Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende satralizumab til behandling af neuromyelitis optica spectrum sygdom (NMOSD)

Vers. 1.0

Bilagsoversigt

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2. Forhandlingsnotat fra Amgros vedrørende satralizumab
3. Medicinrådets vurdering vedrørende satralizumab til behandling af neuromyelitis optica spectrum sygdom (NMOSD), version 1.0
4. Ansøgers endelige ansøgning
5. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
6. Medicinrådets protokol for vurdering vedrørende satralizumab til behandling af neuromyelitis optica spektrum sygdom, version 1.1

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Satralizumab

Neuromyelitis optica spektrum 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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1. Begreber og forkortelser

AIP: Apotekernes indkøbspris

AQP4: Aquaporin 4

DKK: Danske kroner

DRG: Diagnose Relaterede Grupper

SAIP: Sygehusapotekernes indkøbspris

EDSS: *Expanded Disability Status Scale*

MS: *Multipel sklerose*

NMOSD: *Neuromyelitis optica spectrum sygdom*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for satralizumab ca. [redacted] DKK pr. patient sammenlignet med BSC. Ved en gennemsnitlig behandlingslængde på 7,4 år er de gennemsnitlige omkostninger pr. år ca. [redacted] DKK. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 4,6 mio. DKK pr. patient, og med en gennemsnitlig behandlingslængde på 7,4 år er de gennemsnitlige omkostninger pr. år ca. 634.000 DKK.

De inkrementelle omkostninger ved satralizumab er hovedsageligt drevet af lægemiddelomkostninger, som er meget høje. Relativt til lægemiddelomkostningerne fylder de øvrige omkostninger meget lidt, og de væsentligste usikkerheder vedrører derfor lægemiddelomkostningerne.

Konkret er der usikkerhed vedr. antagelser om behandlingsstop og dermed behandlingslængde. I hovedanalysen antages det, at der vil være ca. 1 % af patienterne, der stopper hver måned - svarende til ~12 % årligt, mens der er udført en følsomhedsanalyse, som viser, at de totale inkrementelle omkostninger stiger til [redacted] DKK og [redacted] DKK pr. patient, hvis det antages at hhv. ca. 8 og 10 % stopper behandlingen årligt.

I denne analyse er satralizumab 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 satralizumab. Øvrige usikkerheder er uddybet i afsnit 7 og fylder mindre for det samlede resultat.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af satralizumab som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 8,0 DKK i det femte år.

3. Introduktion

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

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Roche. Medicinrådet modtog ansøgningen den 26. november 2021.

3.1 Patientpopulation

Neuromyelitis optica spektrum (NMOSD) sygdom er en kronisk inflammatorisk og 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 hyppigere 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 et år efter 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.

Fagudvalget finder, at det er vanskeligt at give et præcist estimat af antallet af nye patienter med NMOSD. Medicinrådet 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 [3]. Der foreligger ikke danske data efter 2014. På den baggrund antager fagudvalget, at antallet af patienter, der er kandidater til behandling med satralizumab, 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 satralizumab på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har satralizumab sammenlignet med placebo for patienter med neuromyelitis optica spektrum sygdom?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for satralizumab sammenlignet med *best supportive care* (BSC). Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Sammenligningen mellem satralizumab og BSC er primært lavet på baggrund af data fra det kontrollerede dobbeltblindede fase III-studie SAkuraStar [4], hvori patienterne blev randomiseret til behandling med enten satralizumab monoterapi eller placebo. Placebo-armen i SAkuraStar anvendes som kilde for effektiviteten af BSC i den sundhedsøkonomiske model.

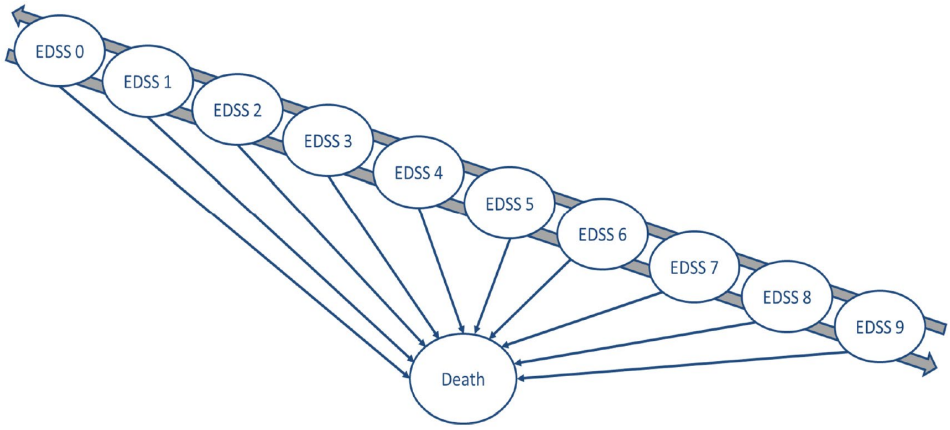
4.1.1 Modelbeskrivelse

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

Ansøgers model består af 10 *Expanded Disability Status Scale* (EDSS)-stadier, og patientens bevægelser igennem modellens stadier bestemmes af transitionssandsynligheder. Se Figur 1.

Ansøger antager, at den initiale fordeling af patienter mellem EDSS-stadierne i dansk klinisk praksis er identisk med fordelingen i SAkuraStar [4]. I hver cyklus kan en patient enten forblive i det nuværende EDSS-stadie, progrediere til højere EDSS-stadie, opnå sygdomsforbedring til et lavere EDSS-stadie, stoppe behandling med satralizumab eller opleve et attak. Se Figur 1 for de forskellige sygdomsstadier og hvordan patienten kan bevæge sig mellem de forskellige stadier.

Modellen har en cykluslængde på 4 uger, hvilket ansøger argumenterer er passende, da cykluslængden er tilpas kort til at opfange udviklingen i sygdommen. Ansøger anvender desuden *half-cycle correction*.



Figur 1. Illustration af modelstrukturen

Medicinrådets vurdering af ansøgers model

Medicinrådet vurderer, at modelstrukturen i ansøgers model afspejler patienternes forløb og accepterer derfor tilgang vedr. modelstruktur.

4.1.2 Modelantagelser og -beskrivelse

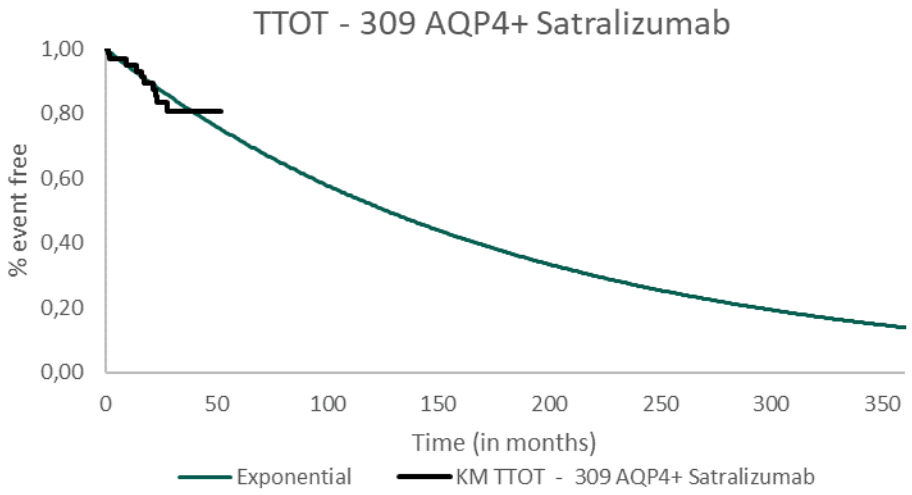
I hver cyklus kan patienterne enten dø, forblive i nuværende EDSS-stadie, progrediere til højere EDSS-stadie eller have sygdomsforbedring til et lavere EDSS-stadie. Transitionssandsynlighederne for at forblive i nuværende EDSS-stadie, progrediere til højere EDSS-stadie eller regrediere til et lavere EDSS-stadie er baseret på data for NMOBase [5]. NMOBase er et webbaseret globalt register, designet til klinisk forskning blandt patienter med NMOSD. Ansøger anvender faktiske observationer indeholdt i dette register til at generere årlige transitionssandsynligheder for at patienterne bevæger sig i mellem EDSS-stadier. Disse bliver efterfølgende omregnet til månedlige transitionssandsynligheder, som anvendes i modellen. Disse transitionssandsynligheder er ikke konstante, men afhænger af, hvilket EDSS-stadie patienten befinder sig i. Ansøger antager, at når en patient vil opleve et attak, så vil denne patient også progrediere til et højere EDSS-stadie, og derfor antager ansøger, at hazardratioen for attakraten (0,26), estimeret i SAkuraStar [4], både kan anvendes til at beskrive forskellen i attakraten og sygdomsprogression mellem satralizumab og BSC. Ansøger antager, at effekten på attakraten og sygdomsprogression ikke vil aftage – dvs. effekten er livslang.

Ansøger antager, at transitionssandsynlighederne for at dø ligeledes afhænger af EDSS-stadie. Ansøger tager udgangspunkt i et studie, der undersøger dødeligheden for multiple sklerose (MS) [6], da ansøger mener, at disse patienters dødelighed er sammenlignelig med patienter med NMOSD, men vælger alligevel at øge dødeligheden med 20 %. Dette er baseret på et interview med [redacted].

Transitionssandsynlighederne for at stoppe behandling med satralizumab er baseret på *time to treatment discontinuation* (TTOT) data fra SAkuraStar [4]. Her har ansøger ekstrapoleret behandlingslængden med en eksponentiel fordeling, se [redacted]. Med en

eksponentiel fordeling vil transitionssandsynligheden for at stoppe behandling være konstant og svarer til, at ca. 0,5 % af patienterne stopper hver måned - svarende til ca. 6 % årligt.

[redacted]



Modellen estimerer omkostningerne baseret på det respektive EDSS-stadie, som patienten befinder sig i.

Medicinrådets vurdering af ansøgers modelantagelser

Medicinrådet er bekendt med det webbasereret globale register blandt patienter med NMOSD, NMOBase, og vurderer, at det er rimeligt at anvende faktiske observationer fra dette register til at estimere de årlige baseline transitionssandsynligheder for BSC, se Tabel 1.

Tabel 1. Baseline årlige transitionssandsynligheder for patienter med NMOSD

EDSS	0	1	2	3	4	5	6	7	8	9
0	[redacted]									
1	[redacted]									
2	[redacted]									
3	[redacted]									
4	[redacted]									
5	[redacted]									

6	[redacted]									
7	[redacted]									
8	[redacted]									
9	[redacted]									

Medicinrådet vurderer også, at det er rimeligt at anvende hazard ratioen for attakraten, estimeret i SAkuraStar (0,26) på baseline transitionssandsynlighederne, til at estimere transitionssandsynlighederne for attak for satralizumab. Medicinrådet vurderer, at den væsentligste sygdomsprogression er forbundet med attaker, men vurderer alligevel, at ansøgers antagelser om at anvende den samme hazard ratio for attaker fra SAkuraStar [4]på sygdomsprogression er tvivlsom. I Medicinrådets vurderingsrapport kan effekten af satralizumab på sygdomsprogression ikke kategoriseres, da den relative forskel ikke er statistisk signifikant, om end favoriserer satralizumab. Medicinrådet vælger dog alligevel at acceptere ansøger tilgang, idet modellen ikke indeholder omkostninger til håndtering af den underliggende sygdom, og det dermed ikke har nogen betydning for resultatet. Desuden vurderer Medicinrådet, at ansøgers antagelse om livslang effekt af satralizumab er usikkert, da opfølgningen i studier er for kort til at vurdere, om effekten vil fortsætte resten af livet. Medicinrådet udfører derfor en følsomhedsanalyse, hvor effekten af satralizumab gradvist ophører over 4 år fra år 10.

Medicinrådet vurderer, at ansøgers antagelser om at dødelighed er sammenlignelig med patienter med MS, og at afhængigheden af EDSS-score er rimelig, men vurderer ikke, at ansøgers antagelser om, at dødeligheden er 20 % højere hos NMOSD-patienter end patienter med MS, er rimelig. Medicinrådet fremhæver, at det er vanskeligt at kvantificere den øget dødelighed ift. patienter med MS, da data er sparsomt, men vurderer at dødeligheden er omkring 10 % højere end patienter med MS. Derfor justeres den øgede dødelighed til 10 %. Dette er dog usikkert, og derfor udføres en følsomhedsanalyse, hvor denne justeres.

Medicinrådet vurderer, at ansøgers antagelser vedr. behandlingsstop er underestimeret. Medicinrådet forventer, at mellem 10-15 % af patienterne årligt vil stoppe behandling med satralizumab. Derfor vælger Medicinrådet at øge den månedlige sandsynlighed for behandlingsstop til 1 % (~12 % årligt). Både denne sandsynlighed og antagelsen om en konstant sandsynlighed for at stoppe behandling er dog usikkert, og derfor udføres en række følsomhedsanalyser, hvor transitionssandsynligheden for at stoppe behandling justeres. Den gennemsnitlige behandlingslængde med satralizumab, som anvendes i Medicinrådets hovedanalyse, er 7,4 år.

4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 50 år.

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

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont, da NMOSD er en kronisk sygdom, som kræver livslang behandling, og analysens tidshorisont skal derfor være livslang for at opfange alle væsentlige forskelle i behandlingsomkostninger mellem satralizumab og BSC.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af satralizumab sammenlignet med BSC. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, patientomkostninger og omkostninger forbundet med håndtering af attakker.

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). Doser anvendt i ansøgers analyse er hentet i det respektive produktresumé (SPC). Ansøger antager, at patienter, der modtager BSC, ikke behandles med nogen lægemidler, hvorfor der ingen lægemiddelomkostninger er forbundet med BSC.

Satralizumab:
Opstart: 120 mg satralizumab subkutant ved behandlingsstart, efterfulgt af 120 mg satralizumab på dag 14 og 28.

Vedligeholdelse: 120 mg satralizumab subkutant hver 4. uge.

BSC:
Ingen behandling.

Ansøger har antaget, at der ikke er noget lægemiddelspild forbundet med håndtering af satralizumab, og at alle patienter modtager den fulde dosis indtil behandlingsstop.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
I dansk klinisk praksis anvendes en række lægemidler, som ikke er inkluderet i denne sammenligning. Medicinrådet vurderer derfor, at ansøgers antagelse om, at patienter i BSC-armen ikke modtager lægemiddelbehandling vil underestimere omkostningerne ved komparator og dermed overestimere de inkrementelle omkostninger for satralizumab. Medicinrådet accepterer dog ansøgers tilgang, da disse behandlinger er (off-label).

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

Tabel 2. Anvendte lægemiddelpriser, SAIP (marts 2022)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Satralizumab	120 mg	1 stk.	[redacted]	Amgros

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har inkluderet omkostninger til administration af satralizumab og antager, at patienter kræver oplæring i subkutanadministration af satralizumab, men at patienterne herefter selv vil være i stand til at administrere satralizumab. Derfor har ansøger kun inkluderet omkostninger til oplæring i administration af satralizumab ved de to første administrationer. Disse administrationsomkostninger er inkluderet i form af DRG-takster ved subkutan injektion for patienter med NMOSD og udgør 6.704 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger. Anvendte enhedsomkostninger kan ses i Tabel 3.

Tabel 3. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Frekvens	Kode	Kilde
Oplæring i administration af satralizumab	3.353	Første og anden administration	01MA98	DRG-2021

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostning

Ansøger har inkluderet monitoreringsomkostninger og antager, at patienter bliver monitoreret 2 gange årligt af en neurolog. Ansøger antager, at disse omkostninger er uafhængige af EDSS-score og dermed konstante i modellen. Monitoreringsomkostninger bliver takseret med en DRG-takst, svarende til en neurologisk undersøgelse for patienter med NMOSD, og udgør 3.353 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger. Ansøger benytter frekvenser for uønskede hændelser af grad 3-4 som mål for bivirkningerne. For

satralizumab og BSC har ansøger benyttet de rapporterede bivirkningsrater fra SAkuraStar [4] samt den samlede eksponering af satralizumab (186,5 patientår) og BSC (27,1 patientår) til at udregne en månedlig sandsynlighed. Ressourcerne, brugt i forbindelse med de forskellige bivirkninger, har ansøger baseret på DRG 2021. Ansøger antager for satralizumab, at bivirkningerne kun opstår mens patienterne er i behandling med satralizumab, men det det BSC kan opstår så længe patienten er i live.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger, og bemærker, at de lave bivirkningsfrekvenser gør, at bivirkningsomkostninger udgør meget få omkostninger. Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 4.

Tabel 4. Rapporterede bivirkninger ved behandling med satralizumab og BSC samt enhedsomkostninger for bivirkningerne

	Satralizumab [antal]	BSC [antal]	Enhedsomkostning [DKK]	Kilde
Rygsmerter	1		1.617	DRG 2021 - 08MA98
Øjensmerter	1		964	DRG 2021 - 02MA01
Influenza	1		1.862	DRG 2021, 03MA98
Neutropeni	1		3.114	DRG 2021, 16MA98
Pulmonal sepsis	1		2.676	DRG 2021, 18MA98
Akut øvre luftsvejsinfektion	1		1.862	DRG 2021 - 03MA98
Tand absces		1	1.862	DRG 2021 - 03MA98
Svimmelhed	2		5.091	DRG 2021 - 03MA02

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.3 Efterfølgende behandling

Ansøger har ikke inkluderet omkostninger til efterfølgende behandling.

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Medicinrådet accepterer ansøgers tilgang vedr. efterfølgende behandling.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid.

Ansøger antager, at patienter bruger 45 minutter på hospitalet ved første administration af satralizumab, 15 min på hospitalet ved anden administration, men ved tredje administration bruges 15 minutter i hjemmet, og ved fjerde administration og frem bruges 5 minutter i hjemmet.

Ved monitorering antager ansøger, at der bruges 45 minutter på hospitalet.

Derudover anvender ansøger en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 3,52 DKK/km og en gennemsnitlig afstand til hospitalet på 28 km, jf. Medicinrådets værdisætning af enhedsomkostninger.

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

4.2.5 Kommunale omkostninger/omkostninger forbundet med besøg ved egen læge, speciallæge mv.

Ansøger har ikke inkluderet kommunale omkostninger til håndtering af de EDSS-specifikke omkostninger såsom hjemmepleje, transport og besøg af hjemmesygeplejerske.

Medicinrådets vurdering af ansøgers antagelser vedr. kommunale omkostninger
Medicinrådet vurderer, at de EDSS-specifikke omkostninger vil være identiske for satralizumab og BSC, da effekten af satralizumab på sygdomsprogression jf. vurderingsrapporten ikke kan kategoriseres, da den relative effekt ikke er statistisk signifikant. Medicinrådet accepterer derfor, at kommunale omkostninger ekskluderes fra analysen. Selvom effekten af satralizumab på sygdomsprogression ikke er statistisk signifikant, så favoriserer punktestimatet satralizumab, og derfor vil ekskludering af EDSS-specifikke omkostninger, såfremt satralizumab har en effekt på sygdomsprogression, overestimere de inkrementelle omkostninger ved satralizumab. Det skyldes, at de senere EDSS-stadier udgør en stor kommunal omkostning, som kunne undgås eller udskydes.

Medicinrådet accepterer ansøgers tilgang vedr. kommunale omkostninger.

4.2.6 Omkostninger til håndtering af attaker

Ansøger har inkluderet omkostninger til håndtering af attaker. Ansøger antager, at for milde attaker, dvs. attaker der giver en forværring på et EDSS-point, vil 50 % blive indlagt, og 50 % blive behandlet ambulant af en neurolog, men 100 % af patienterne vil blive indlagt ved et svært attak, dvs. attaker der giver en forværring på mere end ét point. Ved indlæggelse behandles patienter med i.v. methylprednisolon over 4 dage, mens det ved ambulante besøg behandles med i.v. sterorid. Ansøger har anvendt DRG-takster til at estimere omkostningerne for disse.

Tabel 5. Ansøgers antagelser vedr. omkostninger til håndtering af attaker

		Frekvens	Omkostning [DKK]	Gennemsnitlig omkostning [DKK]	Kilde
Mildt attak	Indlæggelse	50 %	44.531	23.942	DRG2021 - 01MA07 + 1g methylprednisolon pr. dag i 5 dage
	Ambulant	50 %	3.353		DRG2021 – 01MA07
Svært attak	Indlæggelse	100 %	44.531	44.531	DRG2021 - 01MA07 + 1g methylprednisolon pr. dag i 5 dage
	Ambulant	0 %	3.353		DRG2021 – 01MA07

Medicinrådets vurdering af ansøgers antagelser vedr. omkostninger til håndtering af attaker

Medicinrådet accepterer ansøgers tilgang vedr. omkostninger til håndtering af attaker, men vurderer, at alle milde attaker kan håndteres ambulant, mens Medicinrådet er enige i, at alle svære attakker kræver indlæggelse. Medicinrådet justerer derfor frekvensen for indlæggelse ved milde attakker til 0 %. Medicinrådets antagelser vedr. attakomkostninger fremgår af Tabel 6.

