Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende eculizumab til behandling af neuromyelitis optica spektrum sygdom (NMOSD)

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Eculizumab

Neuromyelitis optica spectrum sygdom (NMOSD)

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
AQP4	Aquaporin 4
BSC	*Best supportive care*
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
EDSS	*Expanded Disability Status Scale*
MS	Multipel sklerose
NMOSD	Neuromyelitis optica spectrum sygdom
SAIP	Sygehusapotekernes indkøbspris

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for eculizumab ca. [redacted] DKK pr. patient sammenlignet med *best supportive care* (BSC). Hvis behandlingsvarigheden i gennemsnit antages at være [redacted], vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK pr. patient. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 28,4 mio. DKK pr. patient.

De inkrementelle omkostninger ved eculizumab er hovedsageligt drevet af lægemiddelomkostninger, som er meget høje. Relativt til lægemiddelomkostningerne fylder de øvrige omkostninger ikke meget, men i absolutte tal udgør omkostninger til administration og patienter ved eculizumab også en stor del.

Der er i modellen en række usikkerheder, som gør det endelige resultat usikkert. Konkret er der usikkerhed vedr. de kommunale og regionale omkostninger til håndtering af det associerede handicap ved en given *Expanded Disability Status Scale* (EDSS-score). I hovedanalysen er disse omkostninger ekskluderet grundet usikkerhed om metode, men der er udført en følsomhedsanalyse, som viser, at de totale inkrementelle omkostninger pr. patient falder med ca. [redacted] DKK, hvis disse omkostninger inkluderes.

Der er ligeledes usikkerhed vedr. antagelser om behandlingsstop og dermed behandlingslængde. I hovedanalysen antages det, at behandling med eculizumab fortsættes efter et attak, mens der er udført en følsomhedsanalyse, som viser, at de totale inkrementelle omkostninger falder med [redacted] DKK pr. patient, hvis behandlingen med eculizumab stoppes ved første attak.

I denne analyse er eculizumab sammenlignet med BSC, hvilket er en konservativ komparator. Fagudvalget vurderer, at der benyttes en række immunsupprimerende lægemidler i dansk klinisk praksis (off label). Disse lægemidler er ikke inkluderet i denne sammenligning som derfor er usikker, og sandsynligvis underestimerer lægemiddelomkostningerne ved komparatoren og dermed overestimerer de inkrementelle omkostninger ved eculizumab.

Øvrige usikkerheder er uddybet i afsnit 7 og fylder mindre for det samlede resultat.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af eculizumab som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 43,1 mio. DKK i år 5.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af eculizumab som mulig standardbehandling på danske hospitaler til patienter med neuromyelitis optica spectrum sygdom (NMOSD).

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Alexion. Vi modtog ansøgningen den 12. februar 2021.

3.1 Patientpopulation

Neuromyelitis optica spectrum sygdom (NMOSD) er en kronisk neurologisk sygdom, der typisk rammer synsnerver og rygmarven. Patienter i Danmark har en medianalder på 35 år ved sygdomsdebut, men NMOSD kan ramme i alle aldre [1]. Sygdommen rammer kvinder tre gange oftere end mænd.

NMOSD er karakteriseret ved inflammation i det centrale nervesystem, der fører til demyelinisering med tab af gliaceller og neuroner og dermed neurologisk funktionstab. Patienter med NMOSD vil i varierende grad have både fysiske og kognitive symptomer såsom synsnedsættelse, dobbeltsyn, spastiske lammelser af arme og/eller ben, føleforstyrrelser, dårlig balance, vandladningsproblemer, forstoppelse, problemer med seksualfunktionen, smerter, træthed samt hukommelses- og koncentrationsproblemer. Patienterne oplever attakker, der kan medføre en vedvarende forværring af symptomer gennem sygdomsforløbet [2]. Omkring 60 % af patienterne oplever et nyt attak inden for det første år efter det første attak. Dette er flere end den gennemsnitlige patient med attakvis multipel sklerose (MS), og attakkerne vil oftere medføre varige skader hos patienter med NMOSD end hos patienter med MS. I modsætning til MS ses milde forløb af NMOSD sjældent. Hos ca. 75-80 % af patienterne med NMOSD er antistoffer mod proteinet aquaporin-4 (AQP4) til stede i blodet.

Ansøger angiver i sin foreløbige ansøgning, at 61 danske patienter er registreret med NMOSD (via personlig kommunikation med den ansvarlige person for Skleroseregistret). Fagudvalget har fra en dansk ekspert i NMOSD fået oplyst, at 39 patienter med NMOSD og AQP4-antistoffer blev registreret i Danmark i perioden 2007-2014 (manuskript under udarbejdelse). Der er ikke danske data efter 2014. På den baggrund antager fagudvalget, at antallet af patienter, der er kandidater til behandling med eculizumab, sandsynligvis ligger under 50 patienter, og at 5 nye patienter årligt vil være kandidater til behandlingen. Dette estimat er forbundet med stor usikkerhed.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

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

Klinisk spørgsmål 1:

Hvilken værdi har eculizumab sammenlignet med placebo for patienter med neuromyelitis optica spectrum sygdom?

4. Vurdering af den sundhedsøkonomiske analyse

Som en del af 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 eculizumab sammenlignet med *best supportive care* (BSC).

Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske sammenligning mellem eculizumab og BSC er primært lavet på baggrund af data fra det kontrollerede dobbeltblindede fase III-studie PREVENT, hvori patienterne blev randomiseret til behandling med enten eculizumab eller placebo. I PREVENT-studiet [3] blev mange af patienterne i både interventions- og komparatorarmen desuden behandlet med immunsupprimerende i kombination med eculizumab eller placebo. Placebo-armen i PREVENT [3] anvendes som kilde for effektiviteten af BSC i den sundhedsøkonomiske model.

Medicinrådets vurdering af det anvendte effektdata
Som beskrevet i vurderingsrapporten, finder fagudvalget det sandsynliggjort, at eculizumab har en effekt, især på attaker. Eculizumab vurderes at have stor merværdi på effektmålet 'årlig attakrate' sammenlignet med placebo. Fordi effekten af eculizumab er anderledes end effekten af placebo på dette effektmål accepterer sekretariatet, at der udføres en sundhedsøkonomiske analyse baseret på PREVENT-data. Som fagudvalget også beskriver i vurderingsrapporten er det dog usikkert, om resultaterne fra PREVENT afspejler dansk klinisk praksis, da flere patienter modtager kombinationsbehandling. Der er derfor også en vis usikkerhed forbundet med at benytte resultaterne fra PREVENT, men samlet set vurderer sekretariatet, at dette data er det bedst mulige.

Medicinrådet accepterer ansøgers anvendelse af effektdata fra PREVENT-studiet i den sundhedsøkonomiske model.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en Markov-model til at estimere omkostningerne forbundet med behandlingen med eculizumab.

Modellen består af en række stadier, som patienten kan befinde sig i for hver cyklus. Ansøgers model består af 10 *Expanded Disability Status Scale* (EDSS)-stadier, og patientens bevægelser igennem modellens stadier bestemmes af transitionssandsynligheder.

Ansøger antager, at den initiale fordeling af patienter mellem EDSS-stadierne i dansk klinisk praksis er identisk med fordelingen i PREVENT [3]. I hver cyklus kan en patient enten forblive i det nuværende EDSS-stadie, dø af andre årsager end et attak, stoppe behandling med eculizumab, opleve et ikke-dødeligt attak, opleve et dødeligt attak eller samtidig stoppe behandling og progrediere til næste EDSS-stadie grundet et attak. Transitionssandsynlighederne for at stoppe behandling med eculizumab, at opleve et attak samt transitionssandsynligheden for at progrediere et EDSS-stadie er alle baseret på PREVENT-studiet [3] for både eculizumab og BSC. Transitionssandsynligheden for hhv. et ikke-dødeligt og dødeligt attak er baseret på Mealy 2018 [4]. Ansøger antager, at alle transitionssandsynligheder er konstante.

Modellen estimerer omkostningerne baseret på det EDSS-stadie, som patienten befinder sig i, da hvert sygdomsstadie er forbundet med forskellige omkostninger til behandlingen af det pågældende handicap.

Modellen har en cykluslængde på 6 måneder, hvilket ansøger argumenterer er passende, da det tillader patienter at progrediere op til to gange om året. Ansøger anvender desuden *half-cycle correction*.

Medicinrådets vurdering af ansøgers modelantagelser
Medicinrådet accepterer ansøgers tilgang vedr. modelstruktur og transitionssandsynligheder, men fagudvalget fremhæver, at et attak vil true syn og førlighed, men at det sjældent vil være dødeligt. Derfor vælger sekretariatet at sætte dødeligheden ved et attak til 0 %. Transitionssandsynlighederne er præsenteret i Tabel 1. Desuden vurderer fagudvalget at den årlige sandsynlighed for attak på 35 % er højere end forventet i dansk klinisk praksis.

Tabel 1. Årlige transitionssandsynligheder for eculizumab og BSC

Behandling	Eculizumab	BSC	Kilde
Attak	5,8 %	35 %	PREVENT
Heraf:			
- Dødeligt	0 %	0 %	Mealy
- Ikke-dødeligt	100 %	100 %	Mealy
EDSS-progression efter attak	[redacted]	[redacted]	PREVENT
Behandlingsstop	4,5 %	N/A	PREVENT

Med fordelingen mellem EDSS-stadier fra PREVENT og transitionssandsynlighederne præsenteret ovenfor bliver den kohorte-simulerede fordeling mellem stadier over tid som præsenteret i Figur 1 for eculizumab og Figur 2 for BSC.

Figur 1. Simulering af fordeling mellem modellens stadier for eculizumab

Figur 2. Simulering af fordeling mellem modellens stadier for BSC

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men justerer sandsynligheden for et dødeligt attak til 0 % og udfører en følsomhedsanalyse af denne samt af baggrundssandsynligheden for attak.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en livslang tidshorisont svarende til 56 år, da den gennemsnitlige patient er 44 år i analysen. Det antages, at alle patienter er døde ved en alder på 100 år.

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
Medicinrådet accepterer ansøgers valgte tidshorisont, da NMOSD er en kronisk sygdom, som kræver livslang behandling, hvorfor analysens tidshorisont skal være tilstrækkeligt lang til, at alle væsentlige forskelle i behandlingsomkostninger mellem eculizumab og BSC opfanges.

4.2 Omkostninger

I det følgende er ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af eculizumab sammenlignet med BSC præsenteret. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger til administration, vaccineomkostninger, patientomkostninger, attakomkostninger samt en samlet omkostning til øvrige omkostninger forbundet med håndtering af de tilhørende EDSS-stadier.

Ansøger har valgt ikke at inkludere omkostninger til håndtering af uønskede hændelser. Ansøger argumenterer for, at dette er et konservativt valg, da frekvensen af uønskede hændelser er højere blandt patienter i behandling med BSC end ved eculizumab. Dette er uddybet i afsnit 4.2.2.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i stadiet.

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). Ansøger antager, at patienter, der modtager BSC, ikke behandles med nogen lægemidler, hvorfor der ingen lægemiddelomkostninger er forbundet med BSC. Ansøger antager desuden, ligesom i PREVENT-studiet, at patienter vil blive behandlet med eculizumab indtil attak, hvorefter behandlingen stopper, og patienterne vil få BSC. Ansøger har ikke inkluderet omkostninger forbundet med lægemiddelspild i analysen.

Dosis anvendt i ansøgers analyse for eculizumab er hentet i det respektive produktresumé (SPC): Eculizumab:
Første 4 uger: 900 mg om ugen (3 x 300 mg)
Uge 5: 1.200 mg (4 x 300 mg)
Uge 7 og frem: 1.200 (4 x 300 mg) hver 2. uge.

BSC:
Ingen lægemidler.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Fagudvalget forventer, at patienter i behandling med eculizumab ofte vil fortsætte behandlingen efter et attak. Derfor vælger sekretariatet ikke at inkludere behandlingsstop ved attak i hovedanalysen, men i stedet præsentere dette som en følsomhedsanalyse. Sekretariatet antager i stedet, at behandlingen stoppes, når patienterne når til EDSS 8-9, jf. Medicinrådets protokol vedr. eculizumab [5].

Ansøgers antagelse om, at patienter i komparator armen ikke modtager lægemiddelbehandling vil overestimere de inkrementelle omkostninger for eculizumab. Sekretariatet accepterer dog valget, da det er dikteret af protokollen.

Fagudvalget pointerer, at der potentielt vil kunne være et lægemiddelspild forbundet med anvendelse af eculizumab i praksis grundet forkert opbevaring og/eller håndtering af lægemidlet. Fagudvalget kan ikke kvantificere, hvor stort et potentielt lægemiddelspild forventes at være.

Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 2.

Tabel 2. Anvendte lægemiddelpriser, SAIP (maj 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Eculizumab	300 mg	1 stk.	[redacted]	Amgros

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger, men vælger ikke at anvende antagelsen om behandlingsstop med eculizumab ved attak i hovedanalysen. Dette scenarie præsenteres dog i en følsomhedsanalyse. Desuden bemærker Medicinrådet, at der i dansk klinisk praksis anvendes en række lægemidler, som ikke er inkluderet i denne sammenligning, hvorfor lægemiddelomkostningerne sandsynligvis er underestimeret.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger for eculizumab, men ikke BSC. Ansøger antager, at det tager 25-45 minutter at administrere eculizumab, og ansøger takserer denne omkostning med en DRG-takst. Ansøger antager, at omkostningen til administration er konstant, og at patienter skal møde op på hospitalet ved hver administration.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger, men bemærker, at ansøger ikke har inkluderet testomkostninger forbundet med identificering af, om NMOSD-patienterne er AQP4-antistofpositive. Idet testen allerede i dag foretages på nationalt plan, accepterer Medicinrådet ansøgers ekskludering af omkostninger forbundet med antistoftest. De anvendte enhedsomkostninger kan ses i Tabel 3.

Tabel 3. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Årlig frekvens [antal]	Kode	Kilde
Administrationsomkostninger 1 år	3.353	28	01MA98	[DRG-2021]
Administrationsomkostninger 2 år+	3.353	26	01MA98	[DRG-2021]

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostninger

Ansøger har ikke eksplicit inkluderet omkostninger til monitorering af håndtering af eculizumab, men antager, at patienterne vil blive monitoreret som en del af administrationen. For løbende monitorering af udviklingen i sygdommen har ansøger inkluderet en separat omkostning til håndtering af NMOSD-sygdommen, som afhænger af det respektive EDSS-stadie. Disse er beskrevet i afsnit 144.2.6.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger.

Bivirkningsomkostninger

Ansøger anvender uønskede hændelser som proxy for bivirkninger, men har ikke inkluderet omkostninger forbundet med håndtering af bivirkninger, da ansøger argumenterer for, at frekvensen af uønskede hændelser er højere blandt patienter i BSC end for patienter i behandling med eculizumab. Denne argumentation er baseret på PREVENT-studiet [3]. Ekskludering af bivirkningsomkostningerne er derfor jf. ansøger en konservativ tilgang, som underestimerer de inkrementelle omkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Medicinrådet bemærker, at værdien af eculizumab på effektmålet ikke kunne kategoriseres på de kvantitative data. Fagudvalget er bekymret for alvorlige og dødelige infektioner med meningokokker, hvorfor eculizumab fik en negativ værdi på effektmålet. Sekretariatet er derfor ikke enig i, at denne tilgang er et konservativt estimat, men vælger dog alligevel at acceptere ansøgers tilgang, da det er vanskeligt at kvantificere disse omkostninger. Sekretariatet fremhæver, at ekskludering af uønskede hændelser bidrager med usikkerhed til det endelige resultat.

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men fremhæver, at dette bidrager med usikkerhed til det endelige resultat.

4.2.3 Vaccinationsomkostninger

Idet virkningsmekanismen ved eculizumab øger patientens følsomhed for meningokokinfektion, skal patienterne som udgangspunkt vaccineres mod serogruppe A, C, Y, W 135 og B forud for behandling med eculizumab [6]. Ansøger har inkluderet

lægemiddel- og administrationsomkostninger forbundet med injektion af vaccinerne Bexsero® og Nimenrix®, se Tabel 4. Ansøger antager, at patienten vil modtage vaccinerne over to konsultationer hos egen praktiserende læge.

Tabel 4. Omkostninger forbundet med vaccine mod meningokokinfektion

	Bexsero® [DKK]	Nimenrix® [DKK]	Reference
Lægemiddelomkostninger	[redacted]	[redacted]	Amgros
Totale administrationsomkostninger	292,50 kr.		www.plo.dk, Honorartabel Almen Praksis pr. 01.10.2020

Derudover har ansøger inkluderet de patientomkostninger, som antages at være forbundet med injektion af vaccinerne, se afsnit 4.2.4.

Medicinrådets vurdering af ansøgers antagelser vedr. vaccinationsomkostninger
Medicinrådet accepterer ansøgers tilgang vedr. vaccinationsomkostninger.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrationsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid. Ansøger antager, at den samlede tid pr. besøg er to timer. Derudover har ansøger også inkluderet patientomkostninger forbundet med injektion af meningokok-vaccinerne samt hospitalsindlæggelse og kontrolbesøg grundet attak. Vedrørende vaccineinjektionerne antager ansøger, at patienten vil modtage disse hos egen praktiserende læge, og at tidsforbruget sammenlagt er 1 time. For attak antager ansøger, at patienterne vil bruge henholdsvis 10 timer på en indlæggelse og 2 timer på efterfølgende kontrolbesøg.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time, mens der for transportomkostningerne anvendes en gennemsnitlig afstand til nærmeste hospital på 28 km, som takseres med 3,44 kr./km, jf. Medicinrådets værdisætning af enhedsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid, men patienttid ved indlæggelse efter attak justeres, da fagudvalget vurderer, at den samlede patienttid udgør 30 timer. Desuden ekskluderes patienttiden ved kontrolbesøg efter attak, jf. afsnit 4.2.7. De anvendte patientomkostninger kan ses i Tabel 5, mens transportomkostningerne kan ses i Tabel 6.

Tabel 5. Estimat af effektiv patienttid

	Patienttid [timer]	Årlig frekvens [antal]	Enhedsomkostning pr. time [DKK]	Total [DKK]
Administrationsbesøg år 1	2	28	179	10.024
Administrationsbesøg år 2+	2	26	179	9.308
Meningokok-vacciner	1	-	179	179
Indlæggelse grundet attak	30	-	179	5.370

Tabel 6. Transportomkostninger

	Transport [KM]	Årlig frekvens [antal]	Enhedsomkostning pr. time [DKK]	Total [DKK]
Administrationsbesøg år 1	28	28	3,44	2.697
Administrationsbesøg år 2+	28	26	3,44	2.504
Meningokok-vacciner	28	-	3,44	96,32

Medicinrådet accepterer ansøgers tilgang vedr. patient- og transportomkostninger, men justerer patienttid ved indlæggelse efter attak til 30 timer og ekskluderer patientomkostninger ved kontrolbesøg efter attak.

4.2.5 Kommunale omkostninger

Ansøger har inkluderet kommunale omkostninger, men antager, at disse afhænger af EDSS-stadie og ikke af, om patienterne er i behandling med eculizumab eller BSC. Ansøger antager, at de kommunale omkostninger forbundet med håndtering af patienter med NMOSD ikke afviger fra de kommunale omkostninger ved håndtering af patienter med multipel sklerose (MS) og dermed kan bruges som en proxy for de kommunale omkostninger ved patienter med NMOSD. Baseret på denne antagelse anvender ansøger de kommunale omkostninger fra det danske *cost of illness-studie, Vestergaard et al.* [7], der estimerer de samlede omkostninger ved MS-patienter afhængig af EDSS-stadie, til at estimere de kommunale omkostningerne for patienter med NMOSD. De kommunale omkostninger i *Vestergaard et al.* [7] inkluderer omkostninger til hjemmehjælp, transport, besøg af sygeplejerske samt køb af hjælpemidler (f.eks. installation af

lift/elevator i bil eller bolig og rullestol). I hverken *Vestergaard et al.* [7] eller ansøgers ansøgning er enhedsomkostningerne og frekvenserne opgjort.

Medicinrådets vurdering af ansøgers antagelser vedr. kommunale omkostninger
Sekretariatet accepterer ikke de kommunale omkostninger præsenteret i Vestergaard et al. [7]. Ansøger præsenterer de samlede årlig kommunale omkostninger for de respektive EDSS samt nogle udvalgte aggregerede frekvenser (på tværs af EDSS) samt nogle udvalgte enhedsomkostninger. Baseret på disse oplysninger er det hverken muligt at validere enhedsomkostningerne, de respektive frekvenser eller fremgangsmåde. Fagudvalget er dog enige i, at med ansøgers antagelse om, at de kommunale omkostninger ved et givent EDSS-stadie er uafhængige af, om en patient har MS eller NMOSD, hvilket fagudvalget grundlæggende er enig i. Derfor vælger sekretariatet at præsentere en følsomhedsanalyse, hvor de kommunale omkostninger baseret fra Vestergaard et al. [7] er inkluderet, men understreger, at denne følsomhedsanalyse er meget usikker, da antagelserne ikke kan verificeres. De anvendte omkostninger i følsomhedsanalysen er præsenteret i Tabel 7.

Tabel 7. Årlige kommunale omkostninger anvendt i følsomhedsanalysen

	EDSS 0-3	EDSS 4-6	EDSS 7-9
Kommunale omkostninger (inkl. hjælpemidler) [DKK]	3.110	15.752	208.891

Medicinrådet accepterer ikke ansøgers tilgang vedr. kommunale omkostninger og vælger derfor at ekskludere dem fra hovedanalysen. Medicinrådet vælger dog at præsentere en følsomhedsanalyse, hvor ansøgers estimat for kommunale omkostninger er inkluderet.

4.2.6 EDSS-specifikke omkostninger

Ansøger har valgt at inkludere en række omkostninger i analysen, som er specifikke for det pågældende EDSS-stadie. Til at estimere de EDSS-specifikke omkostninger anvender ansøger den samme reference som til estimeringen af de kommunale omkostninger, *cost of illness*-studiet Vestergaard et al. De samlede omkostninger forbundet med håndtering af det respektive EDSS-stadie inkluderer omkostninger forbundet med ambulatoriebesøg, indlæggelser, monitorering og tests, men i hverken *Vestergaard et al.* [7] eller i ansøgers ansøgning er enhedsomkostningerne og frekvenserne opgjort.

Medicinrådets vurdering af ansøgers antagelser vedr. EDSS-specifikke omkostninger
Sekretariatet accepterer ikke de EDSS-specifikke omkostninger præsenteret i Vestergaard et al. [7], da det ligeledes ikke er muligt at validere hverken enhedsomkostningerne, de respektive frekvenser eller fremgangsmåde. Fagudvalget er dog blevet konsulteret med ansøgers antagelse om, at de EDSS-specifikke omkostninger ved et givent EDSS-stadie er uafhængige af, om en patient har MS eller NMOSD, hvilket fagudvalget grundlæggende er enig i. Derfor vælger sekretariatet at præsentere en følsomhedsanalyse, hvor de EDSS-specifikke omkostninger baseret på Vestergaard et al. [7] er inkluderet, men understreger, at denne følsomhedsanalyse er meget usikker, da

antagelserne ikke kan verificeres. De anvendte omkostninger i følsomhedsanalysen er præsenteret i Tabel 8.

Tabel 8. EDSS-specifikke omkostninger

	EDSS 0-3	EDSS 4-6	EDSS 7-9
Indlæggelse	6.866	17.754	26.579
Ambulatoriebesøg	989	943	1.832
Konsultation	10.231	14.595	12.289
Test	3.542	8.226	958

Medicinrådet accepterer ikke ansøgers tilgang vedr. EDSS-specifikke omkostninger og vælger derfor at ekskludere dem fra hovedanalysen. Medicinrådet vælger dog at præsentere en følsomhedsanalyse, hvor ansøgers estimat for EDSS-specifikke omkostninger er inkluderet.

4.2.7 Omkostninger ved attakker

I analysen har ansøger inkluderet omkostninger forbundet med, at patienterne som følge af et enten ikke-dødeligt eller et dødeligt attak vil udgøre en omkostning for hospitalet. I denne sammenhæng antager ansøger, at 67 % af de patienter, som oplever et attak, vil blive indlagt, uanset om det er et ikke-dødeligt eller et dødeligt attak. Endvidere antager ansøger, at patienter, som oplever et ikke-dødeligt attak, vil blive tilbudt to ambulante kontrolbesøg på hospitalet.

Medicinrådets vurdering af ansøgers antagelser vedr. attakomkostninger
Fagudvalget vurderer, at 50 % af patienterne vil blive indlagt som følge af et attak, men vurderer, at patienter ikke vil blive tilbudt to ambulante kontrolbesøg på hospitalet efterfølgende. De anvendte attakomkostninger er præsenteret i Tabel 9.

Tabel 9. Attakomkostninger

	Enhedsomkostning [DKK]	Rate	DRG-kode	Kilde
Indlæggelse	40.744	50 %	01MA07	[DRG-2021]

Medicinrådet accepterer ansøgers tilgang vedrørende attakomkostninger, men vælger at justere indlæggelsesrate fra 2/3 til 50 % samt at ekskludere efterfølgende ambulante kontrolbesøg.

4.3 Følsomhedsanalyser

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

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. De udførte følsomhedsanalyser fremgår af Tabel 10.

Tabel 10. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Alder og handicap ved baseline	Justeres til 35 år og EDSS 0 som baseline
Baseline EDSS-distribution	Scenarie med hver EDSS-score fra 0 til 9 som baseline
Hazard ratio	Anvendelse af nedre og øvre konfidensintervaller
Årlig baggrundsrisiko for attak	Anvendelse af nedre og øvre konfidensintervaller
Sandsynlighed for EDSS-progression ved attak	Reduceres med 50 % og øges med 50 %
Sandsynlighed for dødeligt attak	Justeres til 0,07 og 0,14
Rate for behandlingsophør	Reduceres med 50 % og øges med 50 %
Behandlingsophør efter attak	Scenarie 1: Ingen behandlingsophør Scenarie 2: Behandlingsophør, hvis handicap forværres
Infusionsomkostninger	Reduceres med 50 % og øges med 50 %
EDSS-omkostninger	Anvendelse af nedre og øvre konfidensintervaller
Attakomkostninger	Reduceres med 50 % og øges med 50 %
Tidshorisont	Justeres til 10, 20 og 30 år

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Sekretariatet vurderer, at ansøgers følsomhedsanalyser er relevante og belyser usikkerhederne i modellen, og derfor vælger sekretariatet ligeledes at præsentere et udsnit af disse. Sekretariatet ekskluderer følsomhedsanalyserne relateret til EDSS, da alle EDSS-specifikke omkostninger er ekskluderet fra hovedanalysen, og derfor har EDSS-baseline ingen indflydelse på hovedanalysen. Dog vælger sekretariatet at udføre en følsomhedsanalyse, hvor de EDSS-specifikke omkostninger og kommunale omkostninger fra Vestergaard et al. [7] er inkluderet, samt en følsomhedsanalyse, hvor patienter stopper behandling med eculizumab efter første attak, og en følsomhedsanalyse, hvor dødeligheden ved attak sættes til 7 %.

Medicinrådet accepterer ansøgers valg af følsomhedsanalyser og vælger at præsentere et udsnit af disse samt en følsomhedsanalyse hvor patienter stopper behandling med

eculizumab efter første attak, en følsomhedsanalyse hvor dødeligheden ved attak er 7 % og en følsomhedsanalyse hvor EDSS-specifikke og kommunale omkostninger er inkluderet.

4.4 Opsummering af basisantagelser

I Tabel 11 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 11. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Sammenligning	Eculizumab sammenlignet med BSC	Eculizumab sammenlignet med BSC
Tidshorisont	56 år	56 år
Diskonteringsrente	3,5 % (år 1-35) 2,5 % (år 36+)	3,5 % (år 1-35) 2,5 % (år 36+)
Inkluderede omkostninger	Lægemiddelomkostninger Administrationsomkostninger EDSS-omkostninger Kommunale omkostninger Omkostninger ved attakker Patientomkostninger	Lægemiddelomkostninger Administrationsomkostninger - - Omkostninger ved attakker Patientomkostninger
Dosering	Eculizumab: Uge 1-4: 900 mg hver uge Uge 5 og frem: 1.200 mg hver anden uge	Eculizumab: Uge 1-4: 900 mg hver uge Uge 5 og frem: 1.200 mg hver anden uge
Inkludering af spild	Nej	Nej
Andre væsentlige antagelser	Behandlingsstop med eculizumab indtil attak 7 % dødelighed ved attak	Fortsat behandling med eculizumab efter attak 0 % dødelighed ved attak

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, der er gennemgået ovenfor.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse. Hvis behandlingsvarigheden i gennemsnit antages at være [redacted] år, vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK pr. patient. Størstedelen af omkostningerne forekommer dog de første 15 år af behandlingsforløbet.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 28,4 mio. DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 12.

Tabel 12. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC, DKK, diskonterede tal

	Eculizumab	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	793.391	191.059	602.332
EDSS-specifikke omkostninger	0	0	0
Patientomkostninger	107.255	25.356	81.899
Kommunale omkostninger	0	0	0
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 13.

Tabel 13. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Alder justeres til 35 år	[redacted]

Scenarie		Inkrementelle omkostninger
Hazard ratio mellem eculizumab og BSC varieres	Nedre konfidensinterval	[redacted]
	Øvre konfidensinterval	[redacted]
Årlig baggrundsrisiko for attak varieres	Nedre konfidensinterval	[redacted]
	Øvre konfidensinterval	[redacted]
Sandsynlighed for fatalt attak varieres	Øges til 7 %	[redacted]
	Øges til 14 %	[redacted]
Rate for behandlingsophør	Reduceres med 50 %	[redacted]
	Øges med 50 %	[redacted]
Behandlingsophør	Scenarie 1: Behandlingsstop ved attak	[redacted]
	Scenarie 2: Behandlingsophør, hvis handicap forværres	[redacted]
Infusionsomkostninger	Reduceres med 50 %	[redacted]
	Øges med 50 %	[redacted]
EDSS-specifikke omkostninger (både kommunale og regionale)		[redacted]
Omkostninger ved attakker	Reduceres med 50 %	[redacted]
	Øges med 50 %	[redacted]
Tidshorisont varieres	10 år	[redacted]
	20 år	[redacted]
	30 år	[redacted]

6. Budgetkonsekvenser

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

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

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

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, at der i indeværende år er 43 patienter, der lever med NMOSD i Danmark, som kandiderer til behandling med eculizumab. Ansøger baserer estimatet for det prævalente patientantal på en beregning, hvori følgende parametre indgår: det danske folketal, NMOSD-prævalens, andel AQP4-antistofpositive patienter og andel patienter med recidiverende sygdom. Foruden de prævalente patienter antager ansøger, at 5 nye patienter årligt vil blive diagnosticeret med NMOSD og kandidere til behandling med eculizumab. Ansøger baserer estimatet for antal incidente patienter pr. år på Medicinrådets *Protokol for vurdering af eculizumab til behandling af NMOSD*.

Vedrørende markedsoptag antager ansøger, at eculizumab i dansk klinisk praksis primært vil tilbydes til patienter med en høj attakrate. Ansøger vurderer i denne sammenhæng, at 26 % af de prævalente patienter, som i dag modtager off label-behandling, vil have en høj rate af attakker. Et markedsoptag på 26 % svarer til, at 11 prævalente patienter vil blive tilbudt behandling med eculizumab i dansk klinisk praksis. Ansøger antager dog, at der i år 1 kun vil være 2 prævalente patienter, der opstarter behandling med eculizumab, hvis lægemidlet anbefales. Endvidere antager ansøger, at 3 prævalente patienter vil starte i behandling med eculizumab i år 2, 3 og 4.

Ansøger anvender det samme procentvise estimat for markedsoptaget (26 %) for incidente patienter, svarende til, at 1 nydiagnosticeret NMOSD-patient vil opstarte behandling med eculizumab pr. år.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal og markedsoptag, hvis eculizumab hhv. anbefales som mulig standardbehandling, og hvis ikke eculizumab anbefales. Fagudvalget vurderer, at ansøgers antagelser er acceptable, men understreger samtidig, at der er usikkerheder forbundet med at definere eksakte tal for antallet af patienter, der i dansk klinisk praksis vil blive tilbudt behandling med eculizumab ved en anbefaling. Grundet usikkerhederne har fagudvalget ikke mulighed for at definere mere præcise estimater for patientantallet og markedsoptaget, end hvad ansøger antager.

Medicinrådet vælger at anvende ansøgers antagelser i sin hovedanalyse, hvilket svarer til patientantallene i Tabel 14.

Tabel 14. Medicinrådets estimat af antal patienter (både incidente og prævalente) pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales ikke		
Eculizumab	0	0	0	0	0
BSC	43	48	53	58	63
			Anbefales		
Eculizumab	2	6	10	14	15
BSC	41	42	43	44	48

Medicinrådet accepterer ansøgers tilgang til patientantal og markedsoptag, men understreger, at disse estimater er behæftet med stor usikkerhed.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af eculizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 15.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 43,1 mio. DKK i år 5.

Tabel 15. 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 eculizumab er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med BSC. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostninger for eculizumab.

EDSS-specifikke omkostninger:
Der er i modellen stor usikkerhed vedrørende omkostningerne til håndtering af patienternes handicap, hvilket er udtrykt ved EDSS. Ansøger antager, at omkostningerne er afhængige af EDSS, og antager desuden alt andet lige, at omkostningerne til håndtering af en patient med NMOSD med en given EDSS ikke afviger fra en patient med MS med samme EDSS. Derfor anvender ansøger det danske *cost of illness*-studie, Vestergaard et al. [7], vedr. MS-patienter til at estimere de løbende EDSS-specifikke omkostninger (både regionale og kommunale). Fagudvalget er overordnet enig i den antagelse, men fremhæver, at antagelsen vil bidrage med usikkerhed til modellen. Desuden fremhæver sekretariatet, at priser, frekvenser og fremgangsmåde ikke er tilgængelige i hverken Vestergaard et al. [7] eller i ansøgers ansøgning, hvorfor det ikke er muligt at verificere eller validere omkostningerne og antagelserne. Grundet den manglende redegørelse vurderer sekretariatet, at inkludering af de EDSS-specifikke omkostninger (både regionale og kommunale) vil bidrage med mere usikkerhed, end hvis de inkluderes. Det har ikke været muligt for ansøger at levere bedre data eller redegøre yderligere for disse omkostninger. Sekretariatet har udført en følsomhedsanalyse, hvor de EDSS-specifikke omkostninger er inkluderet, hvilket resulterer i, at de inkrementelle omkostninger falder fra ca. [redacted] DKK til ca. [redacted]. DKK. Grundet de meget høje lægemiddelomkostninger vil det både ved inkludering og ekskludering af de EDSS-specifikke omkostninger være lægemiddelomkostningerne, der driver de inkrementelle omkostninger.

Behandlingsstop:
I modellen er der usikkerhed vedr. behandlingsstop. Ansøger har antaget, at behandlingen med eculizumab stopper efter første attak, mens fagudvalget forventer, at det er en individuel vurdering, men at man ofte vil fortsætte behandlingen med eculizumab efter attak. Idet lægemiddelomkostningerne driver de samlede omkostninger i modellen, vil behandlingsstop – og dermed behandlingslængden – have betydning for resultatet. De inkrementelle omkostninger falder fra ca. [redacted] DKK til ca. [redacted] DKK pr. patient, hvis det antages, at behandling med eculizumab stoppes ved attak. Der er derfor usikkerhed vedr. behandlingslængden, hvilket grundet de høje lægemiddelomkostninger reducerer de inkrementelle omkostninger med ca. [redacted] pr. patient.

Komparator:
Valg af komparator har ligeledes stor betydning for resultatet. I denne analyse er eculizumab sammenlignet med BSC, som ikke indeholder aktiv behandling, hvilket er en konservativ komparator. Fagudvalget vurderer, at der benyttes en række lægemidler i dansk klinisk praksis (off label), og fagudvalgets erfaring er, at disse lægemidler har en vis effekt, selvom der ikke er evidens af høj kvalitet fra større randomiserede kliniske

studier. Disse lægemidler er ikke inkluderet i denne sammenligning, og derfor vil denne sammenligning være usikker og sandsynligvis underestimere lægemiddelomkostningerne ved komparatoren og dermed overestimere de inkrementelle omkostninger ved eculizumab.

Attaksandsynligheder og dødelighed:
Fagudvalget fremhæver, at der er usikkerhed vedr. de årlige attaksandsynligheder samt dødelighed blandt patienter med attak. Fagudvalget forventer, at de faktiske sandsynligheder er lavere, men det er ikke muligt for fagudvalget at kvantificere et mere konkret estimat. Der er udført en følsomhedsanalyse, som viser, at ved anvendelse af den nederste værdi i konfidensintervallet for årlige attaksandsynlighed [redacted] de inkrementelle omkostninger med ca. [redacted] DKK pr. patient. Ligeledes viser en følsomhedsanalyse, at de inkrementelle omkostninger [redacted] med ca. [redacted] DKK ved en dødelighed ved attak på 7 %, som er antaget af ansøger.

Bivirkninger:
Slutteligt er der usikkerhed vedr. omkostningerne til håndtering af bivirkninger. Ansøger anvender uønskede hændelser fra PREVENT [3] som en proxy for bivirkninger, og idet der er færre uønskede hændelser ved eculizumab end ved placebo i PREVENT [3], argumenterer ansøger for, at det er en konservativ tilgang at ekskludere bivirkningsomkostninger. Fagudvalget fremhæver dog, at den relative risiko mellem eculizumab og placebo i PREVENT-studiet ikke er statistik signifikant, og at fagudvalget er bekymret for alvorlige og dødelige infektioner med meningokokker. Sekretariatet er derfor ikke enig i, at denne tilgang er et konservativt estimat, men mener, at det blot bidrager med yderligere usikkerhed til modellen. Samtidig vurderer sekretariatet, at en eventuel inkludering af omkostninger til håndtering af bivirkninger sandsynligvis ikke vil rykke de inkrementelle omkostninger signifikant.

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. juni 2021	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 56 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 16.

Tabel 16. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Eculizumab	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	730.887	181.674	549.213
EDSS-specifikke omkostninger	639.068	587.139	51.929
Patientomkostninger	89.096	10.663	78.433
Kommunale omkostninger	1.015.171	1.352.392	-337.221
Totale omkostninger	[redacted]	[redacted]	[redacted]

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 eculizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 17.

Tabel 17. 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]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	23.06.2021
Leverandør	Alexion
Lægemiddel	Eculizumab (Soliris)
Ansøgt indikation	Til behandling af patienter med neuromyelitis optica spectrum sygdom (NMOSD), som er anti-aquaporin-4 (AQP4) antistof-positive med relaps af sygdom.

Forhandlingsresultat

Amgros har ikke opnået nogen rabat gennem forhandlingen og eculizumab indkøbes derfor fortsat til AIP:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP	Rabatprocent ift. AIP
Eculizumab	300 mg	1 stk.	34.273	-	0%

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi ikke har mulighed for at forhandle en rabatteret pris på nuværende tidspunkt. Vi forventer derfor ikke at kunne få en bedre pris såfremt eculizumab ikke anbefales til standardbehandling. Denne vurdering baserer vi på følgende punkter:

- Eculizumab er godkendt til andre indikationer: paroksystisk nocturnal hæmoglobinuri, atypisk hæmolytisk uræmi syndrom og refraktær generaliseret myasthenia gravis. Dette er også årsagen til at leverandøren omsatte for cirka 35 mio DKK i 2020 og ikke vil tilbyde en yderligere rabat.
- Det koster cirka 3,5 mio DKK i rene lægemiddelpriser at behandle med eculizumab i et år.
- [redacted]

[redacted]

Konklusion

Det er Amgros vurdering at vi ikke har opnået den bedst mulige pris og at den eksisterende pris er urimeligt høj.

Relation til markedet

Der er på nuværende tidspunkt ingen konkurrence på dette område, men Roche har sendt en foreløbig ansøgning på satralizumab til behandling af neuromyelitis optica spectrum sygdom, i september 2020.

Status fra andre lande

Norge: Under behandling[1].

UK: NICE var ikke i stand til at lave en anbefaling i september 2020 angående eculizumab, grundet manglende evidens.[2]

[1] Eculizumab (Soliris) - Indikasjon II (nyemetoder.no)
[2] Eculizumab for treating relapsing neuromyelitis optica (terminated appraisal) (nice.org.uk)

2021-05-26

Soliris in NMOSD.

Alexion Pharma's comment to Danish Medicine Council draft assessment reports

Alexion Pharma is grateful for the opportunity to comment on the draft assessment reports on Soliris in NMOSD.

The main purpose of the pivotal trial (PREVENT) was to show efficacy and safety of Soliris in NMOSD indication with time to recurrent attack being the primary endpoint. Secondary endpoints supplied important additional evidence but the interpretation of these if made difficult by the fact that – as an orphan disease – there are no disease specific instruments to document progression of disability or health-related quality of life.

With this in mind, we find that the Expert Committee has expressed a balanced view of the available evidence for the efficacy of Soliris in the NMOSD indication.

There is a highly significant and clinically relevant reduction in the risk of having recurrent attacks and other evidence suggest that the reduction in attacks will slow down disease progression and improve quality of life.

The assessment of clinical safety of Soliris highlights the concern for infections occurring during treatment with Soliris - especially meningococcal infection. Alexion Pharma would like to re-emphasize that no cases of meningococcal infections was observed in PREVENT or the open-label extension study (PREVENT OLE) and that the rates of meningococcal infection observed in international pharmacovigilance data early on in the clinical use of Soliris decreased over time from 0.57/ 100 PY in 2008 to 0.16/ 100 PY in 2016.[1]

Alexion Pharma acknowledge the Expert Committees expressed concern of the safety in clinical practice and would strongly suggest that the DMC and Expert Committee seek further information on this issue from Danish clinical practice where Soliris has been used for a decade to treat other orphan disease.

- Søren Schwartz Sørensen (Professor in nephrology and transplantation medicines, Rigshospitalet) and Henrik Fredriksen Professor in hematology, OUH and Chairman of the Danish Hematology Society) both have long-standing experience in managing treatment with Soliris in a Danish clinical practice.

Alexion Pharma further acknowledge that off-label treatments are used in prevention of NMOSD attacks in Denmark. For that reason, the patient forecast assumes that Soliris is reserved for patients with high attack rates despite current treatment. This positioning of Soliris in Danish clinical practice was supported by the Expert Committee.

Alexion Pharma strongly urge that the *Medicinrådet* will recommend Soliris in this small group at high risk of further attacks and the associated high risk of developing further severe debilitating disabilities.

1.Socie G, Caby‐Tosi MP, Marantz JL, Cole A, Bedrosian CL, Gasteyger C, et al. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. Br J Haematol. 2019;185(2):297-310.

Medicinrådet

Medicinrådets vurdering vedrørende eculizumab til behandling af neuromyelitis optica spectrum sygdom (NMOSD)

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. maj 2021
Dokumentnummer	114057
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 8. juni 2021

1. Medicinrådets konklusion

Medicinrådet vurderer, at værdien af eculizumab sammenlignet med placebo til patienter med NMOSD ikke kan kategoriseres efter Medicinrådets metoder. Datagrundlaget er en direkte sammenligning, men designet gør, at vurderingen af de fleste effektmål er forbundet med stor usikkerhed.

Medicinrådet finder, at eculizumab kan have en effekt på attakker, men det er ikke dokumenteret om det påvirker sygdomsprogressionen. Samtidig er Medicinrådet bekymret for infektionsrisikoen. Medicinrådet formoder på den baggrund, at eculizumab kan være et bedre alternativ for patienterne end ingen behandling

Rådet bemærker, at andre immunsupprimerende lægemidler også formodes at have en effekt på at forhindre eller forsinke attakker hos patienter med NMOSD, og at de også kan medføre bivirkninger. Der er erfaring med disse lægemidler og håndtering af bivirkningerne i dansk klinisk praksis. Det er på baggrund af data ikke muligt at vurdere, om eculizumab er et bedre, ligeværdigt eller dårligere behandlingsalternativ end disse

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 (f.eks. 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

AQP4	Aquaporin 4
CI:	Konfidensinterval
EDSS	*Expanded Disability Status Scale*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention-to-treat*
MCS	*Mental component score*
MS	Multipel sklerose
MSQL-54	*Multiple Sclerosis Quality of Life-54*
NMOSD	Neuromyelitis optica spektrum sygdom
OR:	*Odds ratio*
PCS	*Physical component score*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per Protocol*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
SD	Standard deviation
SMD	*Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af eculizumab til neuromyelitis optica spectrum sygdom er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Alexion Pharma. Medicinrådet modtog ansøgningen den 12. februar 2021.

De(t) kliniske spørgsmål er:

Hvilken værdi har eculizumab sammenlignet med placebo for patienter med neuromyelitis optica spectrum sygdom?

3.1 Neuromyelitis optica spectrum sygdom

Neuromyelitis optica spectrum sygdom (NMOSD) er en kronisk neurologisk sygdom, der typisk rammer synsnerver og rygmarven. Patienter i Danmark har en medianalder på 35 år ved sygdomsdebut, men NMOSD kan ramme i alle aldre [1]. Sygdommen rammer kvinder tre gange oftere end mænd.

NMOSD er karakteriseret ved inflammation i det centrale nervesystem, der fører til demyelinisering med tab af gliaceller og neuroner og dermed neurologisk funktionstab. Patienter med NMOSD vil i varierende grad have både fysiske og kognitive symptomer såsom synsnedsættelse, dobbeltsyn, spastiske lammelser af arme og/eller ben, føleforstyrrelser, dårlig balance, vandladningsproblemer, forstoppelse, problemer med seksualfunktionen, smerter, træthed samt hukommelses- og koncentrationsproblemer. Patienter oplever attakker, der kan medføre en vedvarende forværring af symptomer gennem sygdomsforløbet [2]. Den væsentligste sygdomsprogression er således knyttet til attakker, og det er uvist, om sygdommen også progredierer i perioder uden attakker. Omkring 60 % af patienterne oplever et nyt attak inden for det første år efter det første attak. Dette er flere end den gennemsnitlige patient med attakvis multipel sklerose (MS), og attakkerne vil oftere medføre varige skader hos patienter med NMOSD end hos patienter med MS. I modsætning til MS ses milde forløb af NMOSD sjældent.

Sygdommens kliniske fremtræden deler mange ligheder med MS, men adskiller sig især ved, at den underliggende patologi er forskellig. Hos NMOSD er det primært astrocytterne, der er mål for kroppens immunreaktion, hvor det hos MS er oligodendrocytter, der rammes. I begge tilfælde fører det til skader på neuroner i det centrale nervesystem, der fører til de symptomer, som er beskrevet ovenfor. Hos patienter med NMOSD bliver rygmarv og synsnerve ofte ramt – derfor er synsproblemer og tværsnitssyndrom hyppige og alvorlige manifestationer af sygdommen. Et NMOSD-attak kan true patientens førlighed eller syn, men ofte vil akut behandling af attakker med kortikosteroider eller evt. plasmaferese have en effekt på patientens funktionsniveau.

Hos ca. 75-80 % af patienter med NMOSD er antistoffer mod proteinet aquaporin 4 (AQP4) til stede i blodet. AQP4 er især til stede på astrocytternes endefødder [3,4]. Hos patienter med antistoffer mod AQP4 sker en aktivering af immunsystemet, som forårsager tab af astrocytterne, men inflammationen medfører også tab af oligodendrocytter og demyelinisering, og der ses ophobning af komplement i relation til læsionerne.

For patienter med NMOSD er den væsentligste sygdomsprogression forbundet med attakker. Fagudvalget finder det vanskeligt at vurdere, om sygdomsprogression også foregår uafhængigt af attakker.

Ansøger angiver i sin foreløbige ansøgning, at 61 danske patienter er registreret med NMOSD (via personlig kommunikation med den ansvarlige person for Skleroseregistret). Fagudvalget har fra en dansk ekspert i NMOSD fået oplyst, at 39 patienter med NMOSD og AQP4-antistoffer blev registreret i Danmark i perioden 2007-2014 (manuskript under udarbejdelse). Der er ikke danske data efter 2014. På den baggrund antager fagudvalget, at antallet af patienter, der er kandidater til behandling med eculizumab, sandsynligvis ligger under 50 patienter, samt at 5 nye patienter årligt vil være kandidater til behandlingen. Dette estimat er dog forbundet med stor usikkerhed.

3.2 Eculizumab

Eculizumab er et monoklonalt antistof, der virker ved at hæmme dannelsen af komplementkompleks C5b-9. Komplementsystemet er en del af immunforsvaret og består af omkring 20 forskellige proteiner. Disse kan aktiveres i en kaskadereaktion og signalere til andre dele af immunsystemet. Aktivering af komplementsystemet kan lede til inflammation. Eculizumab kan derfor forhindre aktivering af immunsystemet.

900 mg eculizumab skal administreres intravenøst én gang om ugen i fire uger i en opstartsfase. Fra den femte uge skal 1.200 mg gives intravenøst hver anden uge.

Eculizumab øger, på grund af sin virkningsmekanisme, risikoen for infektion med meningokokker (*Neisseria meningitidis*), der er forbundet med alvorlige og livstruende infektioner som meningitis og sepsis. Patienter i behandling med eculizumab skal derfor være vaccineret mod meningokokker to uger inden behandlingsstart.

Behandlingen med eculizumab har til formål at mindske antallet af attakker og dermed forebygge sygdomsprogression.

Eculizumab har af European Medicines Agency (EMA) fået betegnelsen ”orphan drug” og fik i 2019 følgende indikationsudvidelse:

“Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease”

Eculizumab havde i forvejen indikationerne paroksystisk nocturnal hæmoglobinuri, atypisk hæmolytisk uræmisk syndrom og refraktær generaliseret myasthenia gravis.

3.3 Nuværende behandling

Målet med den nuværende behandling er at forsinke/hindre attakker og dermed også hindre varig funktionsnedsættelse samt at bedre livskvaliteten.
Selvom der ikke er andre lægemidler med indikationen NMOSD, betragter fagudvalget det som væsentligt at tilbyde patienter behandling, da attakker kan give varige funktionsnedsættelser. Der benyttes en række lægemidler i dansk klinisk praksis (off label), og fagudvalgets erfaring er, at disse lægemidler har en vis effekt, selvom der ikke er evidens af høj kvalitet fra større randomiserede kliniske studier.

Dansk standardbehandling af patienter med NMOSD kan opsummeres således: De fleste patienter sættes først i behandling med azathioprin (oralt cytostatikum, der hæmmer leukocytproliferation, herunder T- og B-celler) og skiftes til rituximab (CD20-depleterende, som fjerner immunforsvarets B-celler og en mindre del af T-celler) ved fortsat sygdomsaktivitet. Ved bivirkninger kan der skiftes til mycophenolat mofetil (oralt cytostatikum der hæmmer leukocytproliferation, herunder T- og B-celler). Flere klinikker er begyndt at anvende rituximab som førstelinjebehandling, men den første behandling kan også være mycophenolat mofetil eller azathioprin. Hvis der er bivirkninger, kontraindikationer, eller hvis ovenstående lægemidler ikke er effektive, er alternative behandlingsmuligheder yderst begrænsede. En del patienter har andre autoimmune sygdomme, hvilket der skal tages højde for ved valg af behandling.

Valg af komparator

Valget af komparator har været vanskeligt, da der ikke er andre godkendte lægemidler til indikationen. Medicinrådet har derfor valgt at sammenligne med placebo. Fagudvalget har i vurderingen af eculizumab taget højde for, at denne sammenligning ikke er retvisende i forhold til dansk klinisk praksis, da patienterne ofte modtager behandling med andre immunsupprimerende lægemidler som anført ovenfor. Fagudvalget vil tage dette i betragtning, så vurderingen af eculizumab giver et så retvisende indtryk af effekten af eculizumab i forhold til klinisk praksis som muligt. Fagudvalget vil vurdere effekten af den nuværende behandling og derefter sammenligne effekten af eculizumab med nuværende behandling.

4. Metode

Medicinrådets protokol for vurdering vedrørende eculizumab 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.

Ansøgningen baserer sig på den artikel, der er angivet i protokollen samt EMAs EPAR [5]:

- Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 381(7):614-625

Ansøger har desuden indsendt data fra to konferenceabstracts, som baserer sig på samme kliniske studie som den publicerede artikel, og upublicerede data-on-file fra samme studie:

- Berthele A, Pittock S, Fujihara K, Kim HJ, Levy M, Palace J, et al. Impact of eculizumab on reported quality of life in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: findings from the PREVENT study. ECTRIMS; Stockholm 2019.
- Palace J, Pittock S, Berthele A, Fujihara K, Kim H, Levy M, et al. Impact of eculizumab on disability measures in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: phase 3 PREVENT study. ECTRIMS; Stockholm2019

Disse data besvarer effektmål i protokollens kliniske spørgsmål og lever op til Medicinrådets principper for anvendelse af upublicerede data. (Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser (medicinraadet.dk)). Data-on-file er markeret som fortrolige, da ansøger endnu ikke har offentliggjort dem.

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population
PREVENT	Fase III randomiseret, kontrolleret dobbeltblindet studie (time-to-event-studie med median follow-up-tid på 36 uger)	01892345	143 patienter med NMOSD randomiseret 2:1 til eculizumab og placebo

Tabel 2. Baselinekarakteristika

	Eculizumab	Placebo
Alder Middel (SD)	43,9 (13,3)	45 (13,3)
Køn % kvinder	88 (91,7)	42 (89,4)
EDSS Middel (SD)	4,15 (1,65)	4,26 (1,51)
Årlig attakrate ved baseline (gennem 24 måneder før studiestart) Middel (SD)	1,94 (0,9)	2,07 (1,04)
Tidligere behandling (%)		
Kortikosteroider	70,8	63,8
Azathioprin	63,5	55,3
Rituximab	27,1	42,6
Mycophenolate mofetil	28,1	31,9
Behandling ved baseline (%)	78,1	72,3
Ingen	21,9	27,7
Kortikosteroider alene	16,7	23,4
Azathioprin	38,5	27,7
Mycophenolate mofetil	17,7	17
Andet lægemiddel	5,2	4,3

Fagudvalget vurderer, at baselinekarakteristika er godt fordelt mellem de to studiearme. Der er forskel på andelen af patienter, som tidligere har været behandlet med rituximab i de to studiearme, men da de to arme ligner hinanden, hvad angår attakrate og EDSS, skønner fagudvalget, at der ikke er forskel i sygdomsgrad hos de to patientpopulationer.

Patientpopulationen ligner den danske patientpopulation, hvad angår alder, køn og tidligere behandlinger. Fagudvalget mener, at den relativt høje EDSS-score og de mange tidligere behandlinger betyder, at patientpopulationen afspejler de patienter, man vil se i senere behandlingslinjer i Danmark, og ikke nydiagnosticerede patienter.
Fagudvalget gør opmærksom på, at en stor del af patienterne modtager immunsupprimerende behandlinger samtidig med eculizumab i det kliniske studie. I dansk klinisk praksis forventer fagudvalget hovedsageligt at anvende eculizumab som monoterapi. Fagudvalget mener, at man i dansk klinisk praksis vil udvise meget stor

forsigtighed over for kombinationsbehandling og udelukkende kombinere eculizumab med kortikosteroider i kortere tid. Denne forskel mellem studiet og dansk klinisk praksis medfører betydelig usikkerhed på vurderingen af effekten af eculizumab. Den kan muligvis overestimere effekten og medføre bivirkninger i begge behandlingsarme.
Der er i studiet en præspecificeret subgruppe af patienter, som ikke samtidig modtager anden immunsupprimerende behandling. I denne gruppe var der 21 patienter (eculizumab) og 13 patienter (placebo).

5.1.2 Databehandling og analyse

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

Ansøger har indsendt et datagrundlag, der i overensstemmelse med Medicinrådets protokol og dataanalyserne er beskrevet tilstrækkeligt og udført hensigtsmæssigt. Der indgår data på alle ønskede effektmål. Imidlertid er der en række forhold, som kan medføre usikkerhed på de estimater, der er angivet i tabel 3.

Datagrundlaget er et randomiseret, kontrolleret studie med 143 patienter randomiseret 2:1 til eculizumab og placebo. Det kliniske studie er designet som et time-to-event-studie med første attak som primært endepunkt. Ansøgers analyseplan indeholdt en hierarkisk test af et primært endepunkt og seks sekundære endepunkter i en bestemt rækkefølge, deriblandt attakrate og sygdomsprogression.

Studiet blev stoppet efter 23 attakker. Der var en signifikant forskel mellem grupperne på det primære endepunkt og det første sekundære endepunkt, men ikke på det andet sekundære endepunkt (EDSS-score). Der kan ifølge publikationen om det kliniske studie ikke drages konklusioner, efter et endepunkt ikke blev mødt [6]. Designet gør det vanskeligt at vurdere effektmålene EDSS-score, synsskarphed og livskvalitet, da patienterne ikke følges længere efter første attak. Medicinrådet vurderer, at den kvantitative vurdering til brug for kategorisering af merværdi er usikker og forholder sig derfor kvalitativt til resultaterne.

En stor del af patienterne i det kliniske studie blev behandlet med både eculizumab og andre immunmodulerende lægemidler. Det gør det vanskeligt at vurdere effekten af eculizumab alene. Gruppen af patienter, som kun blev behandlet med eculizumab, er en prædefineret subgruppe, men meget lille.

I EMAs EPAR er beskrevet en række protokoldeviationer (138 i 57 patienter). Enkelte af disse kan have betydning for vurderingen af de angivne effektmål (en patient i eculizumab-armen blev behandlet med rituximab under det kliniske studie, og nogle alvorlige uønskede hændelser blev ikke rapporteret inden for 24 timer), men fagudvalget vurderer ikke, at omfanget og alvorligheden af protokoldeviationer medfører yderligere usikkerhed på vurderingen.

For resultater for enkelte effektmål bemærker Medicinrådet:

På effektmålet årlig attakrate er resultatet udregnet ud fra en Poisson regression-analyse, hvori studiepopulationen og historiske data for attakrate indgår. Dette er beskrevet i det kliniske studie af lægemidlet [6]. Det har ikke været muligt at vurdere attakraten på anden vis, da patienterne er blevet censureret, efter de har haft attak, grundet studiets design. Derfor accepterer Medicinrådet denne tilgang.

For effektmålet EDSS-score bemærker Medicinrådet, at der ikke blev set en signifikant forskel i den hierarkiske analyse i det kliniske studie. Ansøger har indleveret data fra et abstract og data on file. Der er i analysen justeret for bl.a. baseline EDSS. Medicinrådet finder tilgangen acceptabel, men vurderer, at resultaterne skal ses i lyset af den manglende signifikans på effektmålet i det kliniske studie. Medicinrådet bemærker, at der er stor usikkerhed på vurderingen af dette effektmål på grund af studiets design.

For effektmålet synsskarphed er der ikke angivet en relativ forskel. Derfor kan effekten af eculizumab ikke kategoriseres på dette effektmål.

Effektmålet livskvalitet er opgjort anderledes end ønsket i protokollen. Derfor kan effekten af eculizumab ikke kategoriseres på dette effektmål efter Medicinrådets metoder, men fagudvalget har forholdt sig kvalitativt til det indsendte data.

For effektmålet bivirkninger er data fra det kliniske studie sparsomme, og fagudvalget har suppleret med data fra patienter behandlet med eculizumab for andre indikationer end NMOSD. Fagudvalget finder, at dette er rimeligt, da dosering af eculizumab er den samme for alle indikationer (fraset paroxysmal nocturnal hæmoglobinuri), hvor dosis er lavere end for de øvrige indikationer.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 1).

Der er nedgraderet for inkonsistens på alle effektmål, da der kun var ét studie. Der er også nedgraderet for indirekthed på alle effektmål, da populationen i studiet adskiller sig fra patienter i dansk klinisk praksis ved bl.a. at blive behandlet med flere lægemidler på én gang. På enkelte effektmål er der nedgraderet for unøjagtighed, da der var brede konfidensintervaller. Den laveste evidenskvalitet for et kritisk effektmål er ”meget lav”, hvilket bliver den samlede konklusion.

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre kategoriseringen. Fagudvalget gør opmærksom på, at flere studier nok ville vise effekten af eculizumab med større sikkerhed, men at det er usandsynligt, at flere studier ville ændre vurderingen af, at eculizumab samlet har en bedre effekt på f.eks. attakrate end placebo – ligesom flere studier sandsynligvis ikke vil ændre fagudvalgets vurdering af bivirkninger.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for klinisk spørgsmål 1

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	
Årlig attakrate	Antal attakker pr. patient om året (0,2 attakker)	Kritisk	-0,33 (-0,35;-0,30)	Merværdi af ukendt størrelse	RR: 0,04 (0,01;0,15)	Stor merværdi	Stor merværdi
Bivirkninger	Andel patienter, der oplever en eller flere alvorlige bivirkninger (5 %-point) Suppleret med kvalitativ beskrivelse af bivirkningsprofil af eculizumab	Kritisk	-9,8 (-22,4;2,9)	Kan ikke kategoriseres	RR: 0,49 (0,21;1,15)	Kan ikke kategoriseres	Negativ værdi Baseret på den kvalitative gennemgang og risikoen for alvorlige og potentielt dødelige infektioner
Vedvarende sygdomsforværring	Gennemsnitlig ændring på EDSS-score (0,2 point pr. år)	Kritisk	[redacted]	Kan ikke kategoriseres	RR: 0,446 (0,182;0,998)	Merværdi af ukendt størrelse	Kan ikke kategoriseres
Synsskarphed	Gennemsnitlig ændring på Snellen-tavle (0,2 point pr. år)	Vigtig	[redacted]	Kan ikke kategoriseres	NA	NA	Kan ikke kategoriseres
Livskvalitet	Gennemsnitlig ændring på SF-36 (0,5 SD)	Vigtig	Opgjort anderledes end ønsket i protokollen PCS: -11,9 (-24,97;1,17) MCS: -3,75 (-19,40;12)	Kan ikke kategoriseres	Opgjort anderledes end ønsket i protokollen PCS: RR 0,52 (0,274;0,955) MCS: RR: 0,83 (0,48;1,31)	Kan ikke kategoriseres	Kan ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres jf. Medicinrådets metoder
Kvalitet af den samlede evidens	Meget lav

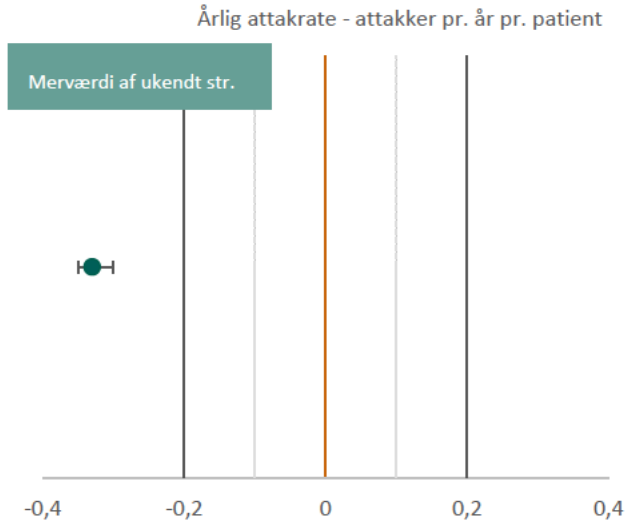
CI = Konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = Relativ risiko.

Årlig attakrate

Som beskrevet i protokollen er effektmålet årlig attakrate kritisk for vurderingen af lægemidlets værdi for patienterne, da patienter med NMOSD ofte kan have relativt mange attakker, som kan medføre varig funktionsnedsættelse.
Et attak defineres som nye eller forværring af eksisterende symptomer af mere end 24 timers varighed i fravær af feber eller infektion, forudgået af en stabil neurologisk tilstand i minimum 30 dage. Symptomerne skal desuden kunne tilskrives sygdommen og skal være ledsaget af objektiv neurologisk forværring [8,9].
Den mindste klinisk relevante forskel er 0,2 attakker pr. patient om året.

Det kliniske studie af eculizumab var designet som et "time-to-event"-studie med første attak som primært endepunkt. Studiet blev afsluttet efter 23 attakker, heraf 20 hos patienter i placebo-armen (43 % af patienterne) og 3 hos patienter i eculizumab-armen (3 %). Fagudvalget bemærker, at vurderingen af attakker i studiet var omhyggelig, og at en komité vurderede hvert potentielt attak.

Den beregnede årlige attakrate var 0,02 hos patienter behandlet med eculizumab og 0,35 hos patienter i placebo-armen. Fagudvalget bemærker, at den årlige attakrate var væsentlig lavere i placebo-armen under studiet end den årlige attakrate hos patienterne ved baseline (ca. 2 attakker/år).



Figur 1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for årlig attakrate. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Den absolutte forskel er vist i figuren ovenfor.

Punktestimatet for den absolutte effektforskel er 0,33 (-0,35;-0,30) attakker pr. år og afspejler en klinisk relevant effektforskel. Derfor er den foreløbige værdi af eculizumabs merværdi af ukendt størrelse vedr. årlig attakrate.

Baseret på den relative effektforskel, som er en RR 0,04 (0,01;0,15), har eculizumab foreløbigt en stor merværdi vedrørende årlig attakrate.

Samlet har eculizumab en stor merværdi på effektmålet årlig attakrate.

Perspektivering: Patienter, som ikke modtager behandling med andre immunsupprimerende lægemidler

I studiet indgik en præspecificeret subgruppe af patienter, der ikke samtidig blev behandlet med andre immunsupprimerende behandlinger end eculizumab. Der var 21 patienter i eculizumab-armen og 13 patienter i placebo-armen. Ingen af patienterne behandlet med eculizumab fik attakker, mens det skete for 7 patienter i placebo-armen. Antallet af patienter er meget småt, men fagudvalget finder, at data indikerer, at eculizumab også er virksomt i at forhindre attakker hos patienter, der ikke modtager anden immunsupprimerende behandling samtidig.

Bivirkninger

Som beskrevet i protokollen er effektmålet bivirkninger et kritisk effektmål, da det belyser, hvor godt patienterne tolererer eculizumab sammenlignet med komparator. Fagudvalget ønskede både en kvantitativ opgørelse opgjort som antal patienter, der oplevede en eller flere alvorlige bivirkninger.

Ansøger har indleveret data for alvorlige uønskede hændelser relateret til behandlingen. Selvom attakker blev udelukket fra analysen, var der 9 patienter i placebo-armen (ud af 47; 19,1 %) og 9 patienter i eculizumab-armen (ud af 96; 9,4 %), som oplevede alvorlige uønskede hændelser, der blev vurderet at være relateret til behandlingen. Fagudvalget har set på en liste over samtlige uønskede hændelser (supplementary appendix til artiklen), som især rummer infektioner. En patient behandlet med eculizumab havde en uønsket hændelse med dødelig udgang (pleural effusion), som blev vurderet at være relateret til behandlingen.

Fagudvalget vurderer, at der i det kliniske studie af eculizumab til NMOSD ikke ses en kvantitativ forskel i bivirkningsprofiler mellem eculizumab og placebo ud fra konfidensintervaller for både den absolutte og relative forskel. Fagudvalget vurderer, at datagrundlaget fra det kliniske studie af eculizumab til NMOSD er lille, og lægger i stedet vægt på erfaringer med lægemidlet til andre patientgrupper. Derfor har fagudvalget baseret sin kategorisering på information fra produktresumeet og EPAR [5,7].

I produktresumeet oplistes en lang række bivirkninger:

Tabel 4. Bivirkninger fra produktresumé

Hyppighed	Bivirkning
Meget almindelige (> 10 %)	Hovedpine
Almindelige (1-10 %)	Anæmi, Leukopeni. Abdominalsmerter, Diarré, Kvalme, Opkastning, Smagsforstyrrelser. Svimmelhed, Temperaturstigning, Træthed. Herpes labialis, Infektion i nedre luftveje, Infektion i øvre luftveje, Influenzalignende symptomer. Artralgi, Myalgi. Tremor. Søvnløshed. Urinvejsinfektion. Hoste, Nasopharyngitis, Orofaryngeale smerter, Pneumoni. Alopeci, Hudkløe, Hududslæt.
Ikke almindelige (0,1-1 %)	Lymfopeni, Trombocytopeni. Tinnitus. Sløret syn. Peritonitis. Anafylaktisk reaktion, Hypersensitivitet. Absces, Infektioner, Sepsis, Svampeinfektioner, Virale infektioner. Infusionsrelaterede reaktioner. Nedsat hæmatokritværdi. Knoglesmerter, Muskelkramper, Rygsmerter, Smerter i ekstremiteter. Paræstesier. Angst, Depression, Humørforstyrrelser. Hæmaturi, Nyrefunktionspåvirkning. Dyspnø. Cellulitis, Erytem, Purpura. Hypertension, Hypotension, Septisk shock, Ødemer.
Sjældne (0,01-0,1 %)	Hæmolyse, Koagulationsforstyrrelser, Myelodysplastisk syndrom. Thyroideapåvirkning. Artritis. Malignt melanom. Trismus. Dermatitis, Impetigo. Hæmatom, Synkope.

EMAs EPAR beskriver, at bivirkningsprofilen for eculizumab ved NMOSD ikke er anderledes end for andre indikationer, men at den underliggende sygdom fører til mange uønskede hændelser.

Fagudvalgets væsentligste bekymring angår sepsis og alvorlige infektioner med meningokokker. Vaccinen vil ikke fuldstændig eliminere risikoen for infektion med meningokokker, da den ikke rammer alle serotyper af bakterien. Desuden kan lægemidlet muligvis også øge risikoen for infektion med andre lignende bakterier.

Selvom det ikke sås i studiet af eculizumab, er det en kendt bivirkning ved lægemidlet og ved andre former for komplementprotein-deficiens, som har medført flere dødsfald. I en publiceret pharmacovigilance-rapport af 10 års brug af eculizumab blev 76 tilfælde af meningokok-infektion beskrevet (0,25 pr. 100 patientår), hvoraf 8 var dødelige [8]. Vaccination mod de hyppigste serotyper af *Neisseria meningitidis* kan reducere risikoen for alvorlig meningokokinfektion, men ikke eliminere risikoen. Således var størsteparten af de patienter, som blev ramt af meningokokinfektion, vaccineret [8]. Udover meningokokker er der en øget risiko for infektion med kapselbærende bakterier og Aspergillus ved behandling med eculizumab [5].

Andre bivirkninger identificeret som bivirkninger med særlig interesse i EPAR'en, udover infektioner og sepsis, er: infusionsreaktioner, hjerteforstyrrelser og angioødem. Infusionsreaktioner optrådte i 9 % i eculizumab-armen (Combined Safety Set), hjerteforstyrrelser i 2 % og angioødem i 4 %.

Samlet vurderer fagudvalget, at bivirkningsprofilen især medfører bekymringer for alvorlige og muligvis dødelige infektioner. Risikoen er så betydelig, og konsekvenserne kan være så alvorlige, at fagudvalget vurderer, at eculizumab har en negativ værdi sammenlignet med ingen behandling.

Vedvarende sygdomsforværring
Som beskrevet i protokollen er effektmålet vedvarende sygdomsforværring, defineret som EDSS-score, et kritisk effektmål.

Expanded Disability Status Scale (EDSS) er en metode til at kvantificere sygdomsforværring i MS og NMOSD. Måleinstrumentet måler ændringer i niveau af sygdomsforværring over tid. EDSS er det instrument, der oftest bruges, både i kliniske studier og i klinikken. EDSS-skalaen går fra 0 (fuld funktion) til 10 (død). Scorer mellem 0,0-3,5 defineres ved patienter, der er i stand til at gå min. 500 m uden nogen hjælp; scorer mellem 3,5-5,5 er patienter med begrænset gangdistance til under 500 m uden støtte; 6,0-6,5 er defineret ved, at patienterne kan gå, men kun med støtte; 7,0-9,5 er defineret ved ophævet gangfunktion og behov for hjælp til daglige aktiviteter.

Effektmålet ønskes opgjort som gennemsnitændring i EDSS-scoren. Den mindste klinisk relevante forskel mellem eculizumab og placebo vurderes af fagudvalget at være en score på 0,2.

Den gennemsnitlige årlige ændring i EDSS-score var [redacted] EDSS/år (forbedring) hos patienter behandlet med eculizumab og [redacted] (forværring) hos patienter i placebo-armen.

Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for ændring i EDSS-score. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Den absolutte forskel er vist i figuren ovenfor.

Punktestimatet for den absolutte effektforskel er [redacted] Da konfidensintervallet overlapper både en negativ og en positiv effekt af eculizumab, kan den foreløbige merværdi ikke kategoriseres for den absolutte effektforskel.

Baseret på den relative effektforskel, som er en RR 0,446 (0,182;0,998), har eculizumab foreløbigt en merværdi af ukendt størrelse vedrørende sygdomsforværring.

Som beskrevet under databehandling gør Medicinrådet opmærksom på, at effektmålet ikke mødte signifikans i den hierarkiske analyse af effektmål. Grundet studiedesignet er der stor usikkerhed på vurdering af effektmålet.

Samlet vurderer fagudvalget, at det kliniske studies design ikke er hensigtsmæssigt til at vurdere sygdomsprogression, og at effekten af eculizumab ikke kan kategoriseres på effektmålet. Den relative effektforskel er dog i favør af eculizumab, og fagudvalget forventer, at effekten på attakker vil medføre en langsommere forværring af sygdommen. Derfor ville en længere opfølgningstid (og et andet studiedesign) måske medføre en tydeligere effekt af eculizumab på sygdomsprogression, men fagudvalget vælger ikke at kategorisere ud fra spekulationer.

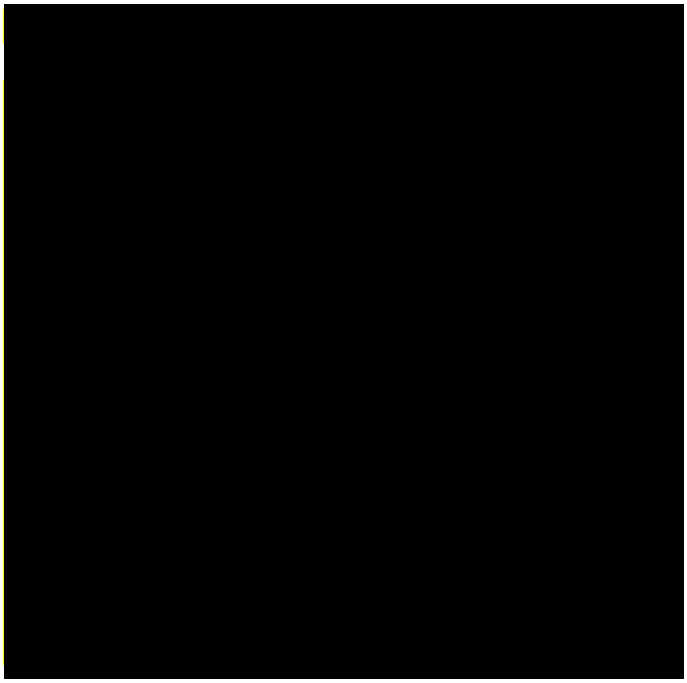
Synsskarphed

Synsproblemer er et væsentligt symptom ved NMOSD, og derfor har fagudvalget valgt i protokollen, at synsskarphed er et vigtigt effektmål. Synsskarphed måles på en Snellen-tavle, og fagudvalget ønsker effektmålet opgjort med "neurostatus scoring" af visuel

funktion, der benyttes i dansk klinisk praksis. Ved denne scoring får patienten 0 point ved normalt syn og 6 point ved den dårligste score, der indikerer en væsentlig forværring af patientens synsevne. Patienter med en score på 6 kan dog stadig have noget af synet intakt. Denne scoring indbefatter synet på begge øjne. Neurostatus scoring af visuel funktion indgår i EDSS som et funktionelt domæne. Fagudvalget er opmærksom på, at der derved er en vis redundans mellem de to vigtige effektmål EDSS-score og synsskarphed, men vurderer, at synsskarphed er så væsentligt for patienter med NMOSD, at effektmålet skal opgøres særskilt.

Den mindste klinisk relevante forskel mellem eculizumab og placebo blev af fagudvalget vurderet at være en forskel i den gennemsnitlige ændring på 0,2 point i løbet af et år. Fagudvalget vurderede, at denne forskel er klinisk relevant, da det vil svare til, at hver femte patient i gennemsnit oplever at undgå en stigning på et point pr. år.

Resultaterne for synsskarphed er ikke publiceret endnu, men ansøger har indsendt data on file fra det kliniske studie. Patienter i eculizumab-armen havde en forbedring [redacted]



Figur 3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for ændring i synsskarphed. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Punktestimatet for den absolutte effektforskel [redacted] Da konfidensintervallet overlapper både en negativ og en positiv effekt af eculizumab, kan den foreløbige merværdi ikke kategoriseres for den absolutte effektforskel. Data er ikke angivet med flere decimaler, og Medicinrådet antager, at afrunding af tal er årsag til at [redacted]

Der er ikke indleveret data for den relative effektforskel.

Samlet kan værdien af eculizumab ikke kategoriseres på effektmålet synsskarphed. Fagudvalget vurderer, ligesom for sygdomsprogression, at studiets design ikke er hensigtsmæssigt til at vurdere dette effektmål.

Livskvalitet
Fagudvalget ønsker effektmålet opgjort med det generiske instrument SF-36.

Fagudvalget har tidligere benyttet Multiple Sclerosis Quality of Life-54 (MSQOL-54) til vurderinger af MS-lægemidler, da det er et sygdomsspecifikt og valideret mål for livskvalitet, der inkluderer selvrapporterede subjektive indikatorer for fysisk, emotionel og social funktionalitet og trivsel [13,14]. MSQOL-54 bygger på SF-36, og da det ikke er valideret i NMOSD, har fagudvalget valgt det generiske instrument. For helbredsrelateret livskvalitet anvendes ofte en mindste klinisk relevant forskel på 0,5 standarddeviationer (SD), og fagudvalget har derfor valgt at anvende en ændring på 0,5 SD som mindste klinisk relevante forskel [16,17].

Ansøger har indleveret data for SF-36 opdelt i "physical component score" og "mental component score" som andel af patienter med "klinisk meningsfyldt forværring". I protokollen bad fagudvalget om at få effektmålet opgjort som gennemsnitlig ændring. Derfor er det ikke meningsfyldt at vurdere resultaterne i forhold til den mindste klinisk relevante forskel og foretage en formel kategorisering af effektmålet.
Resultaterne fra den endelig ansøgning er vist i tabel 1. Fagudvalget bemærker, at begge komponenter tyder på en bedre effekt af eculizumab end placebo på effektmålet, især hvad angår den fysiske komponent.

Værdien af eculizumab kan ikke kategoriseres ud fra Medicinrådets metoder på effektmålet livskvalitet, men fagudvalget bemærker, at data tyder på en bedre effekt af eculizumab på effektmålet.

Perspektivering: Effekter af andre lægemidler

Fagudvalget har kendskab til mindre studier, der undersøger effekten af rituximab og azathioprin til patienter med NMOSD. I et iransk studie blev 86 patienter med NMOSD randomiseret til rituximab eller azathioprin [9]. De fleste resultater i artiklen er rapporteret for de 68 patienter, som gennemførte studiet, der varede 1 år. Ud af 33 patienter, som blev behandlet med azathioprin i et år, oplevede 19 patienter ingen attakker. Det samme var tilfældet for 26 patienter ud af de 35, som i 1 år blev behandlet med rituximab. Fagudvalget gør opmærksom på, at der er mange usikkerheder forbundet med studiet, som vanskeliggør en sammenligning med studiet af eculizumab. Blandt andet var de to arme i studiet signifikant forskellige på flere karakteristika, og kun lidt under halvdelen af patienterne var positive for AQP4-antistoffer.
I et multicenter, randomiseret, dobbeltblindet studie af rituximab i Japan blev 19 patienter randomiseret til rituximab og 19 til placebo [10]. Alle patienter var positive for AQP4-antistoffer og blev fulgt i 72 uger. Ingen af patienterne behandlet med rituximab oplevede attakker, men 3 forlod studiet (tilbagetrækning af samtykke, uønsket hændelse og en patient, som fik et kontraindiceret lægemiddel). I placebogruppen havde 7 patienter attakker.

I et fransk retrospektivt kohortestudie, hvor patienterne blev behandlet med rituximab, mycophenolate eller azathioprin, havde 86 % af patienterne ingen attakker i det første år, og 72 % havde ingen attakker i 3 år [9].
De kliniske studier er små og forbundet med væsentlige usikkerheder, men fagudvalget vurderer samlet set, at de behandlinger, der anvendes i dansk klinisk praksis, har effekt på at forebygge attakker hos patienter med NMOSD og AQP4-antistoffer.
Behandlingerne kan også være forbundet med uønskede hændelser – ofte relateret til, at virkningsmekanismen er immunosuppression. Resultaterne af studierne er i overensstemmelse med fagudvalgets kliniske erfaring. Der er ikke datagrundlag til at sammenligne effekterne af de andre lægemidler med eculizumab i en kvantitativ analyse.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at værdien af eculizumab sammenlignet med placebo til patienter med NMOSD ikke kan kategoriseres efter Medicinrådets metoder. Datagrundlaget er en direkte sammenligning. Det kliniske studie var designet som et time-to-event-studie med første attak som event, og da patienterne ikke blev fulgt efter første attak, er vurderingen af flere effektmål forbundet med stor usikkerhed.

Der er en stor merværdi af eculizumab på effektmålet årlig attakrate, hvor meget få patienter behandlet med eculizumab oplevede attakker i det kliniske studie. På baggrund af det indsendte datagrundlag og designet af det kliniske studie kan værdien på effektmålene sygdomsprogression og synskarphed ikke kategoriseres, og for livskvalitet er der indleveret data, som er opgjort anderledes end ønsket i protokollen, men som dog tyder på en bedre effekt af eculizumab end placebo.

Hvad angår sikkerhed, vurderer fagudvalget, at der især er risiko for infektion med meningokokker og for andre alvorlige infektioner ved behandling med eculizumab. På grund af denne risiko vurderer fagudvalget, at eculizumab har en negativ værdi på effektmålet bivirkninger grundet risikoen for alvorlige og potentielt dødelige bivirkninger trods vaccination.

Fagudvalget finder det sandsynliggjort, at eculizumab har en effekt, især på attakker, sammenlignet med placebo, men er omvendt bekymret for infektionsrisikoen.
Fagudvalget mener samlet set, at eculizumab er et bedre alternativ for patienterne end ingen behandling.

Fagudvalget bemærker, at andre immunsupprimerende lægemidler også formodes at have en effekt på at forhindre eller forsinke attakker hos patienter med NMOSD, og at de også kan medføre bivirkninger. Fagudvalget har erfaring med disse lægemidler og håndtering af bivirkningerne. Det er på baggrund af data ikke muligt at vurdere, om eculizumab er et bedre, ligeværdigt eller dårligere behandlingsalternativ end disse.

6. Andre overvejelser

Fagudvalget ønsker at gøre opmærksom på patientperspektivet i forhold til administration af eculizumab. Ugentlige i.v.-behandlinger i induktionsfasen og senere behandlinger hver anden uge vil være meget indgribende i patienternes dagligdag, men skal naturligvis ses i lyset af sygdommens karakter.

Fagudvalget pointerede i protokollen, at sammenligningen med placebo ikke er retvisende. Derfor har fagudvalget i et perspektiverende afsnit belyst effekten af andre lægemidler, der benyttes til behandling af NMOSD i Danmark. Dette afsnit er indsat ovenfor, da perspektiveringen indgår i fagudvalgets konklusion.

Fagudvalget ønskede også yderligere viden om, hvor godt patienter vaccineret mod *Neisseria meningitidis* er beskyttet under behandling med eculizumab, eftersom vaccinen ikke beskytter mod alle meningokokstammer. Herunder ville fagudvalget gerne have ansøgers overvejelser om behandlingsregimet ved et evt. skift fra rituximab til eculizumab, både i forhold til vaccine og evt. behov for "bridging terapi".

Ansøger beskriver i sin endelige ansøgning vaccinationsprogrammet for patienter, der skal behandles med eculizumab. I det kliniske udviklingsprogram for eculizumab til NMOSD blev der ikke set meningokokinfektioner, men ansøger beskriver også 10 års erfaringer med eculizumab til andre indikationer. Der er rapporteret 76 tilfælde af meningokokinfektion (0,25 pr. 100 patientår), heraf 8 med dødelig udgang. Disse data indgår i fagudvalgets vurdering af effektmålet bivirkninger.

I PREVENT-studiet var det et eksklusionskriterie, hvis en patient var behandlet med rituximab 3 måneder før behandlingen med eculizumab. Ansøger beskriver ikke bridging terapi, men at patienterne, som tidligere var behandlet med rituximab, blev vaccineret tilsvarende andre patienter.

Fagudvalget finder på baggrund af ansøgers indsendte beskrivelser og klinisk erfaring, at meningokokinfektioner er en relevant bekymring ved behandling med eculizumab. Patienterne skal vaccineres inden behandlingen indledes, men det fjerner ikke fagudvalgets bekymring for infektioner.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende multipel sklerose

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Kristian Storr Overlæge, speciallæge i neurologi	Lægevidenskabelige Selskaber og udpeget af Dansk Neurologisk Selskab
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Regionen ser sig repræsenteret af øvrige medlemmer og ønsker derfor ikke at udpege yderligere et medlem	Region Midtjylland
Thor Petersen Overlæge	Region Syddanmark
Said Nasim Ashna Overlæge	Region Sjælland
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Kan ikke opfylde Medicinrådets habilitetskrav	Dansk Neurologisk Selskab
Marie Lynning Patient/patientrepræsentant	Danske Patienter

Sammensætning af fagudvalg	
Malene Krüger Patient/patientrepræsentant	Danske Patienter
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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26. maj 2021	Godkendt af Medicinrådet.

11. Bilag

Bilag 1: Cochrane – risiko for bias

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

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering computer-genereret af 3. part. Baseline karakteristika balanceret.
Effekt af tildeling til intervention	**Lav**	Allokering til interventionsgruppe dobbelt-blindet.
Manglende data for effektmål	**Lav**	Effekten er baseret på *intention-to-treat*-populationen. 16 (17 %) ECU-arm vs. 3 (6 %) placebo forlod studiet. Analyser udført på ITT-population.
Risiko for bias ved indsamlingen af data	**Lav**	Attakker blev vurderet af uafhængige og blindede assessorer bestående af to neurologer og én neuro-ophthalmologist.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	De prædefinerede effektmål passer med de rapporterede effektmål.
Overordnet risiko for bias	**Lav**	

Bilag 2: GRADE

Klinisk spørgsmål 1 – eculizumab sammenlignet med placebo til behandling af NMOSD

Tabel 4. GRADE evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt		Sikkerhed	Vigtighed
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Eculizumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)		
Årlig attakrate												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	96	47	RR: 0,04 (0,01;0,15)	-0,33 (-0,35;-0,30)	⨁⨁◯◯ LAV	KRITISK
Bivirkninger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	96	47	RR: 0,49 (0,21;1,15)	-9,8 (-22,4;2,9)	⨁◯◯◯ MEGET LAV	KRITISK
Vedvarende sygdomsforværring												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	96	47	RR: 0,446 (0,182;0,998)	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
Synsskarphed												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Meget alvorlig[d]	Ingen	96	47	NA	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIG

Sikkerhedsvurdering							Antal patienter		Effekt		Sikkerhed	Vigtighed
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Eculizumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)		
Livskvalitet												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]		Ingen	96	47	PCS: RR 0,52 (0,274;0,955) MCS: RR: 0,83 (0,48;1,31)	PCS: -11,9 (-24,97;1,17) MCS: -3,75 (-19,40;12)		Vigtig
Kvalitet af den samlede evidens			MEGET LAV[e]									

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Der er nedgraderet ét niveau, da der er indirekthed i forhold til en dansk patientpopulation (bl.a. pga. co-medicinering).

[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder én beslutningsgrænse.

[d] Der er medgraderet to niveauer, da konfidensintervallet indeholder to beslutningsgrænser.

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

Medicinrådet

Application for the assessment of clinically added value of Soliris (Eculizumab) for the treatment of adult patients with Neuromyelitis Optica Spectrum Disorder with anti-aquaporin-4 (AQP4) antibody-positive disease

Version 1.1

Contents

1 Basic information

TABLE 1 CONTACT INFORMATION

Name	Mikkel Johansen
Title	Market Access & Policy Director Nordics
Area of responsibility	Primary contact
Phone	+45 5355 6024
E-mail	mikkel.johansen@alexion.com

TABLE 2 OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Soliris
Generic name	Eculizumab
Marketing authorization holder in Denmark	Alexion Pharma Nordics AB
ATC code	L04AA25
Pharmacotherapeutic group	Recombinant humanized monoclonal $IgG_{2/4k}$ antibody
Active substance(s)	Eculizumab
Pharmaceutical form(s)	Concentrate for solution
Mechanism of action	Eculizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and 12 preventing the generation of the terminal complement complex C5b-9. Eculizumab preserves the early components of complement activation that are essential for opsonization of microorganisms and clearance of immune complexes. In patients with Neuromyelitis Optica Spectrum Disorder (NMOSD), uncontrolled terminal complement activation caused by autoantibodies against AQP4 leads to the formation of the MAC and C5a-dependent inflammation which results in astrocyte necrosis and increased permeability of the blood brain barrier, as well as death of the surrounding oligodendrocytes and neurons. Chronic administration results in immediate, complete, and sustained inhibition of terminal complement activity.
Dosage regimen	Initial phase: 900 mg weekly for the first four doses followed by 1200mg the fifth week Maintenance phase: 1200mg once every other week (14 days +/-2days)

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Adult patients with NMOSD who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of disease
Other approved therapeutic indications	• Paroxysmal nocturnal haemoglobinuria (PNH); • Atypical hemolytic uremic syndrome (aHUS); • Refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor antibody-positive (in adults)
Will dispensing be restricted to hospitals?	Soliris must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological, renal, neuromuscular or neuroinflammatory disorders.
Combination therapy and/or co-medication	Due to its mechanism of action, the use of Soliris increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all patients must be vaccinated at least 2 weeks prior to receiving Soliris (SmPC, 2019)
Packaging – types, sizes/number of units, and concentrations	One vial of 30 ml contains 300 mg of eculizumab (10 mg/ml)
Orphan drug designation	Soliris was designated as an orphan drug in NMOSD (EU/3/13/1185 by decisions 5/8 2013 and 21/12 2018)

2 Abbreviations

aHUS	Atypical hemolytic uremic syndrome
ANCOVA	Analysis of co-variance
AQP4	Aquaporin-4
AQP4+	Anti-AQP4 antibody positive
ARR	Annualised relapse rate
AZA	Azathioprine
BSC	Best suportive care
CI	Confidence interval
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FAS	Full analysis set
gMG	Generalized myasthenia gravis
IST	Immunosuppressive therapy
ITT	Intention to treat
KFS	Kurtzke Functional Systems
LSM	Least square means
MC	Medicicines Council
MCS	Mental Component Score
mITT	Modified intention to treat
MMF	mycophenolate mofetil
NMO	neuromyelitis optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
OLE	Open Label Extention

OR	Odds ratio
PCS	Physical Component Score
PI	Product information
PNH	Paroxysmal nocturnal haemoglobinuria
RAC	Relapse adjudication Committee
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short Form - 36

3 Summary

Introduction: This application serves as the basis for the assessment of added clinical value of Eculizumab (Soliris®) for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 antibody-positive (AQP4+) with a relapsing course of disease.

Method: As outlined in the Medicines Council protocol data on the efficacy and safety of eculizumab added to current immunosuppressive therapy (IST) compared to placebo was sourced from the PREVENT study. The PREVENT trial was a double-blind, time-to-event trial where patients were intravenously administered eculizumab (at a dose of 900 mg weekly [7 ± 2 days] for the first four doses starting on day 1, with the fifth dose of 1200 mg, followed by 1200 mg every 2 weeks [14 ± 2 days]) or matched placebo. The study medication, eculizumab or placebo, was added to any existing IST treatment (with the exception of protocol-specified disallowed medications) with the majority of patients on ISTs (76%) at baseline. Patients must have remained on stable dose throughout the study unless they experienced a relapse. With the exception of rituximab, which was prohibited in PREVENT on the basis of the clinical rationale for not using eculizumab and rituximab concomitantly, the distribution and type of ISTs used across randomized treatment groups are broadly reflective of those used off-label in Danish clinical practice. Thus, the placebo arm in the PREVENT trial is considered a reasonable proxy of standard of care.

Results: In the PREVENT study, analysis of the primary endpoint of time to first adjudicated event showed that patients receiving eculizumab had a 94% reduction in risk of relapse; also at 48 weeks, 97.9% of eculizumab treated patients were relapse free (vs. 63.2% of placebo treated patients) demonstrating sustained benefit lasting through ~144 weeks of treatment. Subgroup analysis of the primary outcome in PREVENT showed a similar treatment efficacy across subgroups defined by on-trial IST/ no IST and pre-trial rituximab exposure. Furthermore, a statistically significant reduction in adjudicated ARR with eculizumab compared to placebo with rates of 0.02 and 0.35, respectively (RR: 0.04; p<0.001). Data on the expanded disability status Scale (EDSS) demonstrated an improvement in the overall study population during the PREVENT trial. The difference in least square mean EDSS change from baseline to end of study was numerically in favour of eculizumab (-0.29. 95% CI: –0.59; 0.01). Post-hoc analysis of EDSS showed that 11.5% of patients versus 23.4% in the eculizumab and placebo arm, respectively, experienced disability progression (RR: 0.446. 95% CI: 0.182; 0.998). Analysis of visual acuity (measured by the LSM changes from base line in the Kurtzke Functional System Visual score) showed improvement in both arms (-0.75 and -0.47 in the eculizumab and placebo arm, respectively) but did not reach statistical significance. Fewer patients in the eculizumab arm experienced clinical meaningful worsening of SF-36 Physical Component Score compared to patient in the placebo arm (RR: 0.52. 95% CI: 0.274; 0.955) while the impact on the SF-36 Mental Component Score was smaller (RR: 0.83. 95% CI: 0.48; 1.31).

Overall, in the PREVENT trial, eculizumab was well tolerated and the safety profile was similar to that of standard of care, for which placebo is a proxy. The eculizumab NMOSD trial program did not add any new safety signals to the existing tolerability profile of the drug.

Conclusion: Eculizumab adds clinical value to the treatment of adult patients with AQP4+ NMOSD with a relapsing course of disease compared to current standard of treatment and is the first immunomodulating therapy with robust clinical trial evidence.

4 Literature search

The Medicine Council protocol for assessing the added clinical value of eculizumab in NMOSD[1] stipulates that the clinical evidence should be sourced from the PREVENT trial[2]. Hence, further systematic literature search was not requested.

Databases and search strategy

Not applicable

4.1 Relevant studies

The PREVENT study primary publication (with supplementary appendix) was used as the main source of evidence for this submission (Table 3). In addition data from the eculizumab NMOSD clinical program was sourced from the EPAR[3]. Some of the requested outcomes were not available in these sources and was reported based on conference proceedings [4, 5]. Visual acuity data has not been reported in any form previously and provided as data on file in this application.

TABLE 3 RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. **Pittock, Berthele, Fujihara et al.** N Engl J Med. 381(7):614-625[6, 7]	PREVENT	NCT01892345	Apr 2014 – Jul 2018	1

4.2 Main characteristics of included studies

The clinical evidence was sourced from the PREVENT clinical study. PREVENT is a phase 3, double-blind, time-to-event, randomised trial comparing eculizumab to placebo. The characteristics of the included PREVENT trial are outlined in the following sections and in tabular form in Table A2

4.2.1 Participants

Eligibility

The eligibility criteria for the PREVENT trial included in the submission are shown in Table A2.

In brief, the trial included adults ≥ 18 years of age, diagnosed with NMO (according to 2006 criteria[8]) or NMOSD (according to 2007 criteria[9]) who were AQP4+ with a history of at least two relapses during the previous 12 months or three relapses during the previous 24 months, at least one of which had occurred within the previous 12 months; and a score of 7 or less on the EDSS. Patients who were receiving ISTs for relapse prevention were eligible for inclusion if they were receiving stable dose regimens and must have remained on stable dose throughout the study except in the event of a relapse.

Patient demographics and baseline characteristics

The demographic and other baseline characteristics of the patients included in the FAS in the PREVENT trial are summarised in Table A2

Baseline characteristics were well balanced between treatment arms. The majority of patients were diagnosed with either NMO (75%) or NMOSD (25%) with a high proportion of female patients (91%). All patients were AQP4 +, consistent with the eligibility criteria of the trial, with a mean age of 44.3 years and an average EDSS score of 4. Approximately 50% of all patients were White/Caucasian.

The mean (± SD) ARR in the 24 months before enrolment was 1.99 ± 0.94 (1.94±0.90 for eculizumab and 2.07±1.04 for placebo). A total of 110 (76.9%) patients were on ISTs or immunomodulators at the time of any of the historical relapses. Similarly, 76.2% (n=109) of patients were on ISTs at baseline.

Of the total patients, 133 (93%) had received supportive ISTs prior to the study with 98 (68.5%), 87 (60.8%), 46 (32.2%), and 42 (29.4%) receiving corticosteroids, azathioprine (AZA), rituximab, and mycophenolate mofetil (MMF), respectively.

At noted above, at baseline, the majority of patients randomised to eculizumab and placebo received concomitant supportive ISTs (76.2%) with treatment groups well balanced with this respect (eculizumab 78.1% versus placebo 72.3%). The level of IST use by IST subgroup at baseline between treatment arms was similar. Overall, a total of 34 patients (23.8%) were not under any IST, 27 (18.9%), 50 (35%), 25 (17.5%), and 7 (4.9%) received corticosteroids alone, AZA, MMF, or other therapies with or without corticosteroids, respectively. The largest difference between groups was in the azathioprine with or without corticosteroids (eculizumab 38.5% versus placebo 27.7%).

4.2.2 Study design

Participants (N:143) were randomly assigned in a 2:1 ratio between eculizumab and placebo. Patients were stratified across sites according to the score on the Expanded Disability Status Scale (EDSS) and the use of concomitant immunosuppressive therapy. The treatment details of the interventions (including dosing regimen and duration of treatment) in the trial are presented in Table 4.

The study interventions were administered intravenously over approximately 35 mins. The dosing regimen of eculizumab used in this trial, eculizumab or placebo (at 900 mg) for the first four doses, weekly (7 ± 2 days) for the first 4 weeks, followed by 1200 mg for the fifth dose and then 1200 mg every 2 weeks (14 ± 2 days) thereafter, is consistent with the dose and method of administration as per the eculizumab SmPC.

The study medication, eculizumab or placebo, was added to any existing treatment (with the exception of protocol-specified disallowed medications). The standard of care treatment included the use of concomitant ISTs for relapse prevention. The patient must have been on a stable maintenance dose of the IST before screening and must have remained on that dose throughout the study unless they experienced a relapse. Palliative and supportive care was permitted during the course of the study for underlying conditions as well as recommended standardised relapse treatment.

The 24th adjudicated on-trial relapse was planned to trigger end of study activities. However, the study was terminated after 23 relapses. This action was taken following review of blinded data by the Sponsor, which concluded that terminating the study at 23 on-trial relapses had a low risk of impacting study outcomes. Early termination of the study was not due to concerns over efficacy or safety. [7]

TABLE 4 INTERVENTIONS COMPARED IN THE PREVENT TRIAL

Trial ID	Treatment	Dosing regimen	Duration of treatment	Duration of follow-up
PREVENT	Eculizumab Matched placebo (same buffer, without eculizumab)	• Induction phase: 900 mg IV (3 vials at 300 mg) weekly (every 7 ± 2 days) x 4 followed by 1200 mg (4 vials at 300 mg) 1 week later (7 ± 2 days) for the fifth dose (visit 6/ week 4). • Maintenance phase: 1200 mg IV (4 vials at 300 mg) every 2 weeks (14 ± 2 days) from the sixth dose onwards (visit 7/ week 6).	Time-to-event trial: Duration of treatment until relapse, trial discontinuation, or the end of the trial (approx. 3–4 years).	Follow-up Relapse Evaluation Visits were performed at 1, 4 and 6 weeks after the onset of relapse.

Abbreviations: IV, intravenous; mAb, monoclonal antibody.

4.2.3 Outcomes

Each efficacy parameter included in the primary and secondary endpoint analyses are described below.

The primary efficacy outcome was the time to first adjudicated on-trial relapse. The definition is as follows

- **On-trial relapse:** a relapse that occurs during the study period, defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persisted for more than 24 hours as confirmed by the treating physician. The signs and symptoms must have been attributed to NMO, i.e., not caused by an identifiable cause such as infection, excessive exercise, or excessively high ambient temperature. Isolated changes on magnetic resonance imaging or other imaging investigation with no related clinical findings was not considered an on-trial relapse. The relapse must have been preceded by at least 30 days of clinical stability. The treating physician was not required to wait 24 hours prior to initiating treatment for the relapse.
- **Adjudicated on-trial relapse:** an on-trial relapse that was positively adjudicated by the relapse adjudication committee (RAC).
    - The independent RAC confirmed all on-trial relapse events using objective and consistent clinical criteria described in a relapse adjudication charter. The RAC consists of three independent medical experts in neurology/neuro-ophthalmology who are each experienced in the management of patients with NMOSD. The RAC decided by majority vote whether each relapse met the pre-defined objective criteria for an adjudicated on-trial relapse.

Secondary end points were

1. Adjudicated on-trial ARR
2. Change from baseline in EDSS score at the EOS
3. Change from baseline in mRS score at the EOS
4. Change from baseline in HAI score at the EOS
5. Change from baseline in EQ-5D-3L VAS score at EOS

6. Change from baseline in EQ-5D-3L Index score at EOS

Efficacy analyses was planned to be conducted in the mITT population consisting of all patients randomized and receiving at least one dose of study medication. Since all randomized patients received at least one dose of study medication, ITT and mITT population are the same.

The primary endpoint was tested for between group difference using log-rank test. To control for the overall type-I error at 0.05 for multiple hypothesis tests, fixed sequence hierarchical testing procedure was applied, with the primary end point followed by the six secondary efficacy end points in the order described above.

Stratified Cox proportional-hazards model with the trial group as a covariate was used to estimate the hazard ratio for the primary end point. Randomization strata were based on EDSS score and IST treatment.

Adjudicated ARR was analyzed using Poisson regression analysis with the trial group, historical annualized relapse rate, and randomization strata as covariates.

For the between-group differences in the remaining secondary efficacy end points, stratified, randomization-based nonparametric analysis of covariance that was adjusted for the baseline score on each scale. Least-squares means and 95% confidence intervals were calculated using analyses of covariance after adjustment for the baseline score on each scale and randomization strata. Missing data were replaced by the last-observation-carried-forward method.

5 Clinical questions

5.1 What is the value of eculizumab compared to placebo in treatment of patients with neuromyelitis optica spectrum disease (NMOSD)[1]

5.1.1 Presentation of relevant studies

The clinical evidence was sourced from the PREVENT clinical study comparing eculizumab to placebo. The study is described above in section 4.2 and in tabular form in in Table A2.

5.1.2 Results per study

In line with the Medicine Council protocol, the clinical evidence was sourced from the PREVENT study comparing eculizumab to placebo when added to IST. Results are presented below in section 5.1.3

5.1.3 Comparative analyses

Annualized relapse rate

Table 5 provides details on the outcomes reported on annualized relapse rate in the PREVENT trial. ARR was a secondary endpoint in PREVENT and reported in Pittock et al. (2019). Relapses were defined consistently with the definition requested in the MC protocol. A comparative statistical analysis of ARR in the ITT population was performed using Poison regression with treatment allocation, pre-treatment relapse rate and randomization strata (EDSS score and concomitant immunosuppressive therapy) as explanatory variables.

[1] *Hvilken værdi har eculizumab sammenlignet med placebo for patienter med neuromyelitis optica spectrum sygdom?*

The estimated rate ratio (eculizumab vs placebo) was 0.04 (95% CI: 0.01; 0.15) and the rate difference -0.33 (95% CI: -0.30; -0.35).

TABLE 5. COMPARATIVE RESULTS. ANNUALIZED RELAPSE RATE

Definition	The number of adjudicated relapses divided by the time in years. Treating physicians identified relapses according to the following criteria: a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination that persisted for more than 24 hours, signs and symptoms attributable to NMOSD rather than other causes, and onset preceded by at least 30 days of clinical stability. Changes in imaging were not considered to be an indication of relapse without related clinical findings.[6] Investigator reported relapses were adjudicated by a Relapse Adjudication Committee (RAC) consisting of two neurologists and one neuro-ophthalmologist who were unaware of trial-group assignments and who reviewed all physician determined relapses; adjudications were performed retrospectively and with the same criteria that were used by treating physicians. In addition to physician determined relapses, the RAC considered cases of interest (patients with relapse assessment visit for an event not classified as a relapse, a sentinel adverse event (e.g., adverse events of weakness, sensory changes, especially in a dermatomal distribution, characteristic visual changes of NMO, or pseudo exacerbation of NMO) AND either: a magnetic resonance imaging scan was performed contemporaneously OR neurologic symptoms were treated (by hospitalization or intravenous methylprednisolone for 3 days or fewer) OR contemporaneous objective worsening of the treating physician's neurologic examination).[7]
Methods	According to the predefined statistical analysis plan, all efficacy analyses were to be performed in the modified intention to treat (mITT) population. The mITT population consisted of all randomized patients receiving at least one dose of trial agent. Since all randomized patients was treated with at least one dose of eculizumab or placebo, the analyses were *de facto* conducted in the ITT population of the trial. An on-trial ARR was computed for each patient based on the number of relapse(s) observed and time in the study period for that patient. The statistical analysis was conducted using Poisson regression with treatment group, historical ARR, and randomization strata as covariates. Historical (pre-treatment) ARR was computed for each patient using the historical relapse data for that patient. Randomization stratification were based on EDSS score and use of concomitant immunosuppressive therapy

	A confidence interval for the ARR difference has not been published. For the sole purpose of this application a 95% confidence interval was estimated as $ARR_{Placebo} \times (RR-1)$ evaluated at the 95% confidence interval limits for RR.			
Results				
Statistic [Reference]	**Treatment arm**	**N**	**Observation**	**Confidence interval [p-value]**
RR[6]	Eculizumab	96	0.04	95% CI: 0.01; 0.15
	Placebo	47		
ARR[6]	Eculizumab	96	0.02	95% CI: 0.01; 0.05
	Placebo	47	0.35	95% CI: 0.20; 0.62
	Rate difference		-0.33	95% CI*: -0.35; -0.30

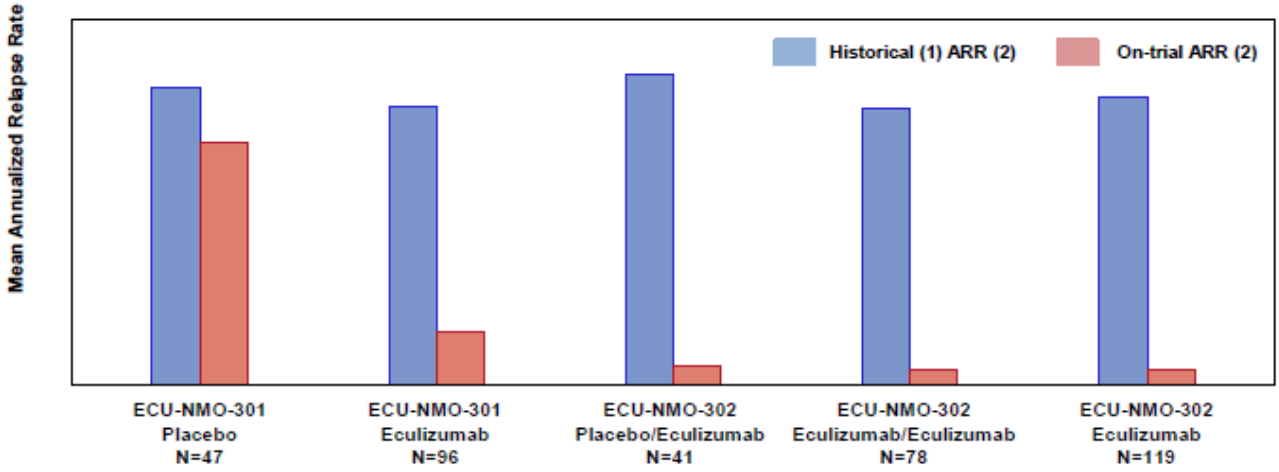
Abbreviations: ARR Annualized relapse rate; CI confidence interval; EDSS Expanded Disability Status Score; ITT Intention to treat; mITT modified intention treatment; NMOSD Neuromyelitis Optica Spectrum Disorder; NMO Neuromyelitis Optica; RAC Relapse Adjudication Committee; RR rate ratio

* The 95% confidence interval for difference in ARR was not reported and were approximated from the published ARR and RR (see outcome Methods above)

The primary endpoint in PREVENT was time to first adjudicated relapse (Hazard ratio 0.06 (p<0.001). At approximately 1 year, 97.9% of patients receiving eculizumab vs. 63.2% of patients receiving placebo were relapse-free. At approximately 3 years, 96.4% of patients receiving eculizumab vs. 45.4% of patients receiving placebo were relapse-free [6] Sub-group analyses are presented in the EPAR Assessment Report (figure 19). [3] The efficacy of eculizumab vs placebo was concluded to be comparable between sub-groups regardless the selected criteria (time since diagnosis, disability burden, relapse history, prior rituximab use, prior IST use, concomitant IST use). [3]

The effect on ARR of eculizumab observed in the PREVENT was further substantiated in the open label extension study (Study ECU-NMO-302). 41 patients from the PREVENT study placebo arm and 78 patients allocated to the PREVENT eculizumab arm entered the OLE study. At the October 2018 data-cut a statistical significant reduction in adjudicated ARR compared to the historical ARR observed 24 months before randomization to PREVENT (mean change in ARR -1.829 (95% CI: -2.098; -1.703 [p-value < 0.0001] from a historical level of 2.013).[3] Figure 1 illustrate the mean ARR in the ECU-NMO-301 (PREVENT) study and the ECU-NMO-302 (PREVENT OLE) study compared to historical rates. The comparison to historical ARR is of specific interest for the MC assessment as 38.5% of patients were treated with rituximab before inclusion in PREVENT.

FIGURE 1 OLE STUDY ECU-NMO-302. MEAN ON-TRIAL ANNUALIZED RELAPSE RATES AS DETERMINED BY THE TREATING PHYSICIAN - FULL ANALYSIS SET



Abbreviations: ARR annualized relapse rate; OLE Open Label Extension study

Note: Analysis based on data cut-off Date of 31 Oct 2018

(1) Based on 24 months prior to screening in PREVENT

(2) The number of relapses for each patient divided by the number of years in the study period for that patient; the mean across all patients is presented.

Source Soliris EPAR. Assessment Report. Figure 26[3]

Side-effects

Serious adverse reactions

Details on the comparative analysis of adverse reactions are reported in Table 6. Data was sourced from the safety reporting in PREVENT and the outcome measure applied is the number of patients with at least one serious treatment emergent adverse reaction assessed by the investigator as related to treatment.

The relative risk of a serious adverse reaction was 0.49 (95% CI: 0.21; 1.15) in the eculizumab arm compared to the placebo arm.

TABLE 6 COMPARATIVE RESULTS. SERIOUS ADVERSE REACTIONS

Definition	Number of patients with at least one serious adverse reaction defined as a serious treatment emergent adverse reaction assessed by the investigator as related to treatment. A treatment adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Serious treatment adverse events were defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolonged an existing hospitalization, resulted in persistent or

	significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event. Relationship to treatment was assessed by the investigator and reported using one of five predefined categories (not related and unlikely, possibly, probably, definitely related, or unknown). Adverse events reported as at least 'possibly' related or 'unknown' were categorized as a related adverse event and were included in the analyses below.
Methods	The number of patients with at least one serious adverse event related to treatment was reported for the safety population in PREVENT. Data below exclude events of NMOSD that were relapses meeting the definition of a serious adverse event. The safety population consist of all randomized patient receiving at least one dose of study treatment. For the sole purpose of this application a comparative statistical analysis of adverse reactions incidence in PREVENT was conducted. The incidence rate and rate ratio were calculated and compared using an unstratified approach. 95% confidence intervals were estimated assuming normal distribution of incidence rates and log-normal distribution of RR.

Results

Statistic [Reference]	Treatment arm	N	Observation	Confidence interval [p-value]
RR[6]	Eculizumab	9 / 96	0.49	95% CI: 0.21; 1.15
	Placebo	9 / 47		
Patients with at least one event[6]	Eculizumab	9 / 96	9.4%	95% CI: 3.5; 15.2
	Placebo	9 / 47	19.1%	95% CI: 7.9; 30.4
	Difference (percentage points)*		-9.8	95% CI: -22.4; 2.9

Abbreviations: CI confidence interval; NMOSD neuromyelitis optica spectrum disorder; RR relative risk

Overall safety profile

The eculizumab clinical program for NMOSD consists of PREVENT and it's open label extension (Study ECU-NMO-302), involving a total of 143 patients. Overall, 137 patients were exposed to eculizumab as of the cut-off date of 31 October 2018 (276.6.8 patient years of exposure).[3]

Eculizumab was well tolerated and the safety profile similar to that of the placebo.

Similar proportions of eculizumab (n = 96) and placebo (n = 47) patients experienced at least one treatment emergent adverse event (TEAE) (91.7% and 95.7%, respectively). The majority (97%) of TEAE's were mild or moderate in severity, and not treatment related. A higher rate of events per 100 PYs was reported in the placebo group versus eculizumab (1160.9 vs. 749.3 per 100 PYs, respectively). Of the TEAEs, 51.0% of eculizumab-treated patients versus 57.4% of patients receiving placebo reported AEs considered related. In the open label extension study, 77.3% patients reported AEs and of them, 33.6% were related AEs.

In the placebo-controlled study upper respiratory infection (29.2% vs 12.8% for eculizumab and placebo, respectively), headache (22.9% vs 23.4%), nasopharyngitis (20.8% vs 19.1%), nausea (16.7% vs 25.5%), urinary tract infection (13.5% vs 21.3%), back pain (14.6% vs 12.8%), diarrhea (15.6% vs 14.9%), were the most frequently reported AEs in both eculizumab and placebo groups. During the open-label extension headache (16%), nasopharyngitis (12.8%), urinary tract infection (8.4%) and upper respiratory infection (8.4%) were also the most frequently reported AEs.

The proportion of patients that experienced at least one treatment emergent serious adverse event (TESAE)s was higher in the placebo compared to eculizumab group (55.3% vs. 31.3%, respectively) with a higher rate of events per 100 PYs in the placebo group (88.4 vs. 30.7 per 100 PYs for eculizumab, respectively). This was primarily driven by the increased incidence of NMOSD related events in the placebo arm compared to the eculizumab group (33.9 vs. 4.1 per 100 PYs, respectively).

Serious adverse reactions include one adverse reaction leading to death in the eculizumab arm. The patient died from infectious pleural effusion (reported as pulmonary empyema), which the investigator categorized as probably related to the trial agent. The associated cultures yielded *Streptococcus intermedius* and *Peptostreptococcus* micros, and the patient had an extensive history of pulmonary disease (including bronchiolitis obliterans requiring tracheostomy, pneumonia, asthma, and obstructive sleep apnea) and was an active smoker. [6]

Adverse events of special interest included infections (meningococcal infections, aspergillus infections, and any serious infection), sepsis, infusion-related reactions, serious cutaneous reactions, cardiac disorders, and angioedema. Similar proportions of eculizumab and placebo patients experienced at least one adverse event of special interest (AESI) (21.9% vs. 21.3%, respectively). A higher rate of events per 100 PYs was reported in the placebo group versus eculizumab (24.5 vs. 16.8 per 100 PYs, respectively). There were no reports of meningococcal infection.

Two patients (both in the placebo group) discontinued the study as a result of one or more TEAEs.

Confirmed disability progression

Disability progression was measured in PREVENT using the Expanded Disability Status Scale (EDSS). [10]

Confirmed disability progression was defined as an increase of at least 2 from a baseline of 0, at least one from a base line score of 1 to 5, and at least 0.5 from a base line of 5.5 or above.

Analysis in the ITT population showed that 11.5% of patients versus 23.4% in the eculizumab and placebo arm, respectively, experienced disability progression (OR: 0.381; 95% CI: 0.146; 0.997; p = 0.0493). In Table

7 the odds ratio is expressed as a risk ratio (RR) using the placebo arm as control rate. This analysis was presented in poster format at the ECTRIMS conference, Stockholm 2019.[5]

On request from the Medicines Council, annualized change in EDSS from baseline to end-of-study was estimated. An annual improvement in the eculizumab group was observed [redacted] while a deterioration was observed in the placebo group [redacted] The difference in the annual change amounts to a [redacted] improvement in the eculizumab arm compared to the placebo arm.

Overall, the avoidance of disability is an important objective in NMOSD treatment. However, multi-system scales such as EDSS developed for multiple sclerosis has not been validated in NMOSD where cerebellar and cerebral functional score are not really applicable, as cognitive and cerebellar dysfunction is limited in NMOSD (EMA, 2015, p 20)[11]. Since disability in NMOSD is a direct consequence of the relapse and spontaneous gradual progression of disability like in MS is very rare in NMOSD, relapses are a clinically relevant measure (EMA, 2015; p 19)[11].

A further complication to the interpretation of EDSS results from PREVENT is that this is an event driven study where patients are follow-up until the first relapse event and the end-of-study EDSS is captured at the relapse follow-up visits (max 6 weeks after event)[6]. Given that EDSS worsening is primarily driven by the occurrence of relapses, the full impact of the relapse on disability may not be manifest at the end-of-study measurement. In the control-arm, patients had an ARR of 0.35. In clinical practice, these patients would have been subject to a risk of subsequent relapses. As a result of the event-driven design, patients in the control-arm was followed for a median of 0.83 years compared to 1.71 years in the eculizumab arm. Hence, had the study design allowed the same follow-up in both arms, a relevant hypothesis would be that the absolute - but also the annualised change from base-line - would be of larger magnitude.

Given the limitation of the instrument (EDSS) in NMOSD in general and given the limitation that PREVENT had an event-driven design, results for the eculizumab arm all indicated that the large reduction in relapse risk (RR: 0.04) had a positive impact on halting development in disability; fewer patients in the eculizumab arm experienced a confirmed disability progression (RR: 0.446; 95% CI: 0.182; 0.998), average EDSS improved in the eculizumab arm compared to an deterioration in the control arm, and the annualized change showed an improvement in EDSS of -0.73 points per year (95% CI: -1.55, 0.09) compared to the control arm.

In the EMA assessment of eculizumab in NMOSD, the CHMP concluded:

At the end of the study, patients on eculizumab reported a mean improvement in the mean EDSS score of -0.18 and patients on placebo reported a mean deterioration in the mean EDSS score of 0.12. It is difficult to give value to these figures, when they are mainly driven by the number of relapses and the lack of progression out of relapses. One of the relevant prognostic factors for disability is the severity of the relapses. Some clues point out a better outcome for eculizumab: more placebo patients than patients treated with eculizumab had major relapses and need of hospitalization due to relapses. However, the disability scales measured during the acute episodes (differences between baseline relapse evaluation and 6 weeks evaluation) did not show differences between arms. (Eculizumab EPAR Assessment Report p 71)[3]

TABLE 7 COMPARATIVE RESULTS. CONFIRMED DISABILITY PROGRESSION

Definition	Disability progression measured using the Expanded Disability Status Scale (EDSS). [10] EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. The Kurtzke functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral) and ambulation are rated in the context of a standard neurological examination, and then these ratings (KFS scores) are used in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score. [10] Confirmed disability progression (worsening of EDSS) was defined as an increase of ≥ 2 from a baseline score of 0, ≥ 1 from a baseline score of 1.0–5.0, or ≥ 0.5 from a baseline score of ≥ 5.5. On request from the DMC the absolute change in disability is here presented as the mean annualized change in EDSS. Absolute change in disability is here presented as the mean annualized change in EDSS (average of individual patients' changes in EDSS from baseline to end-of-study divided by the time in years from baseline to end-of-study). Patients reaching the endpoint of NMOSD relapse were discontinued after post-relapse follow-up visits (up to three weeks after the relapse event).
Methods	In PREVENT, EDSS was assessed at baseline, at weeks 4, 8 and 12, and every 12 weeks. Analysis of worsening of EDSS between baseline and study end was performed using a logistic regression model, adjusting for baseline score and stratified by observed randomization strata. 95% confidence intervals for the mean annualized change in each arm were calculated using *Student-t* distribution for the means. The 95% confidence for the difference between treatment arms was assessed using the t-distribution for the difference and standard error estimated using Satterthwaite approximation. The analysis was performed in the ITT population.

Results

Statistic [Reference]	Treatment arm	N	Observation	Confidence interval [p-value]
Disability progression RR. Poster presented at ECTRIMS 2019 [5]*	Eculizumab	96	0.446	95% CI: 0.182; 0.998
	Placebo	47		
Mean annual EDSS change from base line	Eculizumab	96	[redacted]	[redacted]
	Placebo	47	[redacted]	[redacted]

(Unpublished data on file**)	Difference	[redacted]	[redacted]

Abbreviations: CI Confidence interval, EDSS Expanded Disability Status Scale, ITT Intention to treat, KFS Kurtzke functional systems, LSM least square mean, RR rate ratio, SE Standard Error.

* Rate ratio and 95% CI reported here were calculated from odds ratio (with 95% CI) reported in the source using the method described in the MC Method Handbook version 2.6. [12] Placebo arm rate was applied as control group rate.

** Not previously published. Source: Alexion Pharmaceuticals, Inc. ECU-NMO-301 Final Analysis. Table 409 Annual change in EDSSS score at the End of study. Full analysis set.

Visual acuity

The protocol for assessment of eculizumab in NMOSD request data on eculizumab's effect on visual acuity in the PREVENT study using a 6-point scale based on Snellen chart readings. [1] In PREVENT the KFS visual score was collected as part of the EDSS assessment. The sub-score results have not previously been published but the results are presented in Table 8 as data on file. On the request of the Medicine Council, the change in KFS Visual score was annualized. Patients in both arms had an annual improvement in KFS Visual score per year [redacted] in the eculizumab arm compared to [redacted] in the placebo arm. The difference in annual change from base line to end-of-study show that the improvement was numerically larger in the eculizumab arm [redacted]

It should be noted that the end-of-study assessment of KFS Visual Score was performed no later than 6 weeks following the first relapse which – like described above in section *Confirmed disability progression* – is a complicating factor in the interpretation of the findings. Like EDSS total score, the KFS Visual score cannot be expected to linear, but rather a consequence of relapses over time.

TABLE 8 COMPARATIVE RESULTS. VISUAL ACUITY

Definition	The Kurtzke Functional System Visual score [10] was collected in PREVENT and reported here as a measure of visual acuity. The KFS visual score assigns an ordinal value from 0 to 6 0 - Normal 1 - Scotoma with visual acuity (corrected) better than 20/30 2 - Worse eye with scotoma with maximal visual acuity (corrected) of 20/30- 20/59 3 - Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60-20/99 4 - Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100-20/200; grade 3 plus maximal acuity of better eye of 20/60 or less 5 - Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less 6 - Grade 5 plus maximal visual acuity of better eye of 20/60 or less
Methods	The annualized change in Visual KFS score from baseline to end of study was performed in the ITT population. 95% confidence intervals for the mean annualized change in each arm were calculated using *Student-t* distribution for the means. The 95% confidence for the difference

	between treatment arms was assessed using the t-distribution for the difference and standard error estimated using Satterthwaite approximation. The separate results for the KFS Visual Score in PREVENT have not previously been published and are presented here as data on file.			
Results				
Statistic	**Treatment arm**	**N**	**Observation**	**Confidence interval [p-value]**
KFS Visual score. Annualized change from baseline *	Eculizumab	96	[redacted]	[redacted]
	Placebo	47	[redacted]	[redacted]
	Difference		[redacted]	[redacted]

Abbreviations: ANCOVA Analysis of co-variance, CI confidence interval, KFS Kurtzke Functional System, LSM Least Square Means
* Not previously published. Source: Alexion Pharmaceuticals, Inc. ECU-NMO-301 Final Analysis. Table 410 Annual change in Visual KFS score at the End of study. Full analysis set.

Health related quality of life

As noted in the MC protocol for assessment of eculizumab in NMOSD, there is no NMOSD-specific health related quality of life instrument and the protocol hence suggest the use of the generic Short-Form 36 (SF-36) instrument. SF-36 was collected in PREVENT at baseline, weeks 4, 8 and 12, and every 12 weeks thereafter. SF-36 data was summarized in two components, one of physical health (the physical component score [PCS]) and one of mental health (the mental component score [MCS]).

Analysis of the base line PCS and MCS showed that patients with base line EDSS scores of at least 4 had significantly worse PCS scores than patients with lower EDSS scores. Corresponding differences for the MCS were not significant. [4] These findings indicate that the PSC is sensitive to degree of disability and as a result has the potential to be sensitive to treatment of NMOSD.

The MC protocol's preferred statistic is SF-36 change from base-line[1], however statistical analyses of changes from base-line in SF-36 MSC and PCS have not been reported. Instead, responder analysis of the SF-36 data collected in PREVENT was presented in poster format at the ECTRIMS Conference, Stockholm 2019. This analysis is presented here (Table 9).

The reported odds ratios were for PCS 0.465 (95% CI: 0.229; 0.943 [p-value=0.0337]) and for MCS 0.772 (95% CI: 0.393; 1.517 [p-value=0.4522]). In the placebo group, patients with adjudicated relapses were significantly more likely to have a clinically meaningful deterioration in PCS than those without adjudicated relapses (odds ratio: 0.151; 95% CI: 0.026–0.871; p = 0.0345), while no significant difference in the corresponding analysis for MCS deterioration was observed. [4]. Taken together with the observed relationship between PCS and EDSS scores at baseline this suggest that SF-36 PCS are sensitive to health state and sensitive to treatment, while this may not be the case for SF-36 MCS.

The results expressed in rate ratios are presented in Table 9 as requested in the MC Method Handbook. [12]

TABLE 9 COMPARATIVE RESULTS. HEALTH-RELATED QUALITY OF LIFE

Definition	The SF-36 consists of 36 items organized into eight scales (physical functioning, social functioning, role limitations due to physical health, bodily pain, general health perceptions, mental health, role limitations due to emotional problems, and vitality) and reported health transition. There are two summary measures: one of physical health (the physical component score [PCS]) and one of mental health (the mental component score [MCS]). A responder analysis was performed comparing the rate of patients with clinically meaningful deterioration of health-related quality of life between baseline and end of study. A reduction of 5 points in PCS and MCS sub-scores was defined as a meaningful deterioration of physical and mental health related quality of life, respectively.			
Methods	In PREVENT, SF-36 was assessed at baseline, at weeks 4, 8 and 12, and every 12 weeks. A proportional odds model analysis was conducted for analyses of clinically meaningful changes in PCS and MCS by treatment group. Each model was adjusted for baseline SF-36 scores and baseline EDSS scores. For the purpose of this report the estimated Odds ratios were recalculated and reported as rate ratios using the method outline in the MC Method Handbook version 2.6. [12]. The recalculation was done using the placebo arm rate as comparator rate. 95% CI for percentage patient with deterioration of health-related quality of life, difference in percentage points (with 95% CI) were calculated based on the published results solely for the purpose of this report. The 95% Cis were calculated using normal approximation.			
Results				
Statistic [Reference]	**Treatment arm**	**N**	**Observation**	**Confidence interval [p-value]**
Clinically meaningful deterioration in PCS*	Eculizumab	96	RR: 0.52	95% CI: 0.274; 0.955
	Placebo	47		
% patients with meaningful deterioration in PCS [4]**	Eculizumab	96	9.38%	95% CI: 3.54; 15.21
	Placebo	47	21.28%	95% CI: 9.58; 32.98
	Difference (percentage points)		-11.90	95% CI: -24.97; 1.17
Clinically meaningful	Eculizumab	96	0.83	95% CI: 0.48; 1.31
	Placebo	47		

deterioration in MCS*				
% patients with meaningful deterioration in MCS [4]**	Eculizumab	96	26.04%	95% CI: 17.26; 34.82
	Placebo	47	29.79%	95% CI: 16.71; 42.86
	Difference (percentage points)		-3.75	95% CI: -19.49; 12.00

Abbreviations

* Rate ratio and 95% CI reported here were calculated from odds ratio (with 95% CI) reported in the source [4] using the method described in the MC Method Handbook version 2.6. [12] Placebo arm rate was applied as control group rate.

** 95% CI for percentage patient with deterioration of health-related quality of life, difference in percentage points (with 95% CI) were calculated based on the published results [4] solely for the purpose of this report. The 95% Cis were calculated using normal approximation.

6 Additional information

6.1.1 Relevance of PREVENT in a Danish context

In order to prevent subsequent relapses, patients with NMOSD require immunosuppression. Current standard of care in NMOSD includes the use of azathioprine, mycophenolate mofetil, and rituximab for which there is evidence supporting effectivity coming from observational studies[1].

PREVENT is the first randomized controlled trial of immunomodulation to prevent relapse of NMOSD. In PREVENT, patients with AQP4-IgG–seropositive NMOSD of a relapsing course was treated with eculizumab or placebo in addition to their existing immunosuppressive therapy. Patients have had a mean of 2 annual relapses (between 1 and 6.4) in the past 2 years, most of them (76.9%) while they were being treated. About 31% of patients needed to change their treatment after the last relapse. [3] 76.2% of patients was treated with ISTs at baseline (mainly corticosteroid, azathioprine, mycophenolate mofetil). Whilst the reason as to why the remaining patients were not on concomitant ISTs is unknown, it should noted that the majority (24/32) had been treated with IST prior to the study but had stopped treatment.[3] Treatment with rituximab should have been stopped 3 months prior to recruitment into PREVENT due to incompatibility between its mechanism of action and that of eculizumab. 32.2% had been treated with rituximab prior to entering the PREVENT trial.[3]

PREVENT is the first randomized controlled trial to demonstrate a statistically significant and clinically relevant reduction in relapse risk. Sub-group analyses showed no statistically significant difference in efficacy between sub-groups of patients defined by concomitant IST or historical rituximab treatment.

In addition to the comparative evidence on efficacy and safety of eculizumab added to background IST compared to IST alone, the PREVENT and PREVENT OLE studies allow a comparison of relapse rates during the trials with the historical rate of relapse 24 month prior to the PREVENT baseline during which period one third of patients had been treated with rituximab.

The PREVENT study provides a sound evidence base for assessing the added clinical value of eculizumab in treatment of NMOSD patients with a relapsing course in Denmark. The background therapy allowed in the study is in line with the therapies offered in Denmark [1] and the efficacy and safety is maintained across subgroups of patient irrespective of current therapy and whether the patient was previously treated with rituximab or not.

6.1.2 *Neisseria meningitidis* vaccination

Due to its mechanism of action, the use of eculizumab increases the patient's susceptibility to *Neisseria meningitidis*. Meningococcal disease due to any serogroup may occur.[13]

To reduce the risk of infection, all patients must be vaccinated at least 2 weeks prior to receiving eculizumab unless the risk of delaying eculizumab therapy outweighs the risks of developing a meningococcal infection. Patients who initiate eculizumab treatment less than 2 weeks after receiving a tetravalent meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W 135 and B, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must receive vaccination according to current national vaccination guidelines for vaccination use. [13]

A risk management program is in place to minimize the risk of meningococcal infection. The programme includes

1. All healthcare practitioners who may prescribe eculizumab receive the appropriate educational material.
2. All patients being treated with eculizumab receive a patient safety card.
3. Drug distribution will only be possible after written confirmation that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis.
4. Vaccination reminders are sent to the prescribers.

In the eculizumab clinical program, no cases of meningococcal infection was observed, however, one case of *Neisseria gonorrhoeae* infection was reported in the EPAR[3] The patient recovered after treatment with antibiotics and discontinued treatment. The reported case was considered related to eculizumab treatment.

Furthermore, Socie et al (2019) published pharmacovigilance data from 10-years' experience with eculizumab in the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS) clinical practice. [14] This analysis summarises safety data collected from spontaneous and solicited sources from 16 March 2007 through 1 October 2016. Cumulative exposure to eculizumab was 28 518 patient-years (PY) (21,016 PY in PNH and 7,502 PY in aHUS). Overall, 76 cases of meningococcal infection were reported (0.25/100 PY), including eight fatal PNH cases (0.03/100 PY). The rate of infection decreased over time from 0.57/ 100 PY in 2008 to 0.16/ 100 PY in 2016. Among 49 patients with known serogroup, one patient was recorded as negative in serotypes A, B, C, W135, and Y. [14]

6.1.3 Switch from rituximab to eculizumab

In PREVENT, patient treated with rituximab within the last 3 months were excluded. The rationale for this exclusion criterion was due to the mechanistic effect eculizumab can have on the activity of rituximab, and 3 months was determined by the sponsor and investigators to be a sufficient amount of time between last rituximab dose and study drug initiation.

For the purpose of the Expert Committee assessment, we can provide the following details from the PREVENT Clinical Study Report. Of the 143 patients enrolled in the trial, 46 (32%) had a prior history of rituximab treatment. The median time from last dose of rituximab to first dose of study treatment was [redacted] patients received their last rituximab less than 1 year before first study dose. In this subgroup of patients, the number of reported serious infections/infestations was similar between the treatment groups [redacted]

Of 26 patients with prior rituximab randomized to the eculizumab arm, [redacted] patients received their last rituximab dose less than 6 months prior to eculizumab initiation [redacted]. All [redacted] patients

received their meningococcal vaccination at least 2 weeks prior to eculizumab initiation as required in the protocol.

No cases of meningococcal infection were observed in PREVENT and PREVENT OLE at the latest interim analysis (with 36 patients having more than three years of eculizumab treatment).

In the subgroup of patients previously treated with rituximab (n=[redacted]), the reduction in relapse rate [redacted] was similar to the reduction in the subgroup of patients [redacted] not previously treated with rituximab [redacted]

None of [redacted] patients starting eculizumab less than 6 month after the last dose of rituximab experienced an adjudicated on-trial relapse. All of these [redacted] patients completed the trial and enrolled in the ongoing open-label extension.

To Alexion knowledge, there is no published medical literature that have revealed any contraindications or recommendations on how soon eculizumab can be initiated after previous treatment with rituximab for NMOSD. The decision on how quickly eculizumab can be started after rituximab discontinuation in patients with NMOSD is at the discretion of the prescriber.

Alexion Pharma are available to answer medical questions related to the initiation and management of eculizumab in a meeting with the DMC and/ or the Expert Committee.

7 References

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8 Appendices

Literature search

Not applicable according to protocol

TABLE A1 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	
Exclusion criteria	

Main characteristics of included studies

Study characteristics

TABLE A2 MAIN STUDY CHARACTERISTICS

Trial name	*PREVENT*
NCT number	NCT01892345
Objective	To assess the efficacy and safety of eculizumab compared to placebo in patients with anti-aquaporin-4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD).
Publications – title, author, journal, year	Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder **Pittock SJ, Berthele A, Fujihara K, et al.** *N Engl J Med. 381(7):614-625*
Study type and design	The study is a phase 3 randomized, double-blind, controlled, time to event trial. Participants (N:143) were randomly assigned in a 2:1 ratio between eculizumab and Placebo. Patients were stratified across sites according to the score on the Expanded Disability Status Scale (EDSS) and the use of concomitant immunosuppressive therapy. The trial was completed in July 2018
Follow-up time	The study enrolled patients between April 2014 through October 2017. The trial duration was event driven. Median (range) follow-up was 36 weeks (1; 209) in the placebo arm and 89 weeks (1; 211) in the eculizumab arm
Population (inclusion and exclusion criteria)	Inclusion: 1. Male or female patients aged ≥18 years. 2. Diagnosis of NMO according to 2006 criteria, or neuromyelitis optica spectrum disorder (NMOSD) according to 2007 criteria. 3. AQP-4 antibody-seropositive. 4. At least two historical relapses (as defined by the protocol†) during the 12 months before screening or three relapses during the 24 months before screening with at least one of the three relapses in the 12 months before screening. 5. EDSS score of ≤7. 6. If a patient entered the trial receiving IST for relapse prevention, the patient must have been receiving stable maintenance doses, as determined by the treating physician, before screening and must have continued to receive those doses for the duration of the trial, unless the patient experienced a relapse. 7. Patients must have given written informed consent. 8. Patients must have been able and willing to comply with the protocol requirements for the duration of the trial. 9. Female patients of childbearing potential were to have a negative pregnancy test (serum human chorionic gonadotropin) and patients were required to practice an effective, reliable, and medically approved contraceptive regimen during the trial and for up to 5 months following discontinuation of treatment. Exclusion: 1. Use of rituximab within the 3 months before screening. 2. Use of mitoxantrone within the 3 months before screening. 3. Use of intravenous immune globulin within the 3 weeks before screening.

<table>
<tr><td></td><td>
4. If a patient entered the trial receiving oral glucocorticoid(s) with or without other ISTs, the daily glucocorticoid dose must be no more than prednisone 20 mg/day (or equivalent) before screening, and the patient must continue to receive that dose for the duration of the trial or until the patient experiences a relapse.
5. Pregnant, breastfeeding, or intending to conceive during the trial.
6. Unresolved meningococcal disease.
7. Any systemic bacterial or other infection that was clinically significant in the opinion of the investigator and had not been treated with appropriate antibiotics.
8. Participation in any other investigational drug trial or exposure to other investigational agents, devices, or procedures within the 30 days before screening.
9. Had previously been treated with eculizumab.
10. Hypersensitivity to murine proteins or to one of the excipients of eculizumab.
11. Any medical condition that, in the opinion of the investigator, might have interfered with the patient's participation in the trial, posed any added risk for the patient, or confounded the assessment of the patient.
</td></tr>
<tr><td>Intervention</td><td>Induction Phase: 900 mg IV weekly for 4 weeks, followed by 1200 mg for the fifth dose
Maintenance Phase: 1200 mg IV every 2 weeks</td></tr>
<tr><td>Baseline characteristics</td><td>
Baseline characteristics were well balanced between treatment arms. The majority of patients were diagnosed with either NMO (75%) or NMOSD (25%) with a high proportion of female patients (91%). All patients were AQP4 +, consistent with the eligibility criteria of the trial, with a mean age of 44.3 years and an average EDSS score of 4. Approximately 50% of all patients were White/Caucasian.

The mean (± SD) ARR in the 24 months before enrolment was 1.99 ± 0.94 (1.94±0.90 for eculizumab and 2.07±1.04 for placebo). A total of 110 (76.9%) patients were on ISTs or immunomodulators at the time of any of the historical relapses. Similarly, 76.2% (n=109) of patients were on ISTs at baseline.
<table>
<tr><th rowspan="2">Characteristics</th><th colspan="2">Treatment</th><th rowspan="2">All patients
(N = 143)</th></tr>
<tr><th>Placebo
(N = 47)</th><th>Eculizumab
(N = 96)</th></tr>
<tr><td colspan="4">Demographics</td></tr>
<tr><td>Age, year, mean ± SD</td><td></td><td></td><td></td></tr>
<tr><td>At first dose</td><td>45.0±13.29</td><td>43.9±13.32</td><td>44.3±13.27</td></tr>
<tr><td>At initial clinical presentation</td><td>38.5±14.98</td><td>35.8±14.03</td><td>36.6±14.35</td></tr>
<tr><td>Female, n (%)</td><td>42 (89.4)</td><td>88 (91.7)</td><td>130 (90.9)</td></tr>
<tr><td>Ethnicity, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Hispanic or Latino</td><td>3 (6.4)</td><td>13 (13.5)</td><td>16 (11.2)</td></tr>
<tr><td>Not Hispanic or Latino</td><td>41 (87.2)</td><td>78 (81.3)</td><td>119 (83.2)</td></tr>
<tr><td>Not reported</td><td>1 (2.1)</td><td>4 (4.2)</td><td>5 (3.5)</td></tr>
<tr><td>Unknown</td><td>2 (4.3)</td><td>1 (1.0)</td><td>3 (2.1)</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Asian</td><td>15 (31.9)</td><td>37 (38.5)</td><td>52 (36.4)</td></tr>
<tr><td>Black or African American</td><td>8 (17.0)</td><td>9 (9.4)</td><td>17 (11.9)</td></tr>
<tr><td>White</td><td>24 (51.1)</td><td>46 (47.9)</td><td>70 (49.0)</td></tr>
<tr><td>Other or unknown</td><td>0</td><td>4 (4.2)</td><td>4 (2.8)</td></tr>
<tr><td colspan="4">Disease profile</td></tr>
<tr><td>Diagnosis, n (%)</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

	Neuromyelitis optica	38 (80.9)	69 (71.9)	107 (74.8)
	NMOSD[a]	9 (19.1)	27 (28.1)	36 (25.2)
	EDSS score, mean ±SD§	4.26±1.51	4.15±1.65	4.18±1.59
	History of prior NMOSD relapse			
	Annualised relapse rate during previous 24 mo, mean±SD	2.07±1.04	1.94 ± 0.90	1.99 ± 0.94
	Type of relapse during previous 24 mo, n (%)†			
	Optic neuritis	22 (46.8)	58 (60.4)	80 (55.9)
	Transverse myelitis	42 (89.4)	74 (77.1)	116 (81.1)
	Brainstem symptoms‡	15 (31.9)	18 (18.8)	33 (23.1)
	Cerebral symptoms	5 (10.6)	10 (10.4)	15 (10.5)
	Patients on ISTs or immunomodulators at the time of any of the historical relapses			
	Yes	32 (68.1)	78 (81.3)	110 (76.9)
	No	15 (31.9)	18 (18.8)	33 (23.1)
	Medication profile			
	Any prior medications prior to study treatment, n (%)[b]	45 (95.7)	88 (91.7)	133 (93.0)
	Corticosteroids	30 (63.8)	68 (70.8)	98 (68.5)
	Azathioprine	26 (55.3)	61 (63.5)	87 (60.8)
	Rituximab‖	20 (42.6)	26 (27.1)	46 (32.2)
	Mycophenolate mofetil	15 (31.9)	27 (28.1)	42 (29.4)
	Any ISTs at baseline, n (%)	34 (72.3)	75 (78.1)	109 (76.2)
	None	13 (27.7)	21 (21.9)	34 (23.8)
	Corticosteroids alone	11 (23.4)	16 (16.7)	27 (18.9)
	Azathioprine with or without corticosteroids	13 (27.7)	37 (38.5)	50 (35.0)
	Mycophenolate mofetil with or without corticosteroids	8 (17.0)	17 (17.7)	25 (17.5)
	Other drug with or without corticosteroids¶	2 (4.3)	5 (5.2)	7 (4.9)

Primary and secondary endpoints	The primary efficacy outcome was the time to first adjudicated on-trial relapse. Secondary end points were 1. Adjudicated on-trial ARR 2. Change from baseline in EDSS score at the EOS 3. Change from baseline in mRS score at the EOS 4. Change from baseline in HAI score at the EOS 5. Change from baseline in EQ-5D-3L VAS score at EOS 5. Change from baseline in EQ-5D-3L Index score at EOS
Method of analysis	Efficacy analyses was planned to be conducted in the mITT population consisting of all patients randomized and receiving at least one dose of study medication. Since all randomized patients received at least one dose of study medication, ITT and mITT population are the same. Stratified Cox proportional-hazards model with the trial group as a covariate was used to estimate the hazard ratio for the primary end point. Randomisation strata are defined above. Adjudicated ARR was analysed using Poisson regression analysis with the trial group, historical annualized relapse rate, and randomization strata as covariates.

	For the between-group differences in the remaining secondary efficacy end points, stratified, randomization-based nonparametric analysis of covariance that was adjusted for the baseline score on each scale. Least-squares means and 95% confidence intervals were calculated using analyses of covariance after adjustment for the baseline score on each scale and randomization strata. Missing data were replaced by the last-observation-carried-forward method.
Subgroup analyses	The treatment effect was further studied across randomization strata, age, and sex; by region; and by type of immunosuppressive therapy (IST) at base line (corticosteroid, azathioprine, mycophenolate mofetil, No IST, and prior use of rituximab).

Results per study

Table A3 Results of study PREVENT

Table A3a Results of PREVENT											
Trial name:	PREVENT										
NCT number:	NCT01892345										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized relapse rate	Eculizumab	96	0.02 (0.01; 0.05)	-0.33	-0.35; -0.30	NA	RR: 0.04	0.01; 0.15	NA	*Poison regression controlling for historical ARR and randomisation strata (ITT population).* *95% CI for ARR difference calculated from RR 95 CI applied to placebo group ARR.*	[6]
	Placebo	47	0.35 (0.2; 0.62)								
Patients with at least one SAE	Eculizumab	9/96	9.4% (3.5%; 15.2%)	- 9.8 p.p.	-22.4; 2.9	NA	RR: 0.49	0.21; 1.15	NA	Calculated based on incidence in safety population using unstratified approach. 95% CI for proportion of patients with SAE calculated using normal approximation. 95% CI for RR calculated using log-normal distribution of RR	Incidence: [6] Statistic analysis unpublished
	Placebo	9/47	19,1% (7.9%; 30.4%)								

Disability progression	Eculizumab	96	[redacted]	[redacted]	[redacted]	NA	RR: 0.446	0.182; 0.998	NA	Proportion of patients with confirmed disability progression estimated using logistic regression (controlling for base line EDSS and randomisation strata). Annualized change from base line 95% CI calculated using t-distribution. 95% CI for difference in annualized change calculated using t-distribution and Satterthwaite approximation for standard error.	ECTRIMS 2019 poster[5] Unpublished data on file
	Placebo	47	[redacted]								
KFS Visual score	Eculizumab	96	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	Annualized change from base line 95% CI calculated using t-distribution. 95% CI for difference in annualized change calculated using t-distribution and Satterthwaite approximation for standard error.	Unpublished data on file
	Placebo	47	[redacted]								
Patients with clinical meaningful deterioraton in SF-36, PCS	Eculizumab	96	9.38% (3.54%; 15.21%)	-11.90 p.p.	-24.97; 1.17 p.p.	NA	RR: 0.52	0.274; 0.955	NA	Propotional odds model analysis controlling for SF-36 score and EDSS at baseline RR calculated from OR using placebo arm rate for the comparator. 95% CI for proportion of patient with clinical meaningful deterioration of PCS estimated using normal approximation	ECTRIMS 2019 poster[4] OR calculation and CI previously unpublished
	Placebo	47	21.28% (9.58%; 32.98%)								

	Eculizumab	96	26.04% (17.26%; 34.82%)							Propotional odds model analysis controlling for SF-36 score and EDSS at baseline RR calculated from OR using placebo arm rate for the comparator. 95% CI for proportion of patient with clinical meaningful deterioration of PCS estimated using normal approximation	ECTRIMS 2019 poster[4] OR calculation and CI previously unpublished
Patients with clinical meaningful deterioraton in SF-36, MCS				-3.75 p.p.	-19.49; 12.00 p.p	NA	RR: 0.83	0.48; 1.31	NA		
	Placebo	47	29.79% (16.71%; 42.86%)								

Results per PICO (clinical question)

TABLE A4 RESULTS REFERRING TO CLINICAL QUESTION 1

Table A4 Results referring to scientific question 1								
Results per outcome:		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	
Annualized relapse rate	PREVENT	-0.33	-0.35; -0.30	NA	RR: 0.04	0.01; 0.15	NA	Direct comparison
Patients with at least one SAE	PREVENT	- 9.8 p.p.	-22.4; 2.9	NA	RR: 0.49	0.21; 1.15	NA	Direct comparison
Disability progression	PREVENT	[redacted]	[redacted]	NA	RR: 0.446	0.182; 0.998	NA	Direct comparison

Patients with clinical meaningful deterioraton in SF-36, PCS	PREVENT	-11.90 p.p.	-24.97; 1.17 p.p.	NA	RR: 0.52	0.274; 0.955	NA	Direct comparison
Patients with clinical meaningful deterioraton in SF-36, MCS	PREVENT	-3.75 p.p.	-19.49; 12.00 p.p	NA	RR: 0.83	0.48; 1.31	NA	Direct comparison

Cost and budget impact of eculizumab in NMOSD

Application to the Danish Medicines Council

1.3

2021-02-10

Table of Contents

Executive summary

Purpose To estimate the net present cost of eculizumab in the treatment of adult patients with Neuromyelitis Optica Spectrum Disorder with anti-aquaporin-4 (AQP4) antibody-positive disease compared to treatment with immunosuppressive treatment (IST) alone (best supportive care (BSC)). Furthermore, the five-year regional budget impact is estimated.

Method A Markov health state model was developed to trace the progressive nature of the disease. Health states were defined based on the Expanded Disability Status Scale (EDSS). Progression of disease as well as excess mortality (compared to general population mortality was modelled as a result of events of NMOSD relapse. The risk of relapses in the eculizumab arm was sourced from the phase 3, randomized, placebo-controlled trial PREVENT. The placebo arm in PREVENT was used as source for BSC efficacy. In PREVENT eculizumab and placebo was given on a background of standard IST treatment. Persistence to eculizumab treatment and disease progression as a result of relapses were sourced from PREVENT. Case fatality associated with relapses was estimated based on published observational data and assumed to be the same in both arms of the model. General mortality was sourced from Danish general population lifetables. Cost elements included eculizumab costs, cost of administration, cost of pre-treatment vaccination, relapse cost and health state cost. Costs of managing side-effects were conservatively omitted since a higher incidence of serious adverse events were observed in the placebo arm compared to the eculizumab arm of the PREVENT trial – even after excluding such events that were adjudicated NMOSD relapses. Furthermore, costs were applied from a limited societal perspective as recommended by the guideline for cost-analysis including direct health care cost (regional and community cost) and patient cost associated with treatment but excluding productivity costs. Due to the lack of Danish cost-off-illness studies related to NMOSD patients, the health state cost was based on a Danish study of cost of inpatient, outpatient care and community support for patients with multiple sclerosis. Health state cost by EDSS score was applied to the time in each state calculated using half-cycle correction. Cost of relapse events was estimated using hospitalisation rates in the PREVENT trial. DRG tariffs were applied in the estimation of cost of inpatient and outpatient hospital care. The net-present cost over the patient's remaining lifetime was calculated using 3.5% p.a. years 1-35 and 2.5% hereafter in accordance with the Medicine Council guideline for cost-analysis.

Results The incremental cost per patient was estimated at 24.7 MDKK when evaluated at pharmacy purchase prices. Sensitivity analyses showed that the incremental, societal cost per patient is mainly sensitive to background risk of relapse and treatment efficacy of eculizumab. Furthermore, the incremental cost is sensitive to assumption on discontinuation from eculizumab treatment.

Implication for regional budgets Based on the Medicine Council protocol, the number of prevalent patients eligible for eculizumab treatment is 44 with an incidence of 5 patients per year. According to the Medicines Council protocol, various immunosuppressive and anti-inflammatory treatments such as rituximab are used off-label in Danish Clinical practice. Eculizumab is the first treatment with indication for prevention of relapses in NMOSD and a proven, high efficacy. To form a realistic budget impact, it was assumed that eculizumab in clinical practice primarily will be a treatment for patients with a high frequency of relapses which leave them vulnerable to a fast progression of disability. For these patients, the absolute risk reduction with effective treatment is larger and the impact on patient quality of life greater. Furthermore, patients are more likely to accept a treatment that requires frequent visits the clinic to get infusions. In the analysis it is

assumed that 26% of patients have a high frequency of relapses on the off-label treatments offered today. Hence in the budget impact analysis, it is assumed that a maximum of 11 (26% x 44) of the prevalent patients will be offered treatment with eculizumab in clinical practice and that 1 (26% x 5) incident patient will start treatment each year. Based on these assumptions a realistic budget impact estimate year 1 would be 7.2 MDKK rising to a peak budget impact at 41.1 MDKK year four.

1 Confidentiality

This report contains information that is considered confidential. This includes otherwise unpublished results from post-hoc analyses of clinical trial data or other primary research which were conducted with the sole purpose of informing Health Technology Assessment as well as model output or intermediate results in tabular or graphical form from which the confidential results could be inferred using reverse engineering. Furthermore, confidential information include data from market analysis using primary research or internal assessments.

Confidential information included in this report is marked using MS Word Yellow highlighting as shown in this example. Graphs that should be kept confidential are marked in the caption and surrounding space as shown below.

Caption

2 Cost analysis

2.1 Overview of the economic model

The economic evaluation is a cost analysis of eculizumab compared to Best Supportive Care (BSC) for the treatment of NMOSD. The model employs a Markov cohort analysis to calculate the incremental cost per patient. An overview and rationale of the economic model is as follows:

1. The economic model is setup as a Markov cohort analysis where patients are transitioned between health states defined according to current disability (Expanded Disability Status Scale – EDSS) and treatment received
2. A change in disability (EDSS) is modelled from an incident relapse
3. Eculizumab patients discontinue treatment (and subsequently transition to BSC) as a function of time on treatment according to the clinical trial evidence
4. The baseline population characteristics of the model cohort (mean age, gender distribution, and EDSS distribution) is equal to the PREVENT trials baseline population
5. The pivotal RCT reported a statistically significant treatment benefit for eculizumab in the form of a risk reduction of relapse
6. The economic evaluation translates a risk reduction of relapse to:
    - Slowing the rate of disability progression (EDSS)
    - Lower resource utilisation costs from relapses avoided
7. In turn, delayed disability progression (EDSS) translates to:
    - Lower disease management costs from slowing disability progression to EDSS scores associated with higher disability support costs

The key components of the economic evaluation are provided in Table 1.

Table 1 Key components of the economic evaluation

Component	Claim or assumption
Type(s) of analysis	Cost per patient
Outcomes	Net present cost
Time horizon	Lifetime
Method(s) used to generate results	Markov cohort
Health states	Health states are defined by current disability (EDSS score 0-9) and current treatment (eculizumab – ECU; or best supportive care – BSC) EDSS=0, ECU EDSS=1, ECU EDSS=2. ECU EDSS=3, ECU EDSS=4, ECU EDSS=5, ECU EDSS=6, ECU EDSS=7, ECU EDSS=8, ECU EDSS=9, ECU EDSS=0, BSC EDSS=1, BSC EDSS=2, BSC EDSS=3, BSC EDSS=4, BSC EDSS=5, BSC EDSS=6, BSC EDSS=7, BSC EDSS=8, BSC EDSS=9, BSC Dead, Relapse Dead, General mortality
Cycle length	6 months
Transition probabilities	General mortality, Relapse, EDSS progression, Death due to relapse, discontinuation
Software	Microsoft Excel

Abbreviations: ECU: eculizumab; EDSS: Expanded Disability Status Scale, BSC: best supportive care

2.1.1 Type of economic evaluation

The economic evaluation is a cost-utility analysis which uses a Markov cohort model structure to estimate costs over a lifetime model horizon.

2.1.2 Decision addressed by the economic evaluation

The decision addressed by the economic evaluation is to determine the comparative net present cost of eculizumab versus BSC when administered in a patient cohort with relapsing NMOSD. The economic evaluation is based on a clinical claim of superior efficacy and non-inferior safety for eculizumab, supported by evidence from the PREVENT trial (Pittock et al., 2019) presented in the clinical documentation.

2.1.3 Perspective of the economic evaluation

The economic evaluation takes a limited societal perspective in relation to health-related resource use.

2.1.4 Discounting

Cost and outcomes are discounted within the economic model according the Medicine Council guidelines 3.5% per annum for years 1-35 and 2.5% per annum thereafter.

2.2 Methods and structure of the economic evaluation

2.2.1 Structure of the economic model

The economic evaluation is a Markov cohort analysis where the model cohort is followed through a series of 6-monthly cycles from the time at which treatment is commenced for a lifetime horizon (53 years) or a maximum allowed patient age (100 years).

The Markov model defines the health state of patient based on disability more (i.e. capturing all the symptoms of the disease) rather than just modelling the number of relapses. It should be noted that EDSS does not directly capture the disability associated with optic neuritis due to NMOSD, and hence may understate the benefits of slowing EDSS progression. The scoring of the EDSS instrument is presented in Table 2.

Table 2 Kurtzke Expanded Disability Status Scale (EDSS)

EDSS	Disability description
0	Normal neurological examination.
1	No disability, minimal signs in one FS.
1.5	No disability, minimal signs in more than one FS.
2	Minimal disability in one FS.
2.5	Mild disability in one FS or minimal disability in two FS.
3	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others.
4	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions).
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities.
6	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting.
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting.
7	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day.
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair.
8	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms.
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self-care functions
9	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow.
10	Death due to MS.

Abbreviations: EDSS, Expanded Disability Status Scale; FS, Functional System; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Loss of visual acuity in NMOSD is only partly included in the EDSS as one of the function systems included in the EDSS score. Although the EDSS is not optimal for measuring the progression of NMOSD, it is the best option for economic model in an area with limited data on natural history of the disease. EDSS was measured as a secondary endpoint in PREVENT (see section 2.4.1.2).

The model uses a total of 20 health states (not including death) to track patients over time. Health states are defined based on EDSS (from 0 to 9) and treatment received ('ECU' (eculizumab) or 'BSC' (Best supportive care)). The health state labels are provided above in Table 1.

The possible per cycle transitions of the Markov model cohort are depicted in Figure 1. Patients begin the model receiving either eculizumab or BSC in addition to being allocated a starting EDSS score reflective of the target population.

There patients are at risk of a relapse, which can lead to worsening in disability in a proportion of patients as measured by a progression in EDSS.

Eculizumab patients are at risk of discontinuing therapy each cycle leading to a transition to the corresponding EDSS health state treated with BSC. Furthermore, treatment with eculizumab may be discontinued following a relapse.

Patients are at risk dying each cycle, either due to a fatal relapse or from other causes in the form of general mortality.

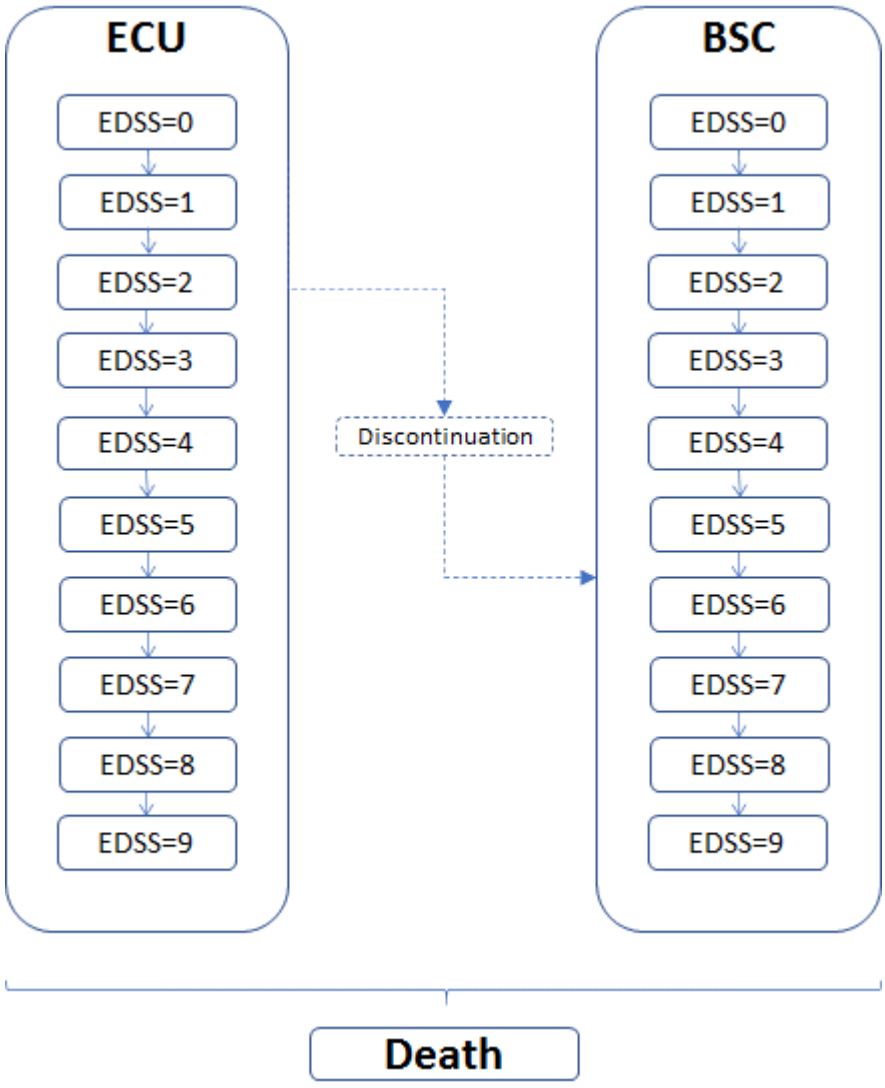


Figure 1 Simplified structure of the Markov model health states and possible transitions

2.2.1.1 Transitions

In each cycle the transitions are calculated in four steps

1. General mortality
2. Among survivors of step 1, the risk of relapse is calculated
3. Patients with relapse are redistributed on health states based on disease progression and relapse related discontinuation from treatment (eculizumab states)
4. General discontinuation from treatment are calculated from patients' distribution (eculizumab trace) following steps 1-3

Separate Markov traces were defined for eculizumab (ECU) and best supportive care (BSC). The difference between the two Markov models is that the ECU contains an additional transition step of discontinuation from ECU treatment.

The model structure uses a sub-structure within all 20 alive health states describing the treatment received (ECU or BSC) and the EDSS (0-9). From all states, patients may die and transition to the absorbing health state 'Death' (EDSS=10 but labelled 'Death' in the model).

Transition step 1. General mortality

In each cycle, the risk of general mortality is first calculated. The risk of all-cause mortality is a function of population characteristics of age and gender and independent of treatment (i.e., no direct treatment effect on mortality is assumed).

Transition step 2. Relapse

For the proportion of the patients alive after step 1, the risk of relapse is calculated. This is calculated as the risk of a fatal and non-fatal event, respectively. Relapse rates and case fatality is independent of EDSS score at start of cycle.

Transition step 3. Redistribution on health state

Patients with no relapse are assumed to stay at the same EDSS level as at start of the cycle.

Patients with a non-fatal relapse will be redistributed on EDSS level to account for disability progression following an event. This is done by assigning transition probabilities to a no change in EDSS (no progression), 1 step or 2 steps increase in EDSS (increase in disability), respectively. Risk of disease progression is independent of EDSS at start of cycle, however, patients in EDSS state 8 can only progress 1 step (with a probability of progression set to the sum of a 1 or 2 step progression probability in lower EDSS states).

For patients in one of the ECU states, treatment may be discontinued following a relapse. The model allows for three models of relapse related discontinuation from eculizumab treatment; No discontinuation following relapse event, discontinuation if disability progression occurred as a consequence of a relapse, or discontinuation following all relapse events. Patients discontinuing treatment following a relapse event is subject to the same risk of EDSS worsening as a consequence of the index event as patients not discontinuing.

In the model, an intermediate distribution of patients on non-death health states are calculated by applying the disease progression/ relapse transition probability matrix to the start-of-cycle, non-death patient distribution multiplied with the probability of surviving step 1 and multiplied by the

probability of a non-fatal event. The start-of-cycle non-death distribution multiplied by the probability of surviving step 1 and multiplied by the probability of being event free is then added to form the updated distribution among survivors following steps 1 through 3. The proportion of patients in the death state is then updated based on the calculated number of patients suffering an in-cycle general mortality event or a fatal relapse event.

Transition step 4. General discontinuation (ECU states)

Patients receiving eculizumab are at risk of discontinuation each cycle of the model independent of suffering a relapse or not. The probability of discontinuation is the same across EDSS states and is applied to each of the non-death, ECU state patient occupancies of the intermediate patient distribution generate in step 4. Patients discontinuing transition to the same EDSS state among the BSC states as the EDSS, ECU state before the discontinuation.

The update following step four forms the end-of-cycle patient distribution on health states and thereby the start-of-cycle distribution of the next cycle.

2.2.2 Cycle length and half-cycle correction

A cycle length of 6-months is employed. A six-month cycle length is sufficiently short to capture EDSS progression and allow up to two EDSS progressions per year. Half-cycle correction is implemented for all state costs.

2.3 Population and settings

2.3.1 Demographic and patient characteristics

Data relevant to the economic model extracted from the PREVENT study included the baseline EDSS distribution (data on file), mean age, and gender distribution of study participants (Pittock et al, 2019). The population characteristics applied in the model are shown in Table 3.

Table 3 Model population characteristics

Parameter	Value
Mean age (years)	44
Proportion female	91%
EDSS distribution	
0	
1	
2	
3	
4	
5	
6	
7-9	

Abbreviations: EDSS=expanded disability status scale
Sources: PREVENT (Pittock et al., 2019 and data on file)

We applied the PREVENT baseline characteristics as the modelled population in the economic model for Denmark. According the Medicine Council protocol the age of symptom onset in Denmark is approximately 35 years of age. The same was observed in PREVENT (36.6 years of age; Pittock et al. 2019). As a consequence, patients in PREVENT had a history of 7.7 years with NMOSD before entering the trial. The treatment history of patients in PREVENT included a number of immunosuppressive and immunomodulating agent which are also used as first-line treatments in

Denmark. For example, one third of the patients had been treated with off-label rituximab in the two year historical record of treatment and relapse events (Eculizumab Assessment Report). From this perspective, the PREVENT can be seen as representative of patients eligible for eculizumab in a Danish setting. In sensitivity analysis we tested the impact of disability on entering the model. Furthermore, we explore a scenario of an incident patient (age 35 and EDSS=0).

2.4 Model transition probabilities or variables, transformation and extrapolation

2.4.1 Transition probabilities and variables

The transition probabilities relevant to the model structure fit into the following categories:

- Probability of relapse
- Probabilities of disability progression (0, 1 and 2 EDSS points)
- Probability of discontinuation
- Probability of fatal relapse
- Probability of all-cause death

2.4.1.1 Probability of relapse

The probability of relapse in the model for the best supportive care arm is populated from the adjudicated annualised relapse rate (ARR) reported in the trial. This annual rate is converted to a 6-monthly probability using the following formula:

$$1 - e^{-rate*time}$$

For eculizumab, treatment efficacy was reported in the primary efficacy analysis of the clinical trial in the form of a relapse risk reduction. The hazard ratio (95% CI) for eculizumab compared to placebo was 0.058 (0.017, 0.197), representing a 94.2% reduction in the risk of relapse. The probability of relapse for BSC and eculizumab is provided in Table 4.

The probability of relapse is assumed to stay constant over the model duration. This is a pragmatic assumption. It is a valid hypothesis that having a relapse may increase the risk of subsequent events, however, no data is available to support this. PREVENT is the main source of relapse risk. This pivotal was event-driven by which patients was followed-up to the first adjudicated relapse. After recording post-relapse information (a maximum of 6 weeks following the relapse), patients were discontinued from the study and – if randomised to placebo – offered to enter an open-label, single-arm eculizumab long-term safety study. Furthermore, the risk of relapse on eculizumab treatment was too low to generate enough events to allow estimation of a potential risk increase after the first event.

Table 4 Probability of relapse

Parameter	Value	Reference
Annual relapse rate for patients treated with BSC (95% CI)	0.350 (0.199, 0.616)	Adjudicated annualised relapse rate (PREVENT)
6-monthly probability of relapse (BSC)	0.161	Calculated
Eculizumab treatment efficacy	0.058 (0.017, 0.197)	Adjusted adjudicated ARR (PREVENT)
6-monthly probability of relapse (ECU)	0.009	Calculated

Abbreviations: ARR: annualized relapse rate; CI: confidence interval; ECU: eculizumab; BSC: best supportive care

Sources: Pittock et al. (2019)

The relapse rate is estimated on a relatively small number of events. According to the sample size calculation, 24 events were needed to estimate a 76% risk reduction with a statistical power of 80%. After a blinded review of the study, it was decided to terminate the study after 23 adjudicated events. The decision was made after considering the impact of early termination on trial participants and trial outcomes. (Pittock et al, 2019, supplementary appendix). Despite the size of the study, the treatment effect is estimated with a high precision as it is seen from the 95% confidence intervals. The background risk and treatment effect in the model is based on the point estimates from PREVENT. In sensitivity analyses the impact on the cost estimates are tested using the confidence interval limits for both parameters.

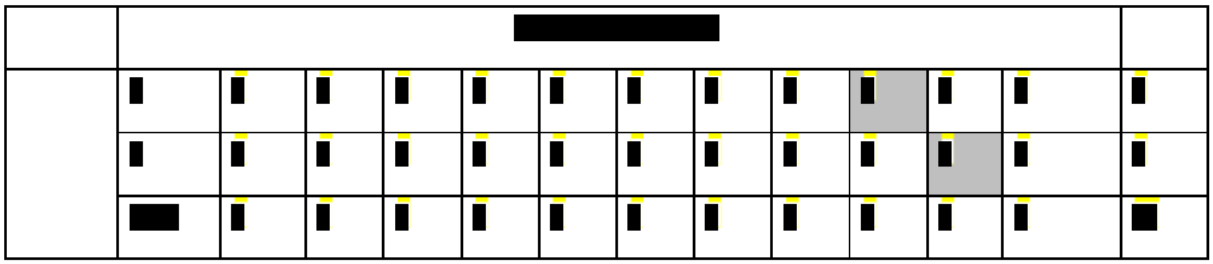
2.4.1.2 Probabilities of disability (EDSS progression) conditional on relapse

Within the model structure, a worsening of disability or EDSS progression, is possible only after a relapse. To populate this model parameter a post hoc analysis of EDSS scores before and after an incident relapse in the PREVENT trial is used to determine the appropriate conditional probability.

Data were analysed for a total of 24 relapses in the trial irrespective of treatment received. Pre- and post- pairs of EDSS scores were reported for 23 out of 24 relapses (1 relapse was missing a post score) (Table 5).

Table 5 Analysis of EDSS pre and post relapse: PREVENT trial

	Post-Relapse EDSS												
Pre-Relapse EDSS													



Abbreviations: ARR: annualized relapse rate; CI: confidence interval; ECU: eculizumab; BSC: best supportive care

Sources: Data on file

Of the 23 relapses, a worsening of pre-relapse EDSS was observed after [redacted] of those relapses, meaning an increase in EDSS score of 1 or more units (Table 6). For simplicity, the model conservatively assumes all EDSS progression is by a single unit (ie 0 to 1, 2 to 3, 3 to 4, etc) in the base case analysis. In sensitivity analysis, alternative assumption including 1 or 2 steps progression is tested.

Table 6 Probability of EDSS progression

Parameter	Value
Relapses (complete data)	[redacted]
Improvement/no change in EDSS post-relapse (%)	[redacted]
Worsening in EDSS post-relapse (%)	[redacted]

Abbreviations: ARR: annualized relapse rate; CI: confidence interval; ECU: eculizumab; BSC: best supportive care

Sources: See Table 5

This variable is tested in sensitivity analysis and is also tested via validation (see Section 2.6.2) to assess ability to predict EDSS progression compared to published sources.

2.4.1.3 Probability of death due to relapse

The relapsing form of NMOSD is associated with an increased risk of mortality, the reasons for which are multifactorial; respiratory failure associated with high cervical myelitis or brainstem involvement; infections, particularly pneumonia predominate. High frequency of attacks and sphincter disturbances early in the disease course, blindness, incomplete recovery from first attack and concomitant autoimmune disorders have all been independently associated with early death. Some patients with NMOSD present with brainstem symptoms due to medullary involvement. In particular, the area postrema clinical syndrome of nausea and vomiting or hiccups, sometimes intractable, with associated medullary lesions on MRI occurs with an incidence of 16 to 43 percent in NMOSD. Brainstem involvement may lead to acute neurogenic respiratory failure and death.

Mortality associated with NMOSD has been studied in several observational studies conducted over the years (Table 7).

Table 7 Observational studies of mortality associated with NMOSD

Study	Country	Diagnostic criteria	Cases selected	Total cases & Gender F/M	Ethnicity	Mean age at onset	Median time to 1st relapse (mo)	Nature of first attack	AQP4 IgG +ve	Median follow-up	Median EDSS	Disease related mortality	Annual mortality: deaths per 100 patient-years
Wingerchuck et al, 1999	US 1950-1997	Wingerchuck 1999	NMO	71	NA	NA	NA	NA	NA	NA	NA	32%	NA
Wingerchuck et al, 2003		Wingerchuck 1999	NMO	80 (57 F/23 M)	NA	41 (6-72)	NA	TM+ON: 12.5% ON: 18.75	NA	14 years	NA	NA	NA
Papais-Alverenga et al 2008	Brazil 1985-2004	1999	NMO	60 (54 F/6 M)	58% Afro Brazilian mixed/black 42% White	NA	NA	TM 43.3%; ON 53.3%; TM+ON 3.4%	NA	8 (0.5 - 30) years)	NA	23.3%	NA
Cabre et al 2009	French WI 2007/2009	Wingerchuk 1999, 2006	NMO	98 (88F/8M)	Hispanic Afro Caribbean	29.5 (11–74)	11.5 (1–300)	NA	32%	9.5 (1-40 years)	NA	24 (25%)	NA
Bichuetti et al 2009	Brazil 2009	Wingerchuk 1999, 2006	NMO relapsing	41 (29F/ 12M)	NA	32.6 (20–60)	NA	TM 41% ON34%ON+TM 24%	41%	1 (0.6-8.3) years	NA	4 (14.3%)	NA
Collengues et al 2010	France 2010	Wingerchuk 2006	NMO. NMOSD	125 (94F/12M)	White=87%;	34.7 (4–66)	12 (30.8-43.1)	TM 45.6% ON 36.8%	54%	8.7 (0.1–39.5) years	NA	4 (3.2%)	NA

Study	Country	Diagnostic criteria	Cases selected	Total cases & Gender F/M	Ethnicity	Mean age at onset	Median time to 1st relapse (mo)	Nature of first attack	AQP4 IgG +ve	Median follow-up	Median EDSS	Disease related mortality	Annual mortality: deaths per 100 patient-years
Asgari et al 2011	Denmark 2011	Wingerchuk 2006	NMO. NMOSD	42 (31F/11M)	White=99%	35.6 (15–64)	NA	TM 59.5% ON 35.7%	62%	6.5 (2–10) years	6.5 (1.0–9)	3 (7.1%)	NA
Jarius et al 2012	Germany 2012	Wingerchuk 2006	NMO. NMOSD	175 (150F/25M)	White=100%	39 (10-81)	8.5 (1-216)	ON 58% ON+TM 8 %	78.3%	0.4 (0–32.5) years	6.5 (1.5–10)	NMO related:5 (2.9%);	NA
Mealy et al 2012	USA 2012	Wingerchuk 2006	NMO. NMOSD	187 (162 F/25M)	White= 47%; AfrAm =37%; Other =16%	40	NA	TM 50.2% ON 35.3%	66.6%	0.46 (0.02–3.2) years	NA	NA	NA
Kitely et al 2012	UK and Japan		NMO. NMOSD	106	UK Japan				100%	6.25 years		NMO related 7%; Overall 9% (	NA
Pandit et al 2013	India 2013	Wingerchuk 2006	NMO. NMOSD	70 (30F/40M)	S. Indian =100%	37.5 (12–65)	12 (4-96)	NA	39%	4.5 (1-13) years	5.5 (1.5–10) 12	12 (17%)	NA
Abdoul Enein et al 2013	Austria 2013	Wingerchuk 1999, 2006	NMO. NMOSD	73 (62F/10M)	White =100%	45.7 (12.3-79.6)	NA	ON 54.2% TM 41.7% ON+TM 4.2%	97%	NA	NA	NA	NA

Study	Country	Diagnostic criteria	Cases selected	Total cases & Gender F/M	Ethnicity	Mean age at onset	Median time to 1st relapse (mo)	Nature of first attack	AQP4 IgG +ve	Median follow-up	Median EDSS	Disease related mortality	Annual mortality: deaths per 100 patient-years
Mealy et al 2018	US	Wingerchuk 2015	MNOSD	427 (367F/60M)	Caucasia=46%; Afr AM =41% Other =13%	39.9 (16.7)			80%	Mean 10.4 years		30 (7%)-all-cause 22 (5%) NMOSD	0.68% - all-cause

Abbreviations: ON, optic neuritis; TM, transverse myelitis;

Historically, NMOSD mortality of 23%-32% has been reported (varying follow-up periods). This higher mortality could be explained by earlier diagnostic criteria which likely only captured the most severe cases.

More recent studies have found mortality rates of between 7% and 13% (varying follow-up periods). The most recent study, in 2018 reported a mortality rate of 7% (Mealy 2018). When adjusted for the duration of follow-up, an annual mortality rate of 0.68 deaths per 100 patient-years with the mean disease duration at time of death being 6.9 years.

For the base-case economic evaluation, the study by Mealy et al. (2018) is used to justify a mortality risk of 7% in relapsing NMOSD patients. A risk of 7.0% was estimated in a cohort of 427 patients with NMOSD across two NMO centres in the USA.

The US-based study is chosen as an estimate of case fatality rates in a Danish population because it is the most recent study. The reported studies in Table 7 showed decreased mortality observed in later studies is considered associated with progress achieved in the diagnosis and treatment of NMOSD. The availability of AQP4 antibody testing now allows early and more accurate diagnosis and where use of plasmapheresis for acute relapses, and preventive immunotherapies, which have been shown to decrease relapse rates in observational studies (Kessler 2016) and which are used in Danish clinical practice.

Mortality in the model is assumed to be constant across all EDSS health states and treatment arms.

2.4.1.4 Probability of all-cause death

All-cause mortality is modelled with the most recent Danish Life tables. Probabilities were weighted to reflect the baseline gender distribution of the model population (see Section 2.3.1).

2.4.1.5 Probability of discontinuation

In the PREVENT trial, a total of 16 (16.75%) eculizumab patients discontinued from the study. When adjusted for study duration discontinuation occurs at a rate of 9.3 per 100 patient-years of follow-up (Pittock et al. 2019; EPAR Variation report table 14). The rate of discontinuation was calculated for the ITT population randomized to eculizumab (N: 96, patient years of follow-up: 172.8; EPAR Variation Report table 14). No discontinuation occurred due to adverse events or relapse, with all discontinuations due to death (n=1), loss of follow-up or patient withdrawal (EPAR Variation Report, p 40). In the extension study PREVENT OLE (ECU-NMO-302) a single patient withdrew from the study drug due to multiple TEAEs.

In the model, a treatment discontinuation rate of 9.3 per 100 treatment years is assumed for the base-case analysis and tested in sensitivity analysis. This is a conservative assumption as it appears the risk of discontinuation with eculizumab is negligible. The cycle probability of discontinuation is calculated using the formula:

$$1 - e^{-rate*time}$$

With a rate of 9.3 per 100 treatment years this gives a cycle probability of 4.5%.

In addition to the general risk of discontinuation it is assumed that patient will discontinue eculizumab in case of a relapse. This is based on the assumption of how the product will be used on Danish clinical practice, however, it not substantiated by evidence.

2.5 Health care resource use and costs

Non-study drug costs in the economic model fall into the following categories of resource use:

- Intervention cost
- Administration costs: Costs incurred during infusion cost of eculizumab
- Health state costs: Costs related to managing level of disability (function of EDSS)
- Relapse costs: Acute costs of treating relapse of disease
- Patient cost: Patient cost and travel cost associated with health care visits

2.5.1 Intervention costs per patients

The economic model is based on the Pharmacy Purchase Price of 34,273 per 300 mg vial of eculizumab (http://medicinpriser.dk, February 2021)

Dosing for eculizumab is as follows:

- First 4 weeks: 900 mg a week (3 x 300 mg vials)
- Week 5: 1200 mg (4 x 300 mg vials)
- Week 7 onwards: 1200 mg (4 x 300 mg vials) every two weeks

The first 5 weeks of the above dosing schedule represent an 'induction' treatment phase, with a 'maintenance' treatment phase describing dosing from week 7 onwards.

For a 6-monthly model Markov cycle incorporating 'induction' (1st cycle of the model), a total of 56 vials of eculizumab are needed at a cost of 1,919,288 DKK, compared to 52 doses for a maintenance treatment cycle (2nd and subsequent cycles) at a cost of 1,782,196 DKK (see Table 8).

Table 8 Cost of eculizumab treatment

Treatment phase	Number of vials per cycle	Total cost per cycle
Induction (1st cycle)	56	1,919,288
Maintenance (2nd cycle onwards)	52	1,782,196

Abbreviations: ECU: eculizumab

2.5.2 Cost of administration

Eculizumab is administered as an intravenous infusion over a period of approximately 25-45 minutes for each dose.

An induction treatment phase consists of weekly infusions (900 mg) for the first four weeks, followed by an infusion in the fifth week (1200 mg), and then 1200 mg infusions every two weeks thereafter. Therefore, a total of 15 infusions are needed for the first 6-montly Markov cycle of treatment, followed by 13 in subsequent cycles.

The infusion costs of eculizumab are presented in Table 9.

Table 9 Cost of eculizumab administration

Treatment phase	Unit cost per ECU infusion*	Number of infusions per cycle	Total cost per cycle
Induction (1st cycle)	3353	15	50,295
Maintenance (2nd cycle onwards)		13	43,589

Abbreviations: ECU: eculizumab
* DRG2021 01MA98 *MDC01 1-dagsgruppe, pat. mindst 7 år*

The unit cost per infusion was estimating using the tariff for DRG group 01MA98 (*MDC01 1-dagsgruppe, patient mindst 7 år*). This cost is assumed to cover the infusion and any routine follow-up and monitoring of the patient's treatment and health. No routine follow-up was specified for the standard of care arm.

Patient cost of eculizumab administration was calculated the same way. Time cost associated with travel, clinic time and infusion was assumed to be 2 hours @ 179 DKK. Travel cost was based on the assumption of 28 km @ 3.44 DKK (2021 tariff, http://skat.dk). This gives a patient cost per contact of 454.32 DKK. The first cycle cost is 6,815 DKK and the following cycles, patient costs amount to 5,906 DKK.

According to the SmPC, vaccines against serogroups A, C, Y, W 135 and B are recommended for patients before initiating treatment with eculizumab (Soliris SmPC, 2020). The cost of vaccination is added to the first cycle administration cost and assumes vaccination with Bexsero® (serogroup B) and Nimenrix® (serogroups A,C, W135 and Y). Bexsero requires two intramuscular injections on two occasions and Nimenrix one. The two injections may be given on the same day (Nimenrix SmPC, Bexsero SmPC). The regional costs consist of vaccine (Bexsero, 1 pack (two syringes) @ DKK 710.42, Nimenrix (5+5+5+5 microgram @ DKK 260.00)). Prices are in PPP and sourced from http://medicinpriser.dk (February 2021). Cost of administration of vaccines assumes two GP visits (@ DKK 143.44) (http://plo.dk). Patient cost associated with vaccines assumes a total of one hour of patient time (@ DKK 179, Medicinrådet (2020a)) and a total of 28 km (@ DKK 3.44, http://skat.dk). The travel distance associated with each visit to a general physician is assumed to be 50% of the distance to hospital (28 km round trip according to Medicinrådet (2020a)). The total cost of pre-treatment vaccination for eculizumab treated patients is DKK 1,262.92 in regional cost and 275.32 in patient cost.

2.5.3 Cost of side-effects

Costs of managing side-effects were conservatively omitted since a higher incidence of serious adverse events were observed in the placebo arm compared to the eculizumab arm of the PREVENT trial – even after excluding such events that were adjudicated NMOSD relapses. Table 10 provides the comparative analysis related to the clinical analysis supporting the Medicine Council scientific question where the placebo arm in PREVENT is defined as the current standard of care. Although not statistically significant there is a clear trend towards a lower risk of serious adverse events in the eculizumab arm.

Table 10 Summary of comparative risk of serious adverse events* (eculizumab vs placebo) in PREVENT

Statistic [Reference]	Treatment arm	Events/ N	Estimate	Confidence interval
Risk Ratio	Eculizumab	9 / 96	0.49	95% CI: 0.21; 1.15
	Placebo	9 / 47		
Patients with at least one event (absolute risk difference)	Eculizumab	9 / 96	9.4%	95% CI: 3.5; 15.2
	Placebo	9 / 47	19.1%	95% CI: 7.9; 30.4
	Difference (percentage points)*		-9.8	95% CI: -22.4; 2.9

* Based on safety analysis in PREVENT. Serious adverse event associated with events classified as NMOSD relapses were omitted.

Source: Pittock et al. (2019)

2.5.4 Health state costs

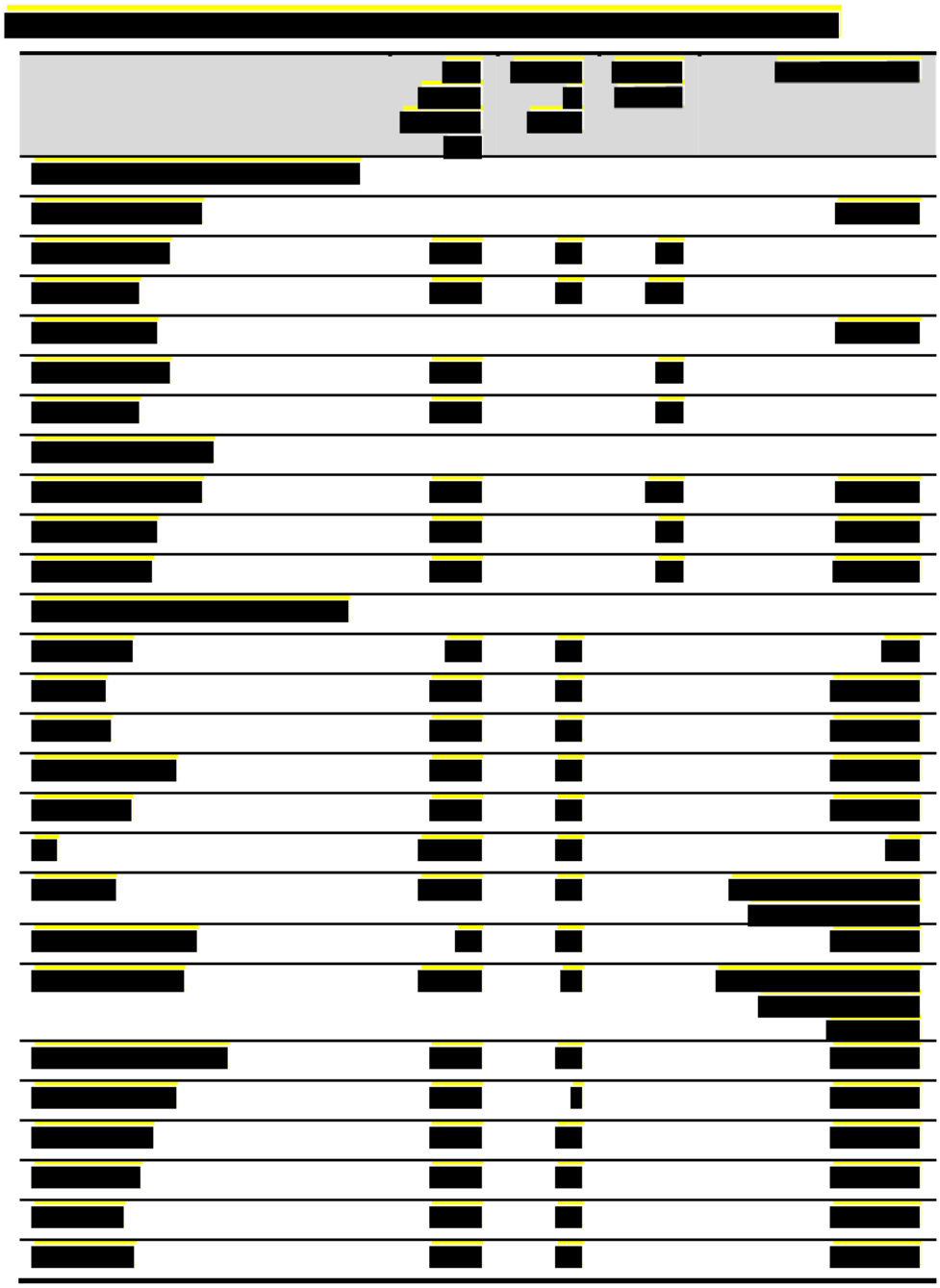
To our knowledge no estimate of cost associated with NMOSD disability is available from Denmark. To estimate the long-term cost associated with NMOSD, cost estimates from a cohort of patients with multiple sclerosis (MS) was applied as a proxy. The EDSS score (which formed the basis for the definition NMOSD health states in this model) was developed to describe the degree of disability in MS. This means that a NMOSD-patient and a MS-patients who have the same EDSS score will have the same overall level of disability. Although the scoring system is the same, it is not given that the cost of care will be the same for a patient with NMOSD as for a patient with MS but with the same level of EDSS. With this uncertainty in mind, cost of medication was omitted as this is likely to be related to management of the disease rather than to management of disabilities.

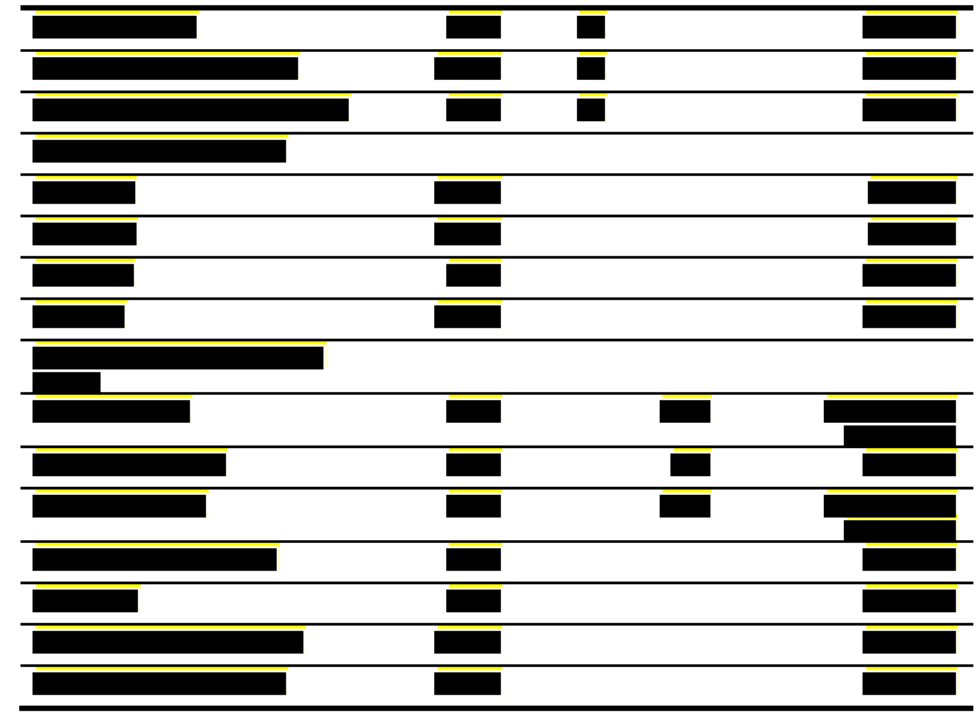
Vestergaard Rasmussen et al. (2017) reported on a retrospective study of resource consumption and quality of life in a sample of 830 patients. The study aimed to estimate all costs related to MS: hospitalization, rehabilitation, consultations, diagnostic procedures and tests, medication, community care, family support and production losses (sick leave, early retirement, invalidity). Data were collected using an online survey among MS patients invited by the national patient organization (Scleroseforeningen). A total of 830 evaluable response were included in the analysis. Average age of the population was 54 years and the average EDSS was 4.2 (42.8%, 40.4% and 17.8% had mild, moderate and severe disability, respectively). Costs were calculated based on year 2015 price levels and included health care cost (inpatient care, day admission, consultations, tests, medication and disease modifying treatments) as well as services and informal care costs (community services, investments, and informal care costs). In addition, social income transfers were estimated.

In the survey health care resource utilization was collected with a 3 months period (Vestergaard Rasmussen et al. 2017). [redacted] show the average health care resource utilization in the survey. Hospitalisation was rare: 3%. of patients were admitted as inpatients, 4% as day admission,

rehabilitation centres were used by 5%. In all, 65% of patients had consultations and 22% had investigations and tests, most often magnetic resonance imaging (MRI) scans (brain 11%, spine 5%) (ibid.). Assistance from community and social services was provided to 17% of patients, evenly spread between home help, transportation and personal assistants (nurse visit). Services were concentrated in the severe group of patients, where personal assistants supported 33% of patients (ibid.). Investments in equipment and devices to aid patients' mobility included house and car modifications (lifts, elevators, ramps, rails), walking aids, and wheelchairs (manual, electric).

House and car modifications were collected from the past 12 months. 190 patients (23%) reported having resource utilization in this category, most often for modifications to the house or the car and walking aids.

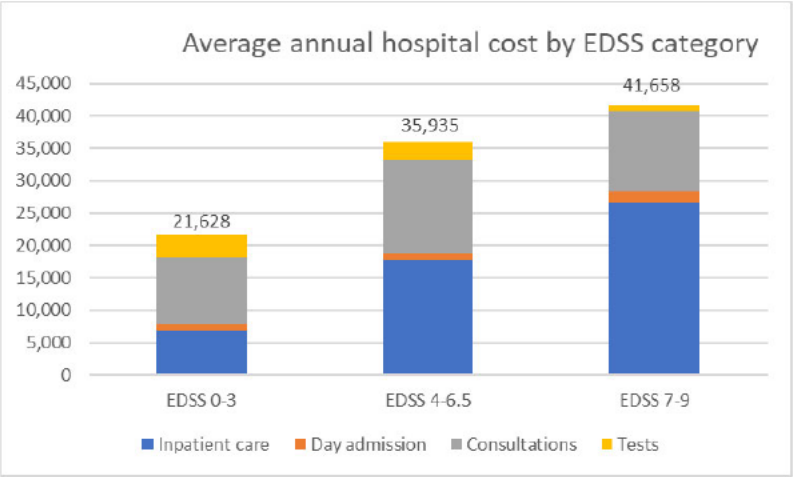


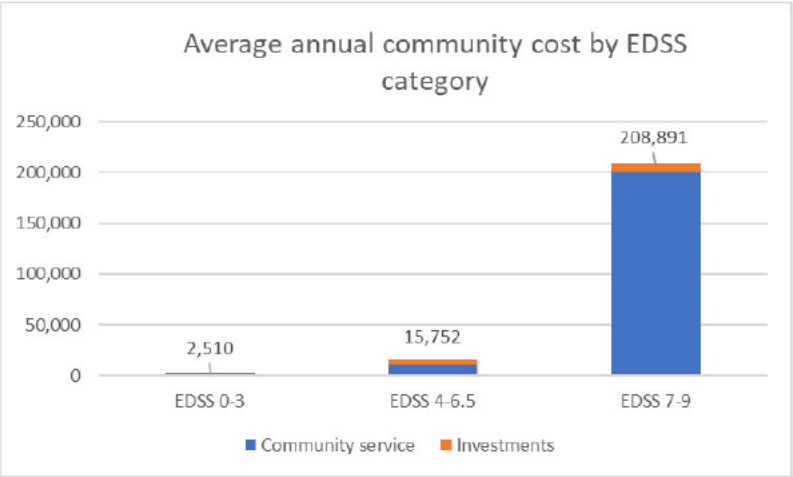


1) Vestergaard-Rasmussen et al. (2017)
2) Kobelt et al. (2017)

Costs were reported as annual cost by applying commonly accepted public unit cost. The complete list of unit costs has not been published but the main elements are available in a methodological paper presenting the European study design (of which the Danish Survey was a sub-study (Kobelt et al. (2017)). For the hospital contacts the Danish survey applied DRG tariffs. For GP visits, the tariff agreement between *Danske Regioner* and *PLO* were used (*Type 1 patient, standard consultation)*. For MS Nurses the *RTLN* wage rates were applied and for community home help and personal assistance (nurse visits) hourly wage rates were applied., i.e., the unit costs per hour (DKK 130 and DKK 370, respectively) were not adjusted to account for patient contact time as stipulated in DMC guidance on cost calculation. This adjustment would have led to a higher cost. Overall, the method for calculating costs appear solid and to be applying commonly accepted methods. The list of authors includes health economists with an extensive experience in international studies of cost of illness and cost-effectiveness.

The survey showed the relationship between EDSS and cost.





Adapted from Vestergaard-Rasmussen et al. (2017)

The estimates of selected health care cost and community cost (excluding informal care cost) from Vestergaard Rasmussen et al (2017) were applied in the model after inflating from 2015 to 2021M01 price levels using the net price index (a total of 3.8% inflation). Health care cost for inpatient care, day care, tests and consultation reported in Vestergaard Rasmussen et al. (2017) were included. Cost associated with Informal care costs estimated in Vestergaard Rasmussen et al. (2017) were not included because it is not possible from the source to separate treatment related cost and general household activities.

Table 12 displays the cost inputs for the health state cost applied in the model. The 95% confidence intervals were tested in scenario analyses.

Table 12 Health state cost applied in the model

EDSS score	Regional cost			Community cost		
	Base case	95% confidence interval*		Base case	95% confidence interval*	
0	22,450	16,089	28,811	2,605	0	6,089
1	22,450	16,089	28,811	2,605	0	6,089
2	22,450	16,089	28,811	2,605	0	6,089
3	22,450	16,089	28,811	2,605	0	6,089
4	37,301	28,618	45,983	16,351	9,423	23,278

5	37,301	28,618	45,983	16,351	9,423	23,278
6	37,301	28,618	45,983	16,351	9,423	23,278
7	43,241	27,212	59,270	216,829	157,480	276,178
8	43,241	27,212	59,270	216,829	157,480	276,178
9	43,241	27,212	59,270	216,829	157,480	276,178

* 95% confidence intervals were calculated from standard deviations presented in Vestergaard Rasmussen et al. (2017) assuming approximately normal distribution of means but truncated to the left at zero.

There are a number of limitations to using the MS based costs by EDSS group in the current cost calculation.

- The Vestergaard-Rasmussen et al. (2017) survey was conducted in patients primarily suffering from relapsing-remitting MS and did not include NMOSD patients. The validity of applying cost from MS in a cost model for NMOSD may be questioned, however, the level of disability is measured using the EDSS in both the survey and in the economic model. For this reason, Alexion believes it is the best available source to approximate the cost of disability associated with NMOSD.

- Some health care cost consultations in the survey may represent cost outside the regional budget. Visits to homeopath (0.6% of patients reported this) are most likely paid by the patients themselves, continence advisor, acupuncturist and massage therapy may be a regional, municipality or patient cost. From the source it is not possible to separate these out so they can be included correctly as either regional, community, or patient cost. However, all of the cost items quality as a societal cost from the limited societal perspective as they are directly related to treatment.

- The study did not report in a level of detail that will allow estimation of cost by EDSS category using current unit cost. However, the study is recent (cost level 2015) and conducted using acceptable sources of unit cost. The year of the unit costs in the source should not by itself disqualify the study.

- In Vestergaard Rasmussen et al. (2017), the 3-month cost of illness in patients reporting a relapse was compared to that of patients not reporting a relapse during the data collection period (in patients with a EDSS score below 6.5). A substantial increase in cost was observed between the two groups amounting to 19,037 DKK (cost excluding disease modifying drugs, invalidity and early retirement) (Vestergaard Rasmussen et al. 2017). It is not possible from the source to identify what proportion of the relapse cost is associated with acute treatment and what amount is associated with health care and community care cost resulting from follow-up cost (health care and community care contacts needed to adapt patient treatment and patient care to the new level of disability). Nor is it possible to estimate the proportion of cost in each level of disability (EDSS strata) associated with relapse. For this reason, no attempt was done to estimate EDSS level cost without acute relapse cost. When applying the MS related cost in the current model this will mean that the relapse cost to some extend will be double counted. This is a conservative assumption given that the model predicts a higher life-expectancy (and hence a higher net-present health state cost) in the eculizumab arm.

- In Vestergaard Rasmussen et al. (2017), patients were treated with first or second generation disease modifying drugs (Vestergaard Rasmussen et al. 2017). The health state cost associated with routine follow-cost and monitoring of these treatments. It is not possible from the source to estimate what proportion of cost is associated with these contacts. This implies that when applying these costs in the NMOSD model, the cost of routine follow-up of eculizumab arm will be double counted. Inclusion of the health state is hence a conservative assumption because drug administration and monitoring are only included in the intervention arm.

- No patient costs associated with treatment of patients due to disability were included in the analysis due to lack of evidence.

2.5.5 Cost of relapse

In PREVENT 2 of 3 adjudicated relapses was associated with a hospitalization (Kim et al. 2019; EPAR Assessment report). The DRG cost of a hospitalization for NMOSD is 40,744 (DRG 01MA07 with or without plasma exchange procedure). The cost of hospitalization involving treatment with immunoglobulin is more than double of that (DRG 01MP07, 106,361 DKK). 6.3% of patients in PREVENT had been treated with i.v. immunoglobulin in the two years before entering the trial (Kim et al., 2019). We conservatively assumed the lower cost of hospitalization but explored the impact of relapse cost in a sensitivity analysis. For fatal events 67% of patients were assumed to be hospitalized at the time of death (same as observed for non-fatal in PREVENT).

All patients with a non-fatal event was assumed to (in addition to any hospitalization) have two outpatients visit (DRG 01MA98) if they were not treated with eculizumab (in which case 1 of the follow-up consultation was assumed to occur at the same visits as the infusion was performed).

Table 13 Calculation of the relapse cost input

	Unit cost	Eculizumab arm	IST alone arm	Notes
Non-Fatal				
% Hospitalized		67%	67%	PREVENT
Direct cost	40,744	1	1	1 hospitalization with NMOSD diagnosis (DRG group 01MA07)
Patient cost (hours)	179	10	10	Assumption
Outpatient follow-up				
Direct cost (outpatients visits)	3,353	2	2	Assumption 2 outpatients with NMOSD diagnosis (DRG group 01MA98)
Patient cost (hours/ visit)	179	2	2	Assumption
Patient cost (km/visit)	3.44	28	28	Assumption
Direct cost of non-fatal relapse		**34,004**	**34,008**	Calculated
Patient cost of non-fatal relapse		**2,108**	**2,108**	Calculated
Fatal				
% Hospitalized		67%		Assumption. Same as non-fatal
Direct cost	40,744	1		1 hospitalization with NMOSD diagnosis (DRG group 01MA07)
Direct cost of fatal relapse		***27,298***		Calculated

2.6 Model validation

2.6.1 Operational validation of the economic model

2.6.1.1 Markov traces – EDSS over time

[redacted] and [redacted] show Markov traces for ECU and BSC treatment arms respectively, depicting the proportion of the cohort with each EDSS score over time. The data is presented as a stacked line chart, with the stacked data representing the proportion of alive patients over time for each treatment arm.

Abbreviations: ECU=eculizumab; EDSS=expanded disability status scale; BSC=best supportive care

Notes: Curves illustrate the proportion of the model cohort with each EDSS score (within-cycle correction)

Abbreviations: ECU=eculizumab; EDSS=expanded disability scale; BSC=best supportive care

Notes: Curves illustrate the proportion of the model cohort with each EDSS score (within-cycle correction)

2.6.1.2 *Markov traces – On treatment (%) and cumulative relapses over time*

An additional Markov trace is presented in Figure 4, depicting the on treatment curve for the ECU treatment arm plotted against the cumulative number of relapses per patient (in each treatment arm) over the model horizon. This figure demonstrates the internal validity of the model in that it shows the inverse relationship between ECU treatment and the cumulative number of relapses in ECU treatment arm.

Abbreviations: ECU=eculizumab; BSC=best supportive care

2.6.2 Other validation techniques

An external validation of the economic model was performed by comparing model outcomes to a results from a published outcome prediction model for a APQ4-IgG positive NMOSD population utilising a large multicentre dataset of 441 patients from the UK, USA, Japan and Martinique (Palace et al, 2019). Of interest to facilitating a validation to the economic evaluation were the two and five-year predicted risks of reaching EDSS ≥ 8 or death. The ability to validate the model against a composite measure that included mortality justified the choice of the EDSS ≥ 8 or death outcome for the validation exercise.

The two and five-year likelihoods of developing an EDSS of ≥ 8 or dying were presented by:

- Patient ethnicity [African, Japanese or Caucasian]
- Gender [female/male]
- Age at onset (≤35 years, 36-48 years, and >48 years), and
- Attack onset type (optic neuritis [ON]; transverse myelitis [TM]; or brainstem [BS]).

Reported outcomes from Palace et al were weighted to best represent the target population, which as described earlier was based on a NMOSD population aged 47 years who are 91% female. For

simplicity and to maximise data reliability, for ethnicity the predicted outcome data for Caucasian female and Caucasian male were used in the validation. Given the modelled evaluation assumed a baseline age of 47 years, data for the 36-48 years and > 48 years patient groups were used in the derivation of weighted risks (equal weights were assumed). Patients in the study were receiving immunosuppressive treatment (IST) consistent with BSC in the economic evaluation.

Palace et al. (2019) did not report an EDSS distribution at time of onset, however because the study reported low incidence of reaching EDSS 6 within 2-years it was assumed that no patients had a baseline EDSS of ≥ 6 for purpose of this validation exercise. Therefore, the baseline model population was standardised to be between EDSS 0 and EDSS 6.

As estimates were presented by attack onset type and individual patient numbers were not known, a lower and upper estimate was used to present a plausible range of values to compare to outcomes from the economic model. The weighted risk of EDSS ≥ 8 or death was estimated to be between 3.9% and 6.3% at two year, and between 8.5% and 13.0% at five-years (Table 14).

Table 14 Derivation of 2 and 5-year risk of EDSS ≥ 8 or death for validation with economic evaluation (Palace et al, 2019)

Parameter	Palace et al patient group				Weighted cohort
Gender	Female	Female	Male	Male	-
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	-
Age	36-48 years	>48 years	36-48 years	>48 years	-
Weight for modelled population	(91% x 50%)	(91% x 50%)	(9% x 50%)	(9% x 50%)	100%
EDSS ≥ 8 or death at:					
2-years (lower-upper)	1.8% - 3.0%	6.5% - 10.0%	1.3% - 2.1%	2.1% - 7.3%	3.9% - 6.3%
5-years (lower-upper)	3.9% - 6.3%	13.4% - 20.1%	4.7% - 7.3%	9.8% - 14.9%	8.5% - 13.0%

Abbreviations: ECU: eculizumab

Source: Palace et al 2019.

For comparison, the economic model estimates a two year outcome of 4.4% and a five-year outcome of 10.9% in the BSC arm when the base-line population is adjusted to the disability distribution in Palace et al. (2019), comfortably fitting within the ranges predicted by Palace et al 2019 [redacted] This exercise therefore validates the rate of EDSS progression and mortality in the comparator arm of the economic evaluation.

2.7 Results of the base-case economic evaluation

2.7.1 Base-case assumptions

Table 15 provides an overview of the key assumptions defining the base case analysis as described in sections 2.3 through 2.5.

Table 15 Key assumptions defining the base-case

Option	Selected base case
Population	ITT population from PREVENT trial by age, gender and EDSS at baseline
Starting age	44
Time horizon	Life-long (56 years)
Discounting	3.5% p.a. up to year 35, 2.5% p.a. thereafter
Relapse rate	Based on PREVENT (adjudicated relapse rate)
Disability progression	[redacted]
Relapse case fatality	7% based on Melay et al. (2018)
Mortality	Relapse related morality in addition to Danish general population mortality
Dosing of eculizumab	According to SmPC
Discontinuation from treatment	9.3 patient per 100 patient years (PREVENT observation) Patients suffering relapse on treatment is assumed to discontinue treatment permanently
Cost of IST	Cost of IST medication has been omitted from both arms as this is assumed to be the same irrespective of treatment with eculizumab or not.
Monitoring of treatment	Monitoring of eculizumab treatment is assumed to take place in relationship to infusions Costs of monitoring of IST (direct and patient cost) have been omitted. Note that this is a conservative assumption given that

	patients in the BSC arm may be expected to been monitored for treatment and disease progression.

2.7.2 Base-case results

Over a lifetime model horizon, the net present value of eculizumab acquisition costs is estimated to total 24.349 MDKK per patient, with administration costs of 600,178 DKK per patient (including vaccinations). By avoiding relapses, eculizumab is associated with cost-offsets of 50,930 DKK. Although eculizumab is predicted to delay disability progression (especially to non-ambulatory levels), eculizumab is associated with an increase in health state cost of 51,929 DKK per patient. This is because patients treated with eculizumab in the model are predicted to increase life-expectancy by 4.2 years as a consequence of delaying time to relapse and reducing the cumulative number of relapses. The total incremental regional cost of treatment with eculizumab is 24.950 MDKK per patient (Table 16). Community cost decreases by 337,221 DKK. Unlike regional health state cost, the community cost associated with progression is increasing much more with increasing disability which means that the eculizumab modelled treatment effect on disability progression outweighs the increase in overall survival.

Patient cost increased with eculizumab treatment by 78,433 DKK per patient. Time and travel cost associated with eculizumab infusion is the main driver of this cost element. The net-present incremental societal cost associated with eculizumab treatment compared to standard IST alone is 24,691,451DKK per patient (Table 16).

Table 16 Disaggregated costs: Health care costs by cost category (DKK)

Type of resource item	Eculizumab + IST	IST alone	Incremental cost
Eculizumab costs	24,349,094	0	24,349,094
Administration costs	600,147	0	600,147
Health state costs	639,068	587,139	51,929
Relapse costs	130,744	181,674	-50,930
Total regional costs	**25,719,052**	**768,813**	**24,950,240**
Community costs	1,015,171	1,352,392	-337,221
Total direct costs	**26,734,224**	**2,121,205**	**24,613,019**
Patient costs	89,096	10,663	78,433
Total societal costs	**26,823,319**	**2,131,868**	**24,691,451**

Abbreviations: IST=Immunosuppressive therapy

2.8 Uncertainty analysis: model inputs and assumptions

2.8.1 Identifying and defining uncertainty in the model

Univariate sensitivity analyses were performed for the following parameter categories:

- Model population characteristics: Age and starting EDSS state; Baseline population distribution of EDSS scores (testing the impact of starting in each of the EDSS state)
- Treatment efficacy: Eculizumab efficacy in preventing relapses
- Event probabilities: background relapse risk, conditional probability of EDSS progression, probabilities of a relapse being fatal, probability of treatment discontinuation
- Cost parameters: infusion, disability, and relapse treatment costs

- Other: discount rate and model duration
- Impact of disability cost elements

2.8.2 Summary of uncertainty analysis

Results of univariate sensitivity analyses are presented in Table 17.

The analyses show that the incremental, societal cost per patient is mainly sensitive to background risk of relapse and treatment efficacy of eculizumab. Furthermore, the incremental cost is sensitive to assumption on discontinuation from eculizumab treatment.

The unit cost of eculizumab infusion has only minor impact as has the health state cost and relapse cost. The analysis is insensitive to disability (EDSS score of the patient) at start of treatment and to time horizon. In a scenario analysis the incremental cost of an incident patient was modelled (assuming an age of 35 at start of treatment and no disability). The result of this scenario is an increased cost of 516,582 DKK compared to the base case (based on the PREVENT baseline characteristics). This scenario is an extreme case, because eculizumab is indicated for NMOSD of a relapsing nature and will not be used before the first relapse has occurred, but shows that the incremental cost of early vs. late use of eculizumab is associated with a limited increase in cost. Nevertheless, the base case analysis is a better reflection of the patient population in Denmark in a situation where cheaper (but off-label) treatment options are likely to be tried first.

Table 17 Sensitivity analyses

Variable/ Assumptions (base-case value)	Sensitivity analysis	Incremental costs (DKK)
Base-case	–	**24,691,451**
Population characteristics		
Age/ disability (PREVENT baseline (age 46 horizon 56) and EDSS distribution)	Incident patient (age 35 (horizon 65) and EDSS 0)	25,208,033
Baseline EDSS distribution (PREVENT baseline distribution)	EDSS 0	24,957,537
	EDSS 1	24,910,746
	EDSS 2	24,841,986
	EDSS 3	24,743,548
	EDSS 4	24,794,365
	EDSS 5	24,652,998
	EDSS 6	24,454,438
	EDSS 7	25,546,300
	EDSS 8	25,546,300
	EDSS 9	25,546,300
Treatment efficacy		
Hazard ratio (0.058)	95% LCL (0.017)	27,027,703
	95% UCL (0.197)	19,022,041
Event probabilities		
Background annual relapse risk (0.35)	95% LCL (0.199)	26,052,076
	95% UCL (0.616)	22,870,151
[redacted]	[redacted]	24,853,324

Variable/ Assumptions (base-case value)	Sensitivity analysis	Incremental costs (DKK)
[redacted]		24,581,580
		24,612,157
Probability of fatal relapse (0.07)	Off (0)	24,227,787
	Doubled (0.14)	24,925,514
Eculizumab discontinuation rate (0.093 p.a.)	Halved (0.0465 per 100 patient years)	35,425,571
	+50% (0.1395 per 100 patient years)	15,297,200
Eculizumab discontinuation after relapse (always stop treatment after relapse)	Stop after relapse if disability worsens	26,389,029
	Never stop treatment after relapse	27,877,207
Costs		
Eculizumab infusion costs (3807.32 DKK per infusion)	Increased by 50%	24,351,436
	Decreased by 50%	25,031,467
Health state costs by EDSS Mean cost by EDSS from Vestergaard Rasmussen et al. (2017)	Lower CI estimates from Vestergaard Rasmussen et al. (2017)	24,771,772
	Upper CI estimates from Vestergaard Rasmussen et al. (2017)	24,612,268
Cost of relapse	Increased by 50%	24,718,411
	Decreased by 50%	24,664,492
Other		
Time horizon (53 years)	10 years	19,287,581
	20 years	23,534,121
	30 years	24,437,468

In a separate sensitivity analysis, each of the included cost elements were tested to estimate the impact on the net-present incremental cost. The analysis was conducted by excluding each cost element in turn and recalculating the NPV cost (Table 18). The increment cost per patient is mainly affected by inclusion of the community cost and – with in this cost-category – almost exclusively by community serves (consisting of 'Home help', 'Transportation' and 'Personal assistance'). Since these elements are most clearly linked to the level disability (and not influenced by the underlying disease and treatment) this supports that inclusion of disability cost (linked to EDSS) from a MS study most likely will not bias the results of the NMSOD analysis.

Table 18 Impact of each disability cost element on incremental cost per patient

Name	Net present cost per patient (DKK)		
	Eculizumab + IST	IST alone	Incremental
Base case	**26,823,319**	**2,131,868**	**24,691,451**
Exclude Inpatient care	26,497,362	1,815,401	24,681,961
Exclude Day admission	26,802,093	2,111,212	24,690,881
Exclude Consultations	26,577,037	1,917,138	24,659,899
Exclude Tests	26,777,718	2,096,582	24,681,136
Exclude All direct EDSS cost	*26,184,251*	*1,544,729*	*24,639,522*
Exclude Community service	25,892,171	865,386	25,026,785
Exclude Investments	26,739,296	2,045,957	24,693,339
Exclude All community costs	*25,808,148*	*779,475*	*25,028,672*
Exclude All state cost	*25,169,080*	*192,337*	*24,976,743*

3 Budget impact analysis

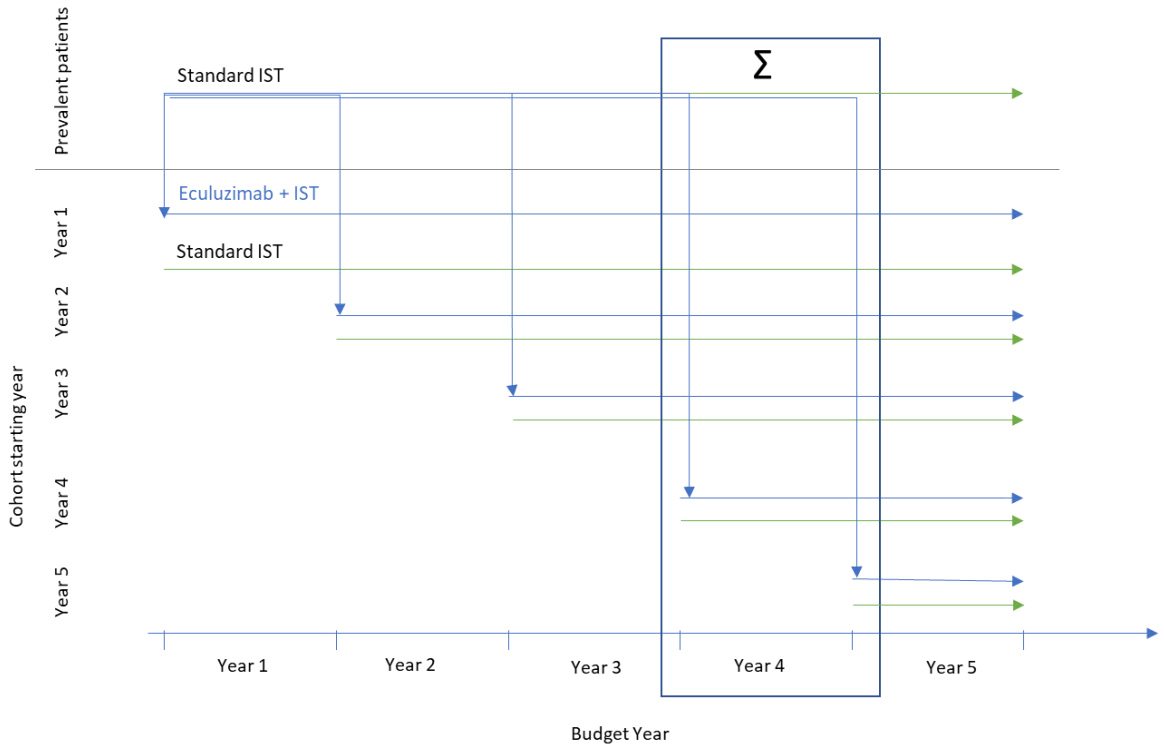
The impact of introducing eculizumab as standard treatment in NMOSD was calculated using a 5-year budget impact model.

The model is illustrated in Figure 6. The population of eligible patients over the next five years consists of a group of prevalent patients and a group of patients that will become diagnosed and eligible for treatment each of the following years. In the scenario without NMOSD, patients (prevalent and incident) will be treated with BSC. The regional cost per year is based on the cost-analysis prediction of undiscounted cost per year. Downstream regional cost will accrue until death and are estimating using the same long-term model as the net-present cost analysis reported above but in the budget impact analysis limited to up to year 5.

For simplicity, prevalent patients are assumed to start BSC treatment year 1. Prevalent patients switching to eculizumab in one of the following years will accrue cost as in the eculizumab + BSC arm of the cost-model and no longer accrue cost as in the BSC alone arm. Incident patient will accrue cost according to the cost-model from the year of starting and up to 5 years.

The budget impact in a given year is captured as the sum in that year. Costs in the budget impact are not discounted and include only total regional cost.

Figure 6 Illustration of budget impact model



Abbreviations: IST Immunosuppressive therapy

3.1 Number of patients

According to the protocol from the Medicines Council, it is stated that there less than 50 Danish patients with NMOSD eligible patients in Denmark and 5 patients are diagnosed yearly..

Based on a population of 5.8 million in Denmark and a prevalence of NMOSD of 1.09 per million (Papp et al., 2018) the number of patients would be 65. 73% of these patients may be assumed to be AQP4 antibody positive (Hamid et al. 2017) and 94.1% to have a relapsing course of disease (Mealy et al. 2012). This would imply that there are 43 patients within the eculizumab indication in Denmark. This is consistent with the Expert Committee assessment. The budget impact analysis is based on 43 prevalent patients and 5 incident eligible patient annually

According to the Medicines Council protocol, various immunosuppressive and anti-inflammatory treatments such as rituximab are used off-label in Danish Clinical practice. Eculizumab is the first treatment with indication for prevention of relapses in NMOSD and a proven, high efficacy. To form a realistic budget impact, it was assumed that eculizumab in clinical practice primarily will be a treatment for patients with a high frequency of relapses which leave them vulnerable to a fast progression of disability. For these patients, the absolute risk reduction with effective treatment is larger and the impact on patient quality of life greater. Furthermore, patients are more likely to accept a treatment that requires frequent visits the clinic to get infusions. In the analysis it is assumed that 26% of patients have a high frequency of relapses on off-label treatments currently used. This assumption is based the totally of Alexion internal market forecast information from other European markets and cannot be further substantiated for the Danish setting. Hence in the budget impact analysis, it is assumed that a maximum of 11 (26% x 43) of the prevalent patients will be

offered treatment with eculizumab in clinical practice. Among the newly diagnosed patients, it is likewise assumed that 26% of patients will be candidates (5 x 26% = 1 patient per year) will be offered treatment within the first 5 years. In sensitivity analysis, the assumption on restricted use in clinical practice is relaxed.

In the budget impact analysis, it is assumed that 2 prevalent patients will be offered treatment in year 1 rising to 3 years 2, 3 and 4 - to a total of 11 patients - and that the number of incident patients will be 1 each year in the coming five years.

Table 19 shows the assumption of number of patients treated with eculizumab+IST and standard IST alone, respectively. The table shows the accumulated number of patients who have started treatment and does not reflect that some patients may stop treatment with eculizumab again within the five-year timeframe.

Table 19 Estimated number of patients

	Year 1	Year 2	Year 3	Year 4	Year 5
			Without recommendation		
Standard IST	43	48	53	58	63
			With recommendation		
Eculizumab+IST	2	6	10	14	15
Standard IST	41	42	43	44	48

Abbreviations: IST Immunosuppressive therapy

3.2 Results

3.2.1 Base case

Table 20 shows the results of the base case budget impact analysis. Based on the assumption on number of eligible patients offered treatment in clinical practice and the uptake assumptions above, the budget impact will be 7.179 million DKK the first year and stabilize over the five years at a level of approximately 41 MDKK per year.

Table 20. Estimated budget impact (regional cost). Drug cost estimated at pharmacy purchasing prices (million DKK)

	Million Kroner (MDKK) per year				
	1	**2**	**3**	**4**	**5**
Scenario with eculizumab	9.090	22.621	34.473	45.081	43.802
Scenario without eculizumab	1.911	2.106	2.298	2.487	2.671
Budget impact	**7.179**	**20.515**	**32.174**	**42.595**	**41.131**

3.2.2 Sensitivity analyses

If only incident patients are treated with eculizumab the budget impact year 5 will be 12 MDKK. If all 43 eligible prevalent patients will start treatment with the first 3 years and all incident patients (5 each year) will start treatment as well, the year five regional budget impact will be 117.4 MDKK.

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Medicinrådet

Medicinrådets protokol for vurdering af eculizumab til behandling af neuromyelitis optica spectrum sygdom

Versionsnr.: 1.0

Medicinrådet

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 deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi 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, 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 ansøgende virksomhed få besked.

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Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
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Indhold

1 Begreber og forkortelser

AQP4	*Aquaporin-4*
AR	*Attakrate*
CDP	*Confirmed Disabilty Progression*
EDSS	*Expanded Disability Status Scale*
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
EQ-5D	*EuroQol-5 Domain*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
ITT	*Intention to treat*
MS	Multipel sklerose
NMOSD	Neuromyelitis optica spectrum sygdom *(Neuromyelitis optica spectrum disease)*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
SD	*Standardafvigelse*
SF-36	*Short Form 36*
SMD	*Standardized Mean Difference*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Alexion Pharma Nordics AB, som ønsker, at Medicinrådet vurderer eculizumab til neuromyelitis optica spectrum sygdom. Vi modtog den foreløbige ansøgning den 11. marts 2020.

2.1 Neuromyelitis optica spectrum sygdom

Neuromyelitis optica spectrum sygdom (NMOSD) er en kronisk neurologisk sygdom, der typisk rammer synsnerver og rygmarven. Patienter i Danmark har en medianalder på 35 år ved sygdomsdebut, men NMOSD kan ramme i alle aldre [1]. Sygdommen rammer kvinder tre gange oftere end mænd.

NMOSD er karakteriseret ved inflammation i det centrale nervesystem, der fører til demyelinisering med tab af gliaceller og neuroner og dermed neurologisk funktionstab. Patienter med NMOSD vil i varierende grad have både fysiske og kognitive symptomer såsom synsnedsættelse, dobbeltsyn, spastiske lammelser af arme og/eller ben, føleforstyrrelser, dårlig balance, vandladningsproblemer, forstoppelse, problemer med seksualfunktionen, smerter, træthed samt hukommelses- og koncentrationsproblemer. Patienter oplever attaker, der kan medføre en vedvarende forværring af symptomer gennem sygdomsforløbet [2]. Omkring 60 % af patienterne oplever et nyt attak indenfor det første år efter det første attak. Dette er flere end den gennemsnitlige patient med attakvis multipel sklerose (MS), og attakerne vil oftere medføre varige skader hos patienter med NMOSD. Hos patienter med NMOSD er synsproblemer meget hyppige.

Sygdommens kliniske fremtræden deler mange ligheder med MS, men adskiller sig især ved, at den underliggende patologi er forskellig. Hos NMOSD er det primært astrocytterne, der er mål for kroppens immunreaktion, hvor det hos MS er neuronernes myelinskeder, der rammes. I begge tilfælde fører det til skader på neuroner i det centrale nervesystem.

Hos ca. 75-80 % af patienter med NMOSD er antistoffer mod proteinet aquaporin-4 (AQP4) til stede i blodet. AQP4 er især til stede på astrocytternes endefødder og er en vigtig del af blod-hjernebarrieren [3,4]. Hos patienter med antistoffer mod AQP4 sker en aktivering af immunsystemet, som forårsager tab af astrocytterne, men inflammationen medfører også tab af oligodendrocytter og demyelinisering, og der ses ophobning af komplement i relation til læsionerne.

Expanded Disability Status Scale (EDSS) er en metode til at kvantificere sygdomsforværring i MS og NMOSD. Måleinstrumentet måler ændringer i niveau af sygdomsforværring over tid. EDSS er det instrument, der oftest bruges, både i kliniske studier og i klinikken. EDSS-skalaen går fra 0 (fuld funktion) til 10 (død). Scorer mellem 0,0-3,5 defineres ved patienter, der er i stand til at gå min. 500 m uden nogen hjælp; scorer mellem 3,5-5,5 er patienter med begrænset gangdistance til under 500 m uden støtte; 6,0-6,5 er defineret ved, at patienterne kan gå, men kun med støtte; 7,0-9,5 er defineret ved ophævet gangfunktion og behov for hjælp til daglige aktiviteter.

Fagudvalget finder, at det er vanskeligt at give et præcist estimat af antallet af nye patienter med NMOSD. Ansøger angiver i sin foreløbige ansøgning, at 61 danske patienter er registreret med NMOSD (via personlig kommunikation med den ansvarlige person for Skleroseregistret). Fagudvalget har fra en dansk ekspert i NMOSD fået oplyst, at 39 patienter med NMOSD og AQP4-antistoffer blev registreret i Danmark i år 2007-2014 (manuskript under udarbejdelse). Der er ikke danske data fra efter 2014. På den baggrund antager fagudvalget, at antallet af patienter, der er kandidater til behandling med eculizumab sandsynligvis ligger under 50 patienter, samt at 5 nye patienter årligt vil være kandidater til behandlingen. Dette estimat er forbundet med stor usikkerhed.

2.2 Eculizumab

Komplementsystemet er en del af immunforsvaret og består af omkring 20 forskellige proteiner. Disse kan aktiveres i en kaskadereaktion og signalere til andre dele af immunsystemet. Aktivering af komplementsystemet kan lede til inflammation. Eculizumab er et monoklonalt antistof, der virker ved at hæmme dannelsen af komplementkompleks C5b-9, som udgør en signalvej i aktiveringen af immunsystemet hos patienter med antistoffer mod AQP4. Eculizumab kan forhindre aktivering af immunsystemet gennem denne mekanisme.

900 mg eculizumab skal administreres intravenøst en gang om ugen i fire uger i en opstartsfase. Fra den femte uge skal 1.200 mg gives intravenøst hver anden uge.

Eculizumab øger risikoen for infektion med meningokokker (Neisseria meningitidis), der er forbundet med alvorlige og livstruende infektioner som meningitis og sepsis. Patienter i behandling med eculizumab skal derfor være vaccineret mod meningitis to uger inden behandlingsstart.

Behandlingen har til formål at mindske antallet af attakker og forebygge sygdomsudviklingen. Det er relevant, da hvert attak kan medføre vedvarende skade.

Eculizumab har af European Medicines Agency (EMA) fået betegnelsen ”orphan drug” og fik i 2019 følgende indikationsudvidelse:

“Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease”

Eculizumab havde i forvejen indikationerne paroksystisk nocturnal hæmoglobinuri, atypisk hæmolytisk uræmisk syndrom og refraktær generaliseret myasthenia gravis.

2.3 Nuværende behandling

Målet med den nuværende behandling er at forsinke/hindre attaker og dermed også hindre varig funktionsnedsættelse samt at bedre livskvaliteten.

Selvom der ikke er andre lægemidler med indikationen NMOSD, betragter fagudvalget det som væsentligt at tilbyde patienter behandling, da attaker kan give varige funktionsnedsættelser. Der benyttes en række lægemidler i dansk klinisk praksis (off label), og fagudvalgets erfaring er, at disse lægemidler har en vis effekt, selvom der ikke er evidens af høj kvalitet fra randomiserede kliniske studier.

Dansk standardbehandling af patienter med NMOSD kan opsummeres således: De fleste patienter sættes først i behandling med azathioprin (oralt cytostatikum der hæmmer leukocytproliferation, herunder T- og B-celler) og skiftes til rituximab (CD20-depleterende, som fjerner immunforsvarets B-celler og en mindre del af T-celler) ved fortsat sygdomsaktivitet. Ved bivirkninger kan der skiftes til mycophenolat mofetil (oralt cytostatikum der hæmmer leukocytproliferation, herunder T- og B-celler). Flere klinikker er begyndt at anvende rituximab som førstelinjebehandling, men den første behandling kan også være mycophenolat mofetil eller azathioprin. Hvis der er bivirkninger, kontraindikationer, eller hvis ovenstående lægemidler ikke er effektive, er alternative behandlingsmuligheder yderst begrænsede. En del patienter har andre autoimmune sygdomme, hvilket der skal tages højde for ved valg af behandling.

3 Kliniske spørgsmål

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

Valg af komparator

Valget af komparator er vanskeligt, da der ikke er andre godkendte lægemidler til indikationen. Fagudvalget har derfor valgt at sammenligne med placebo. Fagudvalget vil i vurderingen af eculizumab tage højde for, at denne sammenligning ikke er retvisende i forhold til dansk klinisk praksis, da patienterne ofte modtager behandling men andre immunsupprimerende lægemidler som anført ovenfor. Fagudvalget vil tage dette i betragtning, så vurderingen af eculizumab giver et så retvisende indtryk af effekten af eculizumab i forhold til klinisk praksis som muligt. Fagudvalget vil vurdere effekten af den nuværende behandling og narrativt sammenligne effekten af eculizumab med nuværende behandling.

3.1 Klinisk spørgsmål 1

Hvilken værdi har eculizumab sammenlignet med placebo for patienter med neuromyelitis optica spectrum sygdom?

Population
Patienter med NMOSD med en EDSS ≤ 7, der har antistoffer mod AQP4 og har oplevet et eller flere attaker.

Intervention
Eculizumab 900 mg i.v. hver uge i fire uger efterfulgt af 1.200 mg i.v. hver anden uge.

Komparator
Placebo.

Effektmål
De valgte effektmål står i tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 1. For hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel. I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Årlig attakrate	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Antal attakker pr. patient om året	Forskel på 0,2 attakker pr. patient om året
Bivirkninger	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever en eller flere alvorlige bivirkninger	Forskel på 5 %-point
			Gennemgang af bivirkningsprofil	Narrativ vurdering
Vedvarende sygdomsforværring	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring på EDSS score	Forskel på 0,2 point på et år
Synsskarphed	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring på Snellen-tavle, opgjort som neurostatus scoring af	Forskel på 0,2 point på et år

			visuel funktion (0-6 point)	
Livskvalitet	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring på SF-36	Forskel på 0,5 SMD

For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.
EDSS: Expanded Disability Status Scale, SMD: Standardized Mean Difference.

3.2.1 Kritiske effektmål

Årlig attakrate
Den årlige attakrate beskriver antal bekræftede attakker pr. patient om året. Fagudvalget betragter dette effektmål som kritisk, da patienter med NMOSD ofte kan have relativt mange attaker, som kan medføre varig funktionsnedsættelse.

Et attak defineres som nye eller forværring af eksisterende symptomer af mere end 24 timers varighed i fravær af feber eller infektion, forudgået af en stabil neurologisk tilstand i minimum 30 dage. Symptomerne skal desuden kunne tilskrives sygdommen og skal være ledsaget af objektiv neurologisk forværring [8,9].

Fagudvalget vurderer, at den mindste klinisk relevante forskel er 0,2 attaker pr. patient om året.

Forebyggelse af attaker er mere væsentligt for patienter med NMOSD end for patienter med attakvis MS. Fagudvalget har i protokoller til attakvis MS benyttet effektmålet *attakrate* som et vigtigt effektmål, med en mindste klinisk relevant forskel på 0,1 attak pr. patient om året. Fagudvalget vurderer, at attakker er en mere væsentlig del af sygdomsforløbet for patienter med NMOSD, og at attakker optræder hyppigere hos disse patienter. Derfor er effektmålet kritisk i denne protokol, og den mindste klinisk relevante forskel er defineret anderledes end i protokoller for attakvis MS.

Bivirkninger
Bivirkninger (adverse reactions, AR) er et kritisk effektmål, da det belyser, hvor godt patienterne tolererer eculizumab sammenlignet med komparator. Fagudvalget ønsker data på nedenstående måleenheder og med længst mulig opfølgningstid:

Alvorlige bivirkninger
Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere alvorlige bivirkninger, er relevant for vurderingen. Da der er mange bivirkninger forbundet med lignende behandlinger, og patienterne i forvejen er meget plaget af symptomer af deres sygdom samt ofte har autoimmun komorbiditet, mener fagudvalget ikke, at det acceptabelt, at en ny behandling medfører markant flere bivirkninger. Fagudvalget vurderer derfor, at den mindste klinisk relevante forskel i andelen af patienter, der får alvorlige bivirkninger, er 5 %-point.

Gennemgang af bivirkningsprofil
Fagudvalget ønsker en gennemgang af eculizumab bivirkningsprofil og bivirkningerne rapporteret for placebo fra det kliniske studie, med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra både de kliniske studier og produktresuméet for eculizumab.

Vedvarende sygdomsforværring
Vedvarende sygdomsforværring (Confirmed Disabilty Progression (CDP)) defineres som en ændring i Expanded Disability Status Scale (EDSS) score på 1 eller på 0,5, hvis baseline EDSS er højere end 5,5.

EDSS er en metode til at kvantificere sygdomsforværring i NMOSD. Måleinstrumentet måler ændringer i niveau af sygdomsforværring over tid. EDSS er det instrument, der oftest bruges, både i kliniske studier og i klinikken. EDSS-skalaen går fra 0 (fuld funktion) til 10 (død). Scorer mellem 1,0-4,5 defineres ved patienter,

der stadig er i stand til at gå uden nogen hjælp, hvorimod scorer mellem 5,0-9,5 er defineret ved, at patienterne ikke kan gå. Det skal dog nævnes, at EDSS ved score ≥ 5 primært måler sygdomsforværring relateret til, om patienterne kan gå, hvorimod funktionsniveauet i overkroppen, det kognitive funktionsniveau, energiniveau og livskvalitet ikke tages i betragtning [5].

Dette effektmål er kritisk, da et centralt mål med behandlingen er at forsinke progression af sygdommen.

Effektmålet ønskes opgjort som gennemsnitændring i EDSS-scoren. Den mindste klinisk relevante forskel mellem eculizumab og placebo vurderes af fagudvalget at være en score på 0,2. Fagudvalget vurderer, at denne forskel er klinisk relevant, da det vil svare til, at hver femte patient i gennemsnit oplever at undgå en stigning i EDSS på et point pr. år.

3.2.2 Vigtige effektmål

Synsskarphed
Synsproblemer er et væsentligt symptom ved NMOSD, og derfor har fagudvalget valgt, at synsskarphed er et vigtigt effektmål. Synsskarphed måles på en Snellen-tavle, og fagudvalget ønsker effektmålet opgjort med neurostatus scoring af visuel funktion, der benyttes i dansk klinisk praksis. Ved denne scoring får patienten 0 point ved normalt syn og 6 point ved den dårligste score, der indikerer en væsentlig forværring af patientens synsevne. Patienter med en score på 6 kan dog stadig have noget af synet intakt. Denne scoring indbefatter synet på begge øjne. Neurostatus scoring af visuel funktion indgår i EDSS som et funktionelt domæne. Fagudvalget er opmærksom på, der derved er en vis redundans mellem de to vigtige effektmål EDSS score og synsskarphed, men vurderer at synsskarphed er så væsentligt for patienter med NMOSD, at effektmålet skal opgøres særskilt.

Den mindste klinisk relevante forskel mellem eculizumab og placebo vurderes af fagudvalget at være en forskel i den gennemsnitlige ændring på 0,2 point i løbet af et år. Fagudvalget vurderer, at denne forskel er klinisk relevant, da det vil svare til, at hver femte patient i gennemsnit oplever at undgå en stigning på et point pr. år.

Livskvalitet
Fagudvalget ønsker effektmålet opgjort med det generiske instrument SF-36.

Fagudvalget har tidligere benyttet Multiple Sclerosis Quality of Life-54 (MSQOL-54) til vurderinger af MS-lægemidler, da det er et sygdomsspecifikt og valideret mål for livskvalitet, der inkluderer selvrapporterede subjektive indikatorer for fysisk, emotionel og social funktionalitet og trivsel [13,14]. MSQOL-54 bygger på SF-36, og da det ikke er valideret i NMOSD, har fagudvalget valgt det generiske instrument.

For helbredsrelateret livskvalitet anvendes ofte en mindste klinisk relevant forskel på 0,5 standarddeviationer (SD), og fagudvalget har derfor valgt at anvende en ændring på 0,5 SD som mindste klinisk relevante forskel [16,17].

Såfremt der ikke foreligger data fra SF-36, foretrækker fagudvalget data fra et andet valideret instrument, som er relevant for patienter med NMOSD, eksempelvis det generiske EQ-5D.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor eculizumab er sammenlignet direkte med placebo.

Medicinrådet har fundet følgende fuldtekstartikel, som indeholder en direkte sammenligning mellem eculizumab og placebo:

- Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 381(7):614-625

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere fuldtekstartikler, men skal konsultere Det Europæiske Lægemiddelagenturs (EMAs) European public assessment reports (EPAR) for eculizumab.

5 Databehandling og -analyse

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 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 (jævnfør 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 (jævnfør 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'- 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.

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 vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

Fagudvalget pointerer, at sammenligningen med placebo ikke er retvisende, da patienter i Danmark behandles med forskellige aktive behandlinger. Dette forhold vil indgå i fagudvalgets vurdering af eculizumab. Fagudvalget vil vurdere effekten af den nuværende behandling og narrativt sammenligne effekten af eculizumab med nuværende behandling.

Fagudvalget ønsker også yderligere viden om, hvor godt patienter vaccineret mod Neisseria meningitidis er beskyttet under behandling med eculizumab, eftersom vaccinen ikke beskytter mod alle meningokok-stammer. Herunder vil fagudvalget gerne have ansøgers overvejelser omkring behandlingsregimet ved et evt. skift fra rituximab til eculizumab, både i forhold til vaccine og evt. behov for "bridging terapi".

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og fagudvalget vil derfor ikke tage stilling til en foreløbig placering af lægemidlet.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende multipel sklerose

Formand	**Indstillet af**
Lars Kristian Storr Overlæge, speciallæge i neurologi	Lægevidenskabelige Selskaber, Dansk Neurologisk Selskab
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Thor Petersen Overlæge	Region Midtjylland
Egon Stenager Professor, centerleder, klinikchef	Region Syddanmark
Said Nasim Ashna Overlæge	Region Sjælland
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11 Versionslog

Version	Dato	Ændring
1.0	17. august 2020	Godkendt af Medicinrådet.