A	N/A	26 (96,3)	39 (95,1)
	Asiatisk	N/A	N/A	6 (86)	6 (100)	0	0
Vægt (Kg)		87,6 (20,4)	84,9 (21,4)	57 (10)	73 (16)	N/A	N/A
BMI (kg/m2)		30,4 (6,7)	29,3 (6,8)	22 (5)	29 (6)	31,0 (7,8)	27,5 (7,7)
Anfaldsfrekvens per måned i run-in perioden		3,06 (1,56)	2,91 (1,12)	2,0 (1,1)	2,5 (1,5)	3,5 (2,3)	4,0 (3,3)
Anfalds-frekvens kategorier ved baseline (anfald per måned), n (%)	≥ 2	30 (75)	27 (68)	4 (57)	3 (50)	20*	29*
	< 2	10 (25)	12 (30)	3 (43)	3 (50)	7 (25,9)	12 (29,3)

Alle værdier er opgivet i mean (SD), medmindre andet er angivet, QD = Én gang dagligt, Q2W = Hver 2. uge, *Kategori 2 - < 3 + ≥ 3.

Fagudvalget vurderer, at baselinekarakteristika i APeX-2 og HELP er sammenlignelige, fraset at flere kvinder er inkluderet i HELP placebo-armen end i de øvrige arme. For APeX-J ses, at studiet hovedsageligt inkluderede asiatiske patienter, at der deltog en overvægt af kvinder, at vægten/BMI i interventionsgruppen var lavere end i de øvrige studiearme, ligesom anfaldsfrekvensen i run-in var lavere i begge arme i forhold til de øvrige.

Baseret på fagudvalgets erfaringer med andre lægemidler end berotralstat til behandling af HAE er der ikke grund til at tro, at behandlingseffekten er forskellig mellem kvinder og mænd. Imidlertid er det uklart, om køn har betydning for behandlingseffekten af berotralstat (se afsnit 5.1.4 ”Anfaldsfrekvens”). Fagudvalget bemærker også, at i APEX-2

er en stor andel af patienterne blevet behandlet med androgener, inden de deltog i studiet (150 mg: n = 21 (53 %), placebo: n = 25 (63 %). Til sammenligning er det uklart, hvor stor en andel patienter i HELP som blev behandlet med androgener før studiestart (dog maksimum 10,7 %). Det er velkendt, at ophør med behandling med androgener kan føre til øget anfaldsfrekvens i tiden umiddelbart efter ophør. Det er uvist, om dette har indflydelse på anfaldsfrekvensen i studiet og forventes i så fald at forekomme i alle behandlingsarme.

De øvrige observerede forskelle forventes ikke at have nogen klinisk betydning, og det bemærkes, at patientgrundlaget i APEX-J kun er n = 13 sammenlignet med APEX-2 n = 80. Fagudvalget har samlet vurderet, at studierne er tilstrækkeligt ens og kan danne grundlag for en sammenlignende kvantitativ analyse.

Fagudvalget vurderer, at patienterne i de kliniske forsøg er tilstrækkeligt repræsentative for den danske patientpopulation.

5.1.2 Databehandling og analyse

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

Ansøger har indsendt en indirekte sammenlignende analyse baseret på data fra følgende studier:

- APeX-2+APeX-J vs. HELP (hvor data for berotralstat er samlet via meta-analyse)

Derudover har ansøger udført en sensitivitetsanalyse, hvor data fra APeX-J er ekskluderet. Analysen inkluderer de samme effektmål som hovedanalysen, og adskiller sig kun ved at ekskludere APEX-J, som kun inkluderer japanske patienter:

- APeX-2 vs. HELP

De indirekte sammenligninger blev baseret på Buchers indirekte analyser med placebo som den fælles komparator. Opfølgningstiden for berotralstat var 24 uger og for lanadelumab 26 uger. Fagudvalget har valgt at tage udgangspunkt i den sammenlignende analyse, som bygger på data for berotralstat fra både APEX-J og APEX-2 ud fra de betragtninger, at etnicitet ikke forventes at have indflydelse på effekt og bivirkninger, og at der herved indgår det størst mulige placebo-kontrollerede datamateriale i vurderingen. Dernæst er design og effektmål ens i studierne.

I Medicinrådets protokol for vurdering af berotralstat [14] efterspurgte Medicinrådet en gennemgang af sværhedsgraden af de tilbageværende anfald (gennembrudsanfald) ved berotralstat og lanadelumab. Det har ikke været muligt for ansøger at levere dette, da data opgøres forskelligt. I stedet har ansøger leveret følgende data:

- Antallet af patienter med mindst et larynx-anfald under behandling med berotralstat/lanadelumab.
- Relativ reduktion i raten af moderate/svære HAE-anfald per måned.

Fagudvalget vurderer, at alvorligheden af gennembrudsanfaldende bliver tilfredsstillende belyst ved brug af disse data.

Derudover bemærker fagudvalget, at datagrundlaget for vurderingen af berotralstat overfor lanadelumab er yderst spinkelt (APeX-2: n = 80, APeX-J: n = 13, HELP: n = 86). Det er noteret, at registreringen af HAE-anfald varierer imellem studierne, idet APeX-2 og APeX-J anvender en tidsramme på 48 timer fra starten af et anfald, hvor indenfor et nyt andet anfald ikke kan registreres, mens HELP anvender en tidsramme på 24 timer. Om det har betydning for effektestimaterne, er uklart. Ligeledes anvendes forskellig metodik til at indsamle information om HAE-anfald. I APeX-2 og APeX-J blev patienterne hver dag mindet om at notere symptomer på anfald i en elektronisk dagbog, mens det i HELP var op til patienten selv at informere om anfald indenfor 72 timer fra anfaldets start. Det er også uklart, om dette i praksis har betydning for effektestimaterne.

Samlet set vurderer Medicinrådet, at de tilgængelige data kan anvendes i vurderingen af berotralstat.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

I vurderingen er der nedgraderet for risiko for bias, da der er forskelle i baselinekarakteristika, som muligvis har betydning for effekt. Ligeledes er det muligt, at patienter og personale kan ræsonnere sig frem til patientens behandling baseret på anfaldsmønstret (bilag 1). Der er nedgraderet for inkonsistens, da vurderingen baseres på to studier for berotralstat med meget få patienter samt ét studie for lanadelumab, som også inkluderer meget få patienter. Desuden er der nedgraderet for unøjagtighed, da kravet om optimal information size ikke er overholdt, og da konfidensintervallerne for estimaterne er meget brede, hvilket resulterer i, at grænserne for klinisk beslutningstagen krydses.

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

I Tabel 3 herunder fremgår de absolutte og relative effektforskelle for sammenligningen af berotralstat (APeX-2 + APeX-J) og lanadelumab (HELP), som anvendes i Medicinrådets vurdering af klinisk spørgsmål 1.

Tabel 3 - Resultater for klinisk spørgsmål 1: Sammenligning APeX-2, APeX-J (berotralstat (24 ugers opfølgning)) og HELP (lanadelumab (26 ugers opfølgning))

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel [95 % CI]	Foreløbig værdi	
Anfalds-frihed	Andel af patienter, som oplever en 100 % reduktion i anfaldsfrekvens (anfaldsfrihed) fra baseline (10 %-point)	Kritisk	[redacted]	Kan ikke kategoriseres	[redacted]	Kan ikke kategoriseres	Kan ikke kategoriseres
Helbreds-relateret livskvalitet	Ændring fra baseline målt med Angioedema Quality of life Questionnaire (AE-QoL) (6 point)	Kritisk	MD: -9,13 [-22,92; 4,66]	Kan ikke kategoriseres			Kan ikke kategoriseres
	Andel af patienter, som oplever en forbedring på 6 point fra baseline (Anvendes til bestemmelse af den relative effektforskel. Der er derfor ikke fastsat en MKRF)				[redacted]	Kan ikke kategoriseres	
Anfalds-frekvens	Gennemsnitlig procentvis reduktion i antallet af HAE-anfald pr. måned (15 %-point)	Vigtig	Δ% RaR: -41,4 %-point [-94,2; -14,6]	Negativ merværdi	RaR: 4,18 [2,12; 8,25]	Negativ merværdi	Negativ merværdi
	Gennemgang af sværhedsgraden af de tilbageværende anfald (gennembruds-anfald) ved de to behandlinger[†]						
Bivirkning-er	Andel patienter, der ophører behandling grundet bivirkninger (10 %-point)	Vigtig	ARR: -0,1 %-point [-1,7; 61,0]	Kan ikke kategoriseres	RR: 0,94 [0,03; 35,17]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Kvalitativ gennemgang af lægemidlernes bivirkningsprofil						
Konklusion							
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres						
Kvalitet af den samlede evidens	Meget lav						

ARR = absolut risk reduktion, CI = konfidensinterval, MD = mean difference, RaR = rate ratio, RR = relativ risiko, Δ% RaR = forskel i procentvis rate reduktion.

Anfaldsfrihed

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

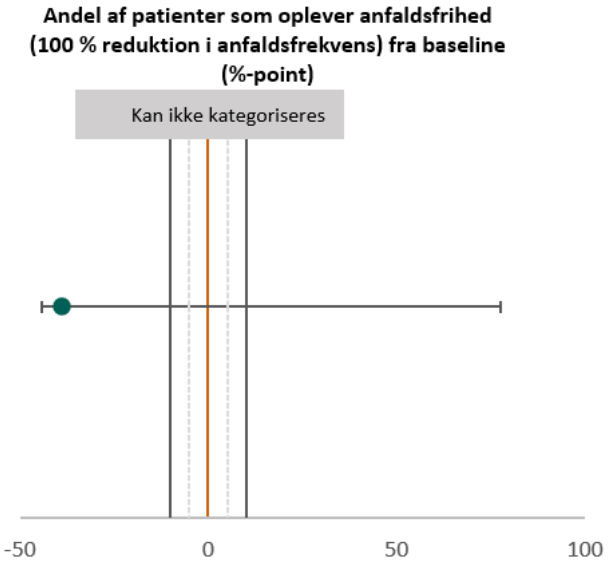
Tabel 4 viser resultater pr. studie for effektmålet anfaldsfrihed. Disse resultater er grundlaget for den indirekte sammenlignende analyse mellem berotralstat og lanadelumab.

Tabel 4 - Andel af patienter, som oplever en 100 % reduktion i anfaldsfrekvens (anfaldsfrihed) fra baseline (%)

Berotralstat				Lanadelumab	
APeX-2 [8]		APeX-J [11]		HELP [12]	
Berotralstat 150 mg QD (n = 40)	Placebo (n = 40)	Berotralstat 150 mg QD (n = 7)	Placebo (n = 6)	Lanadelumab 300 mg Q2W (n = 27)	Placebo (= 41)
[redacted]	[redacted]	[redacted]	[redacted]	12/27 (44,4)	1/41 (2,4)

Ansøgers indirekte analyse viser, at mens 44,4 % af patienterne behandlet med lanadelumab bliver anfaldsfri, er den tilsvarende andel 5,8 % for berotralstat (beregnet baseret på [redacted]), hvilket tilsvarer en absolut risikoreduktion på [redacted]. Det vil sige, at [redacted] færre opnår anfaldsfrihed ved behandling med berotralstat sammenlignet med lanadelumab. Konfidensintervallet for dette estimat er meget bredt, hvilket betyder, at estimatet er usikkert. Derfor kan den foreløbige værdi af berotralstat vedr. anfaldsfrihed ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i Figur 1 nedenfor.



Figur 1 - Punktestimat og 95 % konfidensinterval for den absolutte forskel for patienter, som oplever anfaldsfrihed (en 100 % reduktion i anfaldsfrekvens) fra baseline. De optrukne linjer

indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Punkestimatet for det relative effektestimat [redacted] indikerer ligeledes, at lanadelumab er mere effektivt end berotralstat, men da konfidensintervallet krydser 1 og desuden er meget bredt, er dette ikke konklusivt. Det er således ikke muligt at kategorisere berotralstat i henhold til Medicinrådets metoder vedr. anfaldsfrihed.

Fagudvalget vurderer, at berotralstat aggregeret ikke kan kategoriseres vedr. anfaldsfrihed, da de komparative estimater ikke tillader dette (for stor usikkerhed). Punktestimatet indikerer, at berotralstat er mindre effektivt, i forhold til hvor stor en andel patienter, som opnår anfaldsfrihed.

Helbredsrelateret livskvalitet

Som beskrevet i protokollen er effektmålet livskvalitet kritisk for vurderingen af lægemidlets værdi for patienterne, fordi HAE under anfald såvel som mellem anfald påvirker patientens livskvalitet. Vurderingen bliver baseret på den samlede score målt med Angioedema Quality of life Questionnaire (AE-QoL), og en forskel på 6 point vurderes at være klinisk betydende [15]. Effektmålet ønskes både opgjort som 1) ændring fra baseline målt til *end of study* med Angioedema Quality of life Questionnaire (AE-QoL), og 2) andel af patienter, som oplever en forbedring på 6 point fra baseline.

Ændring fra baseline målt på AE-QoL

Tabel 5 viser resultater pr. studie for AE-QoL-ændring fra baseline til *end of study**, hvor en negativ værdi er udtryk for forbedret livskvalitet. Disse resultater er grundlaget for den indirekte sammenlignende analyse mellem berotralstat og lanadelumab.

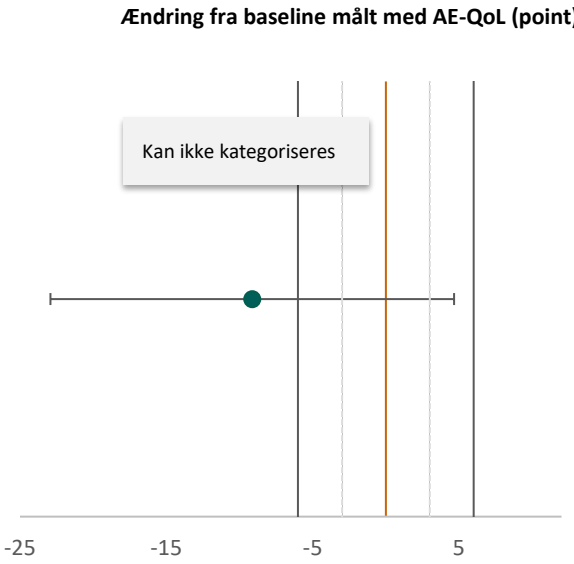
Tabel 5 - Ændring fra baseline til *end of study målt med AE-QoL**

Berotralstat				Lanadelumab	
APeX-2 [8]		**APeX-J** [11]		**HELP** [12]	
Berotralstat 150 mg QD (n = 40) LSM (SE)	**Placebo (n = 40) LSM (SE)**	**Berotralstat 150 mg QD (n = 7) LSM (SE)**	**Placebo (n = 6) LSM (SE)**	**Lanadelumab 300 mg Q2W (n = 27) LSM (CI)**	**Placebo (n = 41) LSM (CI)**
-14,59 (2,59)	-9,69 (2,64)	-15,82 (6,42)	3,18 (6,83)	-21,29 (-28,21; -14,37)	-4,72 (-10,46; 1,02)

*Behandlingsvarighed i APEX-2 og APEX-J er 24 uger. Behandlingsvarighed i HELP er 26 uger.

På baggrund af den indirekte analyse mellem berotralstat og lanadelumab er der beregnet en absolut mean difference på -9,13 point [-22,92; 4,66]. Det vil sige, at patienterne i behandling med lanadelumab i gennemsnit oplevede en forbedret livskvalitet målt med AE-QoL sammenlignet med berotralstat. Punktestimatet afspejler en klinisk relevant forskel, idet den overstiger 6 point. Dog er konfidensintervallet meget bredt, hvilket betyder, at estimatet er usikkert. Derfor kan den foreløbige værdi af berotralstat vedr. ændring i AE-QoL fra baseline ikke kategoriseres.

Den absolutte forskel er afbildet i Figur 2 nedenfor:



Figur 2 - Punktestimat og 95 % konfidensinterval for den absolutte forskel i ændringer fra baseline målt på AE-QoL. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Andel af patienter, som oplever en forbedring på 6 point fra baseline
Denne opgørelse af helbredsrelateret livskvalitet er medtaget i vurderingen, da Medicinrådet ønsker et estimat for den relative effektforskel mellem berotralstat og lanadelumab, og der er derfor ikke fastsat en mindste klinisk relevant forskel.

Tabel 6 viser resultater pr. studie for andel af patienter, som oplever en forbedring på 6 point fra baseline på et hvilket som helst tidspunkt i studiets forløb. Disse resultater er grundlaget for den indirekte sammenlignende analyse mellem berotralstat og lanadelumab.

Tabel 6 - Andel af patienter, som oplever en forbedring på 6 point fra baseline (%)

Berotralstat				Lanadelumab	
APeX-2 [8]		**APeX-J** [11]		**HELP** [12]	
Berotralstat 150 mg QD (n = 40)	**Placebo (n = 40)**	**Berotralstat 150 mg QD (n = 7)**	**Placebo (n = 6)**	**Lanadelumab 300 mg Q2W (n = 27)**	**Placebo (n = 41)**
[redacted]	[redacted]	[redacted]	[redacted]	21/26 (80,77)	14/38 (36,84)

Ansøgers analyse viser, at den relative risiko for at opnå en 6-points forbedring i AE-QoL score er RR[redacted] ved sammenligning af berotralstat med lanadelumab. Det bemærkes, at der er stort placeborespons i APEX-2. Punktestimatet for den relative risiko indikerer, at sandsynligheden for en klinisk relevant forbedring (ændring på 6

point) er halvt så stor i berotralstatgruppen. Dog er konfidensintervallet bredt, og estimatet er behæftet med usikkerhed, hvorfor værdien ikke kan kategoriseres.

Samlet set vurderer fagudvalget, at den samlede værdi af berotralstat vedr. helbredsrelateret livskvalitet formelt set ikke kan kategoriseres, da der er for stor usikkerhed forbundet med de komparative estimater. Det nuværende datagrundlag indikerer, at behandling med berotralstat er forbundet med ringere helbredsrelateret livskvalitet sammenlignet med lanadelumab.

Anfaldsfrekvens
Som beskrevet i protokollen er effektmålet anfaldsfrekvens vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det primære behandlingsmål med rutinemæssig forebyggelse er at reducere frekvensen af HAE-anfald. Effektmålet ønskes både opgjort som 1) gennemsnitlig procentvis reduktion i antallet af HAE-anfald pr. måned, og 2) gennemgang af sværhedsgraden af de tilbageværende anfald (gennembruds-anfald) ved de to behandlinger karakteriseret ved henholdsvis mild, moderat og svær sværhedsgrad.

Ansøger har ikke haft mulighed for at levere de efterspurgte data for gennembrudsanfald (punkt 2), da data ikke er sammenlignelige på tværs af studier. I stedet har ansøger leveret følgende data:

- Antallet af patienter med mindst et larynx-anfald under behandling med berotralstat/lanadelumab.
- Relativ reduktion i raten af moderate/svære HAE-anfald pr måned.

Reduktion i antallet af HAE-anfald pr. måned
Tabel 7 viser den gennemsnitlige ændring i antallet af HAE-anfald pr. måned. Disse resultater er grundlaget for den indirekte sammenlignende analyse mellem berotralstat og lanadelumab.

Tabel 7 - Gennemsnitlig ændring i antallet af HAE-anfald pr. måned (%)

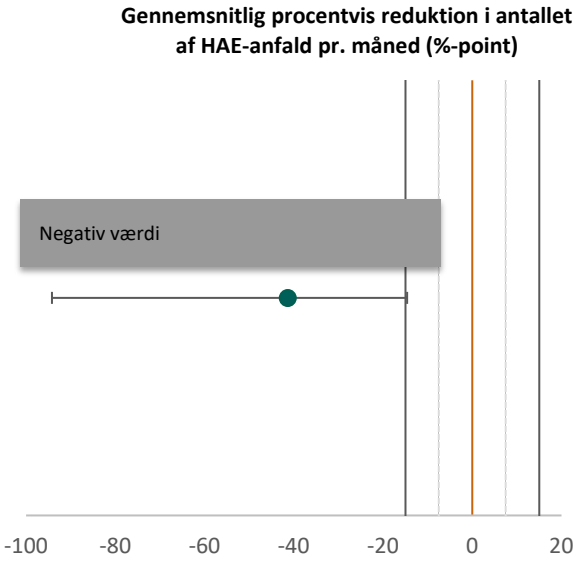
	Berotralstat						**Lanadelumab**		
	APeX-2 [8]			**APeX-J** [11]			**HELP** [12]		
	BERO 150 mg QD (n = 40)	**Placebo (n = 40)**	**Forskel**	**BERO 150 mg QD (n = 7)**	**Placebo (n = 6)**	**Forskel**	**LANA 300 mg Q2W (n =27)**	**Placebo (n = 41)**	**Forskel**

Baseline	3,06	2,91	-	2,0	2,5	-	3,5	4,0	-
Ændring fra baseline efter 24 uger (berotral-stat) og 26 uger (lanadelu-mab)	[redacted]	2,35	**44,2 %-point (23;59,5)**	1,11	2,18	**49,1 %-point (20,4; 67,5)**	[redacted]	1,97	**87 %-point (76; 93)**

Rate ratioen RaR: 4,18 [2,12; 8,25] indikerer, at berotralstat er associeret med en højere anfaldsrate end lanadelumab. På baggrund af dette estimat har berotralstat foreløbigt en negativ værdi vedr. reduktion i antallet af HAE-tilfælde pr. måned.

På baggrund af den indirekte analyse er der beregnet en absolut forskel i procentvis ratereduktion på -41,4 %-point (95 % CI:-94,2; -14,6), hvilket viser, at berotralstat er associeret med en mindre reduktion i anfaldsrate end lanadelumab. Konkret ses det, at i HELP reduceres anfaldsraten med 87 % ved lanadelumab sammenlignet med placebo. Baseret på den absolutte forskel i ratereduktion på -41,4 %-point betyder det, at anfaldsraten reduceres med 45,6 % for berotralstat. Forskellen på 41,4 %-point kan også omregnes til en forskel i anfaldsrate på 0,83 anfald per måned (95 % CI: 0,29 to 1,88).

Den absolutte forskel er afbildet i Figur 3 nedenfor.



Figur 3 - Punktestimat og 95 % konfidensinterval for den absolutte forskel for den gennemsnittelige procentvise reduktion i antallet af HAE-tilfælde pr. måned. De optrukne linjer

indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Estimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel (MKRF: 15 %-point), men da denne er til fordel for lanadelumab, tildeles berotralstat foreløbigt en negativ værdi.

Ansøgers *open-label extension*-studie (APEX-S) viser, at gruppen af patienter, som fortsætter behandlingen med berotralstat 150 mg efter 24 uger, har fortsat gavn af behandlingen op til uge 96, hvor studiet afsluttes, og at effekten måske øges yderligere over tid [10]. Tilsvarende viser *open-label extension*-data for lanadelumab (HELP OLE), at patienterne også her har fortsat gavn af behandlingen efter 33 måneders behandling [13].

Fagudvalget hæfter sig ved, at EMAs gennemgang af data for berotralstat [5] viser ringere effekt af berotralstat hos kvinder sammenlignet med mænd. Konkret ses en rate reduktion på -33,0 % hos kvinderne i studiet behandlet med berotralstat 150 mg, mens den tilsvarende reduktion i gruppen af mænd var -65,6 %. En tilsvarende forskel blev også fundet for 110 mg. Da datamaterialet er yderst spinkelt, er det uklart, om dette er et validt fund, og EMA konkluderer, at de nuværende data er inkonklusive.

Gennemgang af andelen af patienter med larynx-anfald samt rater for moderat/svære anfald per måned
Ifølge ansøgers analyse er risikoen for at opleve et larynx-anfald ved behandling med berotralstat sammenlignet med lanadelumab [redacted]. Forskellen mellem grupperne er [redacted].

En indirekte analyse mellem berotralstat og lanadelumab af forekomsten af moderate/svære anfald viser en højere anfaldsrate for berotralstat sammenlignet med lanadelumab ([redacted]). Dette er i overensstemmelse med behandlingseffekten set for den overordnede anfaldsrate (rate ratio, RaR: 4,18 [2,12; 8,25]). Den beregnede forskel i moderate/svære anfald pr. måned er [redacted]

Fagudvalget vurderer, at berotralstat aggregeret har en negativ merværdi vedr. reduktion i antallet af HAE-anfald pr. måned, fordi berotralstat er mindre effektivt til at forebygge anfald baseret på de tilgængelig data med en opfølgningstid på 24-26 uger. Her var en procentvis ratereduktion på 45,6 % ved behandling med berotralstat og 87 % ved behandling med lanadelumab (Rate ratio, RaR: 4,18 [2,12; 8,25]). Tilsvarende ses også en højere anfaldsrate for berotralstat sammenlignet med lanadelumab, hvad angår moderate/svære anfald ([redacted]). Fagudvalget bemærker, at larynx-anfald forekommer med samme frekvens for berotralstat og lanadelumab [redacted], men at der er for få events i studierne til at effekten på larynx-ødem reelt kan vurderes. Desuden bemærkes, at effekten af berotralstat 150 mg synes at blive opretholdt fra uge 24-96 hos de patienter, som oplevede en effekt ved uge 24.

Bivirkninger
Som beskrevet i protokollen er effektmålet bivirkninger vigtigt for vurderingen af lægemidlets værdi for patienterne. Effektmålet ønskes både opgjort som 1) andel patienter, der ophører behandling grundet bivirkninger, og 2) kvalitativ gennemgang af lægemidlernes bivirkningsprofil.

Andel patienter, der ophører behandling grundet bivirkninger
Der blev kun registreret ét tilfælde af behandlingsophør som følge af en uønsket hændelse (TEAE, *Treatment Emergent Adverse Event*) i APeX-2. Denne hændelse (*asymptomatic transaminase level increase*) var muligvis/sandsynligvis relateret til berotralstat 150 mg. I APeX-J og HELP var der ingen events i henholdsvis berotralstat 150 mg-armen og i lanadelumab 300 mg Q2W-armen.

Ansøger har foretaget en indirekte analyse af behandlingsophør som følge af uønskede hændelser (TEAE, *Treatment Emergent Adverse Events*). Den relative risiko RR: 0,94 [0,03; 35,17] indikerer, at der er lige stor sandsynlighed for ophør med behandling grundet en uønsket hændelse for de to lægemidler. Den absolutte effektforskel er opgjort til -0,1 %-point [-1,7; 61,0]. Da datagrundlaget for den indirekte analyse er yderst beskedent, er estimaterne behæftet med så stor usikkerhed, at værdien af berotralstat ikke kan kategoriseres. 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.

Kvalitativ gennemgang af lægemidlernes bivirkningsprofil
I EMA's produktresumé for berotralstat beskrives de mest almindelige bivirkninger (≥ 1/10) ved brug af berotralstat som smerter i maven (21 %), diarré (15 %) og hovedpine (13 %). De gastrointestinale bivirkninger fortog sig uden medicinsk behandling og blev kategoriseret som milde eller moderate. Bivirkningerne blev fortrinsvis rapporteret i 1.-3. måned af behandlingen. Af almindelige bivirkninger (≥ 1/100 til < 1/10) ses opkastning, gastroøsofageal refluks, flatulens, udslæt på hud samt forhøjede leverværdier (ALAT og ASAT). Der ses tilsvarende sikkerhedsprofil for unge mellem 12 – 18 år, der vejede mindst 40 kg. [16].

I APeX-2 var der ingen alvorlige uønskede hændelser (SAE) eller alvorlige bivirkninger (SAR) i gruppen behandlet med berotralstat 150 mg.

I EMA's produktresumé for lanadelumab beskrives den mest almindelige bivirkning (≥ 1/10) ved brug af lanadelumab som reaktion på injektionsstedet (52,4 %). Af disse var 97 % af mild sværhedsgrad. Af almindelige bivirkninger (≥ 1/100 til < 1/10) ses overfølsomhed (kløe, ubehag og snurren i tungen), svimmelhed, makulopapuløst udslæt, myalgi, øget alanin- eller asparat-aminotransferase. Der ses en tilsvarende sikkerhedsprofil for unge mellem 12–18 år [17].

I HELP var der én alvorlig uønsket hændelse (SAE) i armen behandlet med lanadelumab 300 mg Q2W, infektion ved kateter. Der blev ikke registreret nogen alvorlige bivirkninger i studiet.

Både for berotralstat og lanadelumab foreligger der *open-label* data med en længere opfølgningstid, som belyser sikkerhedsprofilerne. Efter 96 ugers behandling med berotralstat og 33 måneders behandling med lanadelumab ses ingen relevante ændringer i de beskrevne sikkerhedsprofiler [10][13].

Fagudvalget bemærker, at berotralstat er associeret med en række klinisk relevante lægemiddelinteraktioner, mens der ikke er beskrevet relevante interaktioner ved brug af lanadelumab. Berotralstat er en mild inhibitor (hæmmer) af CYP2C9, hvilket kan betyde reduceret effekt af hormonale kontraceptiva, der kræver CYP2C9 for at omdannes fra prodrug til en aktiv metabolit, fx desogestrel.

Fagudvalget vurderer, at berotralstat formelt set ikke kan kategoriseres vedr. bivirkninger, da datagrundlaget er meget spinkelt og dermed ikke tillader en kategorisering. De to behandlinger har forskellige sikkerhedsprofiler jævnfør deres forskellige administrationsmåder og virkningsmekanismer. Berotralstat er således primært associeret med gastrointestinale hændelser, mens der ved lanadelumab ses reaktioner ved injektionsstedet. Begge behandlinger vurderes at være veltolererede, idet der ses få og milde bivirkninger. Fagudvalget vurderer på det foreliggende datagrundlag, at de to behandlinger er ligeværdige, hvad angår bivirkninger.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af berotralstat sammenlignet med lanadelumab til rutinemæssig forebyggelse af tilbagevendende anfald af arveligt angioødem ikke kan kategoriseres på det nuværende datagrundlag.

Fagudvalget vurderer, at berotralstat er et dårligere behandlingsalternativ end lanadelumab, fordi det samlet set vurderes mindre effektivt til at forebygge angioødemanfald. Samtidig ses også en mindre forbedring i helbredsrelateret livskvalitet ved sammenligning med lanadelumab. Dog mener fagudvalget, at berotralstat er et behandlingstilbud, som har værdi i klinikken, idet det er den første orale behandling til forebyggelse af angioødem. De øvrige behandlinger, som aktuelt anvendes i klinikken (lanadelumab og C1-esteraseinhibitor), administreres subkutant. Ikke alle patienter har tilstrækkelig effekt af den nuværende behandling, og det gælder også, at nogle patienter har væsentlige gener ved den subkutane administrationsvej. For disse patienter er berotralstat et velkomment behandlingsalternativ.

Fagudvalget vurderer, at berotralstat er lige så veltolereret som lanadelumab, om end bivirkningsprofilen er anderledes grundet forskellige administrationsmåder og virkningsmekanismer.

Fagudvalget vurderer, at berotralstat er mindre effektivt til at reducere antallet af HAE-anfald pr. måned, baseret på de tilgængelig data med en opfølgningstid på 24-26 uger. Her sås en procentvis ratereduktion på 45,6 % ved behandling med berotralstat og 87 % ved behandling med lanadelumab (Rate ratio, RaR: 4,18 [2,12; 8,25])**.** Det svarer til en

forskel i anfaldsrate på 0,83 anfald per måned (95 % CI: 0,29 to 1,88) mellem de to behandlinger. Effektdata viser også, at 44,4 % af patienterne behandlet med lanadelumab bliver anfaldsfri, mens den tilsvarende andel er 5,8 % for berotralstat.

Ansøgers *open-label extension*-studier (APeX-2 part 2 og 3) viser, at gruppen af patienter, som fortsætter behandlingen med berotralstat 150 mg efter 24 uger, har fortsat gavn af behandlingen op til uge 96, hvor studiet afsluttes, og at effekten måske øges yderligere over tid [9,10]. Tilsvarende viser *open-label extension*-data for lanadelumab (HELP OLE), at patienterne også her har fortsat gavn af behandlingen efter 33 måneders behandling [13].

Fagudvalget hæfter sig ved, at EMAs gennemgang af data for berotralstat [5] viser ringere effekt af berotralstat hos kvinder sammenlignet med mænd. Konkret ses en anfalds-ratereduktion på -33,0 % hos kvinderne i studiet behandlet med berotralstat 150 mg, mens den tilsvarende reduktion i gruppen af mænd var -65,6 %. En tilsvarende forskel blev også fundet for 110 mg. Da datamaterialet er yderst spinkelt, er det uklart, om dette er et validt fund, og EMA konkluderer, at de nuværende data er inkonklusive.

Fagudvalget bemærker, at berotralstat er associeret med en række klinisk relevante lægemiddelinteraktioner (herunder mini-piller (desogestrel)), som der bør være opmærksomhed på i klinikken.

Fagudvalgets vurdering er baseret på en indirekte analyse af data fra studierne APEX-J, APEX-2 og HELP, hvor henholdsvis berotralstat og lanadelumab er sammenlignet med placebo. Der findes ikke direkte sammenlignende studier. Da estimaterne fra den indirekte analyse er behæftet med stor usikkerhed grundet et meget lille datagrundlag, har fagudvalget ikke fundet det muligt formelt set at kategorisere værdien af berotralstat overfor lanadelumab. Evidensens kvalitet vurderes at være meget lav.

6. Andre overvejelser

Anfaldsfrekvens i subgrupper

På baggrund af et ønske fra Medicinrådet har ansøger indsendt subgruppedata baseret på patienternes anfaldsfrekvens ved baseline (< 2 vs. ≥ 2 per måned). Ansøger har indsendt to opgørelser, én, der viser den procentvise ændring i anfaldsfrekvensen for berotralstat og placebo for de ønskede subgrupper, og én, der præsenterer rate ratioen mellem lanadelumab 300 s.c. mg hver 2. uge og placebo for subgrupper med baseline anfaldsfrekvens på ´1 - < 2´, ´2 ≤ - < 3´ og ´≥ 2´ per måned. Ansøger argumenterer for, at der ikke kan laves en statistisk analyse, som sammenligner berotralstat og lanadelumab, da subgrupperne er opgjort forskelligt, ligesom patienter i HELP blev ekskluderet ved en baseline anfaldsfrekvens på < 1 om måneden, hvilket ikke var tilfældet for patienterne i APeX-2.

Ansøger konkluderer på baggrund af den kvalitative sammenstilling, at den relative effekt af berotralstat eller lanadelumab vs. placebo er numerisk lavere (ikke statistisk

signifikant) for patienter med højere anfaldsfrekvens ved baseline. Ansøger tilføjer, at den langtidseffekt, som blev observeret for hele populationen i APeX-2, også ses i subgruppen med baseline på ≥ 2 anfald per måned.

Fagudvalget vurderer, at for begge lægemidler understøtter det nuværende datagrundlag, at effekten af behandlingen ikke i betydende grad er afhængig af patientens udgangspunkt (anfaldsfrekvens ved baseline).

Compliance

For patienter med HAE er der tale om en ny administrationsvej, når en oral behandling som berotralstat godkendes. Fagudvalget ønsker derfor information om adhærens til behandlingen.

Ansøger har indsendt information om adhærens til behandlingen med berotralstat (*compliance*) i de kliniske studier. Den gennemsnittelige compliance ved uge 24 var for berotralstat 150 mg QD [redacted] og [redacted] for placebo. Ved uge 48 var den gennemsnittelige compliance [redacted] for de patienter, som fik berotralstat. Årsagen til non-compliance er ikke blevet studeret.

Fagudvalget vurderer, at data viser en god adhærens ved behandlingen over tid, hvilket er i god overensstemmelse med den uproblematiske bivirkningsprofil.

Håndtering af varierende sygdomsaktivitet

Da det er velkendt, at patienternes sygdomsaktivitet kan variere over tid, har Medicinrådet efterspurgt information om erfaringer med øget dosis for berotralstat over den anbefalede dosis på 150 mg hos patienter med periodisk øget anfaldsfrekvens.

Ansøger oplyser, at berotralstat ikke bør anvendes i dosis, der overstiger de anbefalede 150 mg uanset årsag. Ansøger oplyser også, at i et fase 2-studie (*dose finding study*, APeX-1), blev doser op til 350 mg dagligt testet. Selvom kallikrein inhiberingen blev øget med højere dosering, var dette ikke korreleret med anfaldsraten ved doser over 125 mg dagligt [5].

Fagudvalget tager dette *ad notam*.

7. Relation til behandlingsvejledning

Der findes på nuværende tidspunkt ikke en relevant behandlingsvejledning. Medicinrådet godkendte d. 28. april 2021 en protokol for udarbejdelsen af en kommende behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende arveligt angioødem

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

Medicinrådets sekretariat

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

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26. januar 2022	Godkendt af Medicinrådet

11. Bilag

Bilag 1: Cochrane – risiko for bias

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

Tabel 8 - Vurdering af risiko for bias i Zuraw et al., 2021, APeX-2, NCT03485911

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Forbehold**	Patienterne er randomiseret 1:1:1 til enten berotralstat 110 mg eller 150 mg placebo én gang dagligt. Randomisering foregik via et interaktivt webbaseret randomiseringssystem (Veracity Logic, Chapel Hill, NC) af blindet studiepersonale. Randomiseringen var stratificeret ud fra baseline anfaldsfrekvens. Der er tendens til forskelle i visse baselinekarakteristika, f.eks. kønsfordeling, andel i de forskellige BMI-kategorier og tidligere forebyggende behandling med androgener. Det er muligt, at den ulige kønsfordeling har indflydelse på effektestimaterne, da subgruppeanalyser indikerer, at effekten af berotralstat muligvis er mindre hos kvinder end hos mænd. Det er også velkendt, at ophør med behandling med androgener kan føre til øget anfaldsfrekvens i tiden umiddelbart efter ophør. Det er uvist, om dette har indflydelse på anfaldsfrekvensen i studiet og forventes i så fald at forekomme i alle behandlingsarme.
Effekt af tildeling til intervention	**Forbehold**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får, men det er muligt, at patienter og personale kan ræsonnere sig frem til, om patienten modtager aktiv behandling baseret på patientens anfaldsmønster.
Manglende data for effektmål	**Lav**	Alle effektivitetsanalyser blev udført på intention to treat-populationen, defineret som alle randomiserede patienter eksponeret for aktiv behandling eller placebo. Sikkerhedsanalyser blev udført på sikkerhedspopulationen, som omfattede alle patienter, der modtog en eller flere doser af studiemedicin; analyser blev udført i henhold til den faktiske modtagne behandling. Der er transparent og sammenligneligt frafald i alle behandlingsarme.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Analyser udført efter den statistiske analyseplan.

Bias	Risiko for bias	Uddybning
Overordnet risiko for bias	**Forbehold**	Der er samlet set forbehold vedr. risiko for bias, da ubalance i visse baselinekarakteristika (primært kønsfordelingen og tidligere androgenbehandling) medfører forbehold i forhold til effektestimaterne. Det er også muligt, at patienter og personale kan ræsonnere sig frem til patientens behandling baseret på anfaldsmønstret.

Tabel 94 - Vurdering af risiko for bias i Ohsawa et al., 2021, APeX-J, NCT03873116

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Forbehold**	Patienterne er randomiseret 1:1:1 til enten berotralstat 110 mg eller 150 mg placebo én gang dagligt. Randomisering foregik via et interaktivt randomiseringssystem. Randomiseringen var stratificeret på baseline anfaldsfrekvens. Der er tendens til forskelle i visse baselinekarakteristika, f.eks. vægt, baseline anfaldsfrekvens og tidligere forebyggende behandling med androgener. Det er muligt, at den ulige kønsfordeling har indflydelse på effektestimaterne, da subgruppeanalyser indikerer, at effekten af berotralstat muligvis er mindre hos kvinder end hos mænd. Det er velkendt, at ophør med behandling med androgener kan føre til øget anfaldsfrekvens i tiden umiddelbart efter ophør. Det er uvist, om dette har indflydelse på anfaldsfrekvensen i studiet og forventes i så fald at forekomme i alle behandlingsarme.
Effekt af tildeling til intervention	**Forbehold**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får. Men det er muligt, at patienter og personale kan ræsonnere sig frem til, om patienten modtager aktiv behandling baseret på patientens anfaldsmønster.
Manglende data for effektmål	**Lav**	Størrelsen på studiepopulationen har begrænset statistisk *power.* Alle effektivitetsanalyser blev udført på intention to treat-population, defineret som alle randomiserede patienter eksponeret for aktiv behandling eller placebo. Sikkerhedsanalyser blev udført på sikkerhedspopulationen, som omfattede alle patienter, der modtog en eller flere doser af studiemedicin; analyser blev udført i henhold til den faktiske modtagne behandling. Der er transparent og sammenligneligt frafald i alle behandlingsarme.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får.

Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Analyser udført efter den statistiske analyseplan.
Overordnet risiko for bias	**Forbehold**	Der er samlet set forbehold vedr. risiko for bias, da ubalance i visse baselinekarakteristika (primært kønsfordelingen og tidligere androgenbrug) medfører forbehold i forhold til effektestimaterne. Det er også muligt, at patienter og personale kan ræsonnere sig frem til patientens behandling baseret på anfaldsmønstret.

Tabel 10 - Vurdering af risiko for bias i Banerji et al., HELP, NCT02586805

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Forbehold**	Patienterne er randomiseret 2:1 til henholdsvis lanadelumab eller placebo. For lanadelumab er patienterne desuden 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. Der er tendens til forskelle i visse baselinekarakteristika, f.eks. den historiske anfaldsfrekvens, kønsfordeling og anvendelse af forebyggende behandling op til studiets start.
Effekt af tildeling til intervention	**Forbehold**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får, men det er muligt, at patienter og personale kan ræsonnere sig frem til, om patienten modtager aktiv behandling baseret på patientens anfaldsmønster.
Manglende data for effektmål	**Lav**	Alle effektivitetsanalyser 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.

Bias	Risiko for bias	Uddybning
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet studie. Hverken personale eller patienter har kendskab til, hvilken behandling patienterne får.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Analyser udført efter den statistiske analyseplan.
Overordnet risiko for bias	**Forbehold**	Der er samlet set forbehold vedr. risiko for bias, da det er muligt, at patienter og personale kan ræsonnere sig frem til patientens behandling baseret på anfaldsmønstret. Der er også ubalance i visse baselinekarakteristika, som medfører forbehold i forhold til randomiseringen.

Bilag 2: GRADE

Klinisk spørgsmål 1 – berotralstat sammenlignet med lanadelumab til forebyggende behandling af arveligt angioødem

Tabel 11 - GRADE evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Berotralstat	Lanadelumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Anfaldsfrihed, 24-26 uger												
3	RCT	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Alvorlig[c]	Ingen	[redacted] (5,8 %)	12/27 (44.4%)	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
Helbredsrelateret livskvalitet: Andel patienter som oplever en forbedring på 6 point fra baseline med AE-QoL, 24-26 uger												
3	RCT	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Alvorlig[c]	Ingen	[redacted]	21/27	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
Helbredsrelateret livskvalitet: Ændring fra baseline målt med AE-QoL, 24-26 uger												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Berotralstat	Lanadelumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
3	RCT	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Alvorlig[c]	Ingen	47	27	-	MD -9.13 (22.92; 4.66)	⨁◯◯◯ MEGET LAV	KRITISK
Anfaldsfrekvens: Gennemsnitlig procentvis reduktion i antallet af HAE-tilfælde pr. måned, 24-26 uger												
3	RCT	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Alvorlig[d]		47	27	Rate ratio **4,18** (2,12; 8,25)		⨁◯◯◯ MEGET LAV	VIGTIG
Bivirkninger: Andel patienter der ophører behandling grundet bivirkninger, 24-26 uger												
3	RCT	Ikke alvorlig	Alvorlig[b]	Ikke alvorlig	Alvorlig[c]		1/47 (2.1%)	0/27 (0.0%)	RR 0.94 (0.03 to 35.17)	Absolut risiko-reduktion -0,1 %-point (-1,7; 61,0)	⨁⨁◯◯ LAV	VIGTIG
Kvalitet af den samlede evidens	MEGET LAV[e]											

a. Forskelle i baselinekarakteristika med mulig betydning for effekt af behandling, samt mulighed for at patienter og personale kan ræsonnere sig frem til patientens behandling baseret på anfaldsmønstret.

b. Vurdering baseres på 2 studier for berotralstat med meget få patienter, samt et studie for lanadelumab, som også inkluderer meget få patienter.

c. Konfidensintervallet krydser den kliniske beslutningsgrænse og krav til optimal information size er ikke opfyldt.

d. Krav til optimal information size er ikke opfyldt.

e. Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Application for the assessment of Orladeyo for routine prevention of recurrent attacks of hereditary angioedema in adult and adolescent patients aged 12 years and older.

Contents

Application form version 2.1

1. Basic information

Kontaktoplysninger	
Navn	**Luke Robinson**
Titel	General Manager, UK, Ireland & Nordics
Ansvarsområde	All aspects of submission
Telefonnummer	+44 777 377 95 80 (mobile)
E-mail	LRobinson@biocryst.com

Overview of the pharmaceutical	
Proprietary name	Orladeyo
Generic name	Berotralstat
Marketing authorization holder in Denmark	BioCryst Ireland Limited Block 4, Harcourt Centre, Harcourt Road, DUBLIN 2, D02HW77 Ireland
ATC code	B06AC06
Pharmacotherapeutic group	Other haematological agents, drugs used in hereditary angioedema
Active substance(s)	Berotralstat (as dihydrochloride)
Pharmaceutical form(s)	Hard capsules
Mechanism of action	Berotralstat is an inhibitor of plasma kallikrein. Plasma kallikrein is a serine protease that cleaves high-molecular-weight-kininogen (HMWK), releasing bradykinin, a potent vasodilator that increases vascular permeability. In patients with HAE due to C1-INH deficiency or dysfunction, normal regulation of plasma kallikrein activity is impaired, which leads to uncontrolled increases in plasma kallikrein activity and bradykinin release, resulting in HAE attacks consisting of swelling (angioedema).
Dosage regimen	150 mg once daily
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes, legal code BEGR expected (not confirmed)

Overview of the pharmaceutical	
Combination therapy and/or co-medication	Not applicable
Packaging – types, sizes/number of units, and concentrations	28 hard capsules. Each hard capsule contains 150 mg berotralstat (as dihydrochloride).
Orphan drug designation	Not applicable

2. Abbrevations

ACE	Angiotensin-Converting Enzyme
ALT	Alanine Aminotransferase
ARaR	Absolute rate reduction
ARR	Absolute Risk Reduction
AST	Aspartate Aminotransferase
AE-QoL	Angioedema Quality of Life
BL	Base Line
BMI	Body Mass Index
CSR	Clinical Study Report
CENTRAL	Cochrane Central Register of Controlled Trials
C1-INH	C1 esterase inhibitor
CI	Confidence Interval
DMC	Danish Medical Council
EBM	Evidence Based Medicine
EOS	End of Study
FEM	Fixed effect model
HAE	Hereditary Angioedema
HTA	Health Technology Assessment
IQR	Interquartile Range
ITC	Indirect Treatment Comparison
LLN	Lower Limit of the Normal

LCI	Lower Confidence Limit
LSM	Least Squares Mean
LTP	Long Term Prophylaxis
MD	Mean Difference
MCID	Minimal Clinically Important Difference
NA	Not Applicable
NMA	Network Meta-analysis
OR	Odds Ratio
PICOS	Population Intervention Comparison Outcomes Study
p.p.	Percentage points
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RCT	Randomised Controlled Trial
RaR	Rate ratio
RR	Relative risk
SC	Subcutaneous
SLR	Systematic Literature Review
SOC	Standard of Care
SE	Standard Error
TEAE	Treatment-Emergent Adverse Events
TSQM	Treatment Satisfaction Questionnaire for Medication
UK	United Kingdom
US	United States
UCL	Upper Confidence Limit

3. Summary

Purpose: This application to the Danish Medicines Council (DMC) reports the results from a systematic literature research and comparative analysis of berotralstat 150 mg p.o. od. and lanadelumab 300 mg Q2W in routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

Systematic literature research: The systematic literature research (SLR) identified three phase 3 controlled clinical trials studying prevention of HAE attacks by treatment with berotralstat or lanadelumab at the relevant doses. In all three studies, preventive treatment was compared to placebo. 3 publications were included in the comparative analysis. In addition, data was sourced from the European Public Assessment Reports for each product as well as FDA Multidisciplinary Reviews. For berotralstat, previously unpublished results were included in order to provide the information requested in the DMC protocol.[1]

Comparative analyses: No direct comparison of berotralstat and lanadelumab is available. An indirect treatment comparison was carried out using placebo as a common comparator. For berotralstat the combined data from two phase 3, randomized controlled trials (APeX-2 and APeX-J) were used. In sensitivity analyses, the indirect comparison was conducting using only APeX-2 data. Evidence was not available for all outcomes and comparisons requested in the DMC protocol. To the extent possible data were in these cases sourced from the APeX-2 and APeX-J clinical study reports.

Results: The base case indirect comparison was based on data from approximately 6 months of follow from 47 patients treated with berotralstat 150mg, 27 patients treated with lanadelumab 300mg q2w and a total of 87 patient treated with placebo.

The indirect treatment comparison did not show statistically significant differences in attack freedom, health-related quality of life or treatment discontinuation due to adverse events. For the percent reduction over 6 months in the monthly attack rate relative to placebo, lanadelumab 300mg q2w showed a larger reduction compared to berotralstat 150 mg relative to placebo, however the absolute difference was estimated with wide confidence interval and include the minimal clinically relevant difference defined by the DMC.

Sensitivity analyses excluding the APeX-J study from the indirect treatment comparison showed similar comparative results between berotralstat 150 mg p.o. o.d. and lanadelumab 300mg sc 2qw. In the sensitivity analyses, the indirect treatment comparison of AE-QoL responders showed a statistically significant difference in favor of lanadelumab 300 mg q2w, however, no statistical difference in change from base line of the AE-QoL total score was observed.

Comparison of the safety profile of the two treatments showed that both treatments are well-tolerated with mild side-effects. The type of side-effects differs between treatments, with mild gastrointestinal adverse events (occurring mainly in the first months of treatment) with berotralstat 150 mg and injection site reactions with lanadelumab.

Conclusion: Berotralstat is a potent and highly specific small molecule competitive inhibitor of human plasma kallikrein activity and the first oral, targeted therapy for HAE. The SLR and indirect comparison requested by the DMC found that there are no robust data (due to small patient numbers especially on lanadelumab 300mg q2w, different methodology to record HAE attacks in the trials and the short-term horizon) to suggest statistically significant and clinically meaningful differences on any outcome between berotralstat and the current standard of treatment in Denmark.

4. Literature search

A SLR was conducted to identify relevant clinical trials for evidence synthesis of efficacy, safety and HRQoL outcomes. The SLR was conducted in accordance with the DMC protocol [1] and applying the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [2]

Databases and search strategy

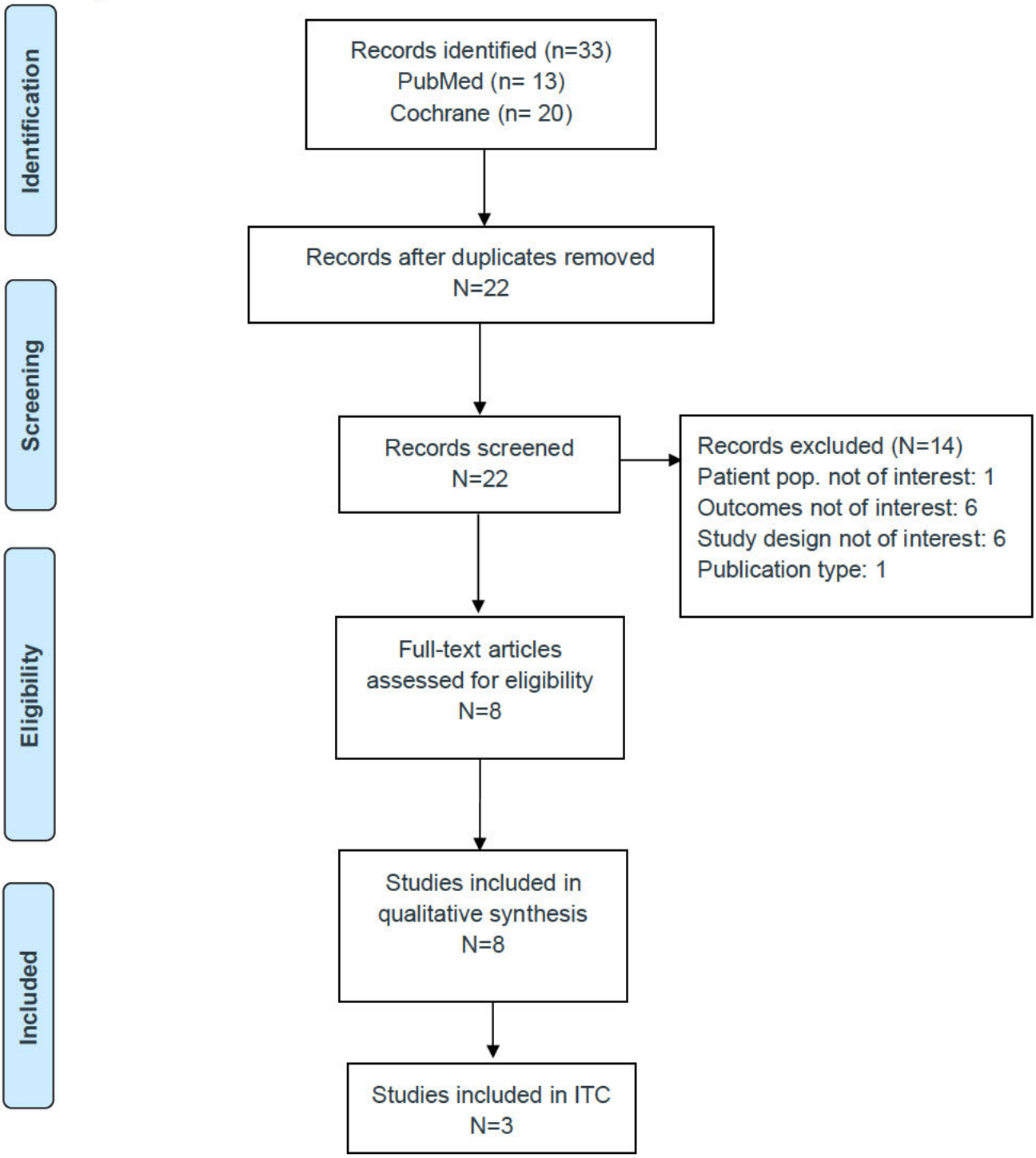
The systematic search was designed to identify randomized controlled trials studying routine prevention of HAE attacks in patients of age 12 or older with berotralstat 150mg o.d. or lanadelumab 300mg Q2W being either intervention or comparator. Details on the search strategy and study selection are provided in appendix A.

Systematic searches for clinical evidence were conducted on 5th April 2021. The databases searched for the clinical SLR included PubMed and CENTRAL (via Cochrane Library) on OVID platform. Details on the search results are shown in appendix A.

The clinical searches yielded 33 records from the electronic literature databases. Following removal of duplicates, there were 22 unique records that were eligible for title and abstract screening. After screening of eight publications retained for full text review, eight publications for five trials were considered eligible for data extraction.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow charts below provide details of the selection process (Figure 1).

Figure 1: PRISMA statement



Abbreviations: ITC, indirect treatment comparison; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Only 3 RCTs (from three publications and two CSRs) were considered for the ITC, since the remaining RCTs/publications did not report any results. Studies with a non-RCT design were not considered eligible for inclusion due to inherent risk of bias and the single-arm, uncontrolled nature of these studies.

The list and details of studies considered for evidence synthesis is provided in section 4.1. Two studies were excluded from ITC.

- APeX-1 (N=77) was a randomised, placebo-controlled, dose response, phase II trial, which evaluated four non-marketed oral doses of berotralstat (62.5 mg, 125 mg, 250 mg, and 350 mg) over four weeks period [3]. As this trial only included non-marketed doses of berotralstat over a short follow-up period of four weeks, the APeX-1 study was not considered for ITC.
- DX-2930-02 (N=37) was a randomised, double-blind, phase I/II trial. Patients were assigned to lanadelumab in sequential subcutaneous dose groups of 30 mg, 100 mg, 300 mg or 400 mg [4]. Due to a short follow-up period of 50 days (7.1 weeks) with primary focus on safety endpoints and the pharmacokinetic profile of lanadelumab, the DX-2930-02 study was not considered for the ITC.

4.1 Relevant studies

Table 1 Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. **Zuraw, Lumry, Johnston, et al.** *Journal of Allergy and Clinical Immunology. 2020*[5]	APeX-2	NCT03485911	February 6, 2018 September 2023
Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: A phase 3 randomized trial. **Ohsawa I, Honda D, Suzuki Y et al**. *Allergy. 2020. DOI: 10.1111/all.14670* [6]	APeX-J	NCT03873116	February 28, 2019 June 2021
Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. **Banerji A, Riedl MA, Bernstein JA et al.** *JAMA. 2018 320(20):2108-2121.*[7]	HELP	NCT02586805	March 3, 2016 April 13, 2017

4.2 Main characteristics of included studies

6.1.1 APeX-2

The APeX-2 (BCX7353-302/ NCT03485911) trial [5] was a phase III, randomised, double-blind, placebo-controlled, parallel-group multicentre trial conducted at 40 sites in 11 countries. Part 1 of the trial, which is reported here, was a 24-week, double-blind evaluation of the efficacy,safety and tolerability of prophylactic berotralstat, 110 mg and 150 mg, administered orally once daily and compared with placebo. Patients were randomised 1:1:1 to receive berotralstat, 110 mg or 150 mg, or placebo administered orally once daily; randomization was stratified by baseline attack rate (≥2 vs <2 attacks per month).

Patients with HAE type 1 or 2 were eligible if aged 12 years or older if living in the United States and Canada, and 18 years or older if living in Europe. A prospective run-in period of up to 70 days was used to determine baseline attack rate. Patients with two or more distinct investigator confirmed HAE attacks requiring treatment or causing functional impairment in the first 56 days of the prospective run-in period were eligible for enrolment. Enrolled patients were required to have access to at least one approved standard of care (SoC) on-demand medication to treat HAE attacks; treatment of attacks followed the patients' usual medical management plan.

The patients in the berotralstat 150 mg group had a lower mean age than patients in the placebo group (40.0 vs 44.5). Female patients constituted 66% of the study sample; 93% of patients were white. The patients in the berotralstat 150 mg group had a higher mean weight (87.6 kg) vs. subjects in the placebo group (84.9 kg). The average baseline attack rate was 3 attacks per month and 75% patients had a history of prophylaxis therapy. Data on HAE attacks were reported by patients and confirmed by investigators.

The primary efficacy endpoint was the rate of investigator-confirmed HAE attacks during the 24-week double-blind treatment period. Investigator-confirmed attack rates were also summarized by month, defined in blocks of 28 days beginning on the first day of dosing. In the berotralstat 150 mg dose group, the rate of HAE attacks was significantly reduced in patients with two or more attacks at baseline (1.76 and 2.92 attacks per month for the 150 mg dose of berotralstat and placebo groups, respectively [P = 0.005]) and patients with fewer than 2 attacks per month at baseline (0.50 and 1.45 attacks per month for the 150 mg dose of berotralstat and placebo groups, respectively [P = 0.009]).

Secondary endpoints were the change from baseline in AE-QoL total scores at week 24, the number and proportion of days with angioedema symptoms through 24 weeks, and the investigator-confirmed attack rates during the effective (steady-state) treatment period (day 8 to end of Part 1).

Exploratory measures included the proportion of responders to the study drug, defined as at least a 50% (prespecified), 70%, or 90% (ad hoc) relative reduction in the rate of investigator-confirmed HAE attacks during treatment compared with the baseline attack rate, proportion of patients with no attacks over 24 weeks (prespecified), and rate of investigator-confirmed HAE attacks treated with on demand medication (prespecified). The rate of on-demand medication use (ad hoc) was also calculated. Satisfaction with treatment was assessed by using treatment satisfaction questionnaire for medication (TSQM scores). Safety outcomes were assessed over the entire treatment period and included the incidence of TEAEs, discontinuations due to TEAEs, serious TEAEs (TESAEs), grade 3 or 4 TEAEs, and grade 3 or 4 laboratory abnormalities.

For further details, see Table A2a in appendix A.

6.1.2 APeX-J

APeX-J (NCT03873116) is a phase III [5], randomised, double-blind, placebo-controlled, parallel- group, 3-part trial conducted in Japan. Patients with a clinical diagnosis of type 1 or 2 HAE underwent a prospective run-in period of 56 days to determine eligibility, allowing enrolment of those with ≥2 expert confirmed angioedema attacks. Patients were randomly assigned (1:1:1) and stratified by baseline attack rate (≥2 vs. <2 expert-confirmed attacks/month between screening and randomization) to receive once-daily berotralstat 110 mg, berotralstat 150 mg, or placebo.

The mean age was 42 years and female patients constituted 84% of the study sample; 94% of patients were Asian. The mean weight was 65 kg. The average baseline attack rate was 2.3 attacks per 4 weeks and 79% patients had a history of prophylaxis therapy. Data on HAE attacks were reported by patients and confirmed by investigators.

The primary efficacy endpoint (the rate of expert-confirmed angioedema events during dosing in the entire 24-week treatment period [Days 1 to 168]) was assessed after the last subject completed Part 1. Berotralstat 150 mg significantly reduced HAE attacks relative to placebo (1.11 vs. 2.18 attacks/ month, p = .003).Secondary endpoints included the number and proportion of days with angioedema symptoms, the rate of expert-confirmed angioedema attacks during dosing in the effective treatment period (steady state, beginning on day 8), and the change from baseline in quality of life at week 24 as assessed by the AE-QoL questionnaire. Exploratory endpoints included the use of on-demand medications to treat angioedema attacks and the proportion of ≥50% responders to study drug. Safety endpoints included TEAEs, TESAEs, grade 3 or 4 TEAEs, grade 3 or 4 laboratory abnormalities, and discontinuations due to TEAEs.

For further details, see Table A2b in appendix A.

6.1.3 HELP

HELP study (DX-2930-03/ NCT02586805) [7] was a randomised, placebo-controlled, parallel-group, phase III trial (N=125). The study compared subcutaneous non-marketed (150 mg every 4 weeks (Q4W)) and marketed doses (300 mg every 4 weeks (Q4W) and 300 mg every 2 weeks (Q2W)) of lanadelumab to placebo over a 26-week period. Patients aged ≥12 years who experienced ≥1 attack per month were included. The mean age was 40.7 years and female patients constituted 70.4% of the study sample; 90.4% of patients were white. The mean weight was 80.7 kg. The average baseline attack rate was 3.9 attacks per 4 weeks and 72% patients had a history of prophylaxis therapy. Data on HAE attacks were reported by patients and confirmed by investigators. The majority of patients had HAE-1 (90.4%), while 9.6% had HAE-2.

The primary endpoint was the total number of investigator confirmed HAE attacks. 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 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 A2c in the appendix.

5. Clinical questions

5.1 What is the value of berotralstat compared to lanadelumab as preventive treatment for patient with hereditary angioedema?

Hvilken værdi har berotralstat sammenlignet med lanadelumab som forebyggende behandling for patienter med arveligt angioødem?

5.1.1 Presentation of relevant studies

The systematic literature search identified no direct comparison to answer the clinical question. Instead, an indirect treatment comparison using Bucher analysis was conducted. The statistical method for the synthesis and indirect treatment comparison are provided in Appendix B.

Consistency with the DMC protocols outcomes of interest considered for the ITC were as follows:

Efficacy	• Attack freedom
	• Distribution of attack severity of break-through attacks*
	  ○ Number of patients reporting at least one laryngeal attack during treatment
	  ○ Relative reduction in monthly rate of moderate/severe HAE attacks
	• Percentage reduction in number of HAE attacks per month

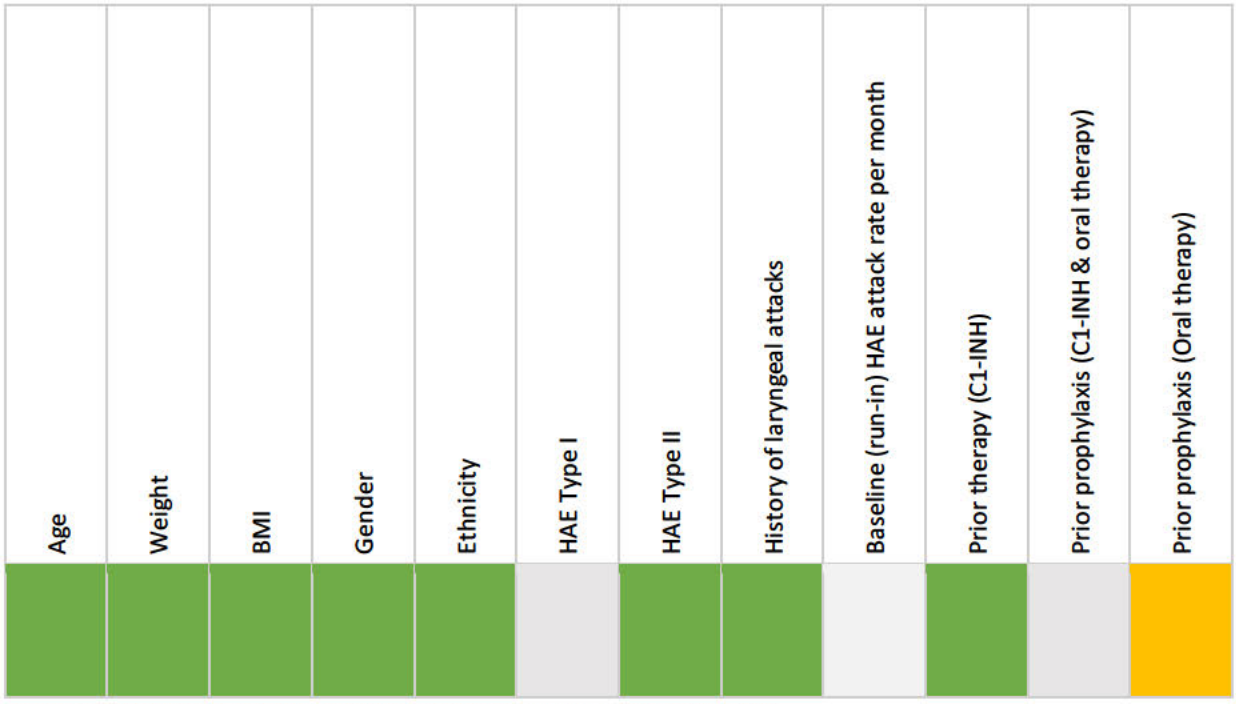
HRQoL	• 6-point improvement in angioedema quality of life questionnaire (AE-QoL) • AE-QoL total score
Safety	• Discontinuation due to treatment-emergent adverse events (TEAEs)

* Distribution of attack severity have not been reported in comparable format for intervention and comparator. Two alternative measures of severity of attack are suggested (number of patients reporting at least one laryngeal attack during treatment and relative reduction in monthly rate of moderate to severe HAE attacks)

The three clinical trials providing results for the indirect treatment comparison are described in section 4.1.1. to 4.1.3 and study characteristics are summarized in Tables A2a through A2c.

5.1.1.1 Differences in patient populations

Heterogeneity was assessed for the main baseline characteristics, an overview is provided in Table 2 categorised by low heterogeneity, heterogeneity and sparse reporting. Histograms for each baseline characteristic are provided in section 8.7.



Green: low heterogeneity, orange: modest heterogeneity, grey: not consistently reported

Heterogeneity was low for most variables except for the baseline (run-in) attack rate and prior therapy. Below are summary descriptions of the heterogeneity assessment for each analysed baseline characteristic:

- *Age, mean (years)*: Age was consistent across all the three included studies [5-7] (Figure B1)
- *Weight, mean (kg)*: Baseline weight was consistent across the BXC7353 studies [5, 6] but not reported in the HELP trial [7] (Figure B2)
- *BMI, mean (kg/m^2)*: BMI was consistent across the included studies [5-7] (Figure B3)
- *Female (%)*: The gender distribution was consistent across the included studies [5-7] (Figure B4)
- *Race (%)*: HELP [7] and APeX-2 [5] studies predominantly included Caucasian patients, whereas APeX-J by nature of its enrolment criteria was conducted exclusively in Asian (Japanese) patients [6] (Figure B5)
- *HAE type*: Only HELP study [7] reported the distribution of HAE type (Figure B6).
- *History of laryngeal attacks (%)*: The proportion of patients with a history of laryngeal attacks at baseline was broadly similar between the APeX-2 [5]and HELP [7] studies, but elevated in APeX-J [6] (Figure B7).
- *Baseline (run-in) attack rate per month*: The attack rate at baseline / during run-in was comparable between berotralstat in APeX-2 and lanadelumab 300mg q2w in HELP, but lower in APeX-J (Figure B8). Notably, the APeX and HELP studies showed different inclusion criterion on the number of baseline attacks per month:
    - *APeX-2*: ≥ 2 investigator confirmed attacks during run-in period of max. 56 days from screening visit [5]
    - *HELP:* ≥ 1 attack per 4 weeks as confirmed during the run-in period [7]
- *Prior prophylaxis (%)*: Included studies differed with respect to prior prophylaxis. APeX-J [6] reported use of oral therapy, while APeX-2 [5] and HELP [7] reported treatment with C1-INH alone or in combination with oral therapy- HELP reported a large proportion of patients not receiving prior long-term prophylactic treatment (Figure B9).

5.1.1.2 Differences in outcome definitions

To assess similarities in outcomes definition, attack definitions and severity rating criteria were compared between trials.

Variation was detected in the time frame specifying a single attack: The APeX-2 trial [5] used 48 hours while the HELP trial used 24 hours[7]. This may entail an underestimation of attack rates in the APeX studies compared to the HELP study.

In the APeX-2 study[5], each subject must have had ≥ 2 HAE attacks during the run-in period of a maximum of 56 days from the screening visit. However, although the inclusion criteria required that subjects should have had a minimum of 2 attacks over the 14 to 56 days of the run-in period to be randomised, some subjects had a baseline attack rate < 1 attack per month. Subjects could have met this inclusion criterion in the 14- to 56-day run-in period, but then had no more attacks in the time between the end of the run-in period and the start of Part 1. In the HELP study[7], each patient must have experienced a baseline rate of ≥1 investigator-confirmed HAE attack per 4 weeks as confirmed during the 4-week run-in period.

In the APeX and HELP studies, attack severity was indicated by the subject in the respective case report form (CRF), with each severity level denoting the following:

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity - some assistance needed
- Severe: Marked limitation in activity, assistance required

In the HELP study, the severity of attacks was reported as the distribution of patients by worst attack severity during follow-up. A similar analysis was not performed in the APeX studies that would allow indirect comparison.

After consultation with the DMC secretariate, it was decided to use the two outcomes "Number of patients with at least one laryngeal attack during treatment" and "Relative reduction in monthly rate of moderate/severe HAE attacks" as a proxy of the "Distribution of attack severity of break-through attacks".

There were also differences in how attack data was collected specifically:

- In the berotralstat studies patients were prompted each day to record signs or symptoms of an attack in an electronic diary. Diary data was automatically uploaded each day and attack data was reviewed by the investigator, who contacted the patient within 48 hrs to review the attack details. In contrast,
- in the lanadelumab study patients or care givers were merely required to notify the site with details of an attack within 72 hrs of onset. According to the published study protocol, study staff solicited information necessary to document an attack. Study staff contacted subjects/ caregivers at pre-specified intervals to solicit for any attacks that may have occurred but were not reported. If desired by the subject, memory aids may have been provided to assist in tracking any HAE attacks subjects experienced.

This significant difference in the collection of the primary endpoint data means that attempts to compare the data between these studies should be treated with caution.

5.1.1.3 Differences in study design

The assessment of differences in study design found that all included studies were double blind, randomised, multicentre, phase III trials (Table A2a to A2a)

In addition, the mix of on-demand therapies permitted in each of the included studies was assessed. Most studies used a similar mix of treatments for management of acute HAE attacks, including C1-INH, conestat alfa, ecallantide, icatibant and tranexamic acid.

5.1.2 Results per study

5.1.2.1 APeX-2

The results per outcome from the APeX-2 study are tabulated in Table A3a. In order meet the request of the DMC protocol, data on several outcomes had to be sourced from unpublished data in the clinical study reports (CSR).

- **Attack freedom:** The number of patients who had 100% reduction in HAE attacks over the 24 weeks was similar across the treatment groups: [redacted] and [redacted] subjects in the berotralstat 150 mg and placebo treatment groups, respectively. Data were sourced from CSR and have not been published.
- **Percentage of patients experiencing an improvement of 6-points from baseline in AE-QoL:** The percentage of patients experiencing an improvement of 6 points from baseline in AE-QoL was comparable across the groups receiving berotralstat 150mg and placebo (berotralstat 150mg: [redacted] vs placebo: [redacted]. The responder rates were based on [redacted] patients in the berotralstat 150 mg arm and [redacted] patients in the placebo arm. If the patients with missing data are counted as non-responders, the resulting responder rates are [redacted] in the berotralstat 150 mg arm and [redacted] in the placebo arm. Data were sourced from CSR and have not been published.
- **Change in QoL assessed by the AE-QoL:** Patients in the group received berotralstat 150 mg showed a higher improvement in mean AE-QoL total score over 24 weeks compared to those receiving placebo, however, the difference was statistically non-significant (mean change (95% CI) in AE-QoL compared with placebo: -4.90 (-12.23, 2.43), $P = 0.188$. [5]

- **Change in attack rate:** At week 24, patients in the group receiving berotralstat 150mg experienced a significantly lower attack rate compared to the group receiving placebo (attack RaR relative to placebo (95% CI): 0.56 (0.41, 0.77); $P < 0.001$) [5]
- **Laryngeal attacks:** The total number of laryngeal attacks was lower in group receiving berotralstat 150 mg [redacted]) compared with the group receiving placebo ([redacted]). Data were sourced from CSR and have not been published.
- **Discontinuations due to TEAEs:** One patient discontinued the treatment due to a TEAEs in both the berotralstat 150mg group as well as the placebo group. [5]

5.1.2.2 APeX-J

The results per outcome from the APeX-J study are tabulated in Table A3b. In order meet the request of the DMC protocol, data on several outcomes had to be sourced from unpublished data in the CSRs.

- **Attack freedom:** [redacted] Data were sourced from CSR and have not been published.
- **Percentage of patients experiencing an improvement of 6 points from baseline in AE-QoL:** A higher number of patients showed an improvement of 6 points in AE-QoL from baseline in the berotralstat 150mg group compared to the placebo group ([redacted] Data were sourced from CSR and have not been published. No patients in the ITT population had missing data.
- **Change in QoL assessed by the AE-QoL:** Patients in the group receiving berotralstat 150 mg showed a higher improvement in mean AE-QoL total score over 24 weeks compared with placebo, however, the difference was statistically non-significant (mean change (95% CI) in AE-QoL compared with placebo: -19.0 (-39.0, -1.0), $P = 0.061$. [6]
- **Change in attack rate:** Patients in group receiving berotralstat 150 mg experienced a significantly lower attack rate compared to those in the placebo group (attack RaR relative to placebo (95% CI): 0.509 (0.325, 0.796); $P = 0.003$)[6]
- **Laryngeal attacks:** The total number of laryngeal attacks was lower in the group receiving berotralstat 150 mg [redacted] compared with the group receiving placebo ([redacted]). Data were sourced from CSR and have not been published.
- **Discontinuations due to TEAEs:** Overall, 17% patients discontinued the treatment due to TEAEs in the placebo group, whereas no patient discontinued treatment in the berotralstat 150 mg group.[6]

5.1.2.3 HELP

The results per outcome from the HELP study are tabulated in Table in the appendix.

- **Attack freedom:** Over the 26-week treatment period, a significantly greater proportion of patients in the lanadelumab treatment groups were attack free compared to the placebo group (44.4% with lanadelumab 300 mg q2w vs 2.4% with placebo).[7]
- **Percentage of patients experiencing an improvement of 6 points from baseline in AE-QoL:** The percentage of patients showing an improvement of 6 points from baseline in AE-QoL was found to be statistically significantly (but the analysis was not pre-specified into the protocol) higher in the group receiving lanadelumab 300mg q2w compared to that receiving placebo (80.77% vs 36.84%, $P = 0.001$). [8] The resulting difference in responder rates is 43.9 percentage points (95% CI: 22.4, 65.5). The responder rates were based on 26 patients in the lanadelumab 300mg Q2W arm and 38 patients in the placebo arm. If the patients with missing data are counted as non-responders, the resulting responder rates are 77.8% in the lanadelumab 300mg q2w arm and 34.1% in the placebo arm and the difference in responder rates 43.6%.
- **Change in QoL assessed by the AE-QoL:** Patients in the lanadelumab 300mg q2w treatment group experienced a significantly higher improvement in mean AE-QoL total score over 26 weeks compared

with patients in the placebo group, with a mean (95% CI) difference of -16.57 (-28.53, -4.62), $P = 0.003$. [7]

- **Change in attack rate:** Statistically significant reductions were observed in the attack rate per month from days 0 through 182; the mean (95% CI) difference in the lanadelumab 300 mg q2w group vs the placebo group was -1.71 (-2.09, -1.33), $P < .001$. The mean (95% CI) RaR for lanadelumab 300 mg q2w relative to placebo was 0.13 (0.07, 0.24), $P < 0.001$. [7]
- **Laryngeal attacks:** Patients in the group receiving lanadelumab 300mg q2w reported a lower number of laryngeal attacks compared to the group receiving placebo (11.1% vs 19.5%). [7]
- **Discontinuations due to TEAEs:** No patients discontinued treatment due to TEAEs in the lanadelumab 300 mg q2w group, compared to one patient in the placebo group.[9]

5.1.3 Comparative analyses

Following the conduct of the feasibility assessment it was concluded that an ITC was methodologically justifiable for the outcomes attack freedom, laryngeal attacks, attack rate, 6-points improvement in AE-QoL, change in AE-QoL total score and discontinuation due to TEAE. This study reports two sets of analyses for each included outcome, one comparing pooled data from APeX-2 and APeX-J with data from HELP, the other comparing APeX-2 and HELP. For some of the outcomes data from the pooled data-sets from APeX-2 and APeX-J were available in the Orladeyo Public assessment report[10] or from unpublished data in the APeX-J clinical study report. The analysis of pooled data was prespecified based on Japanese regulatory requirements. Where pooled data was available, these were used in the ITC, where not available a meta-analysis of the two trials were used (see Appendix B for further method description). Indirect comparison was carried out using Bucher analysis using placebo as the common comparator (see Appendix B for further method description). Sensitivity analyses using APeX-2 data only were performed on all outcomes. Results from the comparison of APeX-2 and HELP are shown in table A4 and in forest plots in Appendix D (Figure D4 and Figure D6 for rate outcomes and continuous outcomes, respectively).

5.1.3.1 Attack freedom

The result of a pairwise meta-analysis of data from APeX-J and APeX-2 studies showed that compared with placebo, berotralstat 150 mg was associated with a higher, non-significant probability of attack freedom [redacted] Figure 2.

Figure 2: Forest plot for attack freedom (APeX-2 and APeX-J)

The result of the Bucher ITC indicated a comparable probability of attack freedom with berotralstat 150 mg and lanadelumab 300 mg q2w (RR [redacted] with the 95% CI crossing unity (i.e. line of no

difference). Table 3 presents the relative and absolute effect estimates with associated 95% CI for the attack freedom outcome as produced by the Bucher ITC, while Figure D1 provide forest plots.

Table 3: Attack freedom – berotralstat 150mg vs lanadelumab 300mg

	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**	
APeX-J APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The pooled RR for APeX-J and APeX-2 studies are synthesized by meta-analysis using fixed effects Mantel-Haenszel method, which was used as an input for calculating RR by ITC using Bucher analysis.

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; ITC, indirect treatment comparison; RR, relative risk

Severity distribution of on-treatment attacks

The DMC have requested information on the distribution of severity of attacks occurring during treatment with the intervention and comparator, respectively. Data on attack severity was collected in all three studies. In the HELP study, data on the distribution based on worst severity of attack during the follow-up have been reported [7] Similar analyses have not been performed in the APeX-2 or APeX-J studies.

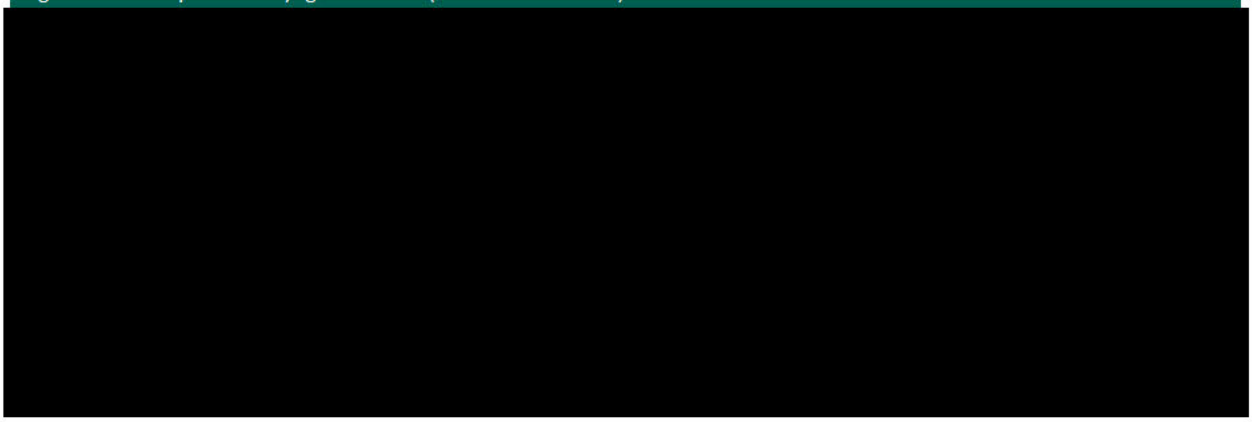
To provide insight into the severity of on-treatment attacks, two analyses were carried out after consultation with the DMC. In the first analysis the proportion of patient reporting at least one laryngeal attack during the treatment follow-up was compared. This analysis is reported below. Secondly, the reduction in the rate of attacks classified as moderate/severe was compared. This analysis is reported in section 5.1.3.4.

Proportion of patients suffering laryngeal attacks on treatment

Data from the studies included in analysis showed a lower number of laryngeal attacks in groups receiving lanadelumab 300 mg q2w or berotralstat 150 mg compared with placebo [7, 11, 12].

Pairwise meta-analysis of data from APeX-2 and APeX-J showed a comparable risk of laryngeal attacks for berotralstat 150 mg versus placebo [redacted] Figure 3.

Figure 3: Forest plot for laryngeal attacks (APeX-2 and APeX-J)



The result of the Bucher ITC indicated a comparable risk of laryngeal attacks with berotralstat 150 mg and lanadelumab 300 mg q2w (Table 4 shows the relative and absolute effect estimates with associated 95% CI for the outcome of laryngeal attacks as produced by the Bucher ITC, while Figure D1 show the forest plot. Sensitivity analysis based on APeX-2 and HELP only are shown in Table A4 and Figure D2 (forest plots). The sensitivity analysis gave a similar RR of laryngeal attacks (berotralstat 150 mg compared to lanadelumab 300mg q2w).

Table 4: Laryngeal attacks – berotralstat 150mg vs lanadelumab 300mg

	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**	
APeX-J APeX-2 HELP							The pooled RR for APeX-J and APeX-2 studies are synthesized by meta-analysis using fixed effects Mantel-Haenszel method, which was used as an input for calculating RR by ITC using Bucher analysis. ARR calculated from RR using % patients having at least one laryngeal attack in the lanadelumab 300mg Q2W arm of the HELP study (11.1%)

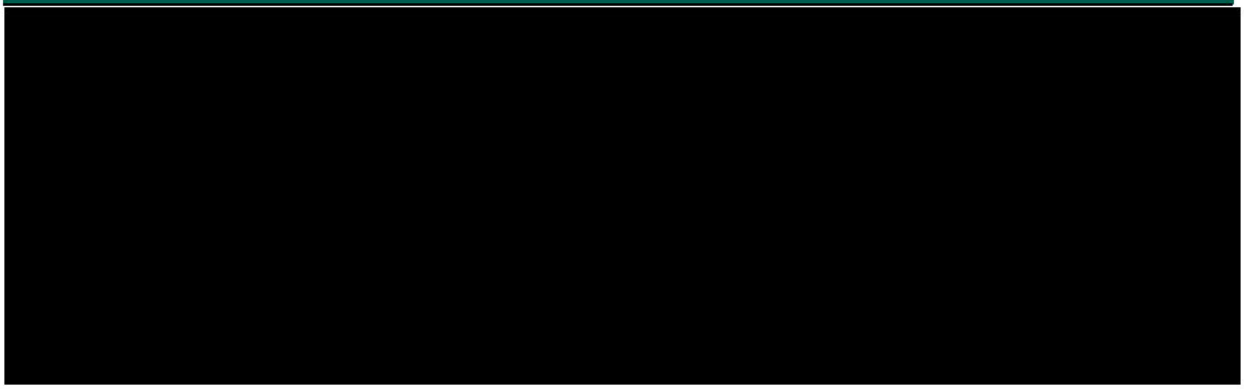
Abbreviations: ARR, absolute risk reduction; CI, confidence interval; ITC, indirect treatment comparison; RR, relative risk

5.1.3.2 Percentage of patients showing an improvement of 6 points from baseline in AE-QoL

In the APeX-2 and HELP study the response rates for the AE-QoL reported were based on patients with complete data (Table A3a, Table A3c). In the ITC, the response rates were calculated based on the ITT population, i.e., assuming that patients with missing data on the AE-QoL instrument are non-responders.
A higher percentage of patients achieved a 6-point improvement in AE-QoL with berotralstat 150 mg or lanadelumab 300 mg q2w compared with placebo [7, 11, 12].

The direct comparison of berotralstat 150 mg and placebo via the pairwise meta-analysis resulted in an RR of [redacted] with corresponding 95% CI of [redacted], indicating a comparable probability of patients achieving a 6-point improvement in AE-QoL with berotralstat 150 mg and placebo (Figure 4).

Figure 4: Forest plot for 6-point improvement in AE-QoL (APeX-2 and APeX-J)



The indirect comparison of berotralstat 150 mg and lanadelumab 300 mg q2w via the Bucher method resulted in an RR of [redacted] with corresponding 95% CI of [redacted] indicating a comparable probability of patients achieving a 6-point improvement in AE-QoL with berotralstat 150 mg lanadelumab 300 mg q2w. Table 5 shows the ARR and RR with associated 95% CI, while Figure D1 show the forest plot from the Bucher ITC. In the sensitivity analysis excluding APeX-J, the RR was estimated at [redacted] (95% CI: [redacted] (Table A4 and Figure D2) indicating a difference in relative effect in favour of lanadelumab 300 mg q2w. It should be noted that the placebo-arm response rate in APeX-2 was high (58%) compared to both HELP (37%) and APeX-J (17%), which questions the reliability of the finding.

Table 5: 6-point improvement in AE-QoL – berotralstat 150mg vs lanadelumab 300mg

	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**	
APeX-J APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Denominator in response rate based on ITT (patients with missing AE-QoL data classified as non-responder) RR for APeX-J and APeX-2 studies synthesized by meta-analysis using fixed effects Mantel-Haenzel method, which was used as input for RR of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method. ARR calculated from RR using % responders in the lanadelumab 300mg Q2W arm of the HELP study (77.8%)

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; ITC, indirect treatment comparison; RR, relative risk

5.1.3.3 Change in QoL assessed by the AE-QoL

AE-QoL total score was improved in patients receiving lanadelumab 300 mg q2w or berotralstat 150 mg compared with placebo in all included studies [5-7].

The indirect comparison of lanadelumab 300 mg q2w and berotralstat 150 mg via the Bucher method showed a lower, but statistically not significant mean relative change in AE-QoL total score from baseline to end of study with berotralstat 150 mg compared to lanadelumab 300 mg (mean difference: -9.13, 95% CI [-22.92, 4.66]. Table 6 shows the mean difference with associated 95% CI for change from baseline to end of study in AE-QoL total score, while Figure D5 show the forest plots. In the sensitivity analysis excluding APeX-J the estimated mean difference was MD: -11.67 (95% CI: -25.69, 2.35; p-value 0.10) (Table A4 and Figure D6). This supports that there is not statistically significant difference in change in QoL between berotralstat 150mg and lanadelumab 300mg q2w.

Table 6: Change from BL to EOS in AE-QoL total score – berotralstat 150mg vs lanadelumab

	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**	
APeX-J APeX-2 HELP	MD: -9.13	-22.92, 4.66	0.19	NA	NA	NA	The pooled MD from APeX-J and APeX-2 studies was used as an input for calculating MD by ITC using Bucher analysis.

Abbreviations: CI, confidence interval; ITC, indirect treatment comparison; MD, mean difference; NA, not applicable

5.1.3.4 Change in attack rate

The studies included in the ITC showed a statistically significant higher percentage reduction in the monthly attack rate with berotralstat 150 mg and with lanadelumab 300 mg q2w compared with placebo [5, 7, 12].

The indirect comparison of berotralstat 150 mg and lanadelumab 300 mg q2w using the Bucher method resulted in a rate ratio (RaR) of 4.18 with corresponding 95% CI of 2.12 to 8.25 (p<0.001), indicating that berotralstat 150 mg is associated with a higher attack rate relative to lanadelumab 300 mg q2w. Table 7 shows the RaR and difference in percentage rate reduction (Δ%RaR) estimates with associated 95% CI for percentage change in attack rate, while Figure D1 shows the forest plots from the Bucher ITC. Using the percentage attack rate difference to placebo in HELP as comparator outcome, the Δ%RaR with berotralstat is 41.4 percentage points lower compared to lanadelumab. The confidence interval includes 15 percentage point defined as the clinically relevant difference in the DMC protocol.

Table 7: Attack rate reduction – berotralstat 150mg vs lanadelumab 300mg q2w

	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**	
APeX-J APeX-2 HELP	Δ%RaR: -41.4 p.p.	-94.2, -14.6	<0.001	RaR: 4.18	2.12, 8.25	<0.001	The pooled RaR for APeX-J and APeX-2 studies reported in APeX-J CSR was used as an input for calculating RaR by ITC using Bucher analysis. Δ%RaR calculated from the % change in attack rate in the

	lanadelumab 300mg q2w arm of the HELP study (87%)

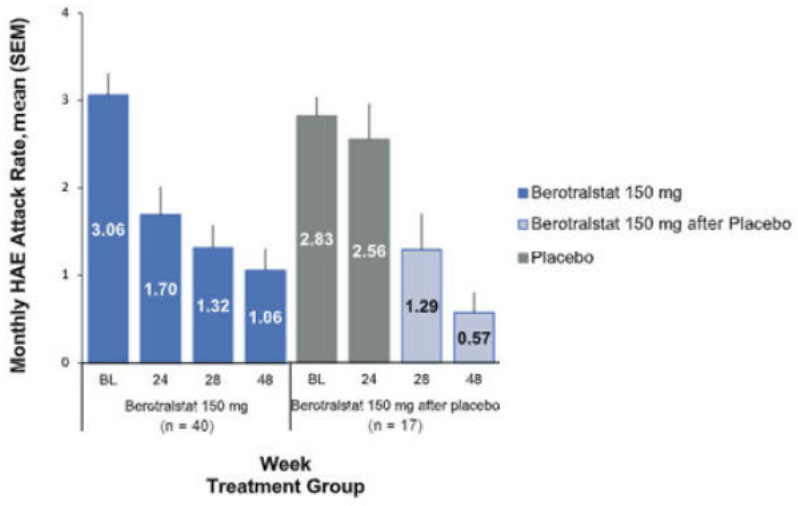
Abbreviations: Δ%RaR, difference in percent rate reduction; CI, confidence interval; ITC, indirect treatment comparison; RaR, rate ratio; p.p. Percentage points

The absolute difference in attack rates per month may be calculated from the lanadelumab 300 mg q2w arm in HELP (0.27 attacks per month). Applying the rate ratio (and 95% CI limits) from the ITC, the difference was estimated at 0.83 attacks per month (95% CI: 0.29 to 1.88).

As indicated in the DMC protocol, the existing placebo-controlled trials have a relative short follow-up relative to the variation in attack rates. For the benefit of the DMC assessment, Biocryst below provides information on the attack rate over the long-term follow-up in APeX-2 (part 2 and part 3).

Figure 5 shows the results from part 2 (48 weeks follow-up) in APeX-2. Among patients who completed 48 weeks of treatment, mean attack rates declined by 67% from baseline to week 48 in the berotralstat 150mg group. In part 2 of the study, the reduction in attack rates observed in part 1 continued or declined further. The decrease in attack rate observed in part 2 demonstrates a clear durability of response to treatment. Among patients who were rerandomized from placebo to berotralstat, the mean monthly attack rate declined and remained consistently low through the 24 weeks of berotralstat therapy (150 mg) in part 2 (week 48: 0.57 attacks/month).[13]

Figure 5 Mean (standard error of the mean) investigator-confirmed HAE monthly attack rates at baseline (BL), 24 weeks, 28 weeks and 48 weeks by treatment arm

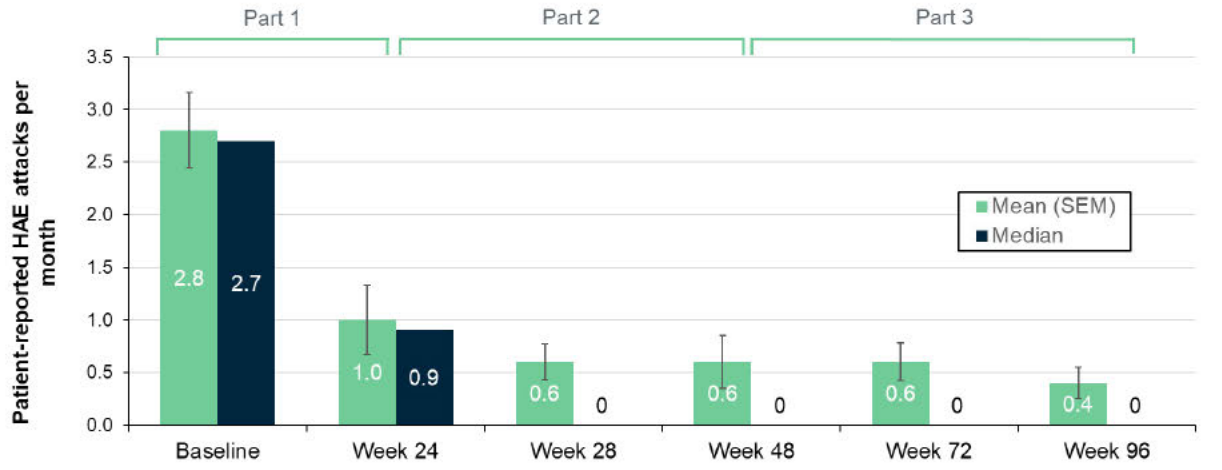


Abbreviations: BL, baseline; SEM, standard error of the mean.

Error bars represents the SEM. Attack rates for the 4 weeks preceding each visit. Adapted from Wedner et al. (2021)[13]

The adjusted mean monthly attack rates at week 96 for patients who completed 96 weeks of treatment with berotralstat 150 mg was 0.35 (SEM: 0.69). These data illustrate that the monthly attack rates were maintained and improved over time (Figure 6).

Figure 6 Adjusted attack rates per month through week 96 - berotralstat 150 mg (mean (SEM) and median)



Monthly Attack Rate is defined as the total number of adjusted HAE attacks experienced during the treatment period adjusted for the length of a month (defined as 28 days) and the number of days the subject was on treatment during that month. The end of Month 6 is defined as the start of Part 2 treatment or the end of Part 1 treatment if the subject does not continue to Part 2. Month 7 is defined as beginning on the day after the end of Month 6 and continuing through Day 196. Remaining months (8 and up) are defined as 28 day intervals. An adjusted attack must include at least 1 symptom of swelling; have a response to the diary question, 'In retrospect, could there be an alternative explanation for your symptoms other than an HAE attack (ie, allergic reaction, viral cold, etc)?' of 'no'; must be unique (attack begins > 24 hours from end of the prior attack), otherwise the event will be combined with and treated as a continuation of the preceding attack; and, if untreated, attack must have a duration > 24 hours. The adjusted attack rate is defined as the total number of adjusted HAE attacks experienced in the period of interest adjusted for the length of a month (defined as 28 days) and the number of days during that period. Data cutoff from February 2021 on patients who have completed 96 weeks of treatment.

Source: Adapted from graph presented at the July 2021 EACCI conference by Kiani et al.

Rate of moderate or severe attacks

To provide further information on the on-treatment attack severity, a sensitivity analysis was performed whereby the percentage reduction in monthly rate of attacks of moderate/severe severity.

APeX-2 and HELP studies showed a lower rate of moderate or severe attacks with berotralstat 150 mg or lanadelumab 300 mg q2w compared with placebo [7, 11].

The indirect comparison of berotralstat 150 mg and lanadelumab 300 mg q2w via the Bucher method resulted in a RaR [redacted] with corresponding 95% CI of [redacted] indicating that the treatment effect on attack of moderate/severe severity is at a similar level to the overall treatment effect on overall attack rate (RaR: 4.18; Table 7). Together with the analysis of proportion of patients reporting laryngeal attacks this supports that the treatments impact on attack severity distribution are similar for berotralstat 150 mg and lanadelumab 300 mg q2w. The conclusion is supported by the sensitivity analysis where APeX-J data was excluded.

Table 8 shows the RR and ARaR estimates with associated 95% CI for percentage change in attack rate, while Figure D3 and Figure D4 show the forest plots from the Bucher ITC for the base case analysis of (APeX-2; APeX-J and HELP) and the sensitivity analysis (APeX-2 and HELP), respectively.

Table 8: Rate of moderate or severe attacks – berotralstat 150mg vs lanadelumab 300mg

	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**	
APeX-J APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The pooled RaR for APeX-J and APeX-2 studies was used as an input for calculating RR by ITC using Bucher analysis. ARaR calculated from the % change in attack rate in the lanadelumab 300mg q2w arm of the HELP study (83%)

Abbreviations: ARaR, absolute rate reduction; CI, confidence interval; ITC, indirect treatment comparison; RaR, rate ratio; p.p. Percentage points

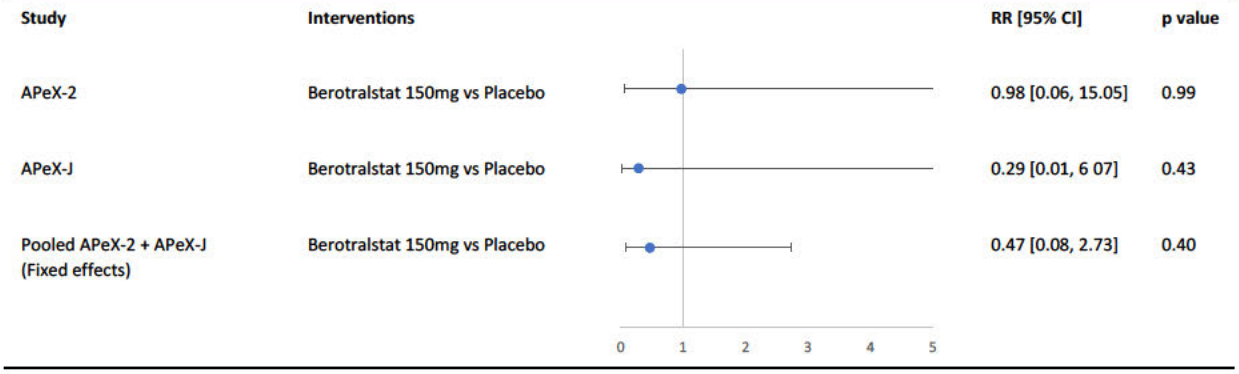
The absolute difference in moderate to severe attacks rates may be calculated from the lanadelumab 300 mg q2w attack rate/ month (0.2) and the RaR (and 95% CI) from the ITC. The estimated difference in moderate/severe attacks/ month was estimated at [redacted]

5.1.3.5 Discontinuations due to TEAEs

In the APeX-J [6] and HELP studies, the number of patients discontinuing treatment due to TEAE were found to be lower in berotralstat 150 mg and lanadelumab 300 mg q2w, respectively, compared to placebo [5, 6]. In APeX-2, the same number of patients discontinued treatment due to TEAE with berotralstat 150 mg and placebo [7].

Pairwise meta-analysis of data from APeX-J and APeX-2 studies showed a lower, non-significant probability of discontinuation due to TEAE with berotralstat 150 mg than placebo (RR: 0.47, 95% CI [0.08, 2.73]), Figure 7. Note that the meta-analysis was performed after using Haldane-Anscombe correction for zero events in the APeX-J trial.

Figure 7: Forest plot for discontinuation due to adverse events (APeX-2 and APeX-J)



The indirect comparison of berotralstat 150 mg and lanadelumab 300 mg q2w via the Bucher method suggests a comparable probability of discontinuation due to TEAE with berotralstat 150 mg and lanadelumab 300 mg q2w (RR: 0.94, 95% CI [0.03, 35.17]). The ITC was carried out after Haldane-Anscombe correction for zero-events in APeX-J and HELP. Table 9 shows the RR and ARR estimates with associated 95% CI for the % of patients discontinuing treatment due to TEAE, while Figure D1 show the forest plot. The ARR was calculated using an assumed comparator rate of 1.8% (the observed rate in the lanadelumab 300 2qW arm in HELP was 0%).

Table 9: Discontinuation due to adverse events – berotralstat 150mg vs lanadelumab 300mg

	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**	
APeX-J APeX-2 HELP	ARR: -0.1 p.p.	-1.7, 61.0	0.97	RR: 0.94	0.03, 35.17	0.97	RR for APeX-J and APeX-2 studies synthesized by meta-analysis using fixed effects Mantel-Haenszel method, which was used as input for RR of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method. Haldane-Anscombe correction applied to APeX-J and HELP datasets in the calculation of RR. ARR calculated from RR using an assumed comparator rate of 1.8%.

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; ITC, indirect treatment comparison; RR, relative risk

5.1.3.6 Safety profiles

Summaries of safety profiles from two products SmPCs are listed in Table 10. For berotralstat, the main adverse events associated with treatment are abdominal pain, diarrhoea and headache. Gastrointestinal abdominal TEAEs were generally grade 1 or 2 and self-limited. Events of vomiting, diarrhea, or abdominal pain had a median duration of 2 days in the 150-mg of berotralstat arm (95% CI: 1.0;7.0) versus 1 day in the placebo arm (95% CI: 0.0;7.0). [5] Gastrointestinal abdominal TEAEs occurred primarily within the first month of treatment. [5]

For lanadelumab the most commonly observed adverse event was injection site reaction. Most of these were recorded as mild intensity. Hypersensitivity reactions (pruritus, discomfort and tingling of tongue) were observed in patients treated with lanadelumab with an incidence of 1.2%. Further discussion of adverse events from the public assessment report risk-benefit assessment in each product's public assessment reports may be found in Appendix C (Table C1).

Table 10 Summary of safety profiles as per product SmPCs

Berotralstat (Orladeyo)	Lanadelumab (Takhzyro)
The most common adverse reactions are abdominal pain (all locations) (reported by 21% of patients) and diarrhoea (reported by 15% of patients). These events were reported primarily in the first 1-3 months of Orladeyo use (median day of onset was day 66 for abdominal pain and day 45 for diarrhoea) and resolved without medicinal product while Orladeyo treatment was continued. Almost all events (99%) of abdominal pain were mild or moderate with a median duration of 3.5 days (95% CI 2-8 days). Almost all events (98%) of diarrhoea were mild or moderate with a median duration of 3.2 days (95% CI 2-8 days).	The most commonly (52.4%) observed adverse reaction associated with TAKHZYRO was injection site reactions (ISR) including injection site pain, injection site erythema and injection site bruising. Of these ISRs, 97% were of mild intensity, 90% resolved within 1 day after onset with a median duration of 6 minutes. Hypersensitivity reaction (mild and moderate pruritus, discomfort and tingling of tongue) was observed (1.2%),

Abbreviations: CI confidence intervals; ISR injection site reaction

Sources: Product SmPC[14, 15]

5.1.3.7 Conclusion

The base case indirect comparison was based on data from approximately 6 months of follow from 47 patients treated with berotralstat 150mg, 27 patients treated with lanadelumab 300mg q2w and a total of 87 patient treated with placebo.

The indirect treatment comparison did not show statistically significant differences in attack freedom, health-related quality of life or treatment discontinuation due to adverse events. For the percent reduction over 6 months in the monthly attack rate relative to placebo, lanadelumab 300mg q2w showed a larger reduction compared to berotralstat 150 mg relative to placebo, however the absolute difference was estimated with wide confidence interval and include the minimal clinically relevant difference defined by the DMC.

Sensitivity analyses excluding the APeX-J study from the indirect treatment comparison showed similar comparative results between berotralstat 150 mg p.o. o.d. and lanadelumab 300mg sc 2qw. In the sensitivity analyses, the indirect treatment comparison of AE-QoL responders showed a statistically significant difference in favor of lanadelumab 300 mg q2w, however, no statistical difference in change from base line of the AE-QoL total score was observed.

Comparison of the safety profile of the two treatments showed that both treatments are well-tolerated with mild side-effects. The type of side-effects differs between treatments, with mild gastrointestinal adverse events (occurring mainly in the first months of treatment) with berotralstat 150 mg and injection site reactions with lanadelumab.

Due to small patient numbers (especially on lanadelumab 300mg q2w), different methodology to record HAE attacks in the trials and the short-term horizon there is limited data that could robustly estimate statistically significant and clinically meaningful differences on any outcome between berotralstat and the current standard of treatment in Denmark.

6. Additional information

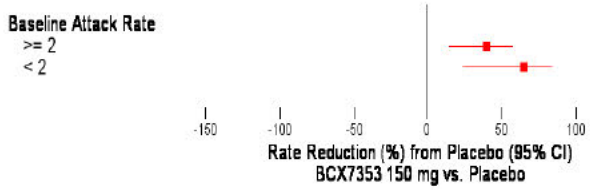
6.1 Outcomes by subgroups

The DMC protocol request data (for berotralstat and lanadelumab) based on subgroups of patients with less than 2 and 2 or more attack per month at base line, respectively. For lanadelumab no results by these subgroups were located. Instead, the RaR by subgroups '1 ≤ rate <2', '2≤ rate <3' and 'rate ≥ 2' were presented in the Takhzyro public assessment report. Note furthermore that in HELP patients with an base-line attack rate of less than 1 per month were excluded, while in the APeX-2 trial patient could have less than one qualifying attack per month (range from 0.86 to 6.67)[10]. These differences prohibit a formal ITC in the subgroups.

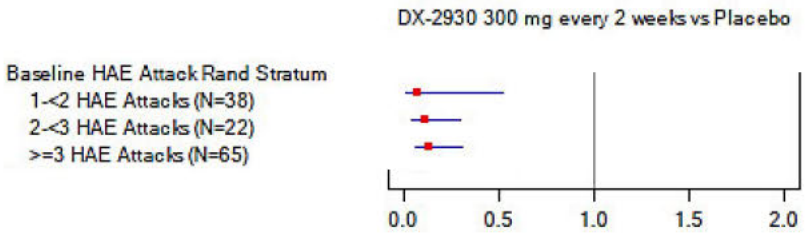
Figure 8 show the subgroup analysis of reduction of attack relative to placebo by subgroup from the APeX-2 (Upper panel) and HELP study (Lower panel), respectively.

Figure 8 Subgroup analysis of reduction in attack rate by baseline attack rate from APeX-2 and HELP

APeX-2 (Investigator-confirmed HAE attack. Entire dosing period. Percent rate reduction. ITT Population)



HELP* (Rate Ratio on Number of Investigator-Confirmed HAE Attacks by Subject Subgroups-ITT Population)



Abbreviations: BCX7353 Berotralstat; CI confidence interval; DX-2930 Lanadelumab; HAE Hereditary Angioedema; ITT intention to treat.

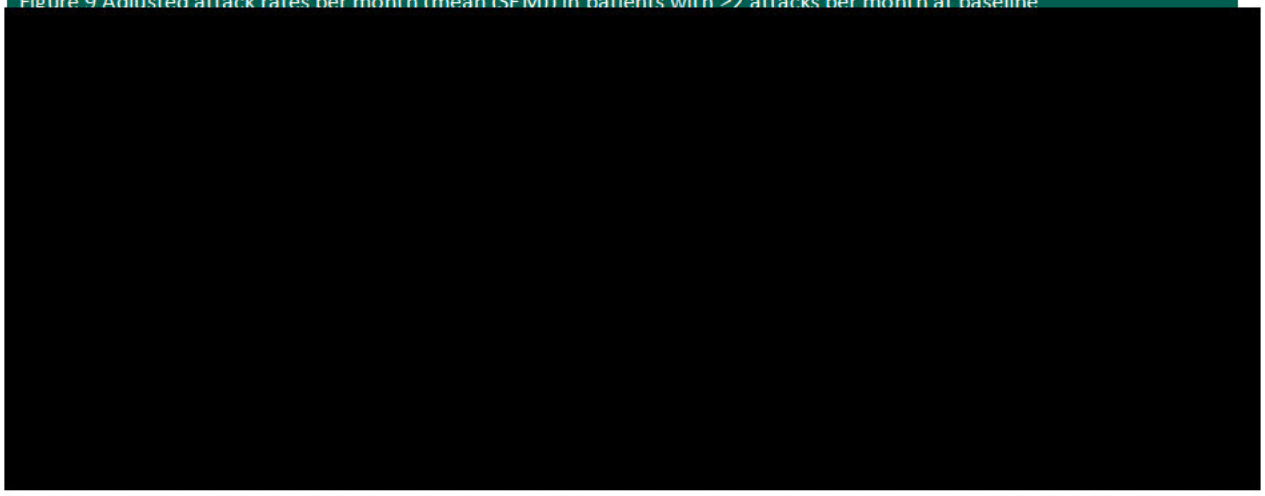
* Patient numbers per strata shown are for the entire ITT population across all 4 arms.

Source. Public assessment reports for Orladeyo (p 94)[10] and Takhzyro (p 50), respectively. [9]

The subgroup analyses show that for both treatments the relative efficacy compared to placebo is numerically lower in patients with a higher attack rate but with overlapping confidence intervals suggesting that the differences are not statistically significant with either treatment compared to placebo.

The maintenance and improve over time in the long-term follow-up of APeX-2 for the overall population (Figure 6) was also observed in patients with a base-line attack rate of 2 or more per month (Figure 9).

Figure 9 Adjusted attack rates per month (mean (SEM)) in patients with >2 attacks per month at baseline



Monthly Attack Rate is defined as the total number of adjusted HAE attacks experienced during the treatment period adjusted for the length of a month (defined as 28 days) and the number of days the subject was on treatment during that month. The end of Month 6 is defined as the start of Part 2 treatment or the end of Part 1 treatment if the subject does not continue to Part 2. Month 7 is defined as beginning on the day after the end of Month 6 and continuing through Day 196. Remaining months (8 and up) are defined as 28 day intervals. Data cutoff from October 2020 on the ITT population.

Source: Biocryst data on file

6.2 Patient compliance with treatment

The DMC have requested information on compliance to berotralstat treatment from the clinical trial program or from other experience with berotralstat treatment. Furthermore, data on reasons to non-compliance are requested.

Table 11 presents an overview of the study drug compliance in the phase 2/3 prophylactic long-term studies. In placebo-controlled phases up to six months, the overall mean compliance with berotralstat 150 mg o.d. was similar to placebo (96.5; SD 8.35) on berotralstat compared (97.0; SD 7.51) to placebo. 89.0% had a calculated drug compliance over 90% on berotralstat 150 mg compared to 87.2% on placebo. Study drug compliance was good through week 48 with a mean (SD) compliance of 96.2 (7.91); 125 of 148 subjects (84.5%) had a calculated compliance between 90% and 110%. This finding was supported by the ongoing open-label, non-randomised safety study in patients aged 12 years and older who received 110 mg or 150 mg berotralstat (NCT03472040). Patients included in the APeX-S study were centrally allocated to receive open-label berotralstat 110 mg or 150 mg. At the time of the interim analysis, a total of 100 patients received berotralstat 110 mg and 127 received 150 mg. Patients were enrolled at 49 sites in 22 countries across the United States, Europe, Israel, Asia, Australia, New Zealand, and South Africa.[16] Over the 48 weeks of treatment, treatment compliance with study drug was high (95% (±9.4)) [16] and similar to the APeX-2 trial in Table 11.

Reasons for non-compliance during berotralstat or placebo treatment has not been studied.

Table 11 Summary of compliance (Phase 2/3 Prophylactic Long-term Studies Safety Population)

	Week 24 overall compliance (%)		Week 48 overall compliance (%)
	Berotralstat 150 mg (N = 184)	Placebo (N = 39)	Berotralstat 150 mg (N = 184)
N	181	39	148
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Compliance was defined as the number of capsules taken/the number expected to be taken multiplied by 100. Day 1 to Week XX was the overall compliance calculated for the interval between Day 1 and the date of the Week XX visit (where XX = 24 or 48) for subjects who discontinued study or completed dosing in that interval. The compliance calculation does not adjust for protocol-allowable drug interruptions.

The results above are previously unpublished data submitted to EMA. Integrated Summary of Clinical Safety, Table S.3.3

6.3 Dosing

In the DMC protocol, Biocryst has been requested to provide information on dose escalation above the recommended dose of 150mg OD during treatment with berotralstat in periods where the patient experience temporarily increased attack frequency.

The hypothesis raised by the DMC is valid but has not been studied. BioCryst cannot recommend any use of berotralstat other than the approved recommended dose of 150 mg p.o. o.d and as per the SmPC and package leaflet, patients are instructed not to take more than one dose per day.[15] Furthermore, in a phase 2 dose finding study (APeX-1), dosages of up to 350 mg o.d. have been tested. Although kallikrein inhibition increases with higher dosing, the attack rate was uncorrelated to kallikrein inhibition at dosages above 125 mg o.d. (Orladeyo Public Assessment Report p 83[10])

7. References

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8. Appendices

Appendix A. Literature search and reported results
Appendix B. Details on the indirect treatment comparison
Appendix C. Summary of unfavourable effects from EPAR risk-benefit assessment
Appendix D. Forest plots from ITC

Appendix A Literature search and reported results

8.1 Literature search

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

Table A1 Inclusion and exclusion criteria

Inclusion criteria	**Population:** Children ≥ 12 years and adults with HAE type I or II **Intervention(s):** BCX7353 150 mg po once daily **Comparator(s):** Lanadelumab 300 mg SC every 2 weeks **Outcomes:** • Attack freedom/ 100%-reduction in attack rate • Severity of on-treatment HAE attacks • % change in attack rate • 90% reduction in attacks rate • % patients achieving 6-point improvement in AE-QoL • Change from BL to EOS in AE-QoL total score • % patients discontinuing treatment due to side-effects **Study design:** RCTs
Exclusion criteria	**Population:** Publications reporting on patient populations in the following categories: • Patients without HAE type I or II • Paediatric patients (aged <12 years) • Patients not indicated for long-term prevention treatment of HAE attacks **Intervention(s):** • Treatments indicated for acute treatment • Publications that do not report data specific to included interventions **Comparator(s):** NA **Outcomes**: Publications that do not report data specific to included outcomes **Study design**: • Uncontrolled clinical trials • Prospective non-randomized controlled interventional studies • Prospective longitudinal observational studies • Retrospective longitudinal observational studies • Cross-sectional studies • Economic models and trial-based economic analyses • Animal studies • In vitro/ex vivo studies

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Table A1 Inclusion and exclusion criteria	
	Publications types: • Case studies • Case reports • Editorials • Letters **Other search limits or restrictions applied:** None

Abbreviations: AE-QoL, Angioedema quality of life questionnaire; BL, baseline; EOS, end of study; HAE, hereditary angioedema; MCID, minimal clinically important difference; RCT, randomized controlled trials; SLR, systematic literature review

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8.1.1 PubMed Search Strategy

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

Search number	Query	Results
1	"Angioedemas, Hereditary"[Mesh]	1,181
2	(C1[tiab] AND Inhibitor*[tiab] AND Deficienc*[tiab]) or (hereditary[tiab] AND (edema*[tiab] or oedema*[tiab] or angioedema*[tiab] or angiooedema*[tiab]))	3,585
3	#1 OR #2	3,674
4	prophyl*[tiab] OR prevent*[tiab]	1,637,591
5	#3 AND #4	709
6	Berotralstat[nm] OR berotralstat[tiab] OR BCX7353[tiab]	6
7	lanadelumab[nm] OR DX-2930[tiab] OR Takhzyro[tiab] OR lanadelumab[tiab]	50
8	#6 OR #7	56
9	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans [mh])	1,299,649
10	#5 and #8 and #9	13

Search was conducted on 5th April 2021

8.1.2 Cochrane Search Strategy

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

ID	Search	Hits
#1	([mh "Angioedemas, Hereditary"]) (Word variations have been searched)	118
#2	(C1 and Inhibitor* and Deficienc*):ti,ab,kw	89
#3	(hereditary and (edema* or oedema* or angioedema* or angiooedema*)):ti,ab,kw or angioneurotic edema:kw	817
#4	[#1-#3]	822
#5	(prophyl* or prevent*):ti,ab or prophylaxis:kw	177556
#6	#4 and #5	271
#7	(berotralstat or BCX-7353 or BCX7353 or orladeyo*):ti,ab,kw	43
#8	(DX-2930 or Takhzyro or lanadelumab):ti,ab,kw	59
#9	#7 or #8	102
#10	#6 and #9	81

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#11	("conference abstract" or review):pt or NCT*:au	397532
#12	#10 not #11	20

Search was conducted on 5th April 2021

8.1.3 Selection of studies

A summary the selection of full-text publications (N=8) are shown below.

Only 3 RCTs (from three publications and two CSRs) were considered for the ITC, since the remaining RCTs/publications did not report any results or where linked to primary publications. Studies with a non-RCT design were not considered eligible for inclusion due to inherent risk of bias and the single-arm, uncontrolled nature of these studies.

#	Author year	Trial acronym	Include/ Exclude	Reason for exclusion
1	Aygören-Pürsün 2018	APeX-1	Exclude	No marketed doses
2	Banerji 2017	DX-2930-02	Exclude	Phase I/II trial with short follow-up
3	Banerji 2018	HELP	Include	
4	Euctr G. B.	HELP (EUCTR)	Exclude	EUCTR reference for HELP trial, hence linked to HELP in data extraction sheet, not extracted
5	Jprn Umin	APeX-J (Jprn Umin)	Exclude	Jprn Umin reference for APeX-J trial, hence linked to APeX-J in data extraction sheet, not extracted
6	Ohsawa 2020	APeX-J (Jprn Umin)	Include	
7	Riedl 2020	HELP	Exclude	Exploratory analysis of HELP trial
8	Zuraw 2020	APeX-2	Include	

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8.2 Main characteristics of included studies

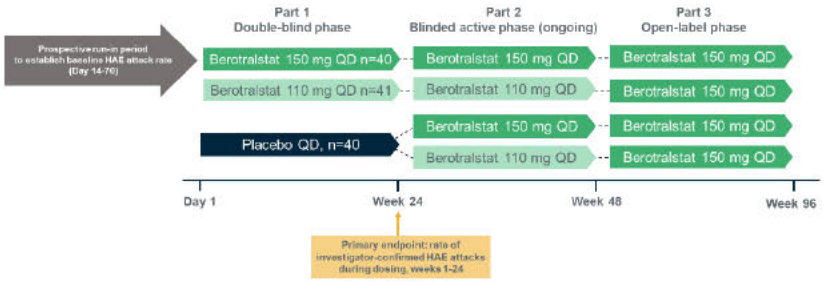
Table A2a Main study characteristics	
Trial name	APEX-2
NCT number	NCT03485911
Objective	To determine the efficacy, safety, and tolerability of berotralstat in patients with HAE
Publications – title, author, journal, year	*Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial.* **Zuraw, Lumry, Johnston, et al.** Journal of Allergy and Clinical Immunology. 2020[5]
Study type and design	APEX-2 is a phase 3, randomized, double blind, placebo-controlled, parallel-group multicenter trial conducted at 40 sites in 11 countries. The study includes three parts. Part 1 has been finalized and is reported in Zuraw, Lumry, Johnston et al (2020).  *HAE, hereditary angioedema; QD, once daily* In part 1, patients were randomized 1:1:1 to receive berotralstat, 110 mg or 150 mg, or placebo administered orally once daily; randomization was stratified by baseline attack rate (>2 vs <2 attacks per month). All patients, investigators, and site and sponsor personnel were blinded to treatment group allocation. Patients were instructed to take the study drug at the same time each day with their largest meal to potentially minimize gastrointestinal side effects. Patients recorded the frequency, duration, location, functional impact, and any treatment of HAE attacks experienced in the previous 24 hours in an electronic diary daily. Investigators contacted patients within 2 business days of each reported attack to discuss and evaluate the event. All investigator confirmed attacks required a symptom of swelling (e.g., visible swelling or symptoms of internal swelling).
Follow-up time	The follow-up time in part 1 (double-blind placebo-controlled) is 24 weeks.
Population (inclusion and exclusion criteria)	**Key Inclusion Criteria:** • A clinical diagnosis of hereditary angioedema Type 1 or Type 2, defined as having a C1-INH functional level and a C4 level below the lower limit of the normal reference range, as assessed during the Screening period. • Subject weight of ≥ 40 kg • Access to and ability to use one or more acute medications approved by the relevant competent authority for the treatment of acute attacks of HAE

Table A2a Main study characteristics

- Subjects must be medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study.
- Subjects must have a specified number of investigator-confirmed attacks during the run-in period of a maximum of 56 days from the Screening visit.
- Acceptable effective contraception
- Written informed consent

Key Exclusion Criteria:

- Pregnancy or breast-feeding
- Any clinically significant medical condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's safety or ability to participate in the study
- Any laboratory parameter abnormality that, in the opinion of the Investigator, is clinically significant and relevant for this study
- Severe hypersensitivity to multiple medicinal products or severe hypersensitivity/ anaphylaxis with unclear aetiology
- Use of C1-INH within 14 days or use of androgens or tranexamic acid within 28 days prior to the Screening visit for prophylaxis of HAE attacks, or initiation of these drugs during the study
- Current participation in any other investigational drug study or received another investigational drug within 30 days of the Screening visit
- Prior enrolment in a berotralstat study

Source: https://clinicaltrials.gov/ct2/show/NCT03485911

Intervention

- Berotralstat 110 mg once daily (N=41)
- Berotralstat 150 mg once daily (N=40)
- Placebo (N=40)

Baseline characteristics

Characteristic	Berotralstat 110 mg (n = 41)	Berotralstat 150 mg (n = 40)	Placebo (n = 40)
Age at consent (y), mean (SD)	40.4 (17.5)	40 (14.0)	44.5 (14.1)
Female sex, no. (%)	30 (73)	23 (58)	27 (68)
Race, no. (%)*			
White	38 (93)	38 (95)	37 (93)
Weight at screening (kg), mean (SD)	78.8 (21.5)	87.6 (20.4)	84.9 (21.4)
Region, no. (%)			
North America	32 (78)	27 (68)	28 (70)
Europe	9 (22)	13 (33)	12 (30)
BMI at screening (kg/m^2, mean (SD)	27.5 (7.3)	30.4 (6.7)	29.3 (6.8)
BMI 18.5-24.9 kg/m^2, no. (%)	19 (46)	8 (20)	12 (30)
BMI 25-29.9 kg/m^2, no. (%)	8 (20)	16 (40)	14 (35)
BMI ≥30 kg/m^2, no. (%)	14 (34)	16 (40)	13 (33)
Baseline investigator-confirmed attack rate, mean (SD)	2.97 (1.36)	3.06 (1.56)	2.91 (1.12)
Baseline investigator-confirmed attack rate, no. (%)			
≥2 attacks/mo	28 (68)	30 (75)	27 (68)
<2 attacks/mo	13 (32)	10 (25)	12 (30)†
Any past prophylactic treatment for HAE, no. (%)	32 (78)	30 (75)	29 (73)

Table A2a Main study characteristics				
	Any prior androgen use, no. (%)‡	19 (46)	21 (53)	25 (63)
	Any prior prophylactic CI-INH use, no. (%)§	16 (39)	21 (53)	16 (40)
	Prior prophylactic treatment use within 30 days of screening, no. (%)	10 (24)	12 (30)	11 (28)
	BMI, Body mass index. **Race was self-reported.* *†A total of 40 patients are in the analysis population; 1 patient was not dosed and therefore has no attack data for Part 1.* *‡Prior androgen use was noted in the patient's HAE medical and medication history and included any of the following: androgens (unspecified), oxandrolone, methyl-testosterone, danazol, and stanozolol.* *§ C1-INH includes plasma-derived and recombinant C1-INH and fresh frozen plasma.*			
Primary and secondary endpoints	Primary endpoint • Rate of expert-confirmed angioedema attacks during the 24-week double-blind treatment period Secondary endpoints: • Number and proportion of days with angioedema symptoms • Rate of expert-confirmed angioedema attacks during dosing in the effective treatment period (steady state, beginning on day 8), • Change from baseline in quality of life at week 24 as assessed by the angioedema quality of life (AE-QoL) questionnaire Explorative endpoints: • Use of on-demand medications to treat angioedema attacks • Proportion of ≥50%; ≥70%; ≥90% responders • Proportion of patients with no attacks over 24 weeks • Rate of investigator-confirmed HAE attacks treated with on-demand medication Rate of on-demand medication use • Satisfaction with treatment was assessed by using TSQM scores Safety endpoints: • Treatment-emergent adverse events (TEAEs) • Treatment-emergent serious adverse events (TESAEs), • Grade 3 or 4 TEAEs • Grade 3 or 4 laboratory abnormalities • Discontinuations due to TEAEs.			
Method of analysis	Primary and secondary efficacy analyses were conducted by using the intent-to-treat population. In the primary analysis, each berotralstat dose was compared with placebo by using a negative binomial model. The number of investigator-confirmed HAE attacks was included as the dependent variable, treatment as a fixed effect, baseline investigator-confirmed attack rate as a covariate, and the logarithm of the duration on treatment as an offset variable. Analysis of the attack rate during the effective dosing period, rate of attacks treated with SOC, and rate of on demand medication use was similarly conducted. Changes in AE-QoL from baseline were assessed with a mixed model for repeated measures with fixed effects for treatment, baseline attack rate, baseline			

Table A2a Main study characteristics	
	AE-QoL, visit, and a visit by treatment interaction and random effect for patient. An unstructured covariance structure was used. Statistical analysis of the proportion of days with angioedema symptoms from investigator confirmed attacks was based on an analysis of covariance model. Analysis of TSQM scores was similar to that for AE-QoL. To account for multiplicity, the Hochberg step-up procedure was used to adjust for the comparison of active drug with placebo for 4 end points and 2 doses. The primary and secondary end points were tested in hierarchic fashion as follows: (1) rate of investigator-confirmed HAE attacks during the 24-week double-blind treatment period, (2) change from baseline in the AE-QoL (week 24 total score), (3) number and proportion of days with angioedema symptoms, and (4) rate of investigator-confirmed HAE attacks during the effective dosing period. The baseline requirements for expert-confirmed attack rate had 2 additional requirements not applied to the entire dosing period on study attacks: (1) attacks had to be unique, and (2) require treatment, medical attention, or cause functional impairment. To allow for a more direct comparison of angioedema attack rates occurring during the baseline and dosing periods, the 2 additional requirements for expert-confirmed baseline attacks were applied programmatically to the on-study expert-confirmed attacks occurring during the dosing period, resulting in an adjusted expert-confirmed attack rate. Adjusted expert-confirmed attack rates were used to compare on study attack rates to baseline attack rates for the exploratory ≥50%, ≥70%, and ≥90% responder endpoints. Safety analyses were done using the safety population. AEs were summarized descriptively by using Medical Dictionary for Regulatory Activities–preferred terms, system organ class, and severity.
Subgroup analyses	Baseline characteristics were assessed for their ability to predict efficacy outcomes as an ad hoc analysis. For the effect of baseline characteristics on the primary analysis, negative binomial regression models were constructed with investigator-confirmed attack rate as the outcome variable and the log of treatment duration as the offset variable. A final multivariable model was obtained by using a stepwise regression process with a 20% significance level for a variable to enter the model and a 15% significance level for a variable to stay in the model. The effect of baseline characteristics on the responder status was evaluated by using logistic regression separately for responses of at least 50% and at least 70% relative reductions, by initially including 1 independent variable at a time in the univariate models

Table A2b Main study characteristics	
Trial name	APeX-J
NCT number	NCT03873116
Objective	To evaluate the efficacy and safety of two dose levels of berotralstat as an oral treatment for the prevention of attacks in subjects with hereditary angioedema
Publications – title, author, journal, year	Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: A phase 3 randomized trial. **Ohsawa I, Honda D, Suzuki Y et al**. Allergy. 2020. DOI: 10.1111/all.14670 [6]
Study type and design	APeX-J is a phase 3, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 11 sites in Japan. Part 1 of the study was a 24-week double-blind evaluation of the efficacy and safety of berotralstat 110 mg and 150 mg for the prophylaxis of HAE attacks compared with placebo. Following completion of 24 weeks of double-blind treatment, patients randomized to placebo were rerandomized 1:1 to berotralstat 110 mg or 150 mg in a double-blind manner (part 2, weeks 25-52) to further evaluate safety and effectiveness. Eligible patients were randomized 1:1:1 to berotralstat 110 mg, berotralstat 150 mg, or placebo into part 1 of the study via an interactive response system. Randomization was stratified by baseline expert-confirmed attack rate (≥2 attacks/month vs. <2 attacks/month) at time of randomization. Expert-confirmed HAE attacks that occurred between screening and first dose were used to calculate a baseline expert-confirmed attack rate for use in the statistical analysis. Study drug assignment was blinded to the investigator, study staff, patients, and clinical research organization staff.
Follow-up time	The study remains ongoing. Data has been presented for the 24-week placebo-controlled period only.
Population (inclusion and exclusion criteria)	<u>Inclusion:</u> • Male and females, 12 years of age or older • A clinical diagnosis of hereditary angioedema (HAE) Type 1 or Type 2, defined as having a C1-INH functional level and a C4 level below the lower limit of the normal (LLN) reference range, as assessed during the Screening period. • Access to and ability to use one or more acute medications approved by the relevant competent authority for the treatment of acute attacks of HAE • Subjects must be medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study. • Subjects must have a specified number of expert-confirmed attacks during the run-in period of 56 days from the Screening visit. • Acceptable effective contraception • Written informed consent <u>Exclusion:</u> • Pregnancy or breast-feeding • Any clinically significant medical condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's safety or ability to participate in the study

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Table A2b Main study characteristics

- Any laboratory parameter abnormality that, in the opinion of the Investigator, is clinically significant and relevant for this study
- Severe hypersensitivity to multiple medicinal products or severe hypersensitivity/ anaphylaxis with unclear etiology
- Use of C1-INH within 14 days or use of androgens or tranexamic acid within 28 days prior to the Screening visit for prophylaxis of HAE attacks, or initiation of these drugs during the study
- Current participation in any other investigational drug study or received another investigational drug within 30 days of the Screening visit
- Prior enrollment in a berotralstat study

Source: https://clinicaltrials.gov/ct2/show/NCT03873116

Intervention

- Berotralstat 110 mg o.d., p.o. (n=6)
- Berotralstat 150 mg o.d., p.o. (n=7)
- Placebo (n=6)

Baseline characteristics

	Placebo (n=6)	Berotralstat		Total (N=19)
Characteristic		**110 mg (N=7)**	**150 mg (n=6)**	
Mean age at time of consent years (SD)	47 (15)	37 (9)	42 (14)	42 (13)
Sex,n (%)				
Male	1 (17)	1 (14)	1 (17)	3 (16)
Female	5 (83)	6 (86)	5 (83)	16(84)
Race, n (%)				
Asian	6 (100)	6 (86)	6 (100)	18 (94)
Other	0	1 (14)	0	1 (5)
Mean weight, kg (SD)	66 (12)	57 (10)	73 (16)	65 (14)
Mean BMI , kg/m^2 (SD)	26 (4)	22 (5)	29 (6)	25 (5)
Mean baseline expert-confirmed angioedema attack rate (SD)[a]	2.4 (1.3)	2.0 (1.1)	2.5 (1.5)	2.3 (1.2)
Categorized baseline expert-confirmed angioedema attack rate , n (%)				
≥2 per month	2 (33)	4(57)	3 (SO)	9 (48)
<2 per month	4(67)	3 (43)	3 (SO)	10 (53)
Any past prophylactic treatment for HAE, n (%)[b]	5 (83)	6 (86)	4(67)	15 (79)
Any C1-INH	1 (17)	1 (14)	1 (17)	3 (16)
Any androgen	0	2 (29)	1 (17)	3 (16)
Tranexamic acid	5 (83)	3 (43)	3 (SO)	11 (58)
Mean age at diagnosis, y (SD)	34(19)	29 (8)	30(17)	31 (14)
Missed work or education in the past year due to HAE, n (%)	5 (83)	5 (71)	4(67)	14(74)

Abbreviations: BMI, body mass index ; C1-INH, C1-esterase inhibitor ; HAE, hereditary angioedema; SD , standard deviation.

[a] Baseline expert-confirmed angioedema attack rate was defined as (total number of expert confirmed angioedema attacks experienced in the period between screening and first date/time of study drug dosing) x 28 /(date of first dose - date of screening+ 1).

[b] Long-term prophylactic therapies for the prevention of HAE attacks are not approved in Japan (except for tranexamic acid). Use of these medications for prophylaxis was likely off label.

Table A2b Main study characteristics	
Primary and secondary endpoints	Primary endpoint • Rate of expert-confirmed angioedema attacks during the 24-week dosing period Secondary endpoints: • Number and proportion of days with angioedema symptoms • Rate of expert-confirmed angioedema attacks during dosing in the effective treatment period (steady state, beginning on day 8), • Change from baseline in quality of life at week 24 as assessed by the angioedema quality of life (AE-QoL) questionnaire Explorative endpoints: • Use of on-demand medications to treat angioedema attacks • Proportion of ≥50%; ≥70%; ≥90% responders Safety endpoints: • Treatment-emergent adverse events (TEAEs) • Treatment-emergent serious adverse events (TESAEs), • Grade 3 or 4 TEAEs • Grade 3 or 4 laboratory abnormalities • Discontinuations due to TEAEs.
Method of analysis	Analyses were conducted in the intent-to-treat population. Comparisons between each berotralstat dose group and placebo in the rate of expert-confirmed angioedema attacks during the entire dosing period were made using a negative binomial regression model. The number of expert-confirmed angioedema attacks was included as the dependent variable, treatment was a fixed effect, baseline monthly angioedema attack rate was a covariate, and the logarithm of duration on treatment was an offset variable. Analysis of the rate of expert-confirmed attacks during the effective dosing period was similarly conducted, as was the number of attacks requiring treatment with on-demand medication. The proportion of days with angioedema symptoms was analyzed using an analysis of covariance model with baseline attack rate as a covariate and treatment included as a fixed effect. Changes from baseline in AE-QoL scores were analyzed using a mixed model for repeated measures with fixed effects for treatment, baseline attack rate, baseline AE-QoL, visit, a visit-by-treatment-interaction effect, and a random effect for patient. Primary and secondary endpoints were tested hierarchically, with the type 1 error rate controlled at the study level using a combination of hierarchical testing and the Hochberg procedure. The rate of expert-confirmed angioedema attacks during the 24-week dosing period was the first endpoint in the hierarchy, followed by the number and proportion of days with angioedema symptoms, the rate of expert-confirmed angioedema attacks during dosing in the effective treatment period, and the change from baseline in AE-QoL. The baseline requirements for expert-confirmed attack rate had 2 additional requirements not applied to the entire dosing period on study attacks: (1) attacks had to be unique, and (2) require treatment, medical attention, or cause functional impairment. To allow for a more direct comparison of angioedema attack rates occurring during the baseline and dosing periods, the 2 additional requirements for expert-confirmed baseline attacks were applied programmatically to the on-study

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Table A2b Main study characteristics	
	expert-confirmed attacks occurring during the dosing period, resulting in an adjusted expert-confirmed attack rate. Adjusted expert-confirmed attack rates were used to compare on study attack rates to baseline attack rates for the exploratory ≥50%, ≥70%, and ≥90% responder endpoints. Safety analyses were performed using the safety population (all patients receiving ≥1 dose of study drug) and are summarized with descriptive statistics.
Subgroup analyses	The pre-planned subgroup analyses for the primary and secondary endpoints were provided by: 1. Sex; 2. Race (white vs. other); 3. Baseline event rate (≥ 2 events/month vs. < 2 events/month); 4. Age group (12 - 17, 18 to 64, ≥ 65 years); 5. Region (North America vs. Japan vs. rest of world); 6. Weight (< median vs. ≥ median); 7. BMI (18.5 to 24.9 kg/m^2 vs. 25 to 29.9 kg/m^2 vs. ≥ 30 kg/m2); 8. Prior androgen use (yes vs. no) A summary of TEAEs by age group was pre-specified.

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Table A2c Main study characteristics	
Trial name	HELP
NCT number	NCT02586805
Objective	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	Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. **Banerji A, MA Riedl, JA Bernstein et al.** JAMA. 2018 320(20):2108-2121.[7]
Study type and design	Phase 3 interventional randomized parallel, quadruple blinded, placebo-controlled study. Patients were enrolled and assigned to interventions using an interactive web-based randomization system. Eligible patients were randomized 2:1 to receive subcutaneously injected lanadelumab or placebo. Randomization was stratified by normalized number of attacks during the run-in period:1 - <2, 2 -< 3, or ≥3 within 4 weeks using a within-stratum block size of 9.
Follow-up time	The prespecified study period on active drug was 26 weeks.
Population (inclusion and exclusion criteria)	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.

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Table A2c Main study characteristics

	• Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3× upper limit of normal, or aspartate aminotransferase (AST) > 3× upper limit of normal, or total bilirubin > 2× 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 every 2 weeks (n=41) All patient received injections every two weeks with those in the Q4W groups receiving placebo in between active treatment.				
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)

Table A2c Main study characteristics					
	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	Primary outcomes: • Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attacks During the 26-week treatment period Secondary outcomes • 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 Exploratory outcomes • Percentage of patients who were attack-free • Number of attack-free days • Responders (50%, 70% and 90% or more reduction in attack rate from run-in) • Number of high morbidity attacks (that is was severe, laryngeal, hemodynamically significant, or resulted in hospitalization) • Maximum attack severity (attack free, mild,moderate,or severe) • Attack location • Attack duration • On-demand medication use to treat attacks • Health–related quality of life using the Angioedema Quality of Life Questionnaire Other outcomes Adverse events and antidrug antibodies.				
Method of analysis	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 5%. The logarithm of the number of days a patient was observed during the treatment period was included as an offset variable in the generalized linear model to adjust for differences in follow-up time.				

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Table A2c Main study characteristics	
	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 (α/3; 2-sided).
Subgroup analyses	According to the statistical analysis plan, subgroup analyses were planned for the primary efficacy endpoint and adverse events (non-HAE attack treatment period AEs, related AEs, and severe AEs). In addition, a subgroup analysis by history of laryngeal attacks were to be performed for the exploratory efficacy endpoint, number of investigator-confirmed laryngeal HAE attacks during the treatment period. The following subgroups were planned to be used: • Age Group (<18, 18 to <40, 40 to <65, ≥65 years) • Sex (Male, Female) • Race Group (White, Other) • Weight Group (<50, 50 to <75, 75 to <100, ≥100 kg) • BMI Group (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m2) • Run-in Period HAE Attack Rate Group (1 to <2, 2 to <3, ≥3 attacks/4 weeks) • HAE Type (Type I, Type II, Unspecified) • Geographic Region (US, Canada, Jordan, Europe) • Type of Long-term Prophylactic Therapy Prior to Study Randomization (C1-INH, Oral Therapy, C1-INH and Oral Therapy, Not on LTP) • History of laryngeal HAE attack (history laryngeal attack, no history of laryngeal attack) For the subgroup analyses conducted for the primary efficacy endpoint, a forest plot depicting the rate ratio and corresponding 95% CI estimated from the Poisson generalized linear model were provided for each active treatment group versus placebo group comparison within each subgroup.

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8.3 Results per study

Table A3a. Results of APeX-2

Trial name:	*APeX-2*
NCT number:	*NCT03485911*

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Attack freedom	Placebo	40	[redacted]							Number of patients with 100% attack reduction were reported per arm.	CSR, Figure 9
	Berotralstat 150 mg	40									
Laryngeal attacks	Placebo	40								Proportions of patients who had ≥ 1 laryngeal event were reported per arm.	CSR, Table 28
	Berotralstat 150 mg	40									
% patients achieving 6-point improvement in AE-QoL	Placebo	40	[redacted]							Proportions of patients achieving 6-point improvement in AE-QoL total score were reported per arm. ARR and RR calculated based on ITT population	CSR, Table 14.2.3.7
	Berotralstat 150 mg	40									

Change from BL to EOS in AE-QoL total score	Placebo	40	LSM (SE): -9.69 (2.64)	-4.90	-12.23, 2.43	0.188	–	–	–	For the change from baseline in AE-QoL total score at week 24, the difference was the LSM difference from a mixed-model repeated-measures analysis with expert-confirmed baseline attack rate, baseline AE-QoL, treatment group, visit and visit × treatment group interaction included as fixed effects, and patient included as a random effect.	Zuraw_2020, Table 2
	Berotralstat 150 mg	40	LSM (SE): -14.59 (2.59)								
Change in attack rate	Placebo	40	2.35 per month	44.2 p.p.	23.0, 59.5	-	RaR: 0.56	0.41, 0.77	<0.001	Rate reduction reported as % from placebo. Investigator confirmed attack rates were analysed using negative binominal regression model with treatment as fixed effect; base-line attack rate as covariate; and ln(treatment duration) as offset variable	HAE rates and %difference: EPAR Table 26
	Berotralstat 150 mg	40	1.31 per month								

										RaR calculated 1-difference in rate reduction	
Rate of moderate or severe attacks	Placebo Berotralstat 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Rate reduction reported as % from placebo. Investigator confirmed attack rates were analysed using negative binominal regression model with treatment as fixed effect; base-line attack rate as covariate; and ln(treatment duration) as offset variable RaR calculated as 1-difference in rate reduction	CSR, Table 14.2.1.29.A
Discontinuations due to TEAEs	Placebo Berotralstat 150 mg	39 40	1 (2.6%) 1 (2.5%)	-0.1 p.p.*	-7.0, 6.9*	–	0.98	0.06, 15.05*	-	Proportions of patients who discontinued due to TEAEs were reported per arm. Note one patient in the ITT placebo group was withdrawn before first dose and excluded from the safety population	Zuraw_2020, Table 3

Abbreviations: CI, confidence intervals; ITC, indirect treatment comparison; LSM, least square mean; MD, mean difference; OR, odds ratio; RaR, Rate ratio; RR, Risk ratio; SE, standard error; TEAEs, Treatment emergent adverse events

* RD with (95% CI) and RR (95% CI) calculated for the purpose of this application only. 95% CI for RD calculated using Normal approximation. 95% CI for RR calculated using normal approximation for ln(RR). In case of zero events in one arm, 0.5 was added to events in both arms for the calculation of RD and RR.

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Table A3b. Results of APeX-J

Trial name: *APeX-J*

NCT number: *NCT03873116*

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Attack freedom	Placebo	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Number of patients with 100% attack reduction were reported per arm. [redacted]	CSR, Table 14.2.4.2
	Berotralstat 150 mg	7	[redacted]								
Laryngeal attacks	Placebo	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Proportions of patients who had ≥ 1 laryngeal event were reported per arm.	CSR, Table 44
	Berotralstat 150 mg	7	[redacted]								
% patients achieving 6-point improvement in AE-QoL	Placebo	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Proportions of patients achieving 6-point improvement in AE-QoL total score were reported per arm.	CSR, Table 14.2.3.7
	Berotralstat 150 mg	7	[redacted]								

Change from BL to EOS in AE-QoL total score	Placebo	6	LSM (SE): 3.18 (6.83)	-19.0	-39.0, -1.0	0.061	–	–	–	For the change from baseline in AE-QoL total score at week 24, the difference was the LSM difference from a mixed-model repeated-measures analysis with expert-confirmed baseline attack rate, baseline AE-QoL, treatment group, visit and visit × treatment group interaction included as fixed effects, and patient included as a random effect.	Ohsawa 2020 Table 2
	Berotralstat 150 mg	7	LSM (SE):-15.82 (6.42)								
Change in attack rate	Placebo	6	2.18 attacks/ month (baseline 2.5)	49.1 p.p.	20.4, 67.5	0.003	0.509	0.325, 0.796	-	Rate reduction reported as % from placebo. Investigator confirmed attack rates were analysed using negative binominal regression model with treatment as fixed effect; base-line attack	Difference in rate reduction. Ohsawa 2020, Table 2
	Berotralstat 150 mg	7	1.11 attacks/ month (baseline 2.0)								

										rate as covariate; and ln(treatment duration) as offset variable RaR calculated as 1-difference in rate reduction	
Rate of moderate or severe attacks	Placebo	6	[redacted] attacks/ month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Rate reduction reported as % from placebo. Investigator confirmed attack rates were analysed using negative binominal regression model with treatment as fixed effect; base-line attack rate as covariate; and ln(treatment duration) as offset variable RaR calculated as 1-difference in rate reduction	CSR, Table 14.2.1.24.A
	Berotralstat 150 mg	7	[redacted] attacks/ month								
Discontinuations due to TEAEs	Placebo	6	1 (17%)	-15.2 p.p.*	-49.9, 19.5*	–	0.29*	0.01, 6.07*	–	Proportions of patients who discontinued due to TEAE were reported per arm. ARR and RR	Ohsawa 2020, Table 3
	Berotralstat 150 mg	7	0								

	calculated using Haldane-Anscombe correction for zero events

Abbreviations: CI, confidence intervals; ITC, indirect treatment comparison; LSM, least square mean; MD, mean difference; RaR, Rate ratio; RR, Risk ratio; SE, standard error; TEAEs, Treatment emergent adverse events

* RD with (95% CI) and RR (95% CI) calculated for the purpose of this application only. 95% CI for RD calculated using Normal approximation. 95% CI for RR calculated using normal approximation for ln(RR). In case of zero events in one arm, 0.5 was added to events/ non-events in both arms for the calculation of RD and RR.

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Table A3c. Results of HELP											
Trial name:	HELP										
NCT number:	NCT02586805										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
Attack freedom	Placebo	41	2.4%	42.0	18.1, 61.8	<0.001	RR: 18.22*	2.51, 132.16*	–	The attack freedom is calculated as number of patients who are attack free.	Banerji_2018, Table 3
	Lanadelumab 300mg Q2W	27	44.4%								
Laryngeal attacks	Placebo	41	8 (19.5%)	-8.4 p.p*.	-25.4, 8.6*	–	RR:0.57*	0.17, 1.96*	–	The absolute difference in effect is estimated using a two-sided t-test.	Banerji_2018, eTable 5
	Lanadelumab 300mg Q2W	27	3 (11.1%)								
% patients achieving 6-point improvement in AE-QoL	Placebo	38	14/38 (36.84%) 14/41 (34.1%) (ITT)	43.6 p.p.*	22.3, 65.0*	–	RR: 2.28*	1.42, 3.65*	-	RR and ARR calculated for the ITT population	G-BA Dossier, Table 4-48
	Lanadelumab 300mg Q2W	26	21/26 (80.77%) 21/27 (77.8%) (ITT)								
Change from BL to EOS in AE-QoL total score	Placebo	38	LSM (SE): -4.72 (-10.46, 1.02)	-16.57	-28.53, -4.62	0.003	–	–	–	Change in total score, from d 0-182 (controlled for baseline scores and are least square means).	Banerji_2018, Table 4
	Lanadelumab 300mg Q2W	26	LSM (SE): -21.29 (-28.21, -14.37)								

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Change in attack rate	Placebo	41	1.97 Attacks/month (baseline 4.0)	87 p.p	76, 93	–	RaR: 0.13	0.07, 0.24	<0.001	Rate ratio is calculated as reduction relative to placebo. Results are from a Poisson regression model accounting for overdispersion	Banerji_2018, Table 2
	Lanadelumab 300mg Q2W	27	0.26 Attacks/month (baseline 3.5)								
Rate of moderate or severe attacks	Placebo	41	1.22 Attacks/month	83 p.p	66, 92		RaR: 0.17	0.08, 0.33	<0.001	Rate ratio is calculated as reduction relative to placebo. Results are from a Poisson regression model accounting for overdispersion Difference in rate reduction calculated as 1-RaR × 100	
	Lanadelumab 300mg Q2W	27	0.20 Attacks/month								
Discontinuations due to TEAEs	Placebo	41	1 (2.4%)	-1.8 p.p*.	-9.2, 5.7*	–	RR: 0.50*	0.02, 11.84*	–	Proportions of patients who discontinued due to TEAE were reported per arm. RD and RR calculated using Haldane-Anscombe correction of zero events	EPAR, Table 23
	Lanadelumab 300mg Q2W	27	0								

Abbreviations: CI, confidence intervals; ITC, indirect treatment comparison; LSM, least square mean; MD, mean difference; RaR, Rate ratio; RR, Risk ratio; SE, standard error; TEAEs, Treatment emergent adverse events

* RD with (95% CI) and RR (95% CI) calculated for the purpose of this application only. 95% CI for RD calculated using Normal approximation. 95% CI for RR calculated using normal approximation for ln(RR). In case of zero events in one arm, 0.5 was added to events/ non-events in both arms for the calculation of RD and RR

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8.4 Results per PICO (clinical question)

Table A4 Results referring to clinical question 1. Berotralstat 150mg OD compared to lanadelumab 300mg Q2W

Results per outcome: ***Attach forest plots and statistical results as a separate file.***
Results from the comparative analysis should be given in the table below, if possible.

		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Attack freedom	APeX-J APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	RR for APeX-J and APeX-2 studies synthesized by meta-analysis using fixed effects Mantel-Haenzel method, which was used as input for RR of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method. [redacted] ARR calculated from RR using % patients achieving 100% reduction in attack rate in the lanadelumab 300mg Q2W arm of HELP as comparator rate (44.4%)
	APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	RR of berotralstat 150mg vs lanadelumab 300mg q2w derived by ITC using Bucher method. ARR calculated from RR using % patients achieving 100% reduction in attack rate in the lanadelumab 300mg Q2W arm of HELP as comparator rate (44.4%).

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Table A4 Results referring to clinical question 1. Berotralstat 150mg OD compared to lanadelumab 300mg Q2W

Results per outcome: ***Attach forest plots and statistical results as a separate file.***
Results from the comparative analysis should be given in the table below, if possible.

		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Laryngeal attacks	APeX-J APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	RR for APeX-J and APeX-2 studies synthesized by meta-analysis using fixed effects Mantel-Haenzel method, which was used as input for RR of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method. ARR calculated from RR using % patients having at least one laryngeal attack in the lanadelumab 300mg Q2W arm of the HELP study (11.1%)
	APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	RR of berotralstat 150mg vs lanadelumab 300mg q2w derived by ITC using Bucher method. ARR calculated from RR using % patients having at least one laryngeal attack in the lanadelumab 300mg Q2W arm of the HELP study (11.1%)
6-point improvement in AE-QoL	APeX-J APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Denominator in response rate based on ITT (patients with missing AE-QOL data classified as non-responder).

Table A4 Results referring to clinical question 1. Berotralstat 150mg OD compared to lanadelumab 300mg Q2W

Results per outcome: ***Attach forest plots and statistical results as a separate file.***
Results from the comparative analysis should be given in the table below, if possible.

	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
							RR for APeX-J and APeX-2 studies synthesized by meta-analysis using fixed effects Mantel-Haenzel method, which was used as input for RR of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method. ARR calculated from RR using % responders in the lanadelumab 300mg Q2W arm of the HELP study (77.8%)
APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Denominator in response rate based on ITT (patients with missing AE-QOL data classified as non-responder) RR of berotralstat 150mg vs lanadelumab 300mg q2w derived by ITC using Bucher method. ARR calculated from RR using % responders in the lanadelumab 300mg Q2W arm of the HELP study (77.8%)

Table A4 Results referring to clinical question 1. Berotralstat 150mg OD compared to lanadelumab 300mg Q2W

Results per outcome: ***Attach forest plots and statistical results as a separate file.***
Results from the comparative analysis should be given in the table below, if possible.

		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Change from BL to EOS in AE-QoL total score	APeX-J APeX-2 HELP	MD: -9.13	-22.92, 4.66	0.19	NA	NA	NA	Pooled MD for APeX-J and APeX-2 studies from APeX-J CSR used as an input for calculating MD of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method.
	APeX-2 HELP	MD: -11.67	-25.69, 2.35	0.10	NA	NA	NA	MD of berotralstat 150mg vs lanadelumab 300mg q2w derived by ITC using Bucher method.
Discontinuations due to TEAEs	APeX-J APeX-2 HELP	ARR: -0.1 p.p.	-1.7, 61.0	0.97	RR: 0.94	0.03, 35.17	0.97	RR for APeX-J and APeX-2 studies synthesized by meta-analysis using fixed effects Mantel-Haenszel method, which was used as input for RR of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method. Haldane-Anscombe correction applied to APeX-J and HELP datasets in the calculation of RR. ARR calculated from RR using an assumed comparator rate of 1.8%.

Table A4 Results referring to clinical question 1. Berotralstat 150mg OD compared to lanadelumab 300mg Q2W

Results per outcome: ***Attach forest plots and statistical results as a separate file.***
Results from the comparative analysis should be given in the table below, if possible.

		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
	APeX-2 HELP	ARR: 1.7 p.p.	-1.7, 226.7	0.75	RR: 1.95	0.03, 127.95	0.75	RR of berotralstat 150mg vs lanadelumab 300mg q2w derived by ITC using Bucher method. Haldane-Anscombe correction applied to HELP dataset in the calculation of RR. ARR calculated from RR using an assumed comparator rate of 1.8%.
% change in attack rate	APeX-J APeX-2 HELP	Δ%RaR: -41.4 p.p.	-94.2, -14.6	<0.001	RaR: 4.18	2.12, 8.25	<0.001	Pooled RaR for APeX-J and APeX-2 studies from APeX-J CSR used as input for RaR of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method. Δ%RaR calculated from the % change in attack rate in the lanadelumab 300mg q2w arm of the HELP study (87%)
	APeX-2 HELP	Δ%RaR: -43.0 p.p.	-129.1, -9.1	0.002	RaR: 4.31	1.70, 10.93	0.002	RaR of berotralstat 150mg vs lanadelumab 300mg q2w derived by ITC using Bucher method. Δ%RaR calculated from the %

Table A4 Results referring to clinical question 1. Berotralstat 150mg OD compared to lanadelumab 300mg Q2W

Results per outcome: ***Attach forest plots and statistical results as a separate file.***
Results from the comparative analysis should be given in the table below, if possible.

		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
								change in attack rate in the lanadelumab 300mg q2w arm of the HELP study (87%)
Rate of moderate or severe attacks	APeX-J APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled RaR for APeX-J and APeX-2 studies from APeX-J CSR used as input for RaR of berotralstat 150mg vs lanadelumab 300mg q2w by ITC using Bucher method. Δ%RaR calculated from the % change in attack rate in the lanadelumab 300mg q2w arm of the HELP study (83%)
	APeX-2 HELP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	RaR of berotralstat 150mg vs lanadelumab 300mg q2w derived by ITC using Bucher method. Δ%RaR calculated from the % change in attack rate in the lanadelumab 300mg q2w arm of the HELP study (83%)

Appendix B. Indirect treatment comparison

For the purpose of this ITC, a frequentist approach using the Bucher method [17] was preferred over a Bayesian approach due to the limited evidence base (n=3 studies) and the low number of interventions of interest. Bucher analysis is used to compare outcomes between two indirect treatments across different studies, where several different interventions are compared to a common comparator (i.e. placebo/SoC). It assumes that the trials included in the ITC are similar with regards to the study population, study design, outcome measurements, and the distribution of treatment effect-modifiers (i.e., study and patient characteristics that have an independent influence on treatment outcome). However, this approach is unsuitable for performing indirect treatment comparisons within more complex networks of treatments with multi-arm trials, for which Bayesian NMA methods are widely used instead [18].

Given the evidence base retrieved from the SLR as described above, pairwise meta-analysis followed by an indirect comparison via the Bucher method was selected as the most appropriate method of evidence synthesis. For ease of review, transparency and reproducibility, all Bucher analyses were conducted in Microsoft® Excel, as described by Tobias et al 2014 (19).

8.5 Bucher indirect treatment comparison

The conducted analyses consisted of outcomes using binary, continuous and rate data.

#	Outcome	Outcome measure
1	Attack freedom	RR, ARR
2	Laryngeal attacks	RR, ARR
3	% reduction in attack rate per month	RaR, ARaR
4	Rate of moderate or severe attacks	RaR, ARaR
5	6-point improvement in AE-QoL	RR, ARR
6	Change from BL to EOS in AE-QoL total score	Mean difference
7	Discontinuation due to TEAE	RR, ARR

Abbreviations: AE-QoL, Angioedema-Quality of Life; ARaR, absolute rate ratio; BL, baseline; EOS, end of study; RaR, rate ratio; RR, relative risk; TEAE, Treatment-emergent adverse events

For binary outcomes, relative effects were expressed as relative risk (RR) or rate ratio (RaR), while absolute effects were estimated in terms of the absolute risk reduction (ARR) to assess the magnitude of the effect size. RR is the most consistent estimate on relative effects and, therefore, preferable over the odds ratio (OR) in cases of variations in event rates between trials.

RR was estimated as

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

Based on the number of events and sample sizes of a given study as presented below.

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Table 15: Contingency table		
	Event	No event
	a	b
	c	d

The corresponding standard error was estimated on the log scale as

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

RR is usually skewed toward the upper end of possible values since the measure cannot take negative values, therefore a logarithmic transformation as the distribution of the log RR was used for the Bucher ITC. The treatment effect of the indirect comparison of active treatments A and B via the common comparator treatment C was estimated as the difference of the treatment effects of the direct comparisons on the log scale as

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

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 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.
The ARR was estimated as

$$ARR = r_c \mathrm{RR} - r_c$$

where r_c represents the rate in the comparator group. Ideally, r_c should reflect the expectations in a Danish context. However, in the absence of robust published data, the observed rates for r_c as reported in the HELP study were considered.

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 calculated at the 95% CI of the RR (as shown above) without logarithmic transformation.

The corresponding p-value is estimated from the transformed CI bounds as

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

Where

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

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 were necessary. SE and z were then estimated as shown for

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ARR, considering the estimates for RR on the log scale. The equation for the p-value is equivalent to ARR, and no back-transformation was necessary.

The measure for attack rate reduction as specified in the DMC protocol is percentage reduction in attack rate (1-RaR). The absolute difference percent reduction in attack rate for berotralstat compared to lanadelumab (Δ%RaR) is calculated as the difference between the indirect estimate of the percentage reduction in attack rate of berotralstat (intervention *A*)

$$1 - RaR_{A\,vs\,B}\, RaR_{B\,vs\,C}$$

and the observed % reduction in attack rate of *B* vs the common comparator *C*

$$1 - RaR_{B\,vs\,C}$$

The difference is hence calculated as

$$\Delta\%RaR = 1 - RaR_{A\,vs\,B}\, RaR_{B\,vs\,C} - (1 - RaR_{B\,vs\,C})$$

Or

$$\Delta\%RaR = RaR_{B\,vs\,C}\,(1 - RaR_{A\,vs\,B})$$

The 95% confidence interval for Δ%RaR is calculated at the 95% confidence for $RaR_{A\,vs\,B}$ from the indirect comparison.

For continuous outcomes, the indirect estimate of the difference in mean outcome of treatment *B* and *C* was estimated as the difference in observed mean differences between treatments *A* and *B* and between *A* and *C*

$$\mu_{BC} = \mu_{AB} - \mu_{AC}$$

With the corresponding variance

$$var(\mu_{BC}) = var(\mu_{AB}) + var(\mu_{AC})$$

A corresponding standard error

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

And 95% CI

$$95\%\ CI_{BC} = \mu_{BC} \pm 1.96 * SE(\mu_{BC})$$

8.6 Meta-analysis

The systematic literature research identified two trials for the intervention (APeX-2 and APeX-J) and one trial for the comparator (HELP)

Table B1: Summary of studies considered for ITC

Study Name	Treatment arms	Follow-up period (cross-over details, if any)	Include/ Exclude for ITC feasibility	Comments
APeX-2 [11]	Berotralstat 110 mg Berotralstat 150 mg Placebo	24 weeks	Include	Comparison of marketed dose (150 mg) of Berotralstat vs placebo will only be considered
APeX-J [11]	Berotralstat 110 mg Berotralstat 150 mg Placebo	24 weeks	Include	Comparison of marketed dose (150 mg) of berotralstat vs placebo will only be considered
HELP [7]	Lanadelumab 150 mg Q4W Lanadelumab 300 mg Q4W	26 weeks	Include	Comparison of marketed dose (300 mg Q4W and Q2W) of lanadelumab

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	Lanadelumab 300 mg Q2W Placebo	vs placebo post cross-over will only be considered

Abbreviations: ITC, Indirect treatment comparison, Q4W every 4 weeks, Q2W every 2 week

The base case analysis considered both the APeX-2 and APeX-J studies. If more than one study is available to inform a direct comparison, 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 [19, 20]. Pooling was conducted by assigning weights wi to the individual studies i, estimated through the inverse variance method, which corresponds to a fixed-effects model. A random effects model assuming variation of the inverse variance method following DerSimonian and Laird was not presented as the between-study variance ($\tau 2$) was zero, given the Cochran's Q statistic was lower than the degrees of freedom. This is expected given there are only two studies available for pooling and event rates in these are very low, implying high variances and low weights.

Continuity correction was applied in instances of zero events in a given trial arm.

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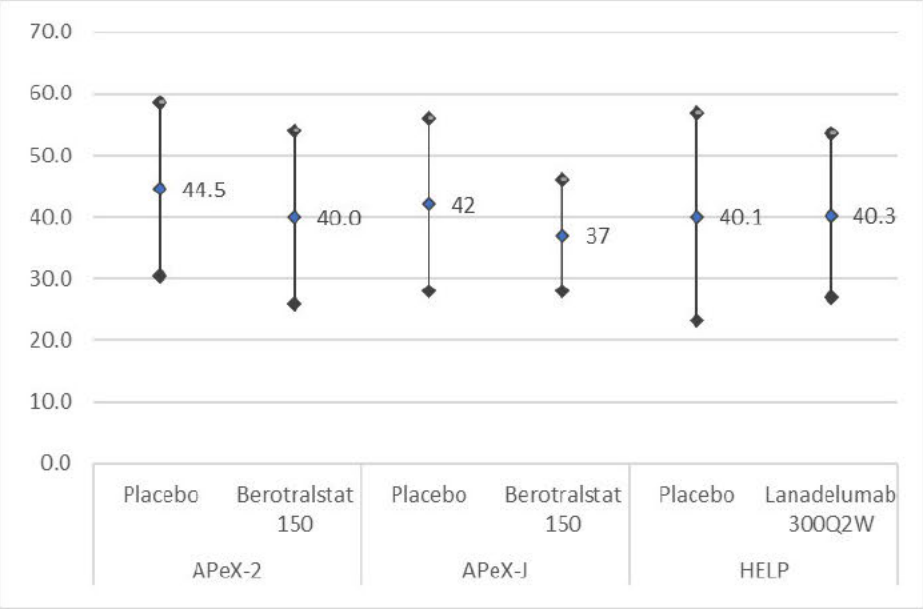
8.7 Assessment of between-study heterogeneity

Figure B1: Between-study heterogeneity: Mean age (± SD)



Abbreviations: Q2W, every 2 weeks; SD, Standard Deviation

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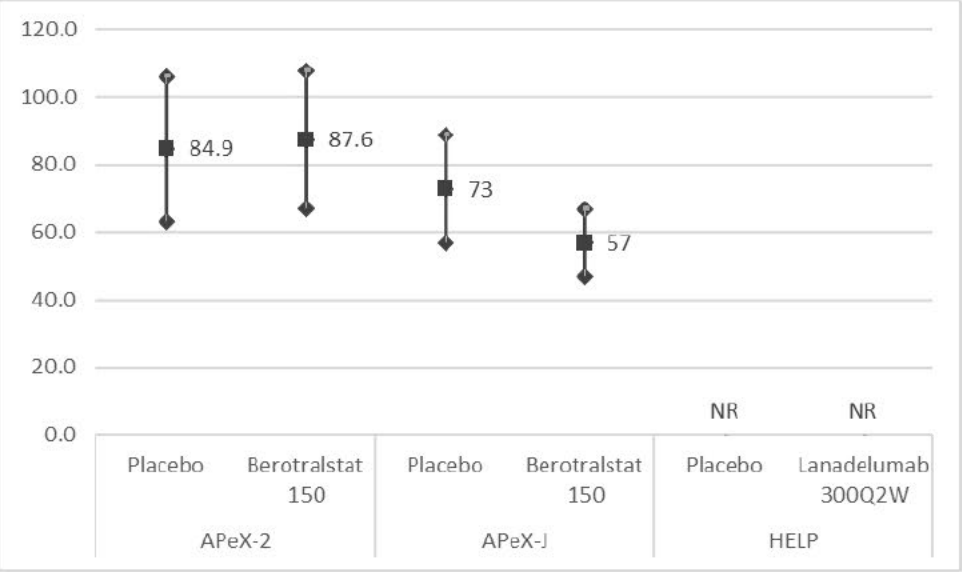
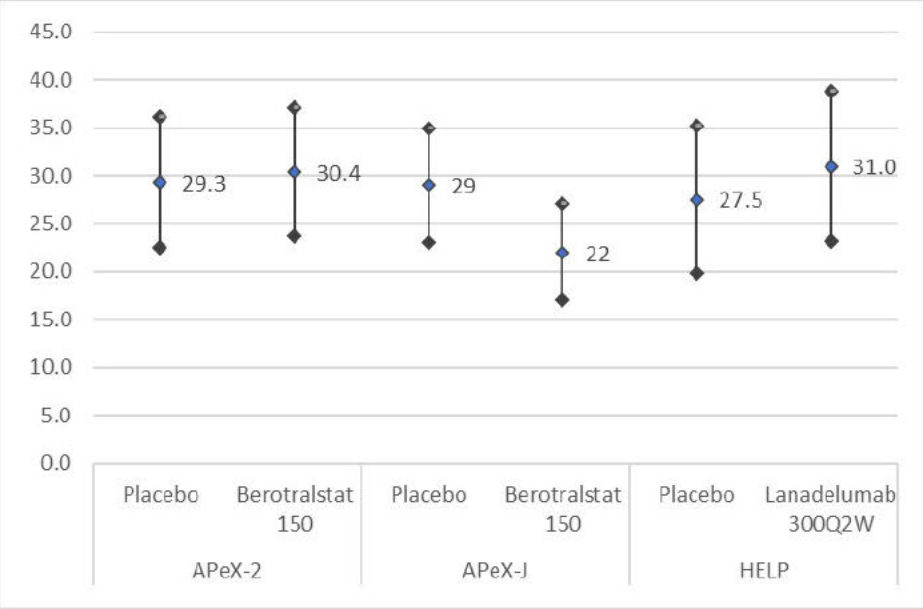
Figure B2: Between-study heterogeneity: Mean weight (kg) ± SD



Abbreviations: NR Not reported; Q2W every 2 weeks; SD, Standard Deviation

Figure B3: Between-study heterogeneity: Mean BMI (kg/m^2) ± SD



Abbreviations: BMI, body mass index; Q2W every 2 weeks; SD, Standard Deviation

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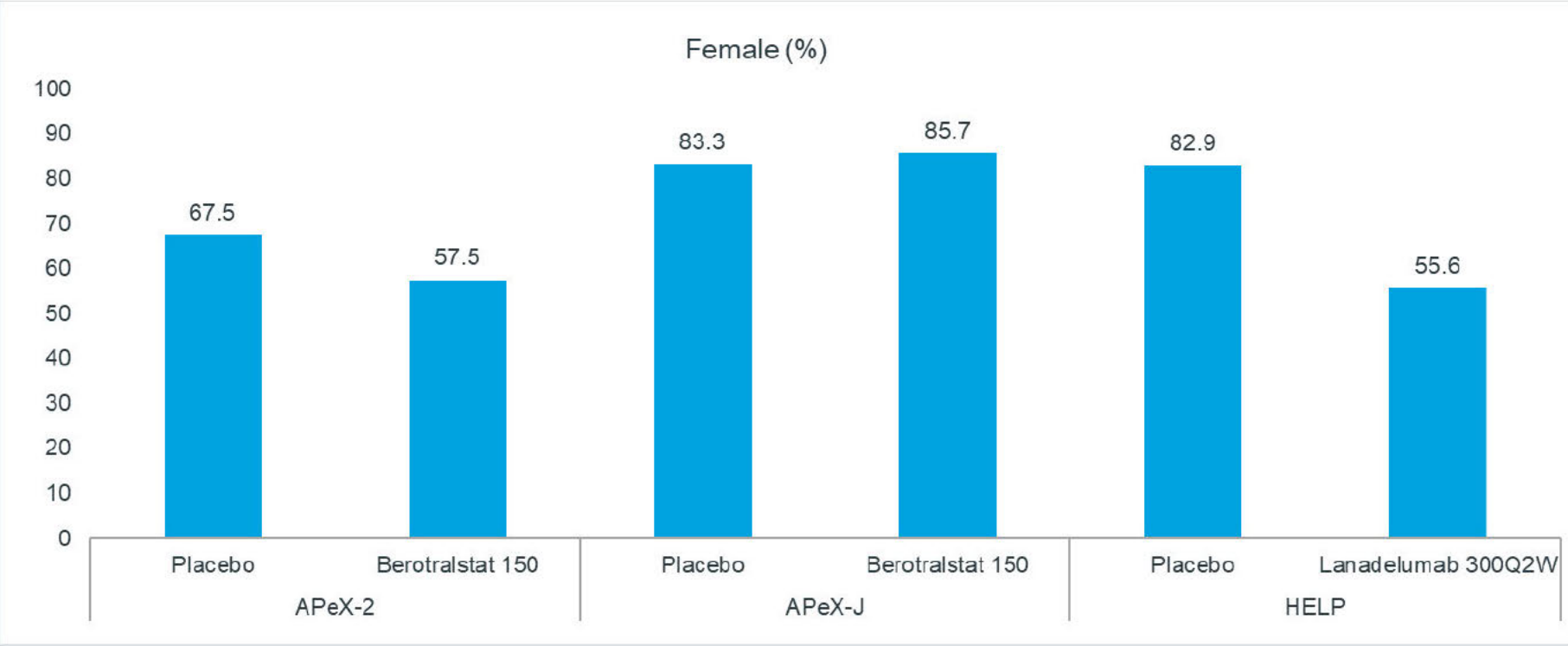
Figure B4: Between-study heterogeneity: Proportion of female



Abbreviations: Q2W every 2 weeks

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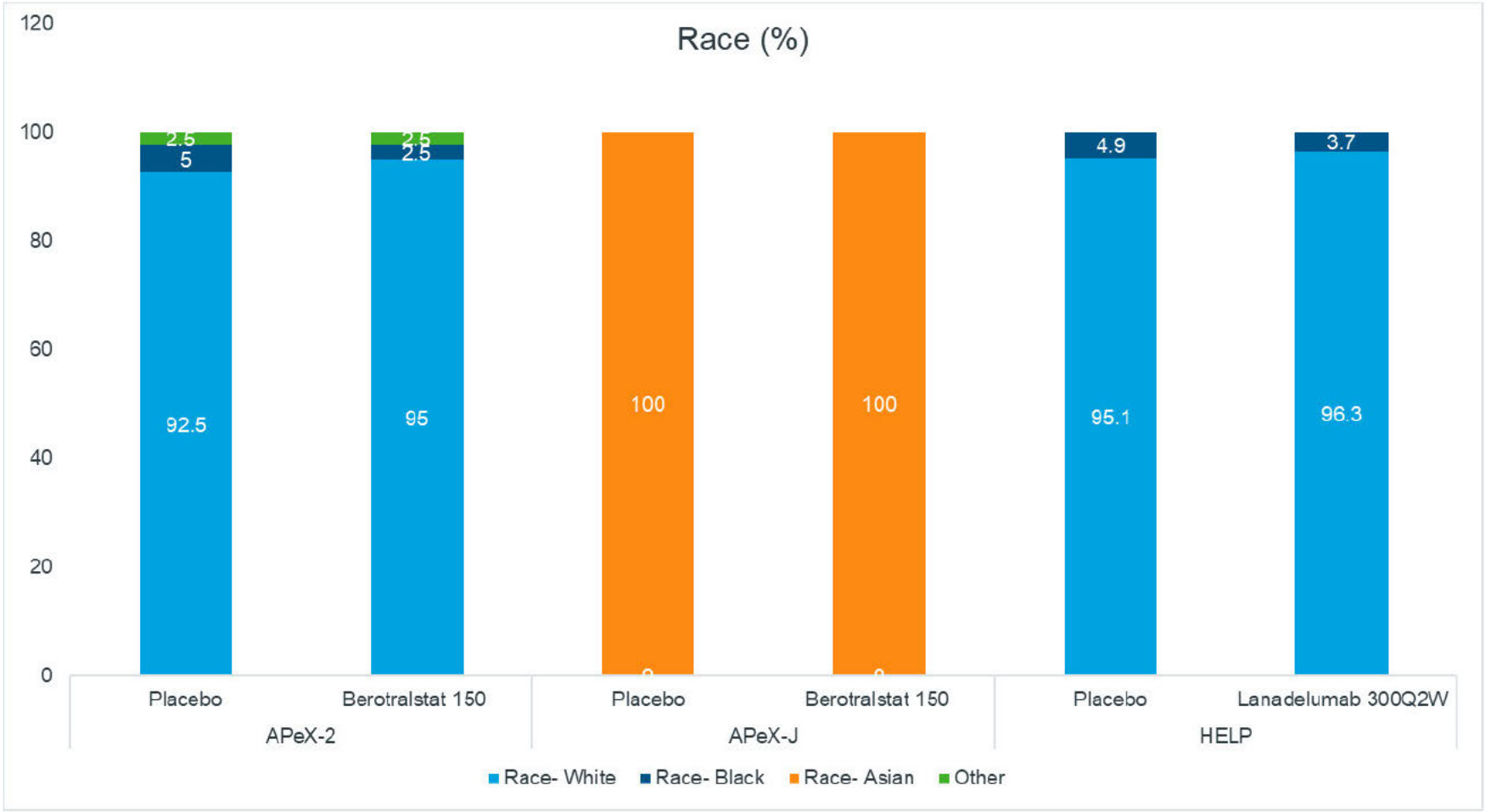
Figure B5: Between-study heterogeneity: Proportion of different race



Abbreviations: Q2W every 2 weeks

*Other in APeX-2 not specified

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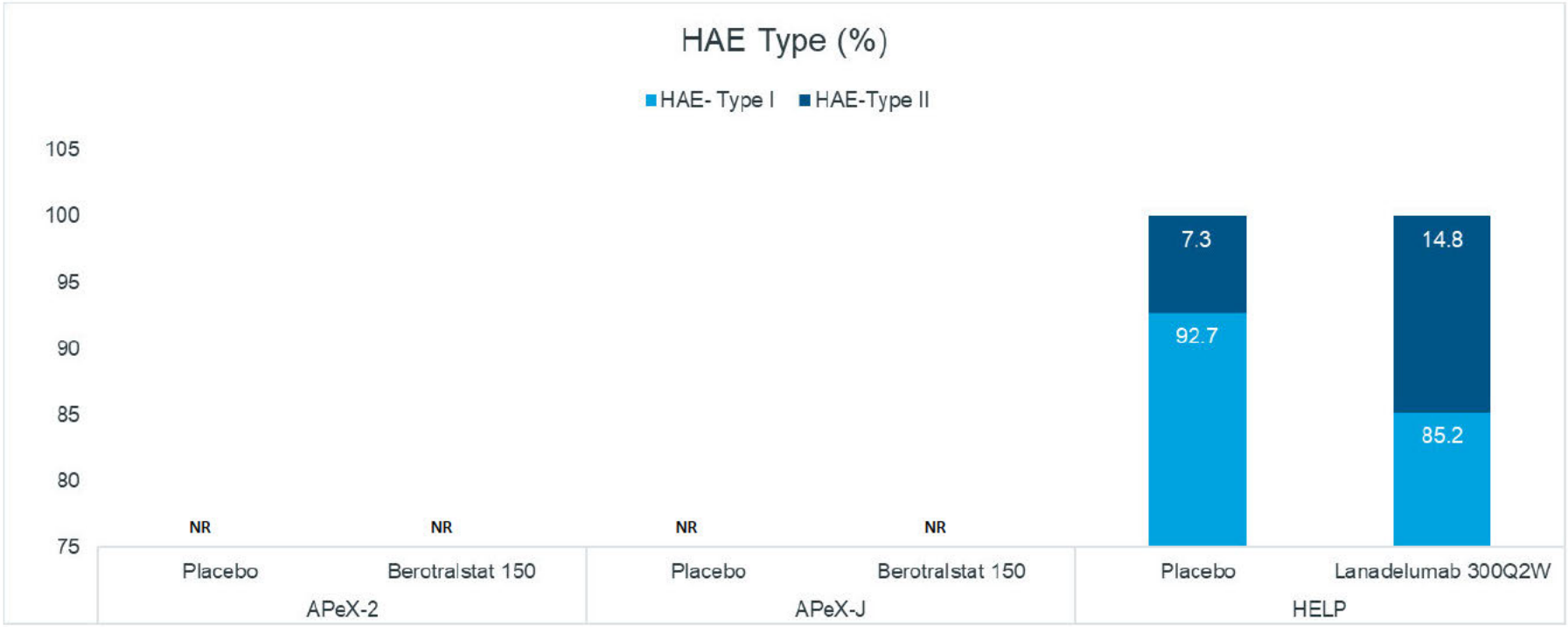
Figure B6: Between-study heterogeneity: Proportion of patients by HAE type



Abbreviations: HAE, hereditary angioedema; NR not reported; Q2W every 2 weeks

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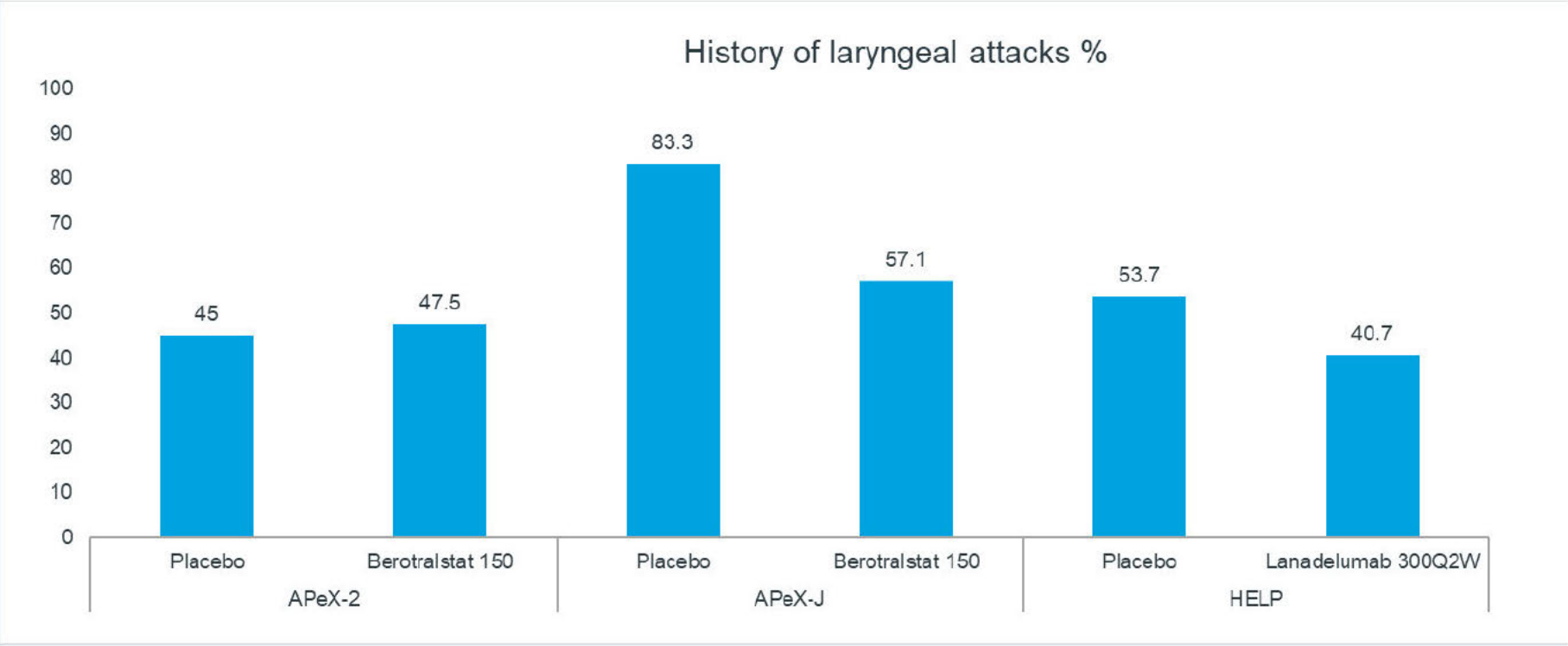
Figure B7: Between-study heterogeneity: Proportion of patients with history of laryngeal attacks



Abbreviations: Q2W every 2 weeks

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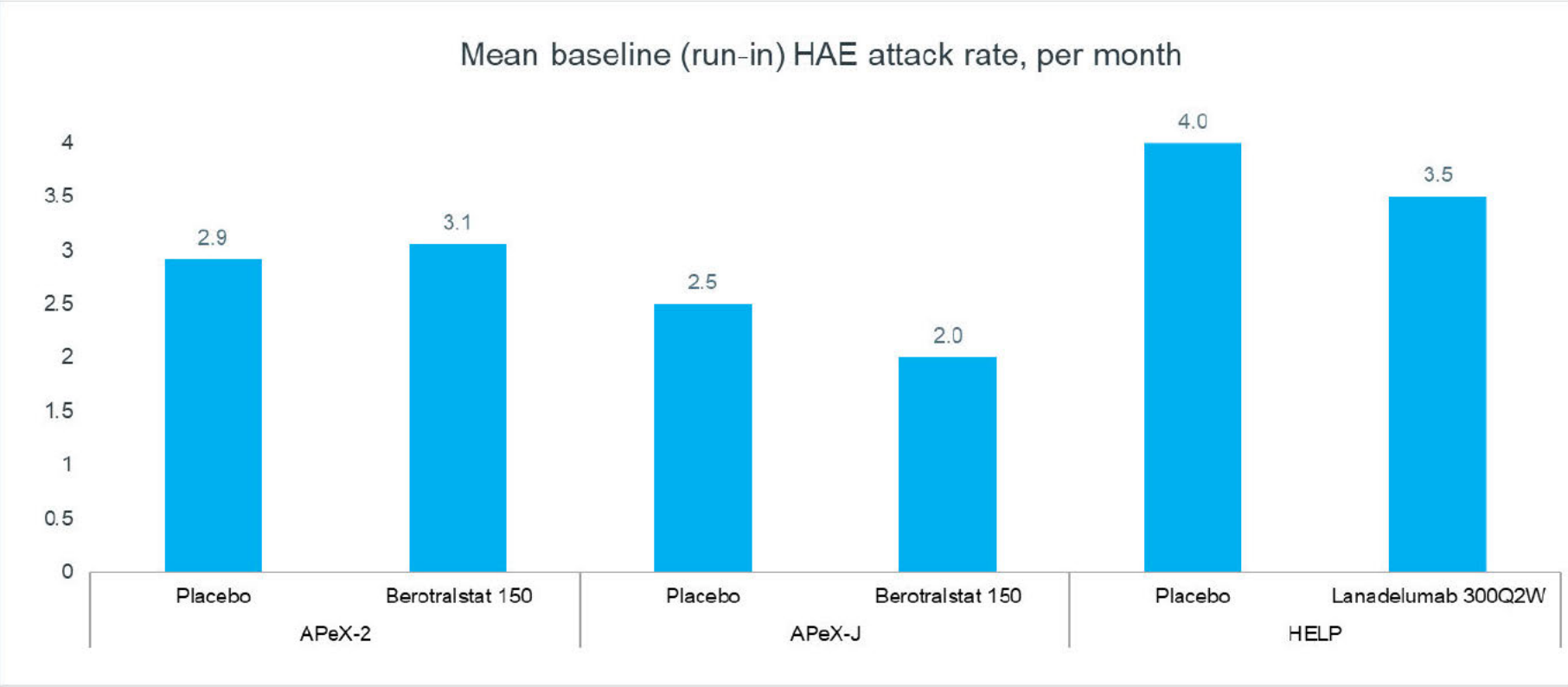
Figure B8: Between-study heterogeneity: Mean baseline (run-in) HAE attack rate, per month



Abbreviations: Q2W every 2 weeks

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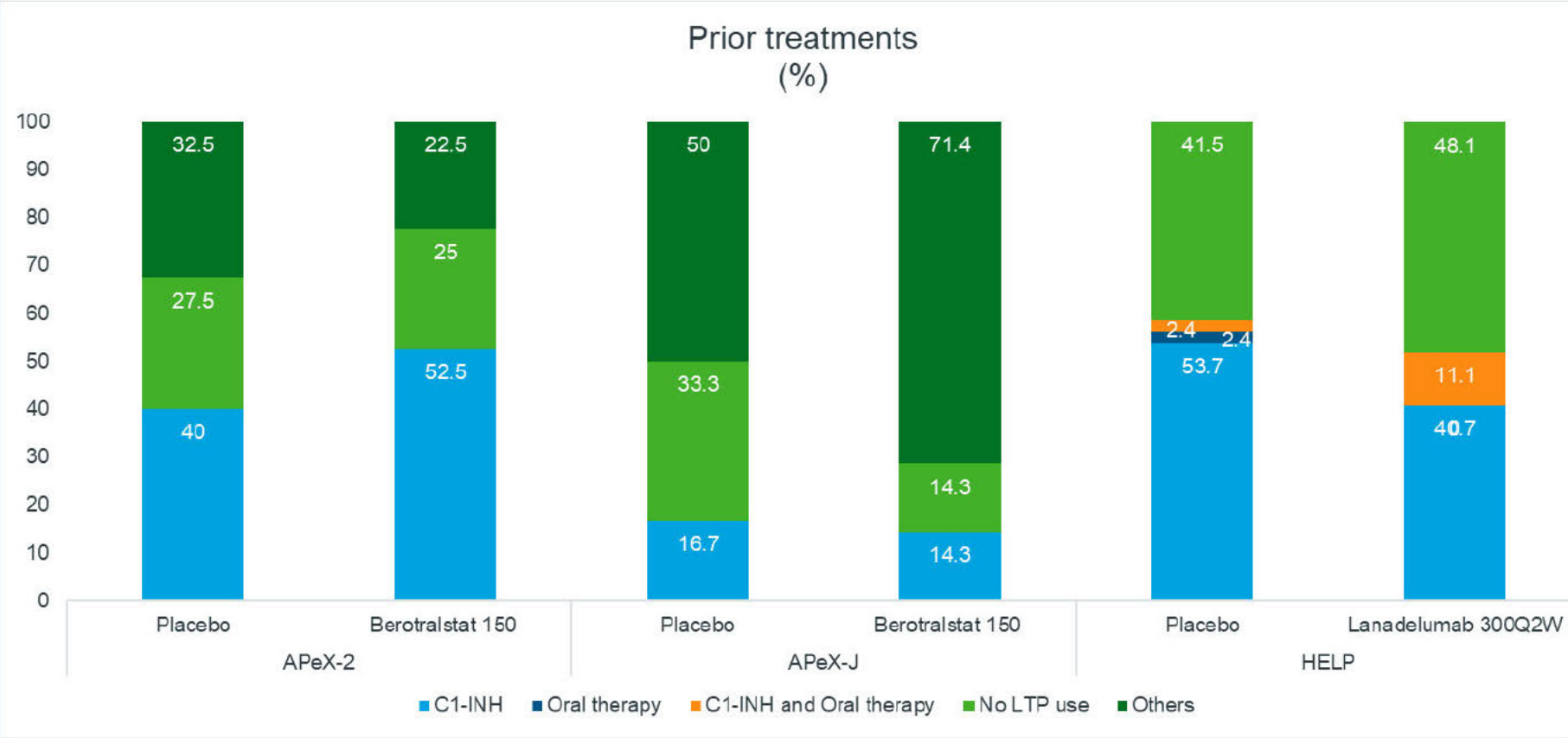
Figure B9: Between-study heterogeneity: Proportion of patients taking prior treatments



Abbreviations: C1-INH: C1-inhibitor; Q2W every 2 weeks

**Others in APeX-2 includes any androgen, conestat alfa, desogestrel, and tranexamic acid*

***Others in APeX-J includes any androgen, goreisan, and tranexamic acid*

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Appendix C. Summary of unfavourable effects from EMA risk-benefit assessment reports

Table C1 Summary of unfavourable effects from the risk-benefit assessments in the products' public assessment reports

Berotralstat [10]

Berotralstat appears to have an acceptable safety profile. Most AEs were mild to moderate in severity, and recovery was documented. The overall rates for AEs and SAEs were low and similar across all treatment arms.

The main unfavourable effects associated with berotralstat are abdominal pain, diarrhoea and headache with a frequency very common. Gastroesophageal reflux, Flatulence vomiting are also reported as common GI effects. These reactions were generally mild rarely led to treatment interruptions.

Drug rash can occur with treatment with a frequency estimated as common.

The most common clinically significant chemistry abnormalities were liver-related abnormalities, (ALT and AST increased). The majority of treatment-emergent liver abnormalities were Grade 1 or Grade 2; however, some patients experienced more marked elevations with treatment-emergent Grade 4 ALT with Grade 3 AST. It acknowledged that these patients remained asymptomatic and that there have not been instances of transaminase elevations with concomitant evidence of jaundice or synthetic dysfunction to date. In studies 204 and 302, the incidence of ALT > 3 × ULN was significantly correlated with prior androgen duration of ≥ 5 years ($p < 0.001$) and recent discontinuation of androgens ($p < 0.001$). The odds of having an elevation were 10.7 × higher for those with ≥ 5 years of exposure (14 of 151 subjects [9.3%]) compared to those with < 5 years duration of exposure (2 of 230 subjects [0.9%]). The odds of having an elevation were 66.0 × higher for those with recent androgen use, defined as discontinuation of androgens within 30 days of commencing berotralstat, (14 of 49 subjects [28.6%]) compared to those without recent androgen use (2 of 332 subjects [0.6%]).

The adolescent group had the lowest proportion of subjects with reported TEAEs, 13 of 16 subjects (81.3%), vs. 283 of 312 adult subjects (90.7%), and 13 of 14 elderly subjects (92.9%). The elderly group had the highest incidence of Grade 3 or Grade 4 TEAEs; 3 of 14 elderly subjects (21.4%), vs. 40 of 312 adult subjects (12.8%), and 2 of 16 adolescent subjects (12.5%). The elderly were the highest proportion of subjects who discontinued study drug due to a TEAE and also had a higher incidence of potentially drug-related hepatic disorders, GI abdominal TEAS, and had a higher incidence of GRADE 3 and Grade 4 laboratory abnormalities compared to adolescents and adults. While the lowest number of adverse events was observed in adolescent population, there remain uncertainty in the safety profile as the number of adolescent patients was very low. There is insufficient data to conclude on the safety in adolescent patients < 40kg.

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Lanadelumab [9]

Safety data are generated from the placebo-controlled pivotal 6-month study DX-2930-03, which included 125 subjects (84 active, 41 placebo). The open-label study DX-2930-04 contributes with long-time data (up to 12 months) in 75 subjects. Overall in the pivotal study, there were more TEAEs in the lanadelumab treated group compared to placebo, 91% vs 76%, more related TEAEs 60% vs 34% and more serious TEAEs 5% vs 0%.

Numerically there is a trend that the highest dose group, 300 mg q2 wks, had more TEAEs and more related TEAEs compared to the other lanadelumab groups. Related TEAEs are dominated by injection site reactions in the lanadelumab group; injection site pain 42%, injection site erythema 9.5%, injection site bruising 6%. Overall pooled data for DX-2930-03 and DX 2930-04 (n=220) shows that Injection Site Reactions were the most frequently reported TEAEs (53% of lanadelumab-treated population).

Hypersensitivity reactions are recorded in the lanadelumab treated population, n=5 in the pivotal study and its extension. In study DX-2930-04, hypersensitivity reactions accounts for 3/5 discontinuations due to adverse events.

There was a dose-dependent increase in aPTT and changes appear from the first measurement after study start, i.e. day 28. These changes were maintained throughout the study period up to day 182. Changes in the 300 mg q2wks group were in the range of 6–8 sec from baseline value of 28 sec (<29% increase). 83/84 lanadelumab treated subjects had aPTT <1.5 x ULN. In DX-2930-04 aPTT was monitored and the change from baseline was increased to a similar extent, at most 5.71 seconds at day 224 on group level. No bleeding events were observed in association with a prolonged aPTT, and no effects on PT, INR were observed in subjects treated with lanadelumab.

Pooled phase 3 safety data shows that elevated ALAT >3X ULN (regardless of baseline - with up to 3X allowed) was reported in 10 subjects. Subjects with elevations were asymptomatic, with no associated hyperbilirubinemia (no Hy's Law cases) or elevated alkaline phosphatase and 5/10 returned to baseline while lanadelumab was continued. No antidrug antibody formation was recorded for the 10 subjects. It is considered unknown whether lanadelumab could potentially be linked with more pronounced liver toxicity in a larger treatment population. Therefore this is a safety concern and included in the RMP as an important potential risk.

Abbreviations: AE Adverse Event; ALAT/ ALT Alanine transaminase; aPTT activated partial thromboplastin time; AST Aspartate transaminase; GI Gastrointestinal; INR International Normalized Ratio; PT thromboplastin time; q2 wks every second week; RMP risk management program SAE Serious Adverse Event; TEAE Treatment emergent adverse event; ULN Upper limit of Normal

Appendix D. Forest plots from ITC

Figure D1: Forest plot for binary outcomes (HELP and APeX-2 + APeX-J)

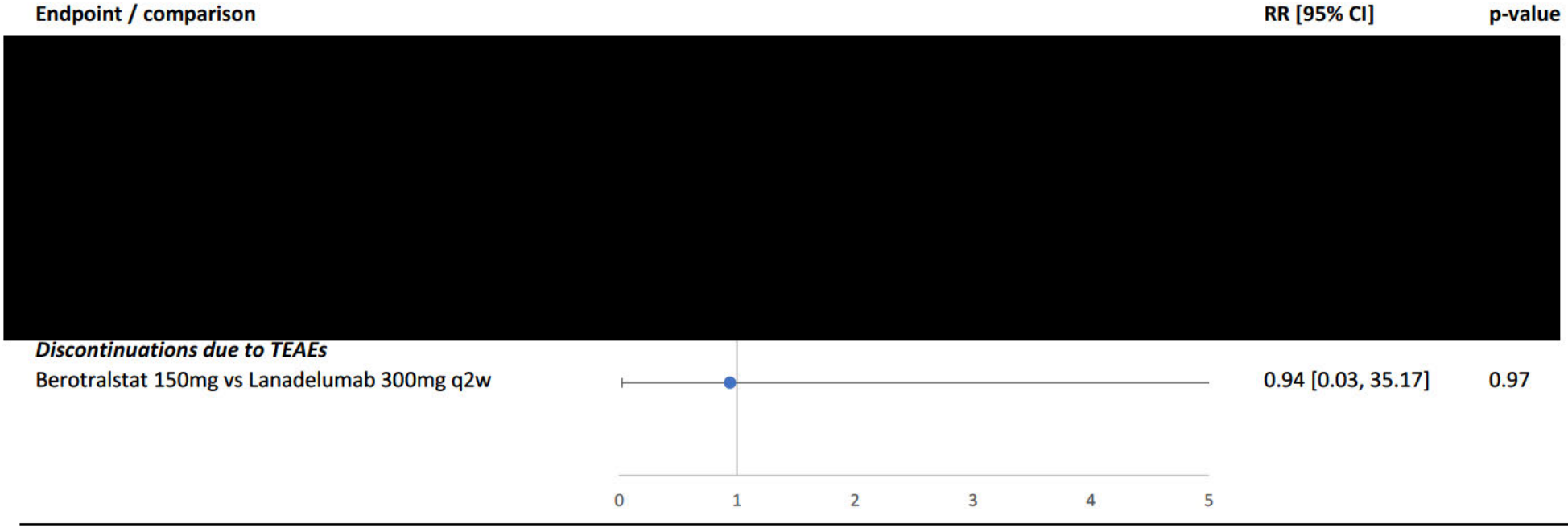

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Figure D2: Forest plot for binary outcomes (HELP and APeX-2)

Endpoint / comparison	RR [95% CI]	p-value
[redacted]		
Discontinuations due to TEAEs		
Berotralstat 150mg vs Lanadelumab 300mg q2w	1.95 [0.03, 127.95]	0.75

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Figure D3: Forest plot for rate outcomes (HELP and APeX-2 + APeX-J)

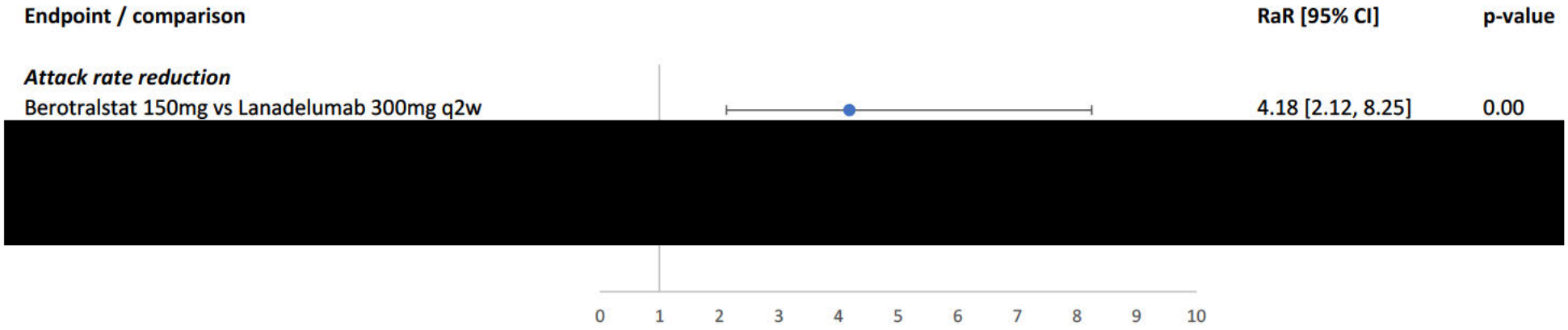

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Figure D4: Forest plot for rate outcomes (HELP and APeX-2)

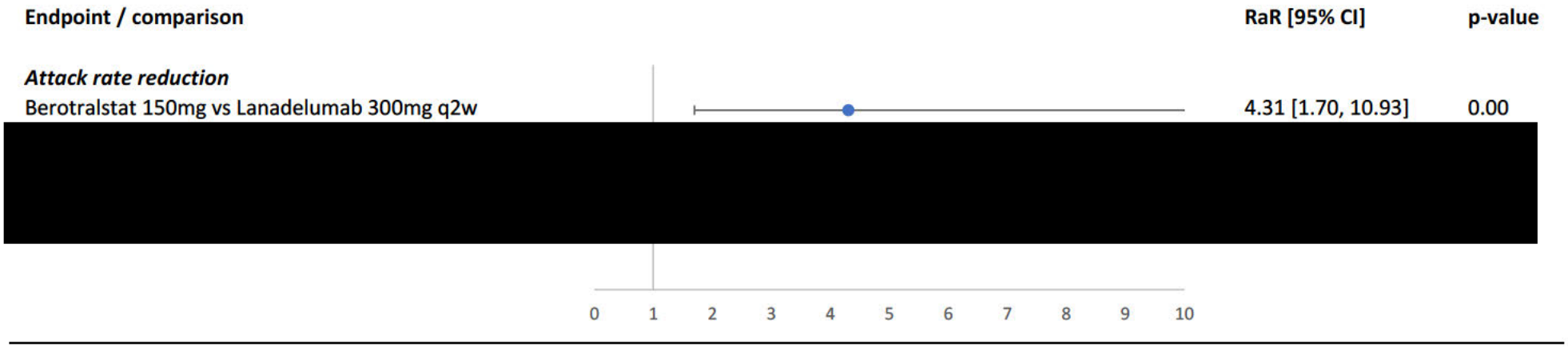

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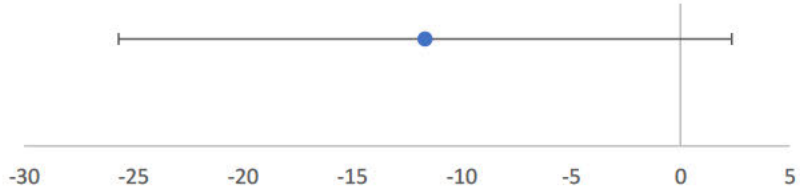
Figure D5: Forest plot for continuous outcomes (HELP and APeX-2 + APeX-J)

Endpoint / comparison		Mean [95% CI]	p-value
AE-QoL total score			
Berotralstat 150mg vs Lanadelumab 300mg q2w		-9.13 [-22.92, 4.66]	0.19

Figure D6: Forest plot for continuous outcomes (HELP and APeX-2)

Endpoint / comparison		Mean [95% CI]	p-value
AE-QoL total score			
Berotralstat 150mg vs Lanadelumab 300mg q2w		-11.67 [-25.69, 2.35]	0.10

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Economic analysis of Orladeyo (berotralstat) for routine prevention of hereditary angioedema attacks

Application to the Medicine Council

1.1

2021-09-01

Contents

Abbreviations

AE	Adverse event
DKK	Danish kroner
DRG	Disease related groups
HR	Hazard ratio
MC	Medicines Council
OD	Once Daily
PO	Peroral
PPP	Pharmacy Purchase Price
Q2W	Every second week
RR	Rate ratio
SC	Subcutaneous
SmPC	Summary of product characteristics
TAE	Treatment emergent adverse event

1 Background

Biocryst is applying to the Medicines Council to commission the use of berotralstat (Orladeyo) for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

The Medicines Council protocol for assessment of added clinical value of berotralstat in this indication states the following scientific question:

- *Hvilken værdi har berotralstat sammenlignet med lanadelumab?[1]*

The protocol specifies a single population of patients with HAE (adults and children 12 years of age and older). The clinical assessment should compare berotralstat at the recommended dose of 150 mg OD PO to lanadelumab at the recommended dose of 300 mg SC every second week (Q2W).[1]

The clinical assessment of berotralstat has been conducted according to the protocol.

Berotralstat was investigated in two phase III studies, APeX-2 is the main efficacy study in the EMA regulatory assessment, while APeX-J is a similarly designed phase III trial in a Japanese population. Both trials were comparing berotralstat in the approved 150mg p.o. o.d. dose compared to placebo.

Lanadelumab was studied in a phase III trial (HELP) comparing various lanadelumab 300 mg Q2W and placebo.

As no head-to-head clinical studies comparing berotralstat with lanadelumab 300mg Q2W exists, an indirect treatment comparison (ITC) was carried using Bucher analysis. The ITC included APeX-2, APeX-J and HELP (see clinical dossier section 4.4.1).

The ITC results for comparison between berotralstat 150mg o.d. and lanadelumab 300mg Q2W showed no statistically significant and clinical meaningful differences with regard to any of the selected outcome (see clinical dossier section 5.1.3). With respect to the attack rate, the relative Rate Ratio was estimated at 4.18 with corresponding 95% CI of 2.12 to 8.25, indicating that berotralstat 150 mg is associated with a higher attack rate relative to lanadelumab 300 mg Q2w ($p<0.001$) at week 24. Using the percentage attack rate difference to placebo in HELP as comparator outcome, the absolute reduction in attack rates compared to placebo with berotralstat is 41.4 percentage points lower compared to lanadelumab. The 95% confidence interval (-14.6 p.p.; 94.2 p.p.) includes 15 percentage points defined as the clinically relevant difference in the DMC protocol.

Comparison of the safety profile of the two treatments showed that both treatments are well-tolerated with mild side-effects. The type of side-effects differs with mild gastrointestinal adverse events (occurring mainly in the first months of treatment) being the main adverse effect associated with berotralstat 150 mg and low-intensity injection site reactions being the main adverse effect associated with lanadelumab treatment.

Overall, the clinical assessment concludes that berotralstat is a relevant new treatment option with efficacy and safety comparable to lanadelumab 300 mg Q2W based on indirect comparison of placebo-controlled trials with up to 6 months of follow-up.

An economic model has been developed to assess the cost per patient of berotralstat as well as the five-year regional budget impact of introducing berotralstat as standard treatment in Denmark. The analysis has been conducted from a partial societal perspective.

2 Cost analysis

Scope of analysis

The main outcome studied is the incremental cost per patients. The scope of analysis is limited to cost associated with choice of treatment (berotralstat 150mg o.d. or lanadelumab 300mg Q2W) and exclude cost elements that are likely to be unaffected by choice of treatment.

A limited societal perspective was applied in costing.

A time horizon was set to life-long treatment in the base case. The horizon was pragmatically chosen as the long-term cost is a multiplication of the annual cost because the two preventive treatments studied do not affect mortality and dosing is constant. In sensitivity analysis over time horizons may be tested.

Cost elements directly associated with choice of treatment include cost of drug and drug administration for long-term prevention and treatment of acute (break-through) attacks. In addition, health care contacts associated with acute treatment of attacks were included.

Excluded cost elements are costs of side effects and disease monitoring cost. There is no evidence to suggest that the interventions are associated with statistically significant or clinically relevant differences in safety. Monitoring of disease is assumed to be the same for both treatments in line with recent HAE cost analyses by the Danish Medicines Council. [2, 3]

2.1 Resource use and unit costs

Cost of medicine

An overview of the dosing of berotralstat and lanadelumab is included is provided in Table 1. Information on dosage, drug administration, and treatment schedules are based on the Medicine Council protocol. [1]

Table 1: Dosing of routine prevention treatments included in the analysis

Product	Recommended dosing
Berotralstat	150 mg peroral once daily
Lanadelumab	300 mg subcutaneous once every second week

Table 2 Available strengths and pack sizes and price per pack (PPP)

Product	Strength and pack size	Pack price
Berotralstat	150 mg 28 capsules	114,398
Lanadelumab	300 mg 1 syringe	99,519.09*

Abbreviations: PPP pharmacy purchase price.
* PPP by April 30th 2021. Medicinpriser.dk

Duration of treatment

In the base case analysis it is assumed that patients are treated life-long. The remaining life-time for patients was based on general population life-table. In the calculation the patient is assumed to be 42 years of age (APeX-2 base line age) and using a 66%: 33% weighting of female: male survival (APeX-2 base line demographics).

Cost of drug administration

The Medicines Council protocol states that current standard of treatment is mainly self-administrated, however, some patient may need assistance at the local hospital.[1] In the cost-analysis it is assumed that this applies for 2 of the estimated 30-40 patients currently treated with lanadelumab which would imply that 6% (2 of 35) will need assisted administration. In addition, patients may need assistance from parent/ caregiver when administrating the treatment at home. No cost associated with assistance in the home were included in the analysis.

Table 3 presents the unit cost per health care contact applied in the model.

Travel cost was calculated based on a 28 km round trip distance for all outpatients visit (@ 3.52 kr/km). [4] Patient time was costed at 179 DKK/ hour.[4] Total time and travel cost associated with regular blood test was assumed to be 50% of the cost associated with an outpatient visit based on the assumption of the patient using a local test facility.

Table 3 Unit cost applied in the cost analysis

Resource	Regional cost	Note	Patient cost	Note
Assisted administration (SC)	185	20 min Nurse time @ 554 DKK/ h[4]	233	28 km travel @ 3.54 DKK/km + 45 min patient time @ 179 DKK/h [4]
Self-administration SC injection	0		15	5 min patient time @ 179 DKK/h[4]
Administration oral drug	0		0	

Cost of monitoring

In line with previous assessments of routine prevention in HAE, it is assumed that the number of monitoring visits and visits associated with drug dispensing will be the same for the two products.[2, 3]

Cost of side-effects

The base case analysis was designed on the premise that treatment with berotralstat is clinically equivalent to lanadelumab with respect to outcomes in the Medicine Council assessment. Consequently, the costs of side-effects were excluded from the analysis.

Treatment of acute attacks

Patients on routine prevention of HAE may suffer break-through attacks. The cost of treating attacks was estimated using the assumptions in the MC's cost assessment of lanadelumab conducted by Amgros[2]. Unit cost applied were updated to 2021 cost-levels using the same sources as in the Amgros analysis. The assumptions and resulting regional and patient cost per attack are shown in Table 4 and Table 5, respectively.

Table 4 Regional cost of attacks (DKK per attack)

Resource	% of treated attacks requiring ressource*	Direct cost	Source:
Firazyr injection	133%	13,589	
GP visit	2%	146.79	Konsultation PLO honorartabel, 2021

Resource	% of treated attacks requiring ressource*	Direct cost	Source:
Outpatient visit	10%	3,114	16MA98: MDC16 1-dags-gruppe, pat. mindst 7 år DRG-takster 2021
Hospital visit	5%	22,545	16MA10: Øvrige sygdomme i blod og bloddannende organer DRG-takster 2021
Cost of treatment*		19,515	
Cost per attack†		16,588	Assuming 85% of attacks require medical treatment[2]

*Applies to attacks requiring treatment.

† Weighted cost (85% of cost of treating attacks assuming zero cost for attacks not requiring treatment)

Table 5 Patient cost of attacks (DKK per attack)

Resource	Patient time (h)	Transport (km)	Assumptions	Total patient cost
Firazyr injection	0.08	0	5 min administration time[2]	15
GP visit	1	14	1 hour travel + clinic time. 14 km travel (50% of hospital visit)[2]	228
Outpatient visit	1	28	1 hour travel + clinic time. 28 km travel [2]	278
Hospital visit	8	28	8 hours travel + clinic time. 28 km travel [2]	1,531
Cost of treatment*				**129**
Cost per attack†				**109**

Note: Unit cost per hour and km sourced from Danish Medicine Council Unit cost catalogue[4]

*Applies to attacks requiring treatment. Weighted sum using the percentages of resource use in Table 4

† Weighted cost (85% of cost of treating attacks assuming zero patient costs for attack not requiring treatment)

There are no available direct comparisons of the clinical efficacy of berotralstat 150 mg OD and lanadelumab 300mg Q2W. Indirect treatment comparison of placebo-controlled trials (1 phase 3 study for lanadelumab and 2 phase 3 studies for berotralstat) suggest that the relative reduction from base line on active treatment compared to the relative reduction on placebo on the short run is higher for lanadelumab compared to berotralstat. However, the indirectness of the evidence adds to the uncertainty of the comparison.

Based on the level of uncertainty – and in anticipation of the Danish Medicines Council final ruling on the overall added clinical value of berotralstat compared to lanadelumab, the base case analysis assumes equivalent on treatment attack rates for both treatments. This assumption is in line with Norwegian authorities' recent decision to include both lanadelumab 300mg Q2W and berotralstat 150mg OD in the same tender class, but is relaxed in sensitivity analyses.

Patient cost

Patient costs were calculated based on patient time spend in connection drug administration and patient time and travel cost associated with health care contacts for acute treatment of break-through attacks as specified above.

Discounting

Costs accrued after year 1 was discounted by 3.5% per year; from year 36-70 by 2.5% per year; thereafter 1.5%. [5]

2.2 Results

Base case assumptions

Table 6 summarized the key base case assumption outlined above.

Table 6 Key base case assumptions

Option	Selected base case
Intervention	Berotralstat 150 mg PO OD
Comparator	Lanadelumab 300 mg SC Q2W
Time horizon	Life-long
Treatment duration	Life-long. Life-expectancy based on general population survival [6] for a 44 old patient (base line age in APeX-2). Population survival was weighted by gender distribution in APeX-2 (66% female; 34% male)[7]
Acute attacks	Equivalent efficacy
Price	Pharmacy purchase price
Discount rate	3.5% per year for cost accrued from year 2 2.5% per year for cost accrued from year 36 1.5% per year for cost accrued from year 71[5]

Abbreviations: PO peroral; OD once daily; Q2W every second week; SC subcutaneous

Base case results

Table 7 show the base case results. Treatment with berotralstat is associated with a saving in net-present cost of 17.4 MDKK per patient.

Table 7 Base case results. Life-term cost per patient(discounted)

	Berotralstat 150 mg PO OD	Lanadelumab 300 mg SC Q2W	Incremental
Medicine	23,507,434	40,900,099	-17,392,665
Hospital cost	0	4,337	-4,337
Total direct cost	**23,507,434**	**40,900,099**	**-17,392,665**
Patient cost	0	11,293	-11,293
Societal cost	**23,507,434**	**40,911,392**	**-17,403,958**

Sensitivity analysis

Table 8 shows the results of a one-way sensitivity analysis of using alternative assumptions.

Table 8 Results of sensitivity analyses (societal cost per patient)

Scenario	Berotralstat	Lanadelumab	Incremental cost
Base case	**23,507,434**	**40,911,392**	**-17,403,958**
Treatment duration 1 year	1,486,624	2,587,260	-1,100,636
Treatment duration 3 years	4,304,657	7,491,652	-3,186,995
Treatment duration 10 years	12,569,902	21,876,151	-9,306,249
Lanadelumab assisted administration 10%	23,507,434	40,915,238	-17,407,804
Lanadelumab assisted administration 0%	23,507,434	40,906,263	-17,398,829

Furthermore, to analyse a scenario where the conclusion of DMC is that the two products are not clinical equivalent the impact of treating acute attack was included. In this analysis, the point estimates from the ITC were applied. The rate ratio of lanadelumab has been reported to be 0.13 compared to placebo (HELP trial [8]) and the rate ratio of berotralstat was estimated at 0.54 (APeX-2 and APeX-J) combined (see main application document). The estimated indirect rate ratio of berotralstat compared to lanadelumab in the Bucher analysis is hence -4.18 (see section 1).

Table 9 show the results of the sensitivity analysis by attack rate without LTP. At PPP, berotralstat 150 mg OD is associated with a cost-saving compared to lanadelumab 300 mg Q2W.

For baseline attack rates below 8 / month the on-treatment attack-rate on berotralstat is less than 4 attack rates per month, which has been defined as the main staring criteria for lanadelumab and subcutaneous C1-inh as preventive treatment by the Danish Medicines Council.[2, 3] This would suggest that the rationale introduction of berotralstat as a first-line treatment and to reserve lanadelumab for patients with insufficient reduction of attack rates on berotralstat treatment.

Table 9 Estimated number of attacks on treatment, incremental cost of acute treatment and incremental societal cost per patient and per year

	Acute attacks (no LTP) per month							
	2	3	3.2 *	4	5	6	7	8
Acute attacks on treatment								
Berotralstat	1.09	1.63	1.76	2.17	2.72	3.26	3.80	4.35
Lanadelumab	0.26	0.39	0.42	0.52	0.65	0.78	0.91	1.04
Incremental annual cost	165,666	248,499	268,713	331,332	414,165	496,998	579,831	662,664
Incremental prevention cost per year (base case)				-1,101,315				
Total cost per year (berotralstat vs lanadelumab)	**-935,649**	**-852,816**	**-832,602**	**-769,983**	**-687,150**	**-604,317**	**-521,484**	**-438,651**

* The baseline attack rate across APeX-2, APeX-J, and HELP (all patients) combined was 3.2[7-9]

3 Budget impact analysis

3.1 Method

The impact of introducing berotralstat as standard treatment in HAE was calculated using a simplified 5-year budget impact model.

The budget impact is simplified in the way that it considers a steady-state population where all patients are either treated with berotralstat or with lanadelumab.

Costs in the budget impact analysis include regional cost only and are not discounted. Mortality was not included in the budget impact analysis.

3.2 Patient numbers and market share

The MC protocol estimate that 30-40 patients are treated with long-term prophylaxis and this consists mainly of lanadelumab[1]. Hence population in the budget impact analysis is assumed to consist of 35 patients all treated with either lanadelumab or berotralstat.

Table 10 Patient number and without recommendation of berotralstat

Year:	1	2	3	4	5
Situation without berotralstat					
Berotralstat	0	0	0	0	0
Lanadelumab	35	35	35	35	35
Situation with berotralstat					
Berotralstat	35	35	35	35	35
Lanadelumab	0	0	0	0	0

3.3 Results

In steady state, the budget impact will result in a decrease in regional expenditure of 38.5 million DKK per year when estimated using current PPP prices (Table 11).

Table 11 Result of budget impact analysis (Million DKK; pharmacy purchase prices)

	Budget year				
Scenario	**1**	**2**	**3**	**4**	**5**
Situation with berotralstat	52.051	52.051	52.051	52.051	52.051
Situation without berotralstat	90.572	90.572	90.572	90.572	90.572
Budget impact	**-38.521**	**-38.521**	**-38.521**	**-38.521**	**-38.521**

4 Conclusion

The introduction of berotralstat offers a cost-saving and a sustainable new treatment option for routine prevention of HAE attacks. The introduction of berotralstat is associated with a societal cost saving over a life-time horizon of 17.4 million DKK per patient at PPP prices. Regional budget impact analysis shows an overall saving of 38.5 MDKK per year when it is pragmatically assumed that all patients currently treated with lanadelumab will switch to berotralstat. Over the 5-years period, the introduction of berotralstat is associated with a total saving of 192,6MDKKK.

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende berotralstat til forebyggende behandling af arveligt angioødem

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

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

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

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

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1. Begreber og forkortelser

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

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra BioCryst Ireland Limited, som ønsker, at Medicinrådet vurderer berotralstat (Orladeyo) til rutinemæssig forebyggelse af tilbagevendende anfald af arveligt angioødem. Medicinrådet modtog den foreløbige ansøgning den 15. december 2020. BioCryst Ireland Limited fik forhåndsgodkendelse (positive opinion) i EMA den 25. februar 2021.

2.1 Arveligt angioødem

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

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

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

Den nøjagtige forekomst af HAE er ukendt, men det anslås, at HAE påvirker ca. 1 ud af 10.000-50.000 personer verden over [1,2]. Aktuelt er der i Danmark registreret ca. 110 patienter, som jævnligt er i kontrol på det Nationale Kompetencecenter for HAE på Odense Universitetshospital. En opgørelse fra 2014 viste, at anfaldsfrekvensen varierede fra, at patienterne var asymptomatiske, andre med få anfald om året og andre patienter med op til 84 anfald om året. Den gennemsnitlige frekvens lå på 17 anfald om året [3].

Den uforudsigelige og potentielt livstruende sygdom påvirker patienternes livskvalitet. Selv mellem anfald, hvor patienterne ellers er symptomfri, oplever mange patienter stadig angst og begrænsninger i de daglige aktiviteter [4]. Mønstret i anfaldene og

sværhedsgraden heraf er for den enkelte patient uforudsigeligt. Sygdomsbyrden mellem anfaldene fylder således rigtig meget for HAE-patienterne. Patienterne tænker ofte: Hvornår kommer det næste anfald, hvor er jeg, har jeg anfaldsmedicin i nærheden, og er jeg overhovedet i stand til at administrere medicinen selv? At leve med HAE har derfor stor betydning for livskvaliteten med risiko for personlige omkostninger i forhold til familie- og arbejdsliv. Netop på grund af den store sygdomsbyrde er det ønskeligt for HAE-patienter, at fremtidige HAE-behandlinger ikke blot holder anfaldshyppigheden nede, men at behandlingen sigter mod at gøre HAE-patienter anfaldsfrie.

2.2 Berotralstat

Berotralstat (Orladeyo) er et oralt lægemiddel, som hæmmer det aktive plasmakallikreins proteolytiske aktivitet og herved mindsker risikoen for angioødemanfald. Hos patienter med HAE-type I og II er den normale regulering af kallikreinaktiviteten nedsat. Dette fører til en ukontrolleret stigning i plasmakallikreinaktiviteten, som, gennem en frigivelse af bradykinin, resulterer i HAE-anfald.

Indikationen for berotralstat (Orladeyo) er rutinemæssig forebyggelse af tilbagevendende anfald af arveligt angioødem. Patienten indtager lægemidlet oralt én gang daglig. En kapsel indeholder 150 mg berotralstat. Lægemidlet betragtes som et *orphan drug*. Berotralstat vil blive givet kontinuerligt gennem flere år. Behovet for forebyggende behandling vurderes løbende, da patienternes sygdomsaktivitet varierer over tid.

2.3 Nuværende behandling

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

Den forebyggende behandling iværksættes i henhold til den gældende internationale guideline fra World Allergy Organization og European Academy Allergy and Clinical Immunology fra 2017 [5]. Jævnfør denne guideline eksisterer der ikke faste kriterier for, hvilke patienter der tilbydes forebyggende behandling. Behovet for forebyggende behandling vurderes under hensyntagen til patientens sygdomsaktivitet, anfaldsfrekvens/sværhedsgrad/lokation, livskvalitet og eventuelt manglende sygdomskontrol ved behandling af akutte anfald. Da alle disse faktorer varierer over tid, bliver behovet for forebyggende behandling vurderet ved hvert kontrolbesøg. Patientens præferencer er også en væsentlig faktor, f.eks. i forhold til administrationsvej.

Til forebyggende behandling bliver to behandlingsprincipper anvendt i Danmark. Det ene princip består i substitution af manglende funktionelt C1-esteraseinhibitor ved et af de to produkter Berinert® eller Cinryze®. Behandlingerne administreres intravenøst og oftest hver 3.-4. dag. Det andet behandlingsprincip består i at hæmme det aktive plasmakallikreins proteolytiske aktivitet, hvorved risikoen for angioødemanfald mindskes. Her anvendes lanadelumab (Takhzyro®), som er et humant monoklonalt antistof. Lanadelumab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af

HAE hos patienter på ≥ 12 år og er anbefalet som mulig standardbehandling af Medicinrådet hos patienter med minimum fire anfald om måneden. Den anbefalede dosis er 300 mg subkutant hver 2. uge.

De fleste patienter administrerer selv deres forebyggende behandling (eventuelt med hjælp fra pårørende). Patienter, der ikke selv behersker teknikken, behandles på lokalt sygehus. Ud af de ca. 110 danske patienter med HAE anslår fagudvalget, at ca. 30-40 patienter får forebyggende behandling, hvoraf hovedparten er i behandling med lanadelumab.

3. Kliniske spørgsmål

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

3.1 Klinisk spørgsmål 1

Hvilken værdi har berotralstat sammenlignet med lanadelumab som forebyggende behandling for patienter med arveligt angioødem?

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

Intervention
Berotralstat 150 mg p.o. én gang daglig

Komparator
Lanadelumab 300 mg s.c. hver 2. uge.

Effektmål
De valgte effektmål fremgår af Tabel 1.

3.2 Effektmål

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

Tabel 1 Oversigt over valgte effektmål

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

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

3.2.1 Kritiske effektmål

Anfaldsfrihed

Det vigtigste for patienterne er at blive anfaldsfrie. Dette vil fjerne den uforudsigelighed, som patienterne lever med, herunder også frygten for larynxødem, som har stor betydning for patienternes livskvalitet. Medicinrådet vil derfor vurdere berotralstats effekt på andelen af patienter, som er anfaldsfrie og anser det som et kritisk effektmål. Medicinrådet ønsker effektmålet opgjort som en forskel i andelen af patienter, som opnår en 100 % reduktion i anfaldsfrekvens fra baseline. I DX-2930-03-studiet med lanadelumab opnår ca. 44 % symptomfrihed [6], men data fra *open label extension*-studiet såvel som national og international klinisk erfaring tyder på, at der er betydeligt flere, som bliver symptomfrie [7,8]. Fagudvalget anslår, på baggrund af disse erfaringer, at ca. 70 % af patienterne opnår symptomfrihed ved behandling med lanadelumab i Danmark. Fagudvalget vurderer på denne baggrund, at en forskel på 10 %-point i andelen, som opnår anfaldsfrihed, er klinisk relevant.

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

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

3.2.2 Vigtige effektmål

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

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

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

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

nye behandlinger er forbundet med bivirkninger af en sådan karakter, at patienterne ophører med behandlingen.

Medicinrådet vil desuden foretage en kvalitativ gennemgang af bivirkningstyperne for berotralstat og lanadelumab med henblik på at belyse bivirkningsprofilerne mht. alvorlighed, håndterbarhed og hyppighed af bivirkningerne. Derfor bedes ansøger bidrage med oversigter over bivirkningsprofilerne for berotralstat og komparator, herunder også diskutere hvordan bivirkningsprofilerne adskiller sig fra hinanden.

4. Litteratursøgning

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

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

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

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

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

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med

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

andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

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

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

5. Den endelige ansøgning

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

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.

- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

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

Narrative analyser

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

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

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

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

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

6. Evidensens kvalitet

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

7. Andre overvejelser

Medicinrådet ønsker, at ansøger fremsender subgruppedata baseret på patienternes anfaldsfrekvens ved baseline. Opdelingen ønskes for patienter med under 2 anfald om måneden ved baseline og patienter med 2 eller flere anfald om måneden svarende til stratifikationen i APeX-2 studiet. Tilsvarende data ønskes også for komparator.

For patienter med HAE er der tale om en ny administrationsvej, når en oral behandling som berotralstat godkendes. Derfor ønsker fagudvalget, at ansøger fremsender information om adhærens til behandlingen med berotralstat (*compliance*), herunder årsager til manglende adhærens. Dette kan f.eks. være fra de randomiserede kliniske studier, *extension*-studier eller eventuel anden erfaring med berotralstat.

Det er også velkendt, at patienternes sygdomsaktivitet kan variere over tid. Såfremt der findes erfaringer med øget dosis for berotralstat over den anbefalede dosis på 150 mg hos patienter med periodisk øget anfaldsfrekvens, ønsker fagudvalget, at ansøger bidrager med information om effekt heraf.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

9. Referencer

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende arveligt angioødem

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

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	16. marts 2021	Godkendt af Medicinrådet

12. Bilag

Bilag 1: Søgestrenge

Søgestreng til PubMed:

#	Søgestreng	Kommentar
#1	"Angioedemas, Hereditary"[Mesh]	Søgetermer for populationen
#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	Berotralstat[nm] OR berotralstat[tiab] OR BCX7353[tiab]	Søgetermer for interventionen
#7	lanadelumab[nm] OR DX-2930[tiab] OR Takhzyro[tiab] OR lanadelumab[tiab]	Søgetermer for komparator
#8	#6 OR #7	Intervention + komparator
#9	(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
#10	#5 and #8 and #9	Samlet søgning

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	[mh "Angioedemas, Hereditary"]	
#2	(C1 and Inhibitor* and Deficienc*):ti,ab,kw	
#3	(hereditary and (edema* or oedema* or angioedema* or angiooedema*)):ti,ab,kw or angioneurotic edema: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	(berotralstat or BCX-7353 or BCX7353 or orladeyo*):ti,ab,kw	Søgetermer for interventionen
#8	(DX-2930 or Takhzyro or lanadelumab):ti,ab,kw	Søgetermer for komparator
#9	#7 or #8	Intervention + komparator
#10	#6 and #9	
#11	("conference abstract" or review):pt or NCT*:au	
#12	#10 not #11	Samlet søgning