Tabel 6. Medicinrådets antagelser vedr. omkostninger til håndtering af attaker

		Frekvens	Omkostning [DKK]	Kilde
Mildt attak	Ambulant	100 %	3.353	DRG2021 – 01MA07

		Frekvens	Omkostning [DKK]	Kilde
Svært attak	Indlæggelse	100 %	44.531	DRG2021 - 01MA07

4.3 Følsomhedsanalyser

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

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

Tabel 7. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Antagelser om behandlingslængden	Alle patienter behandles indtil død
Fordeling anvendt til at ekstrapolere behandlingslængden	Behandlingslængden er estimeret og ekstrapoleret med den sædvandelige parametriske funktion
Antagelser om effekten af satralizumab over tid	Effekten af satralizumab aftager over tid
Tidshorisont	Varierende tidshorisont
Dødelighed ved NMOSD ift. til patienter med MS	Varierende antagelser vedr. dødelig ift. patienter med MS

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vurderer, at ansøgers følsomhedsanalyser beskriver usikkerhederne i modellen, og Medicinrådet vælger derfor at præsentere disse med undtagelse af følsomhedsanalyserne, hvor behandlingslængden ekstrapoleres med andre parametriske fordelinger. Det skyldes, at de øvrige parametriske fordelinger genererer en længere behandlingslængde end den behandlingslængde, som ansøger har brugt i hovedanalysen, og som Medicinrådet allerede vurderer er overestimeret.

Lægemiddelomkostningerne er den parameter, der har størst indflydelse på resultaterne, og derfor har antagelser om behandlingslængden stor betydning for resultatet. Derfor vælger Medicinrådet også at præsentere en følsomhedsanalyse af andelen af patienterne, der stopper behandling hvert år (hhv. 5 % og 10 %).

Medicinrådet accepterer ansøgers følsomhedsanalyser, men disse præsenteres med Medicinrådets øvrige antagelser.

4.4 Opsummering af basisantagelser

I Tabel 8 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 8. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	50 år	50 år
Diskonteringsrate	3,5 % i år < 35 2,5 % i år ≥ 36	3,5 % i år < 35 2,5 % i år ≥ 36
Inkluderede omkostninger	Lægemiddelomkostninger Administrationsomkostninger Monitoreringsomkostninger Attakomkostninger Patient- og transportomkostninger	Lægemiddelomkostninger Administrationsomkostninger Monitoreringsomkostninger Attakomkostninger Patient- og transportomkostninger
Dosering	Satralizumab: Opstart: 120 mg satralizumab subkutant ved behandlingsstart efterfulgt af 120 mg satralizumab på dag 14 og 28. Vedligeholdelse: 120 mg satralizumab subkutant hver 4. uge BSC: Ingen behandling	Satralizumab: Opstart: 120 mg satralizumab subkutant ved behandlingsstart efterfulgt af 120 mg satralizumab på dag 14 og 28. Vedligeholdelse: 120 mg satralizumab subkutant hver 4. uge BSC: Ingen behandling
Behandlingslinje	1. linje	1. linje
Behandlingslængder Satralizumab: BSC:	[redacted] N/A	7,4 år N/A
Inkludering af spild	Ikke inkluderet	Ikke inkluderet

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 8.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted]. DKK i Medicinrådets hovedanalyse. Omkostningerne til behandling med satralizumab er konstante igennem behandlingsforløbet. Ved en gennemsnitlig behandlingslængde på 7,4 år er de gennemsnitlige omkostninger pr. år ca. [redacted] DKK.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 4,6 mio. DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 9.

Tabel 9. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC, DKK, diskonterede tal

	Satralizumab	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	138.841	131.295	7.546
Attakomkostninger	85.836	105.832	-19.996
Bivirkningsomkostninger	719	1.342	-623
Patient- og transportomkostninger	22.055	23.807	-1.752
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 10.

Tabel 10. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie		Inkrementelle omkostninger
Resultatet af hovedanalysen		[redacted]
Sandsynlighed for at stoppe behandling	10 %	[redacted]
	8 %	[redacted]

Scenarie		Inkrementelle omkostninger
Effekten af satralizumab aftager efter 10 år		[redacted]
Tidshorisont	10 år	[redacted]
	20 år	[redacted]
	30 år	[redacted]
Dødelighed ved NMOSD ift. til patienter med MS	20 %	[redacted]
	0 %	[redacted]

6. Budgetkonsekvenser

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

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

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

6.1 Estimat af patientantal og markedsandel

Ansøger antager, at der i indeværende år er 43 patienter, der lever med NMOSD i Danmark, som kandiderer til behandling med satralizumab. Derudover antager ansøger en incidens på ca. 5 patienter om året, ligesom i Medicinrådets afrapportering vedr. eculizumab [7]. Ansøger antager, ligesom i afrapportering vedr. eculizumab, at hvis satralizumab anbefales, vil satralizumab have et markedsoptag på to af de prævalente patienter i det første år, mens tre af de prævalente patienter vil opstarte behandling i år 2, 3 og 4. Desuden antager ansøger, at én af de nydiagnosticerede patienter vil opstarte behandling med satralizumab i år 2, 3, 4 og 5. Således antager ansøger, at der er 15 patienter i behandling i år 5.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal og markedsoptag, hvis satralizumab hhv. anbefales som mulig standardbehandling, og hvis ikke satralizumab anbefales. Medicinrådet 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 satralizumab ved en anbefaling. Grundet usikkerhederne har Medicinrådet 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 præsenteret i Tabel 11.

Tabel 11. Medicinrådets estimat af patientantal pr. år

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

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af satralizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling, [redacted]. Resultatet er præsenteret i Tabel 12.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 8,0 mio. DKK i år 5.

Tabel 12. 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 satralizumab er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med BSC. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne ved satralizumab, og derfor har antagelser vedr. behandlingslængden stor betydning for resultatet. Derudover er der usikkerhed vedr. omkostningerne til komparator.

Behandlingsstop:
I modellen er der usikkerhed vedr. behandlingsstop. Ansøger har antaget, at ca. 6 % af patienterne stopper behandling hvert år, mens Medicinrådet vurderer, at ca. 12 % af patienterne vil stoppe behandling med satralizumab årligt. Idet lægemiddelomkostningerne driver de samlede omkostninger i modellen, vil behandlingsstop – og dermed den gennemsnitlig behandlingslængde – have betydning for resultatet. Følsomhedsanalyserne illustrerer, at andelen af patienter, der årligt stopper behandling med satralizumab, har stor betydning for resultatet. Såfremt den årlige andel, der stopper behandling med satralizumab, reduceres til 8 % og 10 %, så stiger de inkrementelle omkostninger til hhv. [redacted] DKK og [redacted] DKK, men hvis ansøgers antagelser anvendes, stiger de inkrementelle omkostninger yderligere til ca. [redacted] DKK pr. patient. Den gennemsnitlige behandlingslængde har altså stor betydning for de gennemsnitlige inkrementelle omkostninger, mens de gennemsnitlige årlige omkostninger til behandling forbliver det samme uanset antagelser om behandlingslængden.

Komparator:
Valg af komparator har ligeledes stor betydning for resultatet. I denne analyse er satralizumab 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 satralizumab.

Dødelighed:
I modellen modelleres dødelighed for patienter med NMOSD ved at anvende et studie vedr. dødelighed for patienter MS. Denne dødelighed vurderes dog at være underestimeret, og derfor tillægges en ekstra dødelighed. Ansøger tillægger dette en ekstra dødelighed på 20 ift. patienter med MS. Medicinrådet vurderer, at dette er overestimeret og reducerer dette til 10 %, men vurderer også, at dette er meget vanskeligt at kvantificere, da der ikke forelægger større kliniske studier vedr. dødelighed blandt patienter med NMOSD. Dødeligheden har dog kun begrænset effekt på de inkrementelle omkostninger.

8. Referencer

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[7] Medicinrådet. Medicinrådets sundhedsøkonomiske afrapportering vedr. eculizumab. 2021.

9. Versionslog

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

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 50 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 13.

Tabel 13. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Satralizumab	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	137.927	129.545	8.382
Attakomkostninger	133.288	186.950	-53.662
Bivirkningsomkostninger	1.139	1.324	-185
Patient og transportomkostninger	29.896	35.202	-5.305
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 satralizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 14.

Tabel 14. 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	23.03.2022
Leverandør	Roche
Lægemiddel	Satralizumab (Enspryng)
Ansøgt indikation	Behandling af neuromyelitis optica spektrum sygdom (NMOSD)

Forhandlingsresultat

Amgros har opnået følgende pris på satralizumab:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Ubetinget pris der er gældende uanset Medicinrådets anbefaling					
Satralizumab	120 mg injektionsvæske	1 stk.	57.089,97	[redacted]	[redacted]
Betinget pris der er gældende hvis Medicinrådet anbefaler satralizumab					
Satralizumab	120 mg injektionsvæske	1 stk.	57.089,97	[redacted]	[redacted]

[redacted]

[redacted]

Konkurrencesituationen

[redacted]. Nedenstående tabel viser derfor alene de årlige lægemiddelpriser for satralizumab.

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Ubetinget pris					
Satralizumab *(opstartsår)*	Uge 0, 2 og 4: 120 mg IV/2 uge Uge 4 - 52: 120 mg IV/4 uge	120 mg (1 stk.)	[redacted]	[redacted]	[redacted]
Satralizumab *(vedligeholdelsesår)*	120 mg IV/4 uge	120 mg (1 stk.)	[redacted]	[redacted]	[redacted]
Betinget pris					
Satralizumab *(opstartsår)*	Uge 0, 2 og 4: 120 mg IV/2 uge Uge 4 - 52: 120 mg IV/4 uge	120 mg (1 stk.)	[redacted]	[redacted]	[redacted]
Satralizumab *(vedligeholdelsesår)*	120 mg IV/4 uge	120 mg (1 stk.)	[redacted]	[redacted]	[redacted]

Status fra andre lande

Norge: Under vurdering[1].
England: Leverandøren har valgt ikke at indsende den endelige ansøgning til NICE[2].

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/satralizumab
[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10544

[redacted]

Medicinrådet

Medicinrådets vurdering vedrørende satralizumab til behandling af neuromyelitis optica spektrum 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.

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Udgivet af Medicinrådet, 24. februar 2022

1. Medicinrådets konklusion

Medicinrådet vurderer, at værdien af satralizumab, sammenlignet med ingen sygdomsmodificerende behandling til patienter med neuromyelitis optica spektrum sygdom (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 satralizumab 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 satralizumab 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 satralizumab 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 (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

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

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

2. Begreber og forkortelser

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 satralizumab til neuromyelitis optica spektrum sygdom (NMOSD) er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Roche. Medicinrådet modtog ansøgningen den 26. november 2021.

Det kliniske spørgsmål er:

Hvilken værdi har satralizumab sammenlignet med placebo for patienter med neuromyelitis optica spektrum sygdom?

3.1 Neuromyelitis optica spektrum sygdom

Neuromyelitis optica spektrum (NMOSD) sygdom er en kronisk inflammatorisk og 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 hyppigere 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 et år efter 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 oligodendrocytterne, 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 komplementprotein i relation til læsionerne [5].

For patienter med NMOSD er den væsentligste sygdomsprogression forbundet med attakker.

Fagudvalget finder, at det er vanskeligt at give et præcist estimat af antallet af nye patienter med NMOSD. Medicinrådet 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 [6]. Der foreligger ikke danske data efter 2014. På den baggrund antager fagudvalget, at antallet af patienter, der er kandidater til behandling med satralizumab, sandsynligvis ligger under 50 patienter, og at 5 nye patienter årligt vil være kandidater til behandlingen. Dette estimat er forbundet med stor usikkerhed.

3.2 Satralizumab

IL-6 er et signalstof, der har en central rolle i den sygdomsdrevne aktivering af immunforsvaret ved NMOSD. Ved høj sygdomsaktivitet er niveauet af IL-6 højt i cerebrospinalvæsken, og dette formodes at være en drivende faktor for inflammationen, der fører til tab af oligodendrocytter og demyelinisering hos patienter med NMOSD [7,8]. IL-6-medieret aktivering er bl.a. vigtigt for dannelsen af antistoffer med AQP4 [9]. Satralizumab er et monoklonalt antistof, der binder til IL-6-receptoren [10] og dermed også hæmmer inflammationen i cerebrospinalvæsken. Behandlingen har til formål at mindske antallet af attakker og forsinke sygdomsudviklingen. Det er relevant, da hvert attak kan medføre vedvarende skade.

120 mg satralizumab skal administreres subkutant ved behandlingsstart, efter to uger og efter fire uger i en opstartsfase. Derefter skal 120 mg satralizumab administreres subkutant hver fjerde uge.

Satralizumab fik positive opinion af Det Europæiske Lægemiddelagentur (EMA) i april 2021. Satralizumab har følgende indikation:

Satralizumab (Enspryng) er indiceret som monoterapi eller i kombination med immunsuppressiv terapi til behandling af NMOSD hos voksne og unge patienter fra 12 år, som er anti-aquaporin-4 IgG (AQP4- IgG) seropositive.

3.3 Nuværende behandling

Målet med den nuværende behandling er at forsinke/hindre attakker, hindre varig funktionsnedsættelse og forbedre livskvaliteten.

Selvom der ikke er andre anbefalede 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 foreligger evidens af høj kvalitet.

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.

Medicinrådet har vurderet lægemidlet eculizumab til indikationen NMOSD i juni 2021. Eculizumab blev ikke anbefalet (Medicinrådets anbefaling vedr. eculizumab til behandling af neuromyelitis optica spektrum sygdom (NMOSD)-vers. 1.0 (medicinraadet.dk)).

4. Metode

Medicinrådets protokol for vurdering vedrørende satralizumab 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 .

SAkuraStar: Traboulsee, A. et. al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder- a randomized double-blind, multicenter

placebo-controlled phase 3 trial. Lancet Neurology, 2020, 19:402-412, incl. supplementary material. NCT02073279

Disse data adresserer effektmål i protokollens kliniske spørgsmål.

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population
Traboulsee, A. et. al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder- a randomized double-blind, multicenter placebo-controlled phase 3 trial. Lancet Neurology, 2020, 19:402-412	Fase III-randomiseret, kontrolleret dobbeltblindet studie (time-to-event-studie) med median follow-up-tid på 92 uger i satralizumab-armen vs. 48 uger i placebo-armen	NCT02073279	Voksne med NMO eller AQP4-IgG positiv NMOSD med mindst ét attak de sidste 12 måneder og en EDSS-score mellem 0 og 6,5.

Tabel 2. Baselinekarakteristika for SAkuraSTAR (AQP4-IgG seropositiv subpopulation)

Characteristics	AQP4-IgG seropositive population	
	Satralizumab (N=41)	**Placebo (N=23)**
Alder - år	46,0 ± 12,0	40,1 ± 11,5
Alder ved klinisk præsentation - år	40,7 ± 13,5	36,4 ± 11,7
Kvinder (%)	31 (75,6 %)	22 (95,7 %)
Diagnose – antal (%)*		
Neuromyelitis optica	26 (63,4 %)	15 (65,2 %)
Neuromyelitis optica spectrum disorder	15 (36,6 %)	8 (34,8 %)
Årlig attakrate, seneste 12 måneder	0,91 ± 0,50	1,02 ± 0,51
EDSS score	4,02 ± 1,50	3,43 ± 1,55

Characteristics	AQP4-IgG seropositive population	
Etnicitet - antal (%)		
American Indian or Alaska Native	2 (4,9 %)	0
Asiat (ikke-Japan)	7 (17,1 %)	6 (26,1 %)
Afroamerikaner	11 (26,8 %)	3 (13,0 %)
Hvid	19 (46,3 %)	13 (56,5 %)
Anden	2 (4,9 %)	1 (4,3 %)
Tidligere behandling - antal (%)		
B-celle depleterende terapi	5 (12,2 %)	4 (17,4 %)
Immunosuppressiva eller andet	36 (87,8 %)	19 (82,6 %)
Sygdomsvarighed - uger	283,5 ± 354,4	197,1 ± 223,5
Type af seneste attak - antal (%)		
Første attak	5 (12,2 %)	4 (17,4 %)
Relaps	36 (87,8 %)	19 (82,6 %)

Satralizumab – og placeboarmene i SAkuraSTARs prædefinerede AQP4-IgG positive subpopulation er nogenlunde balanceret, taget den meget lille population i betragtning. Der er enkelte skævheder f.eks. ift. køn, hvor der i satralizumab-armen er ~ 75% kvinder, mens det er ~96% i placeboarmen. Etnicitet er heller ikke helt ligeligt fordelt, og der er små forskelle i forudgående behandling, hvor lidt færre i satralizumab-armen har modtaget B-celle-depleterende behandling (12 % vs. 17 %), og lidt flere har modtaget anden immunsuppressiv behandling (88 % vs. 83 %). Derudover er patienternes gennemsnitlige sygdomsvarighed længere i satralizumab-armen (284 dage vs. 197 dage. Den gennemsnitlige EDSS-score er lidt højere i satralizumab-armen (4,0 vs. 3,4 EDSS) og patienterne er en også lidt ældre (46 vs. 40 år). Til sidst er der en mindre forskel i tidligere attakker, hvor der er lidt flere patienter i satralizumab-armen, som har haft mere end ét attak (88 % vs. 83 %).

Overordnet tilfører den lille patientpopulation og de små skævheder i baselinekarakteristika stor usikkerhed til den direkte sammenligning.

Patientpopulationen ligner overordnet den danske patientpopulation, som ligeledes er meget lille (jf. afsnit 3.1). 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.

5.1.2 Databehandling og analyse

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. Ansøger har også vedlagt studiet SAkuraSky, der omhandler patienter, som får kombinationsbehandling med satralizumab og andre immunsupprimerende lægemidler. Dette studie indgår ikke i datagrundlaget, men omtales under "andre overvejelser".

Datagrundlaget er et randomiseret, kontrolleret fase III-studie med en præspecificeret subpopulation af 64 AQP4-IgG seropositive patienter med NMOSD randomiseret 2:1 til satralizumab eller placebo i uge 0, 2, 4 og herefter hver 4. uge. Det kliniske studie er designet som et *time-to-event*-studie med første protokol-definerede attak som primært endepunkt.

Designet af studiet gør det vanskeligt at vurdere effektmålene vedvarende sygdomsforværring, synsskarphed og livskvalitet, da patienterne ikke følges efter første attak. Medicinrådet bemærker, at den kvantitative vurdering til brug for kategorisering af merværdi er usikker og forholder sig derfor også kvalitativt til resultaterne.

Studiet var oprindeligt designet til at slutte efter 44 protokol-definerede attaker, men senere justeret til maksimalt at vare 1,5 år efter sidste patient var blevet randomiseret.

Patienterne i SAkuraSTAR var stratificeret efter forudgående sygdomsmodificerende behandling (B-celle-depleterende vs. immunsuppressiva eller andet) og hvorvidt deres seneste attak før screening var patientens allerførste attak eller ej (*first attack vs. relapse*).

Ift. analysen af årlig attakrate justerer ansøger regressionsmodellen med ovenstående kovariater (forudgående sygdomsmodificerende behandling og seneste attakker) (se også tabel 2 med baselinekarakteristika). Hertil bemærker Medicinrådet, at især seneste attakker har stor betydning for den justerede årlige attakrate. Konkret betyder det, at hvis der er i modellen er en stor andel af patienter med tidligere attakker (vs. *first attack),* så bliver den absolutte justerede attakrate højere, og dermed øges den relative forskel mellem armene. Ansøgers analyse afspejler et *case-mix* med samme fordeling af patienter med tidligere relaps vs. debuterende attak som patientpopulation i studiet. Dvs. 55 patienter har haft tidligere attakker ud af 64 patienter i alt. Den absolutte forskel vedr. årlig attakrate ville altså være mindre, hvis denne andel var mindre i modellen.

Ansøgers analyseplan indeholdt en hierarkisk test af et primært endepunkt og sekundære endepunkter i en bestemt rækkefølge, deriblandt attakrate og sygdomsprogression. Effektanalyser blev udført på *intention-to-treat* (ITT) -populationen.

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 2).

Der er nedgraderet ét niveau ift. inkonsistens, da der kun var ét studie. Der er nedgraderet ét niveau, da der er indirekthed i forhold til en dansk patientpopulation. Der er nedgraderet ét niveau, da konfidensintervallet for et eller flere effektestimater indeholder en beslutningsgrænse. Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

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

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

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

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko

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	-0,43 (95 % CI: - 0,49; -0,28)	Merværdi af ukendt størrelse	RR: 0,2 (95 % CI: 0,09; 0,48)	Stor merværdi	Stor merværdi
Bivirkninger	Andel patienter, der oplever en eller flere alvorlige bivirkninger (5 %-point) Kvalitativ gennemgang af bivirkningsprofil	Kritisk	4,0 (95 % CI:-8,2; 46,5)	Kan ikke kategoriseres	RR: 1,31 (95 % CI: 0,37; 4,58)	Kan ikke kategoriseres	Kan ikke kategoriseres
Vedvarende sygdomsforværring	Gennemsnitlig ændring på EDSS-score (0,2 point pr. år)	Kritisk	-0,35 (95 % CI:-0,81; 0,10)	Kan ikke kategoriseres	HR: 0,34 (95 % CI: 0,14; 0,82)	Moderat merværdi	Kan ikke kategoriseres
Synsskarphed	Kurtzke Functional System (KFS) visual score [Snellen-tavle (0,2 point pr. år)]	Vigtig	0,147 (95 % CI: -0,40; 0,69)	Kan ikke kategoriseres	-	Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	Gennemsnitlig ændring på SF-36 (0,5 SD)	Vigtig	SF-36 MCS: 5,10 (95 % CI: -0,36; 10,57) SF-36 PCS: -0,07 (95 % CI: -3,32; 3,19)	Kan ikke kategoriseres	-	Kan ikke kategoriseres	Kan ikke kategoriseres

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

Årlig attakrate

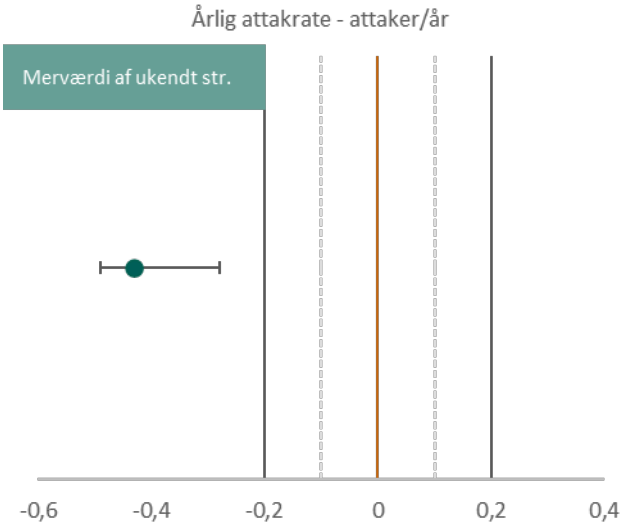
Som beskrevet i protokollen er effektmålet årlig attakrate kritisk for vurderingen af lægemidlets værdi for patienterne, da patienter med NMOSD ofte kan have relativt mange attakker, som kan medføre varig funktionsnedsættelse.

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 satralizumab var designet som et "time-to-event"-studie med første protokol-definerede attak som primært endepunkt. Årlig attakrate blev beregnet på baggrund på det samlede antal attakker, som patienterne oplevede i hver behandlingsarm.

I SAkuraSTAR oplevede 9 ud a f 41 patienter behandlet med satralizumab og 13 ud af 23 patienter behandlet med placebo et attak. Ujusterede attakrater for satralizumab var 0,12 (95 % CI: 0,05; 0,22) og for placebo 0,52 (95 % CI: 0,28; 0,88). Attakrate justeret for tidligere modtaget behandling, og hvorvidt sidste attak for et debuterede attak eller et relaps, var henholdsvis 0,11 (95 % CI: 0,06; 0,21) og 0,53 (95 % CI: 0,31; 0,93).

Fagudvalget bemærker, at den årlige attakrate var væsentlig lavere i placebo-armen under studiet end den årlige attakrate hos patienterne ved baseline (ca. 1 attak/år)



Figur 1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for årlig attakrate. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figuren ovenfor.

Punktestimatet for den absolutte effektforskel er -0,43 (9 5 % CI: -0,49; -0,28) attakker pr. år og afspejler en klinisk relevant effektforskel. Derfor er den foreløbige værdi af satralizumabs merværdi af ukendt størrelse vedr. årlig attakrate.

Baseret på den relative effektforskel, som er en RR 0,20 (0,09; 0,48), har satralizumab foreløbigt en stor merværdi vedrørende årlig attakrate.

Samlet har satralizumab en stor merværdi på effektmålet årlig attakrate.

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

Ansøger har indleveret data for alvorlige uønskede hændelser relateret til behandlingen i SAkuraSTAR for patienter med AQP4-IgG. I satralizumab-armen oplevede syv patienter en alvorlig uønsket hændelse (7/41; 17,1 %), mens 3 patienter i placebo-armen oplevede alvorlige uønskede hændelser (3/23, 13 %). Det giver en absolut forskel på 4,1 %, hvilket er lavere end den mindste klinisk relevante forskel på 5 %-point fastsat i protokollen til vurdering af satralizumab til NMOSD.

Fagudvalget vurderer, at der i det kliniske studie af satralizumab til NMOSD ikke ses en kvantitativ forskel i alvorlige uønskede hændelser mellem satralizumab og placebo. Fagudvalget vurderer, at datagrundlaget fra det kliniske studie af satralizumab til NMOSD er meget lille, og lægger i stedet vægt den kvalitative gennemgang af satralizumabs bivirkningsprofil.

Gennemgang af bivirkningsprofil

De hyppigst indberettede bivirkninger var: hovedpine (19,2 %), artralgi (13,5 %), nedsat antal hvide blodlegemer (13,5 %), hyperlipidæmi (13,5 %) og injektionsrelaterede reaktioner (12,5 %).

Tabel 4. Oversigt over uønskede hændelser i SAkuraSTAR

Placebo (n=23; 26.8 PY)				Satralizumab (n=41; 80.4 PY)		
	No. of patients (%)	No. of AEs	AEs/ 100PY (95% CI)	No. of patients (%)	No. of AEs	AEs/ 100PY (95% CI)
AEs	16 (69.6)	139	519.7 (436.9–613.6)	36 (87.7)	354	440.5 (395.8–488.9)

Placebo (n=23; 26.8 PY)			Satralizumab (n=41; 80.4 PY)		
Serious AEs	3 (13.0)	3	11.2 (2.3–32.8)	7 (17.1)	14	17.4 (9.5–29.2)
Infections	10 (43.5)	42	157.0 (113.2–212.3)	22 (53.7)	75	93.3 (73.4–117.0)
Serious infections	1 (4.3)	1	3.7 (0.1–20.8)	4 (9.8)	4	5.0 (1.4–12.7)

Beskrivelse af udvalgte uønskede hændelser ved behandling med satralizumab som monoterapi (SAkuraSTAR) eller kombination med anden immunsuppressiva (SAkuraSKY). (ud fra EPAR/SmPC)

Infektioner

Hyppigheden af infektioner var højere i begge behandlingsarme, med en lidt højere forekomst i gruppen af patienter behandlet med satralizumab i kombination med immunsuppressiva (68,3 % vs. 61,9 %) og satralizumab som monoterapi (54 % vs. 43,8 %). En højere andel af patienter rapporterede alvorlige infektiøse bivirkninger i satralizumab-behandlingsarmen (9,5 %) sammenlignet med placebo (3,1 %) i SAkuraSTAR-studiet, og der var her tale om nedre luftvejsinfektioner (bronkitis, pneumoni og lungesepsis).

Injektionsrelaterede reaktioner

Injektionsrelaterede reaktioner (IRR) indberettet hos patienter behandlet med satralizumab var overvejende lette til moderate og opstod hyppigst inden for 24 timer efter injektion. De mest almindelige indberettede systemiske symptomer var diarré og hovedpine. De mest almindelige indberettede reaktioner fra injektionsstedet var rødme, erytem, pruritus, udslæt og smerte.

Neutrofile granulocytter

Hos 31,7 % af patienterne behandlet med satralizumab faldt antallet af neutrofilocytter (som monoterapi eller i kombination med immunsuppressiva) sammenlignet med 21,6 % af patienterne behandlet med placebo (eller placebo plus immunsuppressiva). Størstedelen af tilfældene af fald i neutrofilocytter var forbigående eller sporadiske.

Leverpåvirkning

I den dobbeltblindede behandlingsperiode forekom der stigninger i ALAT eller ASAT hos henholdsvis 27,9 % og 18,3 % af patienterne behandlet med satralizumab (som monoterapi eller i kombination med immunsuppressiva), sammenlignet med 12,2 % og

13,5 % af patienterne behandlet med placebo (eller placebo plus immunsuppressiva). Størstedelen af stigningerne var mindre end 3 x øverste referencegrænse, forbigående og afhjulpet uden afbrydelse af behandling med satralizumab. Der forekom stigninger i ALAT eller ASAT > 3 x øverste referenceværdi hos henholdsvis 2,9 % og 1,9 % af patienterne behandlet med satralizumab (som monoterapi eller i kombination med immunsuppressiva). Stigningerne var ikke forbundet med stigninger i total bilirubin. Der forekom stigninger i ALAT over 5 x øverste referenceværdi hos én (1 %) patient, fire uger efter påbegyndelse af behandling med satralizumab i kombination med IST; værdien normaliseredes efter seponering, og behandlingen med satralizumab blev ikke genoptaget hos denne patient.

Kropsvægt

Der blev observeret en stigning i kropsvægten ≥ 15 % fra baseline hos 3,8 % af patienterne i behandling med satralizumab (monoterapi eller i kombination med immunsuppressiva) sammenlignet med 2,7 % af patienterne, som modtog placebo (eller plus immunsuppressiva).

Lipidparametre

10,6 % af patienterne behandlet med satralizumab (som monoterapi eller i kombination med immunsuppressiva) havde stigninger i total kolesterol over 7,75 mmol/l sammenlignet med 1,4 % af patienterne behandlet med placebo (eller placebo plus IST); 20,2 % af patienterne behandlet med satralizumab oplevede stigningerne i triglycerider over 3,42 mmol/l sammenlignet med 10,8 % af patienterne behandlet med placebo.

Perspektivering ift. andre kendte IL-6-receptorantistoffer

Tocilizumab

Tocilizumab er indiceret til patienter med svær til moderat reumatoid artrit i kombination med methotrexat, og derfor bør der tages højde for, at disse patienter ofte modtager anden immunsupprimerende behandling i kombination med tocilizumab. De hyppigst indberettede bivirkninger for tocilizumab i sikkerhedspopulationen var øvre luftvejsinfektioner, nasopharyngitis, hovedpine, hypertension og forhøjet ALAT. De alvorligste bivirkninger var svære infektioner, komplikationer ved diverticulitis og overfølsomhedsreaktioner (ref.: smPC)

Sarilumab

Sarilumab er ligesom tocilizumab indiceret til reumatoid artrit, og de hyppigst observerede bivirkninger med sarilumab i kliniske studier var neutropeni, forhøjet ALAT, erytem ved injektionsstedet, øvre luftvejsinfektioner og urinvejsinfektioner. De mest almindelige alvorlige bivirkninger var infektioner. De hyppigst rapporterede infektioner (5 % -7 % af patienterne) var øvre luftvejsinfektioner, urinvejsinfektioner og nasopharyngitis. De hyppigst observerede alvorlige infektioner omfattede pneumoni og cellulitis. Der er rapporteret tilfælde af opportunistiske infektioner.

I en langtidssikkerhedspopulation med tocilizumab i kombination sygdomsmodificerende lægemidler til kronisk leddegigt var hyppigheden af infektioner og alvorlige infektioner henholdsvis 57,3 og 3,4 hændelser pr. 100 patientår (ref.: smPC)

Konklusion

Sikkerhedsdata for satralizumab er meget begrænset både med hensyn til antal og varighed af eksponering af satralizumab. Det vanskeliggør også identificering af uønskede hændelser ift. særlige sub-patientpopulationer. Der kan tillægges ekstra vægt på bivirkninger, der kan anses som klasseeffekter af anti-IL6-receptor-antistoffer på basis af tilgængelige, større sikkerhedsdatasæt, idet de kliniske data for satralizumab til AQP4-IgG positive NMOSD-patienter er meget begrænset. Her lægger fagudvalget særligt vægt på risikoen for infektioner og alvorlige infektioner.

Fagudvalget vurderer samlet, at værdien af satralizumab ikke kan kategoriseres sammenlignet med placebobehandling til NMOSD.

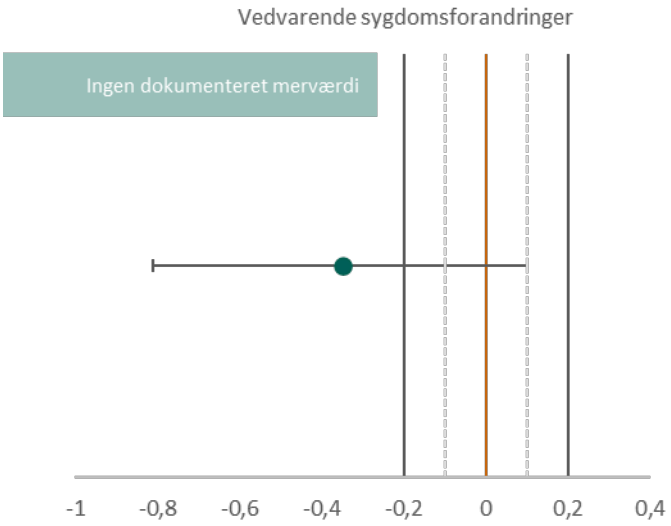
Vedvarende sygdomsforværring
Som beskrevet i protokollen er effektmålet vedvarende sygdomsforværring, defineret som EDSS-score, et kritisk effektmål.

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 satralizumab og placebo vurderes af fagudvalget at være en score på 0,2.

I SAkuraSTAR blev vedvarende sygdomsforandringer målt ved baseline og ved 24 uger og 48 uger samt indenfor 7 dage efter et protokol-defineret attak. Da patienter kun er inkluderet i analysen ved prædefinerede tidspunkter indtil første attak, kan relaps-associeret sygdomsforværring i studiet ikke vurderes ud fra denne type analyse.

Den gennemsnitlige årlige ændring i EDSS-score efter 48 uger var -0,52 (95 % CI: -0,87; -0,16) (forbedring) hos patienter behandlet med satralizumab og -0,17 (95 % CI: -0,60; 0,27) (forbedring) hos patienter i placebo-armen. Den gennemsnitlige forskel i ændring i EDSS-score er -0,35 (95 % CI: -0,81; 0,10). Denne forskel er dog ikke statistisk signifikant, og da konfidensintervallet overlapper både en negativ og en positiv effekt af satralizumab, kan den foreløbige merværdi ikke kategoriseres for den absolutte effektforskel.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for vedvarende sygdomsforværringer. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figuren ovenfor.

Den relative effektforskel mellem satralizumab og placebo er udregnet med en HR på 0,446 (95 % CI: 0,14; 0,82), og giver satralizumab en moderat merværdi vedrørende sygdomsforværring.

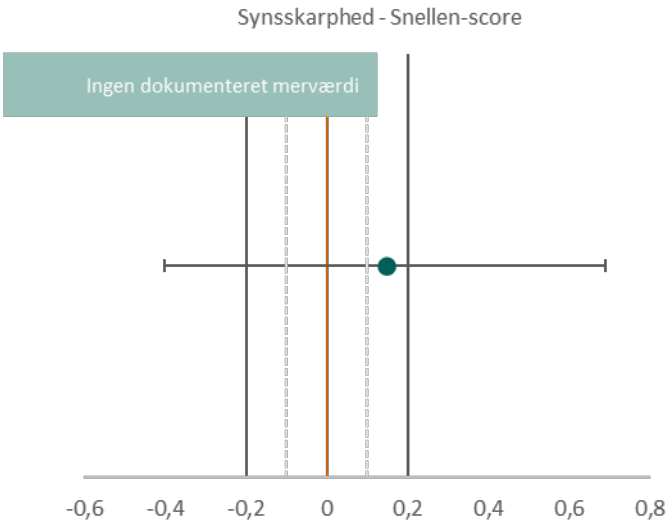
I og med at den mindste klinisk relevante forskel ikke er opnået, vurderer fagudvalget, at værdien af satralizumab sammenlignet med placebo ikke kan kategoriseres efter Medicinrådets metoder. Den relative effektforskel favoriserer dog satralizumab, og fagudvalget forventer, at effekten på attakker vil medføre en langsommere forværring af sygdommen. Derfor ville en længere opfølgningstid måske medføre en tydeligere effekt af satralizumab på sygdomsprogression.

Synsskarphed

Synsproblemer er et væsentligt symptom ved NMOSD, og derfor har fagudvalget valgt i protokollen, at synsskarphed er et vigtigt effektmål. Synsskarphed kan 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 satralizumab 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.

Ansøger har indsendt data on file fra det kliniske studie SAkuraSTAR. Patienter i satralizumab-armen havde en forbedring på -0,18 point (95 % CI, -0,66; 0,31) efter 48 uger, mens forbedringen var -0,32 point (95 % CI: -0,87; 0,23) i placebo-armen.



Figur 3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for synsskarphed. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel 0,15 (95 % CI: -0,40; 0,69). Da konfidensintervallet overlapper både en negativ og en positiv effekt af satralizumab, kan den foreløbige merværdi ikke kategoriseres for den absolutte effektforskel.

Der er ikke indleveret data for den relative effektforskel.

Fagudvalget vurderer, at værdien af satralizumab sammenlignet med placebo ikke kan kategoriseres efter Medicinrådets metoder på effektmålet synsskarphed.

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 on file* for SF-36 opdelt i: *mental component score* (MCS) og *physical component score* (PCS).

Efter 48 uger var den gennemsnitlige ændring fra baseline i MCS-score 5,58 (95 % CI: 1,82; 9,34) i satralizumab-armen og 0,48 (95 % CI: -4,48; 5,44) i placeboarmen. Forskellen mellem armene er 5,10 (95 % CI: -0,36; 10,57). Punktestimatet overstiger mindste klinisk relevante forskel, men konfidensintervallet inkluderer 0, og derfor viser analysen ingen statistisk signifikante forskelle mellem behandlingsarmene i studiet.

Den gennemsnitlige ændring fra baseline i PCS-score var 5,37 (95 % CI: 2,70; 8,03) i satralizumab-armen og 5,43 (95 % CI: -3,32; 3,19) i placebo-armen. Forskellen mellem armene er -0,07 (95 % CI: -0,23; 0,34). Punktestimatet overstiger ikke mindste klinisk relevante forskel, og konfidensintervallet inkluderer 0, og derfor viser analysen ingen statistisk signifikante forskelle mellem studiebehandlingsarme.

Værdien af satralizumab kan ikke kategoriseres ud fra Medicinrådets metoder på effektmålet livskvalitet. Fagudvalget bemærker dog, at konfidensintervallet for den gennemsnitlige forskel i mental livskvalitet (*mental component score*) fra -0,4 til 10,6 mere tyder på en positiv effekt af satralizumab end en negativ effekt, og at en negativ effekt med 95 % sandsynlighed i så fald ville være lille.

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 [11]. 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 satralizumab. 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 [12]. 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 [13].

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 satralizumab i en kvantitativ analyse.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at værdien af satralizumab sammenlignet med placebo til patienter med NMOSD ikke kan kategoriseres efter Medicinrådets metoder. Datagrundlaget er en direkte sammenligning med en prædefineret subpopulation af 64 AQP4-IgG positive patienter. 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 satralizumab på effektmålet årlig attakrate. 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 satralizumab end placebo.

Hvad angår sikkerhed, vurderer fagudvalget, at der er risiko for flere og alvorligere bivirkninger forbundet med satralizumab end med placebo. Der er meget begrænsede sikkerhedsdata for satralizumab, men fagudvalget har perspektiveret ud fra andre kendte IL-6-hæmmere. Den væsentligste bekymring er alvorlige infektioner. Samlet set finder fagudvalget, at hyppigheden af alvorlige bivirkninger forekommer nogenlunde tilsvarende, hvad der er kendt for lægemidler til andenlinjebehandling af attakvis multipel sklerose, men at der er stor usikkerhed forbundet med vurdering af især bivirkningerne.

Fagudvalget finder det sandsynliggjort, at satralizumab har en bedre effekt, især på attakker, sammenlignet med placebo.

Fagudvalget mener samlet set, at satralizumab 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 satralizumab er et bedre, ligeværdigt eller dårligere behandlingsalternativ end disse.

6. Andre overvejelser

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.

Medicinrådet er opmærksom på, at EMA har angivet, at satralizumab kan benyttes både som monoterapi og i kombination med immunsupprimerende behandlinger.

Medicinrådet ønskede i protokollen, at ansøger redegjorde for anvendelsen af satralizumab i kombination med anden immunsupprimerende behandling. Ansøger har vedlagt SAkuraSKY studiet, hvor effekten af satralizumab er sammenlignet i kombination med immunsupprimerende behandling overfor placebo. Medicinrådet vurderer ikke, populationen af patienter, som får kombinationsbehandling, er relevant i forhold til dansk klinisk praksis, men at resultaterne i studiet ikke afviger væsentligt fra resultaterne i SAkuraSTAR angående effekt og bivirkninger af satralizumab.

Til sidst har Medicinrådet anmodet ansøger om at redegøre for, i hvor høj grad satralizumab ligner lægemidlerne tocilizumab og sarilumab, som ligeledes er interleukin 6-hæmmere. Ansøger har ikke lavet en nogen sammenligning, men Medicinrådet har valgt at perspektivere afsnittet vedr. bivirkninger ift. andre velkendte IL-6 receptorantistoffer; tocilizumab og sarilumab. Det indgår i fagudvalgets overordnede vurdering af sikkerheden for satralizumab.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

8. Referencer

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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
Udpegning i gang	Region Sjælland
Matthias Kant Overlæge	Udpeget af formanden
Jeppe Romme Christensen Afdelingslæge	Region Hovedstaden
Hilde Omestad Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
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Kan ikke opfylde Medicinrådets habilitetskrav	Sclerosebehandlingsregistret
Kan ikke opfylde Medicinrådets habilitetskrav	Dansk Neurologisk Selskab
Marie Lynning Patient/patientrepræsentant	Danske Patienter
Malene Krüger Patient/patientrepræsentant	Danske Patienter

Sammensætning af fagudvalg	
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Said Nasim Ashna Overlæge	Region Sjælland
Elisabeth Penninga Overlæge	Dansk Selskab for Klinisk Farmakologi

Medicinrådets sekretariat

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23.02.2022	Godkendt af Medicinrådet.

11. Bilag

Bilag 1: Cochrane – risiko for bias

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

Tabel 5. Vurdering af risiko for bias i SakuraSTAR NCT02073279

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering computer-genereret af 3. part.
Effekt af tildeling til intervention	**Lav**	Allokering til interventionsgruppe dobbelt-blindet.
Manglende data for effektmål	**Lav**	Missing blev imputeret ved *baseline-observation-carried-forward* metode. Sensitivitetsanalyser for *key secondary* effektestimater blev foretaget.
Risiko for bias ved indsamlingen af data	**Lav**	Attaker i studiet var protokoldefineret og vurderet af en *clinical endpoint committee.*
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 – satralizumab sammenlignet med placebo til behandling af patienter med NMOSD

Tabel 6. GRADE evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt		Sikkerhed	Vigtighed
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Satralizumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)		
Årlig attakrate												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	41	23	RR: 0,2 (95 % CI: 0,09; 0,48)	-0,43 (95 % CI: - 0,49; -0,28)	⨁⨁◯◯ LAV	KRITISK
Bivirkninger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	41	23	RR: 1,31 (95 % CI: 0,37; 4,58)	4,0 (95 % CI:-8,2; 46,5)	⨁◯◯◯ MEGET LAV	KRITISK
Vedvarende sygdomsforværring												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	37	14	HR: 0,34 (95 % CI: 0,14; 0,82)	-0,35 (95 % CI:-0,81; 0,10)	⨁◯◯◯ MEGET LAV	KRITISK

Sikkerhedsvurdering							Antal patienter		Effekt		Sikkerhed	Vigtighed
Antal studier	**Studie-design**	**Risiko for bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Satralizumab**	**Placebo**	**Relativ (95 % CI)**	**Absolut (95 % CI)**		
Synsskarphed												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	37	14		0,147 (95 % CI: -0,40; 0,69)	⨁◯◯◯ MEGET LAV	VIGTIG
Livskvalitet												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	37	14		SF-36 MCS: 5,10 (95 % CI: -0,36; 10,57) SF-36 PCS: -0,07 (95 % CI: -3,32; 3,19)		Vigtig
Kvalitet af den samlede evidens			MEGET LAV[d]									

[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.

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

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

Application for the assessment of ENSPRYNG (satralizumab) for neuromyelitis optica spectrum disorder (NMOSD)

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	ENSPRYNG®
Generic name	Satralizumab
Marketing authorization holder in Denmark	Roche Registration GmbH Emil-Barrell-Strasse 1 79639 Grenzach-Wyhlen, Germany
ATC code	L04AC19

Pharmacotherapeutic group	Immunosuppressants, interleukin inhibitors
Active substance(s)	Satralizumab
Pharmaceutical form(s)	Liquid for subcutaneous administration, pre-filled syringe.
Mechanism of action	Satralizumab is a humanized monoclonal antibody that binds to membrane-bound and soluble IL-6 (interleukin-6) receptors, preventing IL-6 from binding, thereby inhibiting IL-6 signalling pathways involved in inflammation. Satralizumab was designed using a novel antibody technology, which allows the antibody to dissociate from the antigen in a pH-dependent manner and then be released into the bloodstream to bind more antigen, prolonging the drug's elimination half-life in plasma.
Dosage regimen	120 mg at weeks 0, 2, and 4, and every 4 weeks thereafter.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Satralizumab is indicated as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Satralizumab can be used as a monotherapy or in combination with either oral corticosteroids (OCs), azathioprine (AZA) or mycophenolate mofetil (MMF).
Packaging – types, sizes/number of units, and concentrations	Prefilled syringe 120 mg satralizumab in 1 ml. 1 single syringe in each package (120mg/ml)
Orphan drug designation	Yes

2. Abbreviations

AE	Adverse event
ARR	Annualized relapse rate
AQP4	Anti-aquaporin-4
AZA	Azathioprine
CCOD	Clinical cut-off date
CI	Confidence interval
DB	Double-blind
EDSS	Expanded disability status scale
EMA	European Medicines Agency
EPAR	European public assessment report
FACIT-F	Functional assessment of chronic illness therapy fatigue score
HR	Hazard ratio
IL-6	Interleukin 6
IgG	Immunoglobulin G
IST	Immunosuppressive therapy
ITT	Intention-to-treat
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorder
OC	Oral corticosteroids
OLE	Open-label extension
OST	Overall satralizumab treatment
PDR	Protocol-defined relapse
PY	Patient-years
RR	Relative risk
SC	Subcutaneous
SPC	Summary of product characteristics
SF-36	36-item Short Form health survey
Th-17	T helper 17 lymphocytes
TRF	Time to first relapse
VAS	Visual analogue scale

3. Summary

INTRODUCTION: ENSPRYNG® (satralizumab) as a monotherapy or in combination with immunosuppressive therapy (IST) was approved by the European Commission on June 24, 2021 for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive. This makes satralizumab the first and only treatment approved for both adults and adolescents with AQP4-IgG seropositive NMOSD in the EU. As these patients are currently treated with "off-label" drugs based on sparse evidence there is a need for new and well-documented treatments in this setting. The approval of satralizumab is based on results from SAkuraSky, a phase 3 trial to evaluate efficacy and safety of satralizumab as add-on therapy compared to placebo in patients with neuromyelitis optica (NMO) and NMOSD, and results from SAkuraStar, a phase 3 trial to evaluate the efficacy and safety of satralizumab monotherapy compared to placebo in patients with NMO and NMOSD. Satralizumab is the only NMOSD treatment that is administered subcutaneously every four weeks, allowing home-dosing after appropriate introduction.

This application, submitted to the Medicines Council on August 30, 2021, provides the basis for the assessment of satralizumab for the treatment of NMOSD in AQP4-IgG seropositive patients.

METHOD: In accordance with the Medicines Council protocol, the randomized controlled trial SAkuraStar is used as the main source of evidence to answer the clinical question. As direct evidence for the efficacy and safety of satralizumab as a monotherapy can be derived from this study, a literature search was not requested in the protocol. In order to provide additional evidence for the efficacy and safety of satralizumab, data from SAkuraSky are also included. Lastly, the European Medicines Agency's (EMA's) European public assessment report (EPAR) and Summary of Product Characteristics (SPC) have been consulted. For the purpose of this submission, comparative analyses are presented for the AQP4-IgG seropositive population, which represents ~70% of the intention-to-treat (ITT) population.

As requested in the protocol, data are presented on annualized relapse rate (ARR), treatment-related adverse events (AEs), persistent disease worsening according to the Expanded Disability Status Scale (EDSS), visual acuity according to the Snellen chart and quality of life according to the 36-Item Short Form health survey (SF-36). In addition, data are provided on time to first protocol-defined relapse (PDR), the primary endpoint in the SAkura studies, which reflects prevention of an occurrence of relapse. Given the potential of a single relapse to cause significant and permanent disability, prevention of the occurrence of a relapse is crucial in the treatment of NMOSD.

RESULTS: Treatment with satralizumab as monotherapy significantly reduced the risk of experiencing a PDR compared to placebo (risk reduction of 74%) in the double-blind (DB) period of SAkuraStar. At week 96, 76.5% of patients treated with satralizumab were relapse-free compared to 41.1% treated with placebo. Analysis of time to first investigator-assessed PDR in the combined DB and open-label extension (OLE) period of the SAkura studies, showed sustained effect of satralizumab on reduction of risk of relapse. Moreover, treatment with satralizumab reduced the adjusted ARR by 90% compared to placebo (rate ratio (RR): 0.10; 95% CI, 0.02 to 0.47; p=0.009) in the DB period of SAkuraStar. No significant differences between satralizumab and placebo were observed for mean change in EDSS score, mean change in visual score and mean change in SF-36 score, within the first 48 weeks of treatment. In terms of interpretation, it is important to note that patients are only included in analyses at 24-week intervals up to the point of PDR, and therefore relapse-associated changes cannot be determined using these measures. Assessment of time to EDSS score worsening in SAkuraStar did however show that treatment with satralizumab significantly reduced the risk of EDSS worsening (HR: 0.34; 95% CI 0.14 to 0.82; p = 0.0124). Overall, similar results were observed in SAkuraSky.

Satralizumab displayed a favourable safety profile in both SAkura studies. Overall, the proportion of patients experiencing adverse events (AEs) and serious AEs were comparable between satralizumab and placebo treatment groups with a slightly higher incidence of events in the satralizumab group. The rates of AEs, including infections and serious infections, were similar between treatment groups. Most reported AEs were mild to moderate.

CONCLUSION: In conclusion, satralizumab as monotherapy showed compelling clinical benefit to AQP4-IgG seropositive NMOSD patients compared with placebo. Supporting the overall use of satralizumab, addition of

satralizumab to immunosuppressive therapy (IST) was also shown to be more efficient than using IST alone. Importantly, satralizumab was demonstrated to be a safe and tolerable therapy.

4. Literature search

The Medicines Council has found that the clinical trial SAkuraStar provides sufficient data to answer the clinical question, and thus a literature search for additional evidence has not been requested in the Medicines Council protocol. Results for the main study population in the trial are published in a peer-reviewed publication [1]. Data for the population in question - the AQP4-IgG seropositive patients - are available in either Traboulsee et al. 2020 and/or EMA's EPAR and SPC for satralizumab or in recent congress presentations. Data on certain outcomes in the subgroup are not yet published. Furthermore, the clinical trial SAkuraSky is included to provide additional information on the efficacy and safety of satralizumab [2]. Both studies are listed in **Table 1**.

4.1 Relevant studies

Table 1 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Traboulsee et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder - a randomized double-blind, multicenter placebo-controlled phase 3 trial. Lancet, 2020, 19:402-412, including supplementary material [1].	SAkuraStar (BN40900)	NCT02073279	Start: August 5, 2014 Completion: March 31, 2021	Main source of evidence
Yamamura et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. NEJM, 2019, 381:2114-24, including supplementary material [2].	SAkuraSky (BN40898)	NCT02028884	Start: February 20, 2014 Completion: March 31, 2021	Supporting evidence

4.2 Main characteristics of included studies

The use of satralizumab was studied in both a monotherapy and combination therapy setting. The design of the randomized controlled trial SAkuraStar, which provides direct evidence for the efficacy and safety of satralizumab monotherapy compared to placebo [1], better reflects current Danish clinical practice. Therefore, in line with the Medicines Council protocol, SAkuraStar will be used as the main source of evidence to answer the clinical question. For the purpose of this submission, analysis of the efficacy outcomes will be presented for the AQP4-IgG seropositive population, which represents ~70% of the ITT population. In terms of safety, results will be presented for both the AQP4-IgG seropositive population and the pooled safety population.

In order to provide additional evidence for the efficacy and safety of satralizumab, results from the trial SAkuraSky, which evaluates the efficacy and safety of satralizumab as add-on therapy to immunosuppressive therapy (IST) compared to placebo and IST [2], are also included. Section 5.1.1 therefore contains a description of both studies. Main characteristics of both studies are presented in **Table A2a** and **Table A2b** in Appendix 9.2.

5. Clinical question

5.1 What value does satralizumab have compared to placebo in AQP4-IgG seropositive patients with neuromyelitis optica spectrum disorder (EDSS < 7 and experienced one or several attacks)?

5.1.1 Presentation of relevant studies

SAkura study design

SAkuraStar and SAkuraSky were similar in study design. Both were phase 3, randomized, double-blind (DB), placebo-controlled, parallel-assignment studies evaluating the efficacy and safety of satralizumab in patients with NMOSD, followed by an open-label extension (OLE) period. Eligible patients were adolescents or adults who had AQP4-IgG seropositive or AQP4-IgG seronegative NMO defined by published criteria [3] or had NMOSD at screening with idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral-segment spinal cord lesions on magnetic resonance imaging) or recurrent or simultaneous optic neuritis in both eyes [4]. The term NMOSD is used to refer to both groups of patients in accordance with 2015 guidelines [5].

In both studies, the ITT population was the primary analysis population for the efficacy analysis and included all patients randomized to either the satralizumab or the placebo group. The primary endpoint was time to first protocol-defined relapse (PDR) in a time-to-event analysis. This endpoint was selected as the natural history of NMOSD suggests that any relapse may potentially be catastrophic to the patient, and that relapse is often accompanied by permanent neurologic impairment [6,7]. Time to first PDR reflects the prevention of an occurrence of relapse, rather than a reduction in the frequency of relapse, making it a suitable primary endpoint. Using this outcome measure also enabled the clinician to change therapy following a relapse, and reduced exposure to ineffective or placebo therapy. Secondary endpoints relevant to the assessment in the Medicines Council were annualized relapse rate (ARR), change in Expanded Disability Status Scale (EDSS) score, visual acuity according to Snellen chart and quality of life measured with the 36-item Short Form health survey (SF-36). These secondary endpoints were measured at baseline and periodically at 24-week intervals up to the point of PDR. Detecting changes in these outcomes during or after a relapse was therefore not possible. Consequently, any observed changes from baseline to every 24 weeks during the DB period stemmed from stable patients who were, by definition, not experiencing relapse symptoms. Adverse events were analysed in the safety analysis population, including all patients who received at least one dose of study treatment. Data are included from the DB period from the first dose of satralizumab up until the clinical cut-off date (CCOD), until 1 day before the first satralizumab dose in the OLE period, withdrawal or loss to follow-up.

Patients who experienced a PDR adjudicated by a Clinical Endpoint Committee could start treatment with satralizumab in the OLE period. Patients who experienced a relapse that did not meet the definition of a PDR were treated with rescue therapy at the discretion of the investigator and continued to receive study treatment in the DB period. At the CCOD of either study, patients who had not experienced a relapse during the DB period were offered to enter the OLE period 4 weeks (± 7 days) after their last dosing in the DB period. Patients who withdrew from the study in the DB period due to clinical relapse continued for a safety follow-up period of 24 weeks from the last dose of study drug.

In the OLE, all patients received open-label treatment with satralizumab at a dose of 120 mg administered subcutaneously at Weeks 0, 2 and 4 and at a maintenance dose of 120 mg subcutaneously every 4 weeks thereafter. To assess persistence of efficacy, the OLE data from patients randomized to satralizumab was analysed to see if the efficacy observed in the DB period was maintained into the OLE period. Safety was evaluated for all patients who received at least one dose of satralizumab in the SAkura trials over the overall satralizumab exposure period, including the DB and OLE periods up to a CCOD of 18 February 2020.

SAkuraStar - NCT02073279

SAkuraStar was designed to evaluate the efficacy and safety of satralizumab monotherapy in adult patients with AQP4-IgG seropositive or seronegative NMOSD. Patients were randomly assigned in a 2:1 ratio to receive either

satralizumab at a dose of 120 mg, or placebo administered subcutaneously at weeks 0, 2, and 4 and every 4 weeks thereafter. Randomization was stratified by prior therapy for relapse prevention (B-cell-depleting therapy vs. immunosuppressants or others) and nature of the most recent attack in the year prior to screening (first attack vs. relapse).

The DB period was initially planned to end after 44 PDRs occurred, based on sample size and power calculations. To prevent prolonged exposure to a drug with unknown risk-benefit balance, the end of the DB period was later modified to include a maximal duration of 1.5 years after random assignment of the last patient enrolled. Patients experiencing a relapse requiring treatment with rescue therapy and/or a PDR adjudicated by a Clinical Endpoint Committee, or those who remained in the trial when the DB period ended, were eligible to enter the OLE period until commercial availability of satralizumab.

Clinical cut-off was 12 October 2018, which was the end of the DB period. At this time, the median treatment duration was 92.3 weeks (80.36 patient-years (PY)) for the satralizumab treated group and 47.6 weeks (26.75 PY) for the placebo treated group. The median duration of exposure in the DB period was longer for patients in the satralizumab group than patients in the placebo group as more patients in the placebo arm relapsed and moved to the OLE than in the satralizumab arm.

Demographic and disease characteristics at baseline in the main study population and the AQP4-IgG seropositive subpopulation are presented in **Table 2** [1] (data on file). Characteristics at baseline are well balanced between the two populations. For both the main and the subpopulation, baseline characteristics were similar between treatment arms, apart from sex and race or ethnicity. This imbalance is however not expected to influence the effect estimates. In the placebo arm in both populations, patients were slightly younger on average than in the satralizumab arm, and in the AQP4-IgG seropositive subpopulation, patients in the placebo arm had a slightly lower EDSS score compared to the satralizumab arm. Overall, based on dialogue with a Danish clinical expert, the trial populations are considered to be representative of a Danish NMOSD patient population [8].

Table 2 Demographic and disease characteristics of participants at baseline in SAkuraStar

Characteristics	Main population		AQP4-IgG seropositive population	
	Satralizumab (N=63)	Placebo (N=32)	Satralizumab (N=41)	Placebo (N=23)
Age - years	45.3 ± 12.0	40.5 ± 10.5	46.0 ± 12.0	40.1 ± 11.5
Age at clinical presentation - years	36.4 ± 10.7	39.3 ± 13.3	NR	NR
Sex - no. (%)				
Male	17 (27%)	1 (3%)	10 (24.4%)	1 (4.3%)
Female	46 (73%)	31 (97%)	31 (75.6%)	22 (95.7%)
Diagnosis - no. (%)*				
Neuromyelitis optica	47 (75%)	24 (75%)	26 (63.4%)	15 (65.2%)
Neuromyelitis optica spectrum disorder	16 (25%)	8 (25%)	15 (36.6%)	8 (34.8%)
AQP4-IgG seropositive - no. (%)	41 (65%)	23 (72%)	NA	NA
Annualised relapse rate in previous 1 yr	1.4 ± 0.6	1.5 ± 0.7	0.91 ± 0.50	1.02 ± 0.51

EDSS score§	3.9 ± 1.5	3.7 ± 1.6	4.02 ± 1.50	3.43 ± 1.55
VAS pain score¶				
Mean ± SD	31.7 ± 28.9	27.6 ± 30.8	NR	NR
Median (range)	25 (0-94)	9 (0-90)	NR	NR
FACIT-F score‖				
Mean ± SD	30.6 ± 11.7	29.7 ± 12.9	NR	NR
Median (range)	30 (6-52)	31 (5-48)	NR	NR
Race or ethnicity - no. (%)				
American Indian or Alaska Native	2 (3%)	0	2 (4.9%)	0
Asian (non-Japanese)	8 (13%)	6 (19%)	7 (17.1%)	6 (26.1%)
Black or African American	13 (21%)	3 (9%)	11 (26.8%)	3 (13.0%)
White	37 (59%)	22 (69%)	19 (46.3%)	13 (56.5%)
Other	3 (5%)	1 (3%)	2 (4.9%)	1 (4.3%)
Previous treatment - no. (%)				
B-cell-depleting therapy	8 (13%)	4 (13%)	5 (12.2%)	4 (17.4%)
Immunosuppressants or other	55 (87%)	28 (88%)	36 (87.8%)	19 (82.6%)
Disease duration - weeks	317.8 ± 340.9	214.7 ± 201.3	NR	NR
Type of most recent attack - no. (%)				
First attack	7 (11%)	4 (13%)	5 (12.2%)	4 (17.4%)
Relapse	56 (89%)	28 (88%)	36 (87.8%)	19 (82.6%)

Data are mean ± SD or n (%). *Patients either had neuromyelitis optica according to published criteria (seropositive or seronegative for antibodies against AQP4-IgG) or had neuromyelitis optica spectrum disorder (AQP4-IgG seropositive status only) according to published criteria with idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral-segment spinal cord lesions on magnetic resonance imaging) or recurrent or simultaneous optic neuritis in both eyes. § Scores on the Expanded Disability Status Scale (EDSS) range from 0 (normal neurologic examination) to 10 (death). ¶ Scores on the visual-analogue scale (VAS) for the assessment of pain range from 0 to 100, with higher scores indicating more pain. ‖ Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) range from 0 to 52, with lower scores indicating more fatigue.

SAkuraSky - NCT02028884

SAkuraSky was designed to evaluate the efficacy and safety of satralizumab added to stable doses of baseline immunosuppressant treatment (IST) in adolescents or adults patients with AQP4-IgG seropositive or -seronegative NMOSD. Patients were randomly assigned in a 1:1 ratio to receive either satralizumab, at a dose of 120 mg, or placebo, administered subcutaneously at weeks 0, 2, and 4 and every 4 weeks thereafter, added to stable IST. The randomization was stratified by baseline ARR (1 vs. >1) and by geographical region (Asia vs. Europe or others).

The DB period was planned to end after the occurrence of 26 PDRs, on the basis of the sample-size and power calculations. Patients who had a relapse that led to treatment with rescue therapy or who had a PDR as adjudicated by the Clinical Endpoint Committee, as well as patients who remained in the trial when the pre-specified number of 26 PDRs had occurred, were eligible to enter the OLE period. The DB period for each patient continued until they received their first dose in the OLE. During the extension period, patients received satralizumab with or without baseline treatment; change or discontinuation of baseline treatment was permitted.

Clinical cut-off was 6 June 2018, which was the end of the DB period. The median treatment duration in the DB period was 121.1 weeks (54.12 PY) for the satralizumab treated group and 31.4 weeks (34.44 PY) for the placebo treated group.

Demographic and disease characteristics at baseline of the main study population and the AQP4-IgG seropositive population are presented in **Table 3** [2] (data on file).

Table 3 Demographic and disease characteristics of participants at baseline in SAkuraSky*

Characteristics	Main population		AQP4-IgG seropositive population	
	Satralizumab+IST (N=41)	Placebo+IST (N=42)	Satralizumab+IST (N=27)	Placebo+IST (N=28)
Age - years				
Mean	40.8 ± 16.1	43.4 ± 12.0	44.4 ± 15.7	43.4 ± 12.9
Range	13–73	14–65	13-73	14-65
Female sex - no. (%)	37 (90%)	40 (95%)	27 (100%)	28 (100%)
Age at clinical presentation - years	35.4 ± 16.9	38.8 ± 12.0	NR	NR
Geographic region - no. (%)				
Asia	16 (39%)	18 (43%)	13 (48%)	13 (46%)
Europe or other†	25 (61%)	24 (57%)	14 (52%)	15 (54%)
Diagnosis - no. (%)‡				
Neuromyelitis optica	33 (80%)	28 (67%)	19 (70%)	14 (50%)
Neuromyelitis optica spectrum disorder	8 (20%)	14 (33%)	8 (30%)	14 (50%)
AQP4-IgG–seropositive status - no. (%)	27 (66%)	28 (67%)	NA	NA
Annualized relapse rate in previous 2 yr	1.5 ± 0.5	1.4 ± 0.5	1.39 ± 0.51	1.41 ± 0.55
EDSS score§	3.83 ± 1.57	3.63 ± 1.32	4.30 ± 1.58	3.70 ± 1.44
VAS pain score¶	27.6 ± 28.2	34.6 ± 26.1	NR	NR
FACIT-F score‖	34.7 ± 10.5)	33.9 ± 11.3	NR	NR
Treatment at baseline - no. (%)				

Oral glucocorticoids	17 (41%)	20 (48%)	14 (52%)	13 (46%)
Azathioprine	16 (39%)	13 (31%)	11 (41%)	11 (39%)
Mycophenolate mofetil	4 (10%)	8 (19%)	1 (4%)	3 (11%)
Azathioprine plus glucocorticoids	3 (7%)	0	0	0
Mycophenolate mofetil plus oral glucocorticoids	1 (2%)	1 (2%)	1 (4%)	1 (4%)

Data are mean ± SD or n (%). There were no significant differences between groups. There were no missing values for any baseline demographic data. Percentages may not total 100 because of rounding. † Other geographic region refers to the United States. ‡ Patients either had neuromyelitis optica according to published criteria (seropositive or seronegative for antibodies against AQP4-IgG) or had neuromyelitis optica spectrum disorder (AQP4-IgG seropositive status only) according to published criteria with idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral-segment spinal cord lesions on magnetic resonance imaging) or recurrent or simultaneous optic neuritis in both eyes. § Scores on the Expanded Disability Status Scale (EDSS) range from 0 (normal neurologic examination) to 10 (death). ¶ Scores on the visual-analogue scale (VAS) for the assessment of pain range from 0 to 100, with higher scores indicating more pain. ‖ Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) range from 0 to 52, with lower scores indicating more fatigue.

5.1.2 Results per study

The Medicines Council has requested data on the following endpoints:

- Annualized relapse rate (ARR) - critical outcome
- Treatment-related adverse events (AEs) - critical outcome
    - Proportion of patients with at least one serious treatment-related AE
    - Review of safety profile of satralizumab
- Persistent disease worsening according to the Expanded Disability Status Scale (EDSS) - critical outcome
- Visual acuity according to the Snellen chart - important outcome
- Quality of life according to the 36-Item Short Form health survey (SF-36) - important outcome

Results per study are summarized in this section and presented in **Table A3a** in Appendix 9.3. In addition, data are provided on time to first PDR, the primary endpoint in the SAkura studies. As described previously, NMOSD patients experience unpredictable relapses, often directly causing accumulating permanent neurological disability and may be associated with limited recovery after each relapse [4,6,7]. Severe relapses can lead to visual impairment (including blindness), difficulties in walking, para- or tetra-paresis, bowel and bladder dysfunction, and sensory loss [4]. Given the potential of a single relapse to cause significant and permanent disability, prevention of the occurrence of a relapse is key in the treatment of NMOSD. In order to evaluate the effect of satralizumab on relapse prevention, Roche urges the Medicines Council to take these additional data into account in the assessment of satralizumab.

According to dialogue with a Danish clinical expert within the field, time to first relapse (TFR) and ARR are the most appropriate measures to evaluate the effect of new medicines for treatment of NMOSD. While TFR reflects the prevention of an occurrence of relapse, ARR reflects the change in the frequency of relapse, and are thus two very different measures of treatment effect on relapse. Furthermore, given the nature of the disease with relapse being the key determinant of permanent neurological impairment, change in EDSS score is not as critical an endpoint as in multiple sclerosis. It is expected that the effect on relapse seen in the SAkura studies will result in a slower progression of the disease but this cannot be concluded at this point in time. Considerations regarding the choice of endpoints in clinical trial designs in NMOSD are discussed in a report developed by EMA in 2015 [9]. From a clinical perspective, both TFR and ARR are found to be the most relevant endpoints, however, TFR is the most appropriate measure to limit exposure to a potentially ineffective drug in a disabling disease, and should therefore be used as primary outcome [9].

Time to first protocol-defined relapse (PDR)

Time to first relapse based on PDR was the primary endpoint in both SAkura studies. Time to first relapse is defined as the time from the date of the randomization until the first occurrence of relapse throughout the DB period. The endpoint reflects the prevention of an occurrence of relapse, which is often accompanied by long-lasting neurological disability. A PDR was defined as a clinical relapse confirmed as PDR by the Clinical Endpoint Committee. In line with the definition in the Medicines Council protocol, a clinical relapse was considered a PDR if new or worsening neurological symptoms attributable to NMOSD persisted for >24 hours and were not attributable to confounding clinical factors. The neurologic symptoms had to meet either of the following:

1. An increase of at least 1.0 point on the EDSS score, or a 2.0 point increase if the baseline EDSS was zero.
2. An increase of at least 2.0 points on one of the appropriate Functional Systems Scores (FSS).
3. An increase of at least 1.0 point on two or more of the appropriate FSS if the baseline score was one or more.
4. An increase of at least 1.0 point in single eye FSS when the baseline score in that eye was one or more.

The basis of comparison for the increase was the score at the most recent EDSS/FSS assessment visit. An appropriate FSS change was one that affected at least one of the following functional systems: pyramidal, cerebellar, brainstem, sensory, bowel/bladder or visual (single eye). Sexual dysfunction and cerebral function did not suffice to establish a PDR. Reoccurrence of symptoms within 31 days was considered part of the same relapse. The reported date of onset of the first relapse was the 'onset date' for the analysis. Relapses regarded as a PDR by the Clinical Endpoint Committee, and followed by confirmation that EDSS/FSS assessment was performed within 7 days after the patient reported the symptoms to the site, were used for the primary analysis. Any potential relapses not evaluated within 7 days were censored from the primary analysis

The Kaplan-Meier method was used to estimate the distribution of time to first PDR for each treatment group. A two-sided log-rank test was used, stratified by previous therapy for the prevention of NMOSD attack (B-cell-depleting therapy vs immunosuppressants or other) and by the most recent attack in the year before screening (first attack vs relapse). Estimates of the treatment effect were expressed as a hazards ratios (HRs) and 95% confidence intervals (CIs) using a Cox proportional hazards model, again stratified by previous therapy and by the most recent attack in the year before screening. Relapse-free rates based on Kaplan-Meier estimates and their 95% CI at 24-week intervals were used to describe the distribution of time to first PDR in addition to the HR. Patients were censored if they discontinued from the DB period, did not experience a PDR at the end date of the DB period or entered the OLE period after having a clinical relapse before implementation of protocol version 5 (November 5, 2015), which required that patients could enter the OLE only after a PDR that was confirmed by the Clinical Endpoint Committee.

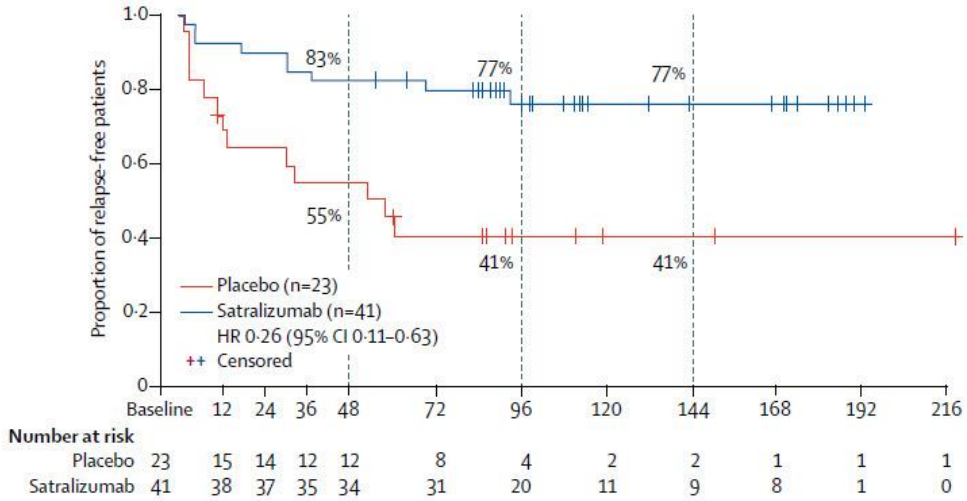
In SAkuraStar, treatment with satralizumab during the DB period led to a statistically significant reduction in the risk of experiencing a PDR by 74% compared to placebo (HR: 0.26; 95% CI, 0.11 to 0.63, p = 0.0014) [1,10,11]. At week 48, the proportion of relapse-free patients in the satralizumab group was 82.9% (95% CI, 67.49 to 91.47) compared with 55.4% (95% CI 32.96 to 73.08) in the placebo group. At week 96, the proportion of patients in the satralizumab group and placebo group was 76.5% (95% CI, 59.22 to 87.21) and 41.1% (20.76 to 60.41), respectively, and remained the same up until the end of the DB period [1,10]. Similar results were observed in SAkuraSky [2,10]. Importantly, treatment with satralizumab reduced the risk of experiencing a severe relapse defined as an EDSS increase ≥ 2 points from the previous EDSS assessment by 79% (HR: 0.21; 95% CI, 0.05 to 0.91; p=0.0231) in SAkuraStar compared to treatment with placebo [10].

Long-term efficacy of satralizumab was assessed in the combined DB and OLE periods of the SAkura studies (CCOD 7 June 2019). As there was no adjudication of PDRs during the OLE period, the definition investigator-assessed PDR was used for efficacy analyses. An investigator-assessed PDR was defined as a relapse determined and reported by the investigator to meet PDR criteria. Analysis of time to first investigator-assessed PDR in the satralizumab group versus the placebo group was based on the original treatment assignment at randomization. Thus, patients who switched from placebo to satralizumab upon entry to the OLE were included in the placebo group, which is likely to reduce the observed difference between groups compared to the DB period. In the pooled analysis, patients originally

randomized to satralizumab had a significant reduction in the risk of experiencing an investigator-assessed PDR by 66% compared to those originally randomized to placebo (HR: 0.34; 95% CI 0.19 to 0.62, p < 0.001) [12].

In conclusion, treatment with satralizumab significantly reduced the risk of experiencing a PDR compared to placebo. At week 96, 76.5% of patients treated with satralizumab were relapse-free compared to 41.1% treated with placebo. A pooled analysis of time to first investigator-assessed PDR showed persistent long-term efficacy of satralizumab.

Figure 1 Time to first PDR during the DB period in the AQP4-IgG seropositive population in SAkuraStar



Patients who did not experience a PDR were censored at the end date of the double-blind period. The dashed lines represent 48 weeks, 96 weeks, and 144 weeks from baseline. The numbers within the figures represent the proportion of relapse-free patients. HR=hazard ratio. NE=not evaluable. Figure from Traboulsee et al. 2020 [1].

Annualized relapse rate (ARR) - critical outcome

The Medicines Council has requested data on the change in ARR and predefined a minimal difference of 0.2 relapse as clinically relevant. ARR, which reflects the annual change in the frequency of relapse, was a secondary endpoint in the SAkura studies.

ARR was calculated based on the total number of PDRs experienced by the patient in each treatment arm, divided by the patient-years at risk for each year of the study period. Patient-year at risk are years calculated using patient event date or censor date. The 95% CI was based on the Poisson distribution. To compare the difference between the two treatment groups, ARR was analysed using a negative binomial regression model with the relapse number as the response variable, and treatment group, prior therapy for prevention of NMOSD attack, and the type of most recent attack in the last year prior to baseline as covariates.

[redacted] ARR adjusted by prior therapy (B-cell-depleting therapy vs. immunosuppressant or others) and most recent attack (first attack or relapse) [redacted] Treatment with satralizumab reduced the adjusted ARR by 90% compared to placebo (rate ratio (RR): 0.10; 95% CI, 0.02 to 0.47; p=0.009) [10]. Similar results were observed in SAkuraSky [10].

In conclusion, treatment with satralizumab led to a statistically significant reduction in adjusted ARR compared to placebo in the DB period.

Treatment-related adverse events (AEs) - critical outcome

In this section, the safety results analysis will be presented in two parts as follows:

- Comparative analyses of serious adverse events (AEs) and serious treatment-related AEs by treatment group in the AQP4-IgG seropositive safety analysis population in the DB period of SAkuraStar.
- Review of the safety profile of satralizumab including descriptive data from the overall satralizumab treatment (OST) period, including all patients who received ≥1 dose of satralizumab in the DB and/or OLE periods of the SAkura studies, in order to present all safety data from patients exposed to satralizumab up to the latest study, CCOD of 18 February 2020.

Proportion of patients with at least one serious treatment-related AE

The Medicines Council has requested data on the change in proportion of patients experiencing a serious treatment-related AE and predefined a minimal difference of 5% as clinically relevant. In addition, for completeness, data are also provided for the rate of serious AEs.

In SAkuraStar, adverse events were analysed in the safety analysis population including all patients who received at least one dose of study treatment. The median duration of treatment exposure in the DB period was 92.3 weeks (80.36 PY) for the satralizumab treated group and 47.6 weeks (26.75 PY) for the placebo treated group.

At CCOD of 12 October 2018, 7 patients (17.1%) in the satralizumab arm and 3 patients (13.0%) in the placebo arm had experienced a serious AE (relative risk (RR): 1.31; 95% CI, 0.37 to 4.58) (data on file). The rate of serious AEs per 100 PY of exposure was 17.42 (95% CI, 9.52 to 29.23) in the satralizumab arm and 11.22 (95% CI, 2.31 to 32.78) in the placebo arm [13]. Only one patient (2.4%) in the satralizumab arm had a serious AE, which was found to be related to treatment. This serious AE was grouped within the System Organ Class (SOC) of infections and infestations or pulmonary sepsis (data on file). The absolute difference between study treatment arms was 2.4% (95% CI is not calculated as the rate in the comparator group is 0%) in favour of placebo, however, the point estimate does not exceed the MCID of 5% prespecified by the Medicines Council expert committee.

In conclusion, no statistically significant differences in the proportion of patients experiencing serious AEs or serious treatment-related AEs were observed between treatment groups in the AQP4-IgG seropositive safety population during the DB period. Long-term safety data from the OST period of SAkuraStar was also assessed up to the CCOD of 18 February 2020. The rate of serious AE per 100 PYs was 12.9 (95% CI, 8.3 to 19.2). This confirmed that longer exposure to satralizumab in the OLE period did not affect the rates of serious AEs [13].

Review of safety profile for satralizumab

In the following the safety profile for satralizumab will be presented. This will include:

- **Safety data from AQP4-IgG seropositive patients in SAkuraStar:** This section will contain data from the DB period and the overall period including the OST in order to present all safety data from patients exposed to satralizumab monotherapy up to the CCOD of 18 February 2020 [13]. Considering the longer overall exposure time to the study treatment in the satralizumab group compared with the placebo group, data is summarized as exposure-adjusted rates in order to adjust for the difference in observation periods between the two groups, which is considered to be an appropriate way to compare the AE profiles.
- **Safety data from the total safety population:** In line with the SPC as requested by the Medicines Council, this section will contain descriptive data from the total safety population from the primary analysis of the DB period and the OST period of SAkuraStar and SAkuraSky. The total exposure of 104 patients treated with

satralizumab during the DB period (41 in SAkuraSky and 63 in SAkuraStar was 193.74 PY). During the DB period in the pooled data set 90 patients treated with satralizumab were exposed up to 23 weeks, 72 patients at least 48 weeks and 48 patients at least 95 weeks. In general, the exposure to satralizumab during the DB period in the pooled data set was longer (median 93.7 weeks) compared to exposure to placebo (median 42.6 weeks). The age of the patients stretches from 13 to 73 years old in the pooled data set from the SAkura studies. Updated safety of satralizumab based on pooled data from the phase 3 studies were presented at EAN 2020 with CCOD June 7, 2019. This included 166 patients exposed to at least one dose of satralizumab with a mean exposure of 133.3 ± 74.5 weeks, 437.7 PYs [14].

Review of safety profile from SAkuraStar, AQP4-IgG seropositive patients

Table 4 provides an overview of the rates of AEs and serious AEs in the AQP4-IgG seropositive population in both the DB period and the OLE period (CCOD 18 February 2020). In SAkuraStar, a total of 64 patients received at least one dose of study treatment (placebo or satralizumab) during the DB period; 23 patients in the placebo group and 41 patients in the satralizumab group with a total of 26.75 PY and 80.36 PY, respectively.

The rate of AEs, serious AEs, infections and serious infections were comparable between the satralizumab group and the placebo group in the DB period of the study, and remained consistent in the OLE period. The most common infections during the OST period (including all patients who received ≥1 dose of satralizumab in the DB period and/or OLE period) were urinary tract infections (35 events, 18.8 (95% CI, 13.1 to 26.1) events/100 PY), upper respiratory tract infections (29 events, 15.6 (95% CI, 10.4 to 22.3) events/100 PY), and nasopharyngitis (14 events, 7.5 (95% CI, 4.1 to 12.6) events/100 PY). Rates of infections and serious infections were evaluated in the OST period for Years 1 to 5, and there was no observed increase in rates over time. Additional information on the safety of satralizumab and placebo groups during the DB period and during the OST period are presented in (**Table 4**) [13].

Table 4 Rates of AEs and serious AEs in the AQP4-IgG seropositive population in the DB and OLE periods

	Double-blind period						OST* period, Satralizumab (n=62; 186.5 PY)		
	Placebo (n=23; 26.8 PY)			Satralizumab (n=41; 80.4 PY)					
	No. of patients (%)	No. of AEs	AEs/ 100PY (95% CI)	No. of patients (%)	No. of AEs	AEs/ 100PY (95% CI)	No. of patients (%)	No. of AEs	AEs/ 100PY (95% CI)
AEs	16 (69.6)	139	519.7 (436.9–613.6)	36 (87.7)	354	440.5 (395.8–488.9)	61 (98.4%)	695	372.7 (345.5–401.5)
Serious AEs	3 (13.0)	3	11.2 (2.3–32.8)	7 (17.1)	14	17.4 (9.5–29.2)	12 (19.4%)	24	12.9 (8.3–19.2)
Infections	10 (43.5)	42	157.0 (113.2–212.3)	22 (53.7)	75	93.3 (73.4–117.0)	35 (56.5%)	148	79.4 (67.1–93.2)
Serious infections	1 (4.3)	1	3.7 (0.1–20.8)	4 (9.8)	4	5.0 (1.4–12.7)	5 (8.1%)	5	2.7 (0.9–6.3)

SAkuraStar, CCOD February 2020. *The overall satralizumab treatment (OST) period refers to all patients who received ≥1 dose of satralizumab in the DB and/or OLE period, up to a CCOD of 18th February 2020 [13] (data on file).

Review of safety profile from the total safety population

The most frequently reported adverse reactions observed were headache (19.2%), arthralgia (13.5%), white blood cell count decreased (13.5%), hyperlipidaemia (13.5%), and injection-related reactions (12.5%) [10].

In both studies, the most commonly reported AEs by SOC were infections and infestations in both treatment groups.

Selected AEs of special interest and safety in special populations

Infections: The incidence rates of infectious AEs were higher in both treatment arms, with a slightly higher incidence in the satralizumab group than the placebo group (SAkuraSky: 68.3% vs 61.9% and SAkuraStar 54% vs 43.8%). A higher proportion of patients reported severe infectious AEs in the satralizumab treatment arm (9.5%, 6.08 events/100 PY) compared to placebo (3.1%, 2.46 events/100 PY) in SAkuraStar.

Serious infections: The incidence of serious infection AEs, under the basket of lower respiratory tract infections, was numerically higher in satralizumab group versus the placebo group (5.68 events/100 PY vs 4 events/100 PY) including bronchitis (3.61 events/100 PY vs 3 events/100 PY), pneumonia (1.55 events/100 PY vs 0 events/100 PY) and pulmonary sepsis (0.52 events/100 PY vs 0 events/100 PY).

Malignancies: Three different types of malignancies were reported in three patients. Two were in the placebo group and one event of squamous cell carcinoma in the satralizumab group was judged as not related to the study drug.

AQP4-IgG seropositive: In the phase 3 studies, the proportion of AQP4-IgG seronegative patients was approximately the intended 30% (AQP4-IgG seropositive: 119 patients; AQP4-IgG seronegative: 59 patients). The incidence of infections in the satralizumab group (102.62 events/100 PY) was lower than in the placebo group (173.24 events/100 PY) in AQP4-IgG seropositive patients [11].

Adolescents: A total of 7 adolescent patients (defined as 12-17 years of age, N=4 in the satralizumab group), representing 3.9% of the total number of patients in the pooled population, were enrolled in SAkuraSky prior to the CCOD. Five adolescent patients reported 28 AEs during the DB period. All AEs were mild or moderate and resolved, and none led to discontinued treatment. Five events experienced by one patient were considered related to study treatment by the investigator.

Pregnancy: There is no data on the use of satralizumab in pregnant women. A global single-arm pregnancy safety study to collect information for 10 years on pregnancy complications and birth outcomes in women exposed to satralizumab during pregnancy in patients with NMOSD is agreed with EMA.

Discontinuation due to AES: AEs leading to discontinuation from treatment were described for eight cases in seven patients. Discontinuations in the DB period were in the satralizumab group of SAkuraSky increased transaminases, decreased neutrophil count and urticaria. In SAkuraStar, one patient treated with satralizumab discontinued treatment due to serious pneumonia, and one patient treated with placebo discontinued due to systemic lupus erythematosus. AEs leading to discontinuation from treatment in the OLE period were in SAkuraSky cases of endocarditis (serious), vasculitis, and infectious enterocolitis (serious). None was reported in SAkuraStar. The case of vasculitis was deemed mild but it had recurred and led to withdrawal.

Updated safety data including the OST

Consistent with the DB period, the most frequently reported AEs in the OST period were those belonging to the SOC Infections and Infestations. The safety profile of satralizumab in the OST period was consistent with the DB period. Overall, the rates of infections (in terms of events per 100 PYs) with satralizumab in the OST periods did not increase over the period of observation in either the SAkuraSky or the SAkuraStar study [14].

Conclusion

Overall, satralizumab displayed a favourable safety profile. The proportion of patients experiencing AEs and serious AEs were comparable in satralizumab and placebo arms with a slightly higher proportion in the satralizumab arm. The

majority of AEs were reported mild to moderate. The rates of AEs, including infections and serious infections, were similar between groups in both the SAkuraStar and SAkuraSky study. There were no deaths and no anaphylactic reactions reported in any of the studies. The overall safety profile for the pooled AQP4-IgG seropositive population was consistent with that reported for the satralizumab group in the DB period [11].

For a more complete presentation of the safety profile, refer to the SPC and the EPAR for satralizumab. The OLE studies are ongoing with a relatively high percentage of patients continuing, so additional long-term safety data can be collected at a later stage.

Persistent disease worsening according to EDSS - critical outcome

The Medicines Council has requested data on the mean change in EDSS score at 1 year and predefined a minimal difference of 0.2 points as clinically relevant. The EDSS is used as a quantitative measure of disability and for the assessment of relapse severity. In the SAkura studies, change in EDSS score was a secondary endpoint. EDSS is scored on a scale of 0-10 with higher scores representing increased disability. EDSS scores were measured at baseline, every 24 weeks during the DB period, and within seven days of a relapse. Because patients are only included in the mean change analysis at pre-specified time points up to the point of PDR, relapse associated disability changes cannot be determined using this measure.

Mean change in EDSS score from baseline to every 24 weeks during the DB period was analysed with a mixed-effect model of repeated measures (MMRM) using a Toeplitz covariance matrix. The MMRM includes treatment group, protocol-specified visit, treatment-by-visit interaction as fixed effects; the baseline measurements as covariates; and visit as a repeated measure.

Mean change from baseline in EDSS score at 24 weeks intervals during the DB period of SAkuraStar is presented in **Table S1** in Appendix 9.5 (data on file). There was no consistent difference in EDSS score from baseline to every 24 weeks between patients receiving satralizumab and those receiving placebo in SAkuraStar (data on file). Similar results were observed in SAkuraSky (data on file). At 48 weeks, the mean change from baseline in EDSS score was -0.52 (SE, 0.18; 95% CI, -0.87 to -0.16) in the satralizumab arm and -0.17 (SE, 0.22; 95% CI, -0.60 to 0.27) in the placebo arm. The difference in mean change in EDSS score between study treatments was -0.35 (SE, 0.23, 95% CI, -0.81 to 0.10, p = 0.12) (**Table 5**) (data on file). The point estimate is favourable towards satralizumab, and does exceed the MCID of 0.2 points prespecified by the Medicines Council expert committee. However, the confidence interval contains 0, and thus, the analysis shows no statistically significant difference between treatments.

Time to EDSS score worsening during the DB period was compared between the satralizumab group and the placebo group. In line with the description in the Medicines Council protocol, EDSS worsening was defined as a worsening of at least 2 points when baseline EDSS score was zero, a worsening of at least 1 point when baseline score was between 1 and 5, or a worsening of at least 0.5 points when baseline EDSS score was above 5. Treatment with satralizumab significantly reduced the risk of EDSS worsening in SAkuraStar (HR: 0.34; 95% CI 0.14 to 0.82; p = 0.0124). In SAkuraSky HR was 0.36 (95% CI, 0.12 to 1.06; p = 0.0529) (data on file).

In conclusion, EDSS scores remained relatively stable across the 24-week intervals in each study treatment arm and no statistically significant differences were observed between treatments. This is consistent with the observation that remaining relapse-free is associated with neurological stability [4]. The risk of EDSS score worsening over time was significantly reduced in patients receiving satralizumab compared to those receiving placebo, which is in line with the results of the primary study endpoint.

Table 5 Change from baseline in EDSS score at 48 weeks during the BD period

	Satralizumab (N=41)	Placebo (N=23)

Baseline		
n	37	14
Mean	4.041 (0.242)	3.179 (0.408)
Week 48		
n	33	12
Adjusted Mean (SE) 95% CI	-0.518 (0.178) (-0.874,-0.162)	-0.165 (0.216) (-0.595,0.265)
Difference in Adjusted Means (SE) 95% CI p-value	-0.353 (0.228) (-0.806,0.100) 0.1249	-

Visual acuity according to Snellen chart - important outcome

The Medicines Council has requested data on the mean change in visual acuity according to Snellen chart at 1 year and predefined a minimal difference of 0.2 points as clinically relevant. Visual acuity measured with the 20-foot Snellen chart was a secondary endpoint in both SAkura studies. Scores were measured at baseline and every 24 weeks during the DB period. Patients are only included in the analysis at pre-specified time points up to the point of PDR, and therefore relapse associated changes in visual acuity cannot be determined.

Mean change in visual score from baseline to every 24 weeks was with a MMRM analysis using unstructured covariance matrix. The MMRM includes treatment group, protocol-specified visit, treatment-by-visit interaction as fixed effects; the baseline measurements and stratification variables as covariates; and visit as a repeated measure. To calculate change from baseline, visual acuity scores were converted to logMAR visual acuity scoring.

Mean change from baseline in visual score at 24 weeks intervals during the DB period of SAkuraStar is presented in **Table S2** and **Table S3** in Appendix 9.5 (data on file). There was no apparent difference between the two treatment groups. Similar results were seen in SAkuraSky (Data on file). At 48 weeks, the mean change from baseline in visual score on the right eye was -0.02 (SE, 0.11; 95% CI, -0.23 to 0.20) in the satralizumab arm and -0.07 (SE, 0.14; 95% CI, -0.34 to 0.20) in the placebo arm. The mean change from baseline in visual score on the left eye was 0.17 (SE, 0.26, 95% CI, -0.35 to 0.69) in the satralizumab arm and 0.18 (SE, 0.24; 95% CI, -0.30 to 0.66) in the placebo arm. The difference between study treatment arms was 0.05 (SE, 0.14; 95% CI, -0.23 to 0.34, p = 0.71) on the right eye and -0.01 (SE, 0.21; 95% CI, -0.43 to 0.40, p = 0.95) on the left eye (**Table 6**) (Data on file). The point estimates on either eye do not exceed the MCID of 0.2 points prespecified by the Medicines Council expert committee. The confidence intervals include 0, and thus, the analyses show no statistically significant differences between study treatment arms.

In conclusion, visual scores remained stable across the 24-week intervals in each study treatment arm, which is consistent with the observation that remaining relapse-free is associated with neurological stability [4].

Table 6 Change from baseline in visual score at 48 weeks during the DB period

	Right eye		Left eye	
	Satralizumab (N=41)	Placebo (N=23)	Satralizumab (N=41)	Placebo (N=23)

Baseline				
n	37	14	37	14
Mean	0.540 (0.120)	0.436 (0.216)	0.653 (0.153)	0.454 (0.228)
Week 48				
n	33	12	33	12
Adjusted Mean (SE) 95% CI	-0.017 (0.108) (-0.234, 0.200)	-0.071 (0.135) (-0.341, 0.199)	0.167 (0.258) (-0.353,0.688)	0.181 (0.239) (-0.299,0.661)
Difference in Adjusted Means (SE) 95% CI p-value	0.054 (0.142) (-0.232,0.339) 0.7074		-0.014 (0.205) (-0.425,0.398) 0.9473	

Quality of life according to SF-36 - important outcome

The Medicines Council has requested data on the mean change in SF-36 and predefined a minimal difference of 0.5 SD as clinically relevant. Health related quality of life measured with SF-36 version 2 was a secondary endpoint in both SAkura studies. Component summary scores (Physical and Mental) and domain scores (Physical functioning, Role limitations due to physical health, Role limitations due to emotional problems, Vitality, Mental Health, Social functioning, Bodily Pain and General health) were derived for the SF-36v2 at baseline and every 24 weeks. In the following, only data for the component summary scores are presented. Scores range from 0-100 and higher scores indicate better quality of life. Patients are only included in the analysis at pre-specified time points up to the point of PDR, and therefore relapse associated changes in quality of life cannot be determined.

Change from baseline in components summary scores to every 24 weeks during the DB period was analysed with a MMRM using unstructured covariance matrix. The MMRM includes treatment group, protocol-specified visit, treatment-by-visit interaction as fixed effects; the baseline measurements and stratification variables as covariates; and visit as a repeated measure.

Mean change in score from baseline at every 24 weeks is presented in **Table S4** and **Table S5** in Appendix 9.5. In general, summary component scores improved from baseline in both treatment groups during the DB period of SAkuraStar. There was a trend towards greater increases in the mental health component summary (MCS) scores in the satralizumab group in comparison to the placebo group, and no differences between groups on the physical component summary (PCS) scores (data on file). There were no consistent differences between the satralizumab and the placebo group in the component summary scores at the 24-week intervals of SAkuraSky (data on file).

At the 48-week interval of SAkuraStar, the mean change from baseline in MCS score was 5.58 (SE, 1.88; 95% CI, 1.82 to 9.34) in the satralizumab arm and 0.48 (SE, 2.46; 95% CI, -4.48 to 5.44) in the placebo arm. The difference between study treatment arms was 5.10 (SE, 2.71; 95% CI, -0.36 to 10.57, p = 0.07) (**Table 7**) (Data on file). The point estimate is favourable towards satralizumab, and does exceed the MCID of 0.5 SD prespecified by the Medicines Council expert committee. The confidence interval includes 0, and thus, the analysis shows no statistically significant differences between study treatments arms. The mean change from baseline in PCS score was 5.37 (SE, 1.32; 95% CI, 2.70 to 8.03) in the satralizumab arm and 5.43 (SE, 1.53; 95% CI, -3.32 to 3.19) in the placebo arm. The difference between study treatment arms was -0.07 (SE, 1.61; 95% CI, -0.23 to 0.34, p = 0.97) (**Table 8**) (Data on file). The point estimate is favourable towards placebo, but does not exceed the MCID of 0.5 SD. The confidence interval includes 0, and thus, the analysis shows no statistically significant differences between study treatments arms.

In conclusion, there was a trend towards greater increases in the MCS scores in the satralizumab group compared to the placebo group, and no differences in PCS scores between groups.

Table 7 Change from baseline in SF-36 MCS scores at 48 weeks during the DB period

	Satralizumab (N=41)	Placebo (N=23)
Baseline		
n	37	14
Mean	46.433 (1.655)	46.444 (2.922)
Week 48		
n	33	12
Adjusted Mean (SE) 95% CI	5.579 (1.875) (1.816,9.342)	0.478 (2.463) (-4.481,5.437)
Difference in Adjusted Means (SE) 95% CI p-value	5.101 (2.709) (-0.363,10.566) 0.0665	

Table 8 Change from baseline in SF-36 PCS scores at 48 weeks during the DB period

	Satralizumab (N=41)	Placebo (N=23)
Baseline		
n	37	14
Mean	39.593 (1.702)	44.092 (3.268)
Week 48		
n	33	12
Adjusted Mean (SE) 95% CI	5.366 (1.319) (2.702,8.030)	5.431 (1.528) (2.343,8.519)
Difference in Adjusted Means (SE) 95% CI p-value	-0.065 (1.606) (-3.315,3.185) 0.9679	

5.1.3 Comparative analyses

Results are described in the previous section (Results per study).

6. Other considerations

6.1 Satralizumab in combination with immunosuppressant treatment

Satralizumab has demonstrated superior efficacy compared to placebo both as monotherapy and in combination with IST. As stated by the Medicines Council, the monotherapy data from SAkuraStar is most representative of the way satralizumab is planned to be used in Denmark. However, the data from SAkuraSky that has also been included in this application shows that addition of satralizumab to IST is more efficient than using IST alone, supporting the overall use of satralizumab in NMOSD.

6.2 Interleukin-6 inhibition in NMOSD

The following section will describe the mode of action for the only EMA approved IL-6 inhibitor in NMOSD; satralizumab. Satralizumab is a recombinant humanised immunoglobulin G2 (IgG2) monoclonal antibody (mAb) that binds to soluble and membrane-bound human interleukin (IL)-6 receptor (IL-6R) and thereby prevents IL-6 downstream signalling through these receptors. IL-6 levels are increased in cerebrospinal fluid and serum of patients with NMO and NMOSD during periods of disease activity. IL-6 functions have been implicated in the pathogenesis of NMO and NMOSD, including B-cell activation, differentiation of B-cells to plasmablasts and production of pathological autoantibodies, e.g. against AQP4, a water channel protein mainly expressed by astrocytes in the CNS, Th17-cell activation and differentiation, T-regulatory cell inhibition, and changes in blood-brain-barrier permeability [10].

Satralizumab was developed using recycling antibody technology, which allows the antibody to dissociate from the receptors at an acidic pH within endosomes, thus allowing it to be released back into the bloodstream to bind to antigen multiple times, thus increasing its half-life in plasma. Satralizumab was engineered to ensure sustained suppression of IL-6 signalling, minimize safety risks, and enable convenient dosing for patients with NMOSD. The antigen-binding fragment (Fab) was engineered for high-affinity binding to the mIL-6R and sIL-6R under neutral pH condition [2,11,15].

6.3 Vaccinations

Live and live-attenuated vaccines should not be given concurrently with satralizumab, as clinical safety has not been established. The interval between live vaccinations and initiation of satralizumab treatment should be in accordance with current vaccination guidelines regarding immunomodulatory or immunosuppressive agents.

No data are available on the effects of vaccination in patients receiving satralizumab. It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating satralizumab treatment [10].

No other vaccinations are required before initiating satralizumab treatment.

7. Conclusion

Satralizumab is the first and only treatment approved for both adults and adolescents with AQP4-IgG seropositive NMOSD in the EU. These patients are currently treated with “off-label” therapies based on sparse evidence. The need for therapeutic options is underlined by the fact that the risk-benefit ratio of unapproved therapies is not yet well

understood. Satralizumab addresses the unmet need in relapse prevention with evidence from the global phase 3 randomized controlled trials SAkuraSky and SAkuraStar. The design of SAkuraStar, which assessed satralizumab in a monotherapy setting, better reflects the current clinical practice in Denmark, and thus SAkuraStar is used as the main source of evidence in this submission. In order to provide additional evidence for the efficacy and safety of satralizumab, results from SAkuraSky, which evaluated satralizumab in an IST add-on setting, is also included.

The evidence presented in this submission demonstrates that satralizumab provides a valuable therapeutic option for patients with AQP4-IgG seropositive NMOSD. Treatment with satralizumab as monotherapy significantly reduced the risk of experiencing a PDR compared to placebo by 74% in the DB period of SAkuraStar. At week 96, 76.5% of patients treated with satralizumab were relapse-free compared to 41.1% treated with placebo. Analysis of long-term efficacy of satralizumab showed a sustained effect on reduction of risk of relapse. Moreover, treatment with satralizumab significantly reduced the frequency of relapse compared to placebo in the DB period of SAkuraStar. No significant differences between satralizumab and placebo were observed for mean change in either EDSS score, visual score and SF-36 score at the 48-week treatment interval. In terms of interpretation, it is important to note that relapse associated changes cannot be determined using these measures as patients were only included in analyses at 24-week intervals up to the point of PDR. Assessment of time to EDSS score worsening in SAkuraStar did however show that treatment with satralizumab significantly reduced the risk of EDSS worsening. Safety analysis of satralizumab in the AQP4-IgG seropositive population and the total safety population, demonstrated that satralizumab is a safe and tolerable therapy. The proportion of patients experiencing AEs and serious AEs were comparable between satralizumab and placebo treatment groups with a slightly higher incidence of events in the satralizumab group. The majority of AEs were reported mild to moderate and the rates of AEs, including infections and serious infections, were similar between treatment groups.

Overall, satralizumab monotherapy has demonstrated superior efficacy compared to placebo in the AQP4-IgG seropositive population, with a favourable safety profile. Data from SAkuraSky - in terms of both efficacy and safety - further supports the use of satralizumab in NMOSD.

8. References

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9. Appendices

9.1 Literature search

A literature search has not been requested in the Medicines Council protocol.

9.2 Main characteristics of included studies

Table A2a Main study characteristics of SAkuraStar	
Trial name	SAkuraStar
NCT number	NCT02073279
Objective	To evaluate the efficacy and safety of satralizumab monotherapy compared to placebo in patients with NMO and NMOSD.
Publications – title, author, journal, year	Traboulsee, A. et. al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder- a randomized double-blind, multicenter placebo-controlled phase 3 trial. Lancet, 2020, 19:402-412, incl. supplementary material.
Study type and design	SAkuraStar was a phase 3, multicenter, randomized, international, double-blind, placebo-controlled parallel assignment study of satralizumab monotherapy (ISTs were prohibited, only rescue therapy allowed). Patients were randomized 2:1 (satralizumab or placebo). Randomization was stratified by prior therapy for relapse prevention (B-cell-depleting therapy or immunosuppressants/others) and nature of the most recent attack in the year prior to screening (patient's first clinical attack vs relapse). The double-blind period was initially planned to end after 44 protocol-defined relapses occurred, based on sample size and power calculations. To prevent prolonged exposure to a drug with unknown risk-benefit balance, the end of the double-blind period was later modified to include a maximal duration of 1.5 years after random assignment of the last patient enrolled. Patients experiencing a relapse requiring treatment with rescue therapy and/or a protocol-defined relapse adjudicated by the Clinical Endpoint Committee, or those who remained in the trial when the double-blind period ended, were eligible to enter an open-label extension period until commercial availability of satralizumab. Status of the SAkuraSTAR as per September 2020: patients can continue in the OLE phase until local approval in the respective study participant country. At this point, they will be offered to participate in SAkura Moon (see below).
Follow-up time	The clinical cut-off was October 12, 2018 (end of blinded phase). The mean treatment duration in the double-blind phase was 92.3 weeks (range 0-202) for the satralizumab treated group and the mean treatment duration was 54.6 weeks (range 2-216) for the placebo treated group. Patients from SAkuraSTAR (and SAkuraSky) will be offered participation in SAkura Moon from local approval of drug. Sakura Moon to begin Q1 2021 until 3 years after FPI (Q1 2024). Estimated cumulative number of patient years by Q1 2024 is 953 (106 patients pooled from both studies).

Population (inclusion and exclusion criteria)	Inclusion criteria: ● Adolescents or adults (aged 18–74 years) with either: 1. Neuromyelitis optica (NMO) as defined by Wingerchuk et al. 2006 criteria with any AQP4-IgG status 2. AQP4-IgG seropositive NMOSD at screening defined by either of the following Wingerchuck 2007 criteria: a) idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord magnetic resonance imaging [MRI] lesion) b) Single, recurrent or simultaneous bilateral optic neuritis ● At least one documented relapse (including first attack) in the last 12 months prior to screening ● Eligible Expanded Disability Status Scale score of 0 to 6.5 at screening Exclusion criteria: ● Clinical relapse onset (including first attack) ≤30 days prior to screening ● Prior treatment with any agent targeting the IL-6 pathway, alemtuzumab, total body irradiation, or bone-marrow transplantation at any time ● Treatment with anti-CD20, eculizumab, anti-B lymphocyte stimulator, or any other MS disease-modifying within 6 months prior to baseline ● Treatment with anti-CD4 agents, cladribine, cyclophosphamide or mitoxantrone within 2 years prior to baseline. ● Treatment with any investigational agent within 3 months prior to baseline. ● A series of exclusions for general safety: a) Pregnancy, lactation or not willing to use study defined contraception during the treatment period and at least three months after study period. b) Surgical procedures within 4 weeks prior to baseline (except minors). c) Other demyelination disease or PML. d) Serious concomitant diseases. e) Known active infection within 4 weeks prior to baseline. f) Chronic active hepatitis B or C. g) History of drug or alcohol abuse within 1 year prior to baseline. h) History of diverticulitis – that may lead to increased risk of complications. i) Active tuberculosis. j) Active interstitial lung disease. k) Receipt of live or live attenuated vaccine within 6 weeks prior to baseline. l) History of malignancy within the last five years. m) History of severe allergic reaction to a biological agent. n) Active suicidal ideation within 6 months prior to screening or suicide attempt within three years prior to screening. ● Exclusion for laboratory abnormalities at screening: a) White blood cells $<3.0x10^3/\mu l$ b) Absolute neutrophil count $<2.0x10^3/\mu l$ c) Absolute lymphocyte count $<0.5x10^3/\mu l$ d) Platelet count $<10x10^4/\mu l$ e) Aspartate aminotransferase or alanine aminotransferase > 1.5 times the upper limit of normal.
Intervention	Satralizumab 120 mg subcutaneously at week 0, 2, and 4, and every 4 weeks thereafter. 63 patients were assigned to satralizumab.
Baseline characteristics	Presented in **Table 2**

Primary and secondary endpoints	The primary efficacy endpoint first protocol-defined relapse in the double-blind period in a time-to-event-analysis. • Protocol-defined relapses are clinical relapses fulfilling specific criteria tailored for NMOSD. Protocol-defined relapses were adjudicated by a Clinical Endpoint Committee masked to treatment assignment. The Key secondary efficacy endpoints were change in Visual Analog Scale (VAS, score 1-100) score for pain and in Functional Assessment of Chronic Illness Therapy Fatigue score (FACIT-F, score 0-52), from baseline to week 24. Additional secondary endpoints were change in scores from baseline to Week 24 in: Short Form Health Survey (SF-36, eight sections with scores transformed to 0 to 100); EuroQol-5 dimensions (EQ-5D, score scale -0.109 to 1); modified Rankin Scale (mRS, scores from 0 to 6); Zarit Burden Interview (ZBI, scored from 0-88); EDSS; visual acuity (Snellen chart), and proportion of relapse-free patients, annualized relapse rate (ARR). Safety outcome measures included incidence and severity of AEs, serious AEs, and selected AEs. Relapses were not categorized as adverse events.
Method of analysis	Efficacy analyses were based on the intention-to-treat population. Primary analysis was planned for the earlier of 44 protocol-defined relapses or 1.5 years after randomization of the last patient. A two-sided log-rank test was used, stratified by prior therapy for prevention of attacks (B-cell-depleting or immunosuppressants/other) and by most recent attack in the year prior to screening (first attack vs relapse). The Kaplan–Meier method was used to estimate the distribution of time to first protocol-defined relapse. Relapse-free rates and their 95% confidence intervals (CIs), in addition to the hazard ratios (HRs), were used to describe the distribution of time to first protocol-defined relapse. Treatment effect was expressed as HRs and 95% CIs using Cox proportional-hazards model. For secondary endpoints ANCOVA was used including the treatment group as a fixed measurement and stratification factors as covariates. Endpoints were analyzed in hierarchical order.
Subgroup analyses	Based on the pre-specified plan in the statistical analysis plan (SAP) for the SAkuraStar study an analysis of time to first protocol-defined relapse were performed (as described above) for the following subgroups: • AQP4-IgG serostatus at screening (positive/negative by Enzyme-Linked ImmunoSorbent Assay [ELISA]) • Baseline ARR • Region • Baseline treatments • ADA (anti-drug antibodies)

Table A2b Main study characteristics - SAkuraSky	
Trial name	SAkuraSky
NCT number	NCT02028884
Objective	To evaluate the efficacy and safety of satralizumab as add-on therapy compared to placebo in patients with NMO and NMOSD

Publications – title, author, journal, year	Yamamura, Y. et. al. Trial of satralizumab in neuromyelitis optica spectrum disorder. NEJM, 2019, 381:2114-24, incl. supplementary material.
Study type and design	SAkuraSky was a phase 3, randomized, multicenter, international, double-blind, placebo-controlled, parallel-assignment trial of satralizumab as add-on therapy to stable doses of baseline immunosuppressant treatment. Patients were randomly assigned in a 1:1 ratio to receive satralizumab or placebo. The randomization was stratified by baseline annualized relapse rate (ARR) and by geographical region (Asia vs Europe/others). The double-blind period was planned to end after the occurrence of 26 protocol-defined relapses, on the basis of the sample-size and power calculations. Patients who had a relapse that led to treatment with rescue therapy or who had a protocol-defined relapse as adjudicated by the clinical end-point committee, as well as patients who remained in the trial when the pre-specified number of 26 protocol-defined relapses had occurred, were eligible to enter the open-label extension period. The double blind-period for each patient continued until they received their first dose in the OLE. During the extension period, patients received satralizumab with or without baseline treatment; change or discontinuation of baseline treatment was permitted. Safety follow-up was until 12 weeks after the last dose (withdrawal visit/end of extension period) and until 24 weeks after the last dose of satralizumab (48 weeks for adolescents) for patients that withdraw due to a relapse. Status of the SAkuraSky as per September 2020: patients can continue in the OLE phase until local approval in the respective study participant country. At this point they will be offered to participate in SAkura Moon (see below).
Follow-up time	Clinical cut-off was June 6, 2018 (end of blinded phase). The mean treatment duration in the double-blind phase was 107.4 weeks (range 2-224) for the satralizumab treated group and the mean treatment duration was 32.5 weeks (range 0-190) for the placebo treated group. Patients from SAkuraSky and SAkuraStar will be offered participation in SAkura Moon from local approval of the drug. SAkura Moon is to begin Q1 2021 until 3 years after FPI (first patient in) (Q1 2024). Estimated cumulative number of patient years by Q1 2024 is 953 (106 patients pooled from both studies).
Population (inclusion and exclusion criteria)	Inclusion criteria: ● Adolescents or adults (aged 12–74 years) with either: 1. AQP4-IgG seropositive or AQP4-IgG seronegative (limited to approximately 30% of the total adult population, aged 18–74 years, in trial) neuromyelitis optica (NMO) as defined by Wingerchuk et al. 2006 criteria, or 2. AQP4-IgG seropositive NMOSD at screening defined by either of the following Wingerchuck 2007 criteria: a) Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord magnetic resonance imaging (MRI) lesion) b) Recurrent or simultaneous bilateral optic neuritis. c) At least two relapses in the 2 years prior to screening, with at least one in the previous 12 months. ● Eligible Expanded Disability Status Scale score of 0 to 6.5 at screening ● Permitted baseline treatments with stable doses for 8 weeks prior to baseline:

	a) Azathioprine b) Mycophenolate mofetil c) Oral corticosteroids ● For patients aged 12-17 either of the following baseline treatments for relapse were permitted: a) Azathioprine + oral corticosteroids b) Mycophenolate mofetil + cortical steroids Exclusion criteria: ● Prior treatment with any agent targeting the IL-6 pathway, alemtuzumab, total body irradiation, or bone-marrow transplantation at any time ● Treatment with anti-CD20 agents, eculizumab, belimumab, or MS disease-modifying treatment within 6 months prior to baseline ● Treatment with anti-CD4 agents, cladribine, or mitoxantrone within 2 years prior to baseline. ● Treatment with any investigational agent within 3 months prior to baseline. ● A series of exclusions for general safety: a) Pregnancy, lactation or not willing to use study defined contraception during the treatment period and at least three months after study period. b) Surgical procedures within 4 weeks prior to baseline (except minors). c) Other demyelination disease or PML. d) Serious concomitant diseases. e) Known active infection within 4 weeks prior to baseline. f) Chronic active hepatitis B or C. g) History of drug or alcohol abuse within 1 year prior to baseline. h) History of diverticulitis – that may lead to increased risk of complications. i) Active tuberculosis. j) Active interstitial lung disease. k) Receipt of live or live attenuated vaccine within 6 weeks prior to baseline. l) History of malignancy within the last five years. m) History of severe allergic reaction to a biological agent. n) Active suicidal ideation within 6 months prior to screening or suicide attempt within three years prior to screening. ● Exclusion for laboratory abnormalities at screening: a) White blood cells <3.0x103/µl

	b) Absolute neutrophil count <2.0x103/µl c) Absolute lymphocyte count <0.5x103/µl d) Platelet count <10x104/µl e) Aspartate aminotransferase or alanine aminotransferase > 1.5 times the upper limit of normal.
Intervention	Satralizumab 120 mg subcutaneously at week 0, 2, and 4, and every 4 weeks thereafter. There were 41 patients assigned to satralizumab.
Baseline characteristics	Presented in **Table 3**
Primary and secondary endpoints	The primary efficacy endpoint was the first protocol-defined relapse in the double-blind period in a time-to-event-analysis. ● Protocol-defined relapses are clinical relapses fulfilling specific criteria tailored for NMOSD. Protocol-defined relapses were adjudicated by a Clinical Endpoint Committee masked to treatment assignment. Key secondary efficacy endpoints were change in Visual Analog Scale (VAS, score 1-100) score for pain and in Functional Assessment of Chronic Illness Therapy Fatigue score (FACIT-F, score 0-52), from baseline to week 24. Additional secondary endpoints were change in scores from baseline to Week 24 in: Short Form Health Survey (SF-36, eight sections with scores transformed to 0 to 100); EuroQol-5 dimensions (EQ-5D, score scale -0.109 to 1); modified Rankin Scale (mRS, scores from 0 to 6); Zarit Burden Interview (ZBI, scored from 0-88); EDSS; visual acuity (Snellen chart), and proportion of relapse-free patients, annualized relapse rate (ARR). Safety outcome measures included incidence and severity of adverse events and serious adverse events. Relapses were not categorized as adverse events.
Method of analysis	Pre-specified efficacy analyses were based on the intention-to-treat population and an event-driven design. The primary analysis was performed after 26 protocol-defined relapses. The time to first protocol-defined relapse for the satralizumab and placebo groups were compared using a two-sided log-rank test, stratified by baseline annualized relapse rate (ARR; 1 vs more than 1) and geographic region (Asia vs Europe/others). A kaplan–Meier analysis was used to estimate distribution of time to first protocol-defined relapse. The treatment effect was expressed by hazard ratio (HR) and 95% confidence interval (CI) using a Cox proportional-hazards model stratified by baseline ARR and geographic region. For secondary endpoints ANCOVA was used including the treatment group as a fixed measurement and stratification factors as covariates. The endpoints were analyzed in hierarchical order.
Subgroup analyses	Based on the pre-specified plan in the statistical analysis plan (SAP) for the SAkuraSky study an analysis of time to first protocol-defined relapse were performed (as described above) for the following sub-groups: ● AQP4-IgG serostatus at screening (positive/negative by Enzyme-Linked ImmunoSorbent Assay [ELISA]) ● Age ● Baseline ARR ● Region

	● Baseline treatments ● Race ● ADA (anti-drug antibodies) The study was not powered for the sub-group analysis (rare disease with limited number of patients enrolled).

9.3 Results per study

Table A3a Results of study SAkuraStar

Trial name:	SAkuraStar										
NCT number:	NCT02073279										
				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**		
Adjusted ARR	Satralizumab	41	0.26 (0.08-0.95)	-2.58	-2.80;-1.51	NA	RR: 0.10	0.02-0.47	0.009	ARR was calculated based on the total number of PDRs experienced by the patient in each treatment arm, divided by the PYs at risk for each year of the study period. The 95% CI was based on the Poisson distribution. To compare the difference between the two treatment groups, ARR was analysed using a negative binomial regression model with the relapse number as the response variable, and treatment group, prior therapy for prevention of NMOSD attack, and the type of most recent attack in the	CCOD: 12 Oct 2018 (DB period) SPC [10], data on file
	Placebo	23	2.85 (0.05-0.22)								

									last year prior to baseline as covariates. The absolute difference and 95% CI were estimated by applying the resulting RR and the ACR of 2.85.	
Serious AEs Patients – no. (%)	Satralizumab	41	7 (17.1%)	4.03	-8.19-46.54	NA	RR: 1.31	0.37-4.58	NA	The safety population included patients who received at least one dose of satralizumab or placebo. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% CI were estimated by applying the resulting RR and the ACR of 13%.	CCOD: 12 Oct 2018 (DB period) Data on file
	Placebo	23	3 (13.0%)								
Serious TRAEs Patients – no. (%)	Satralizumab	41	1 (2.4%)	2.4	NC	NA	NC	NC	NA	The safety population included patients who received at least one dose of satralizumab or placebo. RR and 95% CI as well as 95% CI for the absolute difference are not calculated (NC) as the rate in the comparator group is 0%.	CCOD: 12 Oct 2018 (DB period) Data on file
	Placebo	23	0								
Persistent disease worsening – change in EDSS score at week 48	Satralizumab	33	-0.52 (SE 0.18) -0.87; -0.16	-0.35 (SE 0.23)	-0.81-0.10	0.12	HR: 0.34	0.14-0.82	0.01	Adjusted mean change based on MMRM analysis. Risk of EDSS worsening was expressed as a HR and 95% CI.	CCOD: 12 Oct 2018 (DB period) Data on file
	Placebo	12	- 0.17 (SE 0.22)								

			-0.60-0.27							
Visual acuity according to Snellen chart – change in right eye at week 48	Satralizumab	33	-0.02 (SE 0.11) -0.23-0.20	0.05 (SE 0.14)	-0.23-0.34	0.71	NA	NA	NA	Adjusted mean change based on MMRM analysis; positive numbers indicate improvements in vision. Snellen chart scores were converted to logMAR visual acuity scoring. Unadjusted p-value for pairwise comparison with the control group is presented.	CCOD: 12 Oct 2018 (DB period) Data on file
	Placebo	12	-0.07 (SE 0.14) -0.34-0.20								
Visual acuity according to Snellen chart – change in left eye at week 48	Satralizumab	33	0.17 (SE 0.26) -0.35-0.69	-0.01 (SE 0.21)	-0.43-0.40	0.95	NA	NA	NA	Adjusted mean change based on MMRM analysis; positive numbers indicate improvements in vision. Snellen chart scores were converted to logMAR visual acuity scoring. Unadjusted p-value for pairwise comparison with the control group is presented.	CCOD: 12 Oct 2018 (DB period) Data on file
	Placebo	12	0.18 (SE 0.24) -0.30-0.66								
SF-36 – Change in MCS score at week 48	Satralizumab	33	5.58 (SE 1.88) 1.82-9.34	5.10 (SE 2.71)	-0.36-10.57	0.07	NA	NA	NA	Adjusted mean change based on MMRM analysis. Unadjusted p-value for pairwise comparison with the control group is presented. In order to calculate the MCID, SD is calculated as SD=SE*sqrt(N). SD*0.5 = 4.26	CCOD: 12 Oct 2018 (DB period) Data on file
	Placebo	12	0.48 (SE 2.46) -4.48-5.44								
	Satralizumab	33	5.37 (SE 1.32)	-0.07 (SE 1.61)	-3.32-3.19	0.97	NA	NA	NA		

			2.70-8.03		
SF-36 – Change in PCS score at week 48	Placebo	12	5.43 (SE 1.53) 2.34-8.52	Adjusted mean change based on MMRM analysis. Unadjusted p-value for pairwise comparison with the control group is presented. In order to calculate the MCID, SD is calculated as SD=SE*sqrt(N). SD*0.5 = 2.65	CCOD: 12 Oct 2018 (DB period) Data on file

9.4 Results per PICO (clinical question)

Results are presented in **Table A3a** in Appendix 9.3.

9.5 Additional data

Table S1 Change from baseline in EDSS score at 24 week intervals during the BD period

	Satralizumab (N=41)	Placebo (N=23)
Baseline		
n	37	14
Mean	4.041 (0.242)	3.179 (0.408)
Week 24		
n	36	14
Adjusted Mean (SE) 95% CI	-0.423 (0.176) (-0.776,-0.070)	-0.267 (0.211) (-0.688,0.154)
Difference in Adjusted Means (SE) 95% CI p-value	-0.156 (0.220) (-0.594,0.282) 0.4794	-
Week 48		

n	33	12
Adjusted Mean (SE) 95% CI	-0.518 (0.178) (-0.874,-0.162)	-0.165 (0.216) (-0.595,0.265)
Difference in Adjusted Means (SE) 95% CI p-value	-0.353 (0.228) (-0.806,0.100) 0.1249	-
Week 72		
n	30	7
Adjusted Mean (SE) 95% CI	-0.483 (0.183) (-0.849,-0.117)	0.052 (0.246) (-0.436,0.539)
Difference in Adjusted Means (SE) 95% CI p-value	-0.535 (0.265) (-1.059,-0.010) 0.0461	-
Week 96		
n	18	4
Adjusted Mean (SE) 95% CI	-0.448 (0.200) (-0.847,-0.050)	-0.275 (0.313) (-0.895,0.345)
Difference in Adjusted Means (SE) 95% CI	-0.173 (0.335) (-0.836,0.489)	-

p-value	0.6057	
Week 120		
n	11	2
Adjusted Mean (SE) 95% CI	-0.577 (0.226) (-1.025,-0.129)	-0.621 (0.422) (-1.457,0.215)
Difference in Adjusted Means (SE) 95% CI p-value	0.044 (0.452) (-0.851,0.939) 0.9227	-
Week 144		
n	8	2
Adjusted Mean (SE) 95% CI	-0.159 (0.252) (-0.663,0.346)	-0.899 (0.445) (-1.809,0.012)
Difference in Adjusted Means (SE) 95% CI p-value	0.740 (0.487) (-0.255,1.735) 0.1393	-

The EDSS is scored on a scale of 0-10. Higher scores represent increased disability. Descriptive statistics at baseline include patients with assessment at baseline and at least one post-baseline value. Estimates are from analysis based on MMRM using Toeplitz covariance matrix. Unadjusted p-values for pairwise comparisons with the control group are presented. The output is restricted to Week 144 due low number of observations at later visits leading to non convergence. Data on file.

Table S2 Change from baseline in Visual score on the right eye at 24 week intervals during the DB period

	Satralizumab (N=41)	Placebo (N=23)
Baseline		
n	37	14
Mean	0.540 (0.120)	0.436 (0.216)
Week 24		
n	36	14
Adjusted Mean (SE) 95% CI	-0.004 (0.116) (-0.237,0.229)	-0.156 (0.153) (-0.462,0.150)
Difference in Adjusted Means (SE) 95% CI p-value	0.152 (0.164) (-0.177,0.482) 0.3573	-
Week 48		
n	33	12
Adjusted Mean (SE) 95% CI	-0.017 (0.108) (-0.234,0.200)	-0.071 (0.135) (-0.341,0.199)
Difference in Adjusted Means (SE)	0.054 (0.142)	

95% CI p-value	(-0.232,0.339) 0.7074	
Week 72		
n	30	7
Adjusted Mean (SE) 95% CI	-0.118 (0.094) (-0.309,0.073)	-0.059 (0.099) (-0.260,0.142)
Difference in Adjusted Means (SE) 95% CI p-value	-0.059 (0.109) (-0.282,0.163) 0.5895	-
Week 96		
n	18	4
Adjusted Mean (SE) 95% C	-0.102 (0.143) (-0.391,0.188)	0.010 (0.233) (-0.462,0.483)
Difference in Adjusted Means (SE) 95% CI p-value	-0.112 (0.255) (-0.629,0.405) 0.6626	-
Week 120		
n	11	2
Adjusted Mean (SE)	-0.144 (0.164)	-0.163 (0.280)

95% C	(-0.476,0.188)	(-0.729,0.403)
Difference in Adjusted Means (SE) 95% CI p-value	0.019 (0.294) (-0.576,0.614) 0.9487	-

Visual acuity was measured using Snellen 20-foot wall chart and then converted to logMAR visual acuity scoring. Lower values indicate better visual acuity. Descriptive statistics at baseline include patients with assessment at baseline and at least one post-baseline value. Estimates are from analysis based on MMRM using unstructured covariance matrix. Unadjusted p-values for pairwise comparisons with the control group are presented. The output is restricted to Week 120 due to low number of observations at later visits leading to non convergence. Data on file.

Table S3 Change from baseline in Visual score on the left eye at 24 week intervals during the DB period

	Satralizumab (N=41)	Placebo (N=23)
Baseline		
n	37	14
Mean	0.653 (0.153)	0.454 (0.228)
Week 24		
n	36	14
Adjusted Mean (SE) 95% CI	0.133 (0.255) (-0.383,0.649)	0.181 (0.230) (-0.281,0.644)
Difference in Adjusted Means (SE)	-0.049 (0.188)	

95% CI p-value	(-0.427,0.330) 0.7965	
Week 48		
n	33	12
Adjusted Mean (SE) 95% CI	0.167 (0.258) (-0.353,0.688)	0.181 (0.239) (-0.299,0.661)
Difference in Adjusted Means (SE) 95% CI p-value	-0.014 (0.205) (-0.425,0.398) 0.9473	
Week 72		
n	30	7
Adjusted Mean (SE) 95% CI	0.198 (0.268) (-0.341,0.737)	-0.031 (0.285) (-0.608,0.545)
Difference in Adjusted Means (SE) 95% CI p-value	0.230 (0.263) (-0.304,0.763) 0.3889	
Week 96		
n	18	4
Adjusted Mean (SE)	0.256 (0.273)	-0.081 (0.313)

95% C	(-0.293,0.804)	(-0.713,0.551)
Difference in Adjusted Means (SE) 95% CI p-value	0.337 (0.305) (-0.282,0.955) 0.2767	
Week 120		
n	10	2
Adjusted Mean (SE) 95% C	0.238 (0.274) (-0.315,0.790)	0.081 (0.292) (-0.512,0.673)
Difference in Adjusted Means (SE) 95% CI p-value	0.157 (0.276) (-0.402,0.716) 0.5729	

Visual acuity was measured using Snellen 20-foot wall chart and then converted to logMAR visual acuity scoring. Lower values indicate better visual acuity. Descriptive statistics at baseline include patients with assessment at baseline and at least one post-baseline value. Estimates are from analysis based on MMRM using unstructured covariance matrix. Unadjusted p-values for pairwise comparisons with the control group are presented. The output is restricted to Week 120 due to low number of observations at later visits leading to non convergence. Data on file.

Table S4 Change from baseline in SF-36 mental component scores at 24 weeks interval during the DB period

	Satralizumab (N=)	Placebo (N=)
Baseline		

n	37	14
Mean	46.433 (1.655)	46.444 (2.922)
Week 24		
n	37	14
Adjusted Mean (SE) 95% CI	5.269 (1.767) (1.720,8.818)	2.073 (2.231) (-2.401,6.547)
Difference in Adjusted Means (SE) 95% CI p-value	3.196 (2.388) (-1.603,7.994) 0.1870	
Week 48		
n	33	12
Adjusted Mean (SE) 95% CI	5.579 (1.875) (1.816,9.342)	0.478 (2.463) (-4.481,5.437)
Difference in Adjusted Means (SE) 95% CI p-value	5.101 (2.709) (-0.363,10.566) 0.0665	
Week 72		
n	31	8

Adjusted Mean (SE) 95% CI	5.789 (1.831) (2.106,9.473)	1.181 (2.573) (-4.013,6.375)
Difference in Adjusted Means (SE) 95% CI p-value	4.609 (2.858) (-1.161,10.379) 0.1144	
Week 96		
n	20	4
Adjusted Mean (SE) 95% CI	3.043 (2.208) (-1.435,7.521)	-4.394 (4.049) (-12.704,3.915)
Difference in Adjusted Means (SE) 95% CI p-value	7.437 (4.382) (-1.564,16.438) 0.1014	
Week 120		
n	11	2
Adjusted Mean (SE) 95% CI	6.207 (4.342) (-2.809,15.224)	-25.421 (9.004) (-44.110,-6.732)
Difference in Adjusted Means (SE) 95% CI p-value	31.628 (9.877) (11.099,52.158) 0.0042	

Week 144		
n	9	2
Adjusted Mean (SE) 95% CI	8.899 (2.599) (3.387,14.410)	-10.189 (5.104) (-21.124,0.746)
Difference in Adjusted Means (SE) 95% CI p-value	19.088 (5.499) (7.231,30.944) 0.0040	

The SF-36 component scores range from 0-100. Higher scores indicate better quality of life. Descriptive statistics at baseline include patients with assessment at baseline and at least one post-baseline value. Estimates are from analysis based on MMRM using unstructured covariance matrix. Unadjusted p-values for pairwise comparisons with the control group are presented. The output is restricted to Week 144 due to low number of observations at later visits leading to non convergence. Data on file.

Table S5 Change from baseline in SF-36 physical component scores at 24 weeks interval during the DB period

	Satralizumab (N=)	Placebo (N=)
Baseline		
n	37	14
Mean	39.593 (1.702)	44.092 (3.268)
Week 24		

n	37	14
Adjusted Mean (SE) 95% CI	3.585 (1.400) (0.778,6.393)	4.227 (1.722) (0.776,7.678)
Difference in Adjusted Means (SE) 95% CI p-value	-0.642 (1.816) (-4.291,3.007) 0.7252	
Week 48		
n	33	12
Adjusted Mean (SE) 95% CI	5.366 (1.319) (2.702,8.030)	5.431 (1.528) (2.343,8.519)
Difference in Adjusted Means (SE) 95% CI p-value	-0.065 (1.606) (-3.315,3.185) 0.9679	
Week 72		
n	31	8
Adjusted Mean (SE) 95% CI	5.320 (1.616) (2.075,8.566)	6.819 (2.463) (1.842,11.796)
Difference in Adjusted Means (SE) 95% CI	-1.499 (2.682) (-6.920,3.923)	

p-value	0.5794	
Week 96		
n	20	4
Adjusted Mean (SE) 95% CI	7.721 (1.614) (4.472,10.969)	7.670 (2.668) (2.256,13.085)
Difference in Adjusted Means (SE) 95% CI p-value	0.050 (2.868) (-5.787,5.887) 0.9861	
Week 120		
n	11	2
Adjusted Mean (SE) 95% CI	8.543 (2.207) (4.068,13.017)	14.018 (4.047) (5.751,22.285)
Difference in Adjusted Means (SE) 95% CI p-value	-5.476 (4.416) (-14.500,3.549) 0.2248	
Week 144		
n	9	2
Adjusted Mean (SE) 95% CI	4.524 (1.967) (0.459,8.590)	6.164 (3.490) (-1.287,13.615)

Difference in Adjusted Means (SE)	-1.640 (3.807)	
95% CI	(-9.803,6.523)	
p-value	0.6732	

The SF-36 component scores range from 0-100. Higher scores indicate better quality of life. Descriptive statistics at baseline include patients with assessment at baseline and at least one post-baseline value. Estimates are from analysis based on MMRM using unstructured covariance matrix. Unadjusted p-values for pairwise comparisons with the control group are presented. The output is restricted to Week 144 due to low number of observations at later visits leading to non convergence. Data on file.

ENSPRYNG® (satralizumab) for the treatment of Neuromyelitis Optica Spectrum Disorder (NMOSD)

Health economic technical report for the Danish Medicines Council

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1. EXECUTIVE SUMMARY

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease of the central nervous system characterized by inflammatory lesions in the optic nerves and spinal cord, which can lead to loss of vision and paralysis. Patients with NMOSD frequently experience recurrent attacks, leading to long-term accumulating neurological damage and disability, and a reduced life expectancy. The objective of this technical report is to present the health economic analysis of ENSPRYNG® (satralizumab) for the HTA submission to the Danish Medicines Council (DMC).

Methods

A Markov model, developed in MS Excel 2016, was built to assess the cost-per-patient of satralizumab vs placebo as a new treatment for NMOSD anti-aquaporin-4 IgG (AQP4-IgG) seropositive patients. The Markov model was developed based on patient progression between 10 health states defined by the Expanded Disability Status Scale (EDSS), and death. The model synthesizes available evidence and generates estimates of clinical and economic outcomes based on data from the BN40900 (SAkuraStar) trial. This analysis takes a restrictive societal perspective in Denmark, and estimates outcomes related to costs over a lifetime time horizon of 50 years. The model is discounted annually according to the guidelines provided by the DMC. The model was validated externally by experts and checked by an independent third party.

Baseline EDSS transition probabilities were derived from a natural history study of patients with NMOSD, using the SAkuraStar study inclusion/exclusion criteria. As NMOSD is considered a more aggressive disease than MS, with high mortality risk due to neurogenic respiratory failure, death probabilities compared to the general population (and compared to MS patients) were estimated by adjusting age-specific death probabilities from life tables by means of standardized mortality ratios for MS patients [1], which were in turn corrected by a 20% inflation factor. The treatment effect was modelled as the impact on EDSS transition probabilities (forward transitions only), by applying the hazard ratios (HRs) for time to protocol-defined relapse (PDR), obtained from the SAkuraStar trial to baseline EDSS transition rates. At each model cycle, the proportion of patients remaining alive and discontinuing treatment was estimated by means of time to treatment discontinuation data for satralizumab obtained from the SAkuraStar trial. Costs were included as per the guidelines by the DMC and included treatment cost, administration cost, adverse event costs, monitoring costs, and patient and transportation cost. The uncertainty of the results was explored in scenario analyses. Furthermore, to comply with the method guidelines by the DMC, a budget impact model has been embedded within the cost-per-patient model.

Results

The analysis estimated an incremental cost of satralizumab compared to placebo of [redacted] over a lifetime horizon. The estimated budget impact of recommending satralizumab as a potential standard treatment for the population described in the clinical question was [redacted] in year 5. Both estimates based on the base case assumptions.

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5. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic neurological disease that typically affects the optic nerve and spinal cord. Patients in Denmark have a median age of 35 at the onset of the disease, but NMOSD can affect patients of all ages [2]. The disease affects women three times more often than men.

NMOSD is characterized by inflammation in the central nervous system that leads to demyelination with loss of glial cells and neurons and thus leading to loss of neurological function. Patients with NMOSD will in varying degrees have both physical and cognitive symptoms such as visual impairment, double vision, spastic paralysis of extremities, sensory disturbances, poor balance, urination problems, constipation, problems with sexual function, pain, fatigue, and memory and concentration problems. Patients with NMOSD experience attacks that can lead to a persistent worsening of symptoms throughout the disease [3]. The most significant disease progression is linked to attacks, and it is unknown whether the disease progresses during periods without attacks. 60% of the patients will experience a new attack within a year of the first attack. This is more than the average patient with relapsing multiple sclerosis (MS), and the attacks will more often cause permanent damage in patients with NMOSD than in patients with MS. In contrast to MS, mild courses of NMOSD are rarely seen.

The clinical manifestation of the NMOSD shares many similarities with MS but differs in particular in that the underlying pathology is different. In NMOSD, it is primarily the astrocytes that are targets for the body's immune response, whereas in MS it is oligodendrocytes that are affected. In both cases, it leads to damage to neurons in the central nervous system leading to the symptoms described above. In patients with NMOSD, the spinal cord and optic nerve are often affected - therefore, vision problems and cross-sectional syndrome are frequent and severe manifestations of the disease. An NMOSD attack can threaten the patient's mobility or vision, but the often acute treatment of attacks with corticosteroids or possibly plasmapheresis influence the patient's functional level.

Approximately 75-80% of patients with NMOSD have antibodies to the protein aquaporin 4 (AQP4) present in the blood. AQP4 is particularly present on the astrocytes' end feet [4, 5]. In patients with antibodies to AQP4, activation of the immune system occurs, which causes loss of the astrocytes, but the inflammation also leads to loss of oligodendrocytes and demyelination, and accumulation of complement protein is seen concerning the lesions [6].

Roche has developed satralizumab (SA 237), a monoclonal antibody that binds to the interleukin 6 (IL-6) receptors playing a central role in the disease activation of the immune system by NMOSD. Satralizumab has been studied as both a monotherapy and as a treatment combined with immunosuppressants and was approved by EMA on June 24, 2021, based on data from the trial program:

- **SAkuraSky** (SA-307JG/BN40898) is a multicenter, randomized, addition-to-baseline-treatment, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of satralizumab in patients with NMO/NMOSD [7]; ClinicalTrials.gov identifier: NCT02028884.

- **SAkuraStar** (SA-309JG/BN40900) is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of satralizumab as a monotherapy in

patients with NMO/NMOSD [Report No. 1089825 June 2019]; [8] ClinicalTrials.gov identifier: NCT02073279.

Satralizumab is indicated for the treatment of AQP4-IgG seropositive NMOSD patients from the age of 12 years and above. The results from SAkuraSky and SAkuraStar studies demonstrated that satralizumab is an efficacious and safe treatment for patients with NMOSD who are AQP4-IgG seropositive.

5.1 Decision problem (Clinical questions)

The DMC has presented one clinical question in the protocol [9]:

- What value does *satralizumab* have compared to *placebo* in patients with Neuromyelitis Optica Spectrum Disorder?

This clinical question was presented for the population defined as: "Patients with NMOSD with an EDSS < 7, who have antibodies against AQP4 and have experienced at least one attack".

5.2 Objective

The economic model was developed to estimate the incremental costs per patient as well as the budget impact of satralizumab as a treatment for AQP4-IgG seropositive NMOSD patients as defined by the clinical questions in the protocol [9]. The model will utilize a restricted societal perspective, thereby including drug costs, drug administration costs, hospital costs, patient and transportation costs as defined by the methodological guidance from the DMC [10].

The economic analysis was based on the evidence from the phase 3 trial BN40900 (SAkuraStar) for investigating the efficacy and safety of satralizumab as monotherapy as per the protocol received from the DMC.

6. Clinical trial: BN40900 (SAkuraStar) Study

6.1 Trial design

The BN40900 (SAkuraStar) study is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of satralizumab as a monotherapy against placebo in patients with NMOSD/NMO. The design of the trial is shown in **Figure 1** and described in **Table 1**.

Figure 1 Design of BN40900 (SAkuraStar) study.

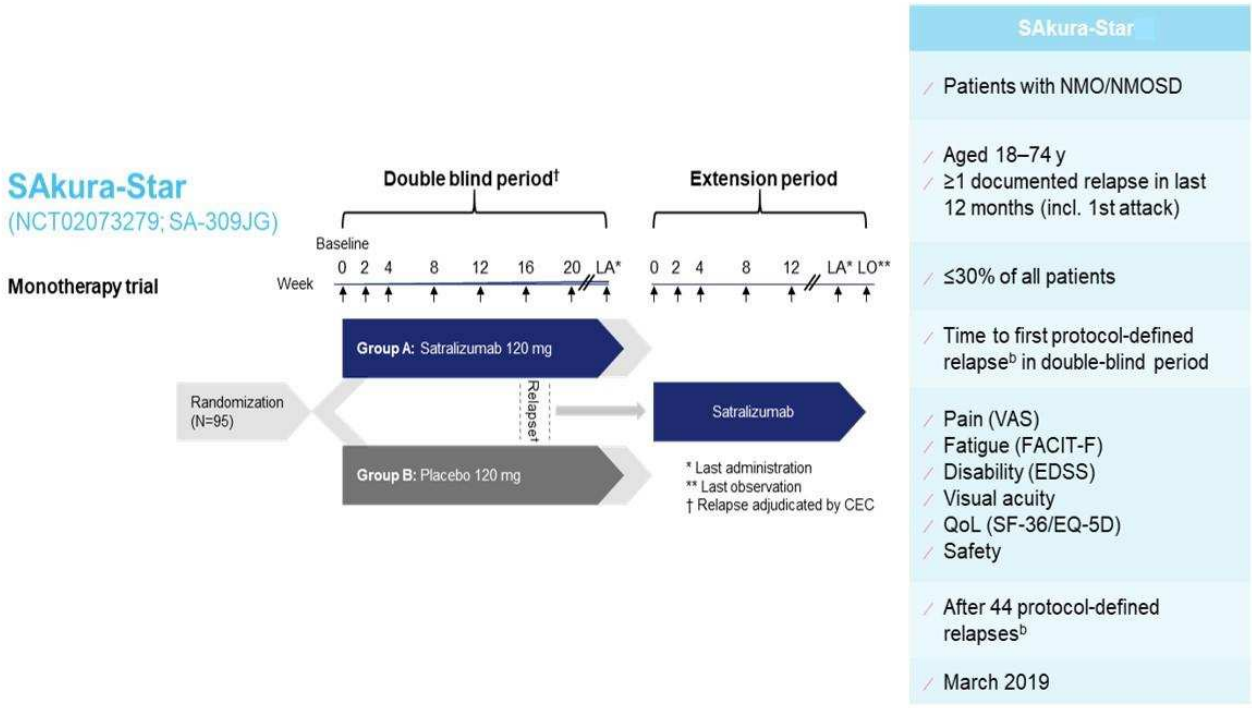


Table 1 Summary of the study design with respect to efficacy evaluation.

Study no. (Phase II and III)	SAkuraStar (SA-309JG/BN40900) (phase 3) NCT02073279
Study design, control type	*Prospective, 2:1 randomized, multicenter, multinational, double-blind, placebo-controlled study*
Population	Patients with NMO and NMOSD
Number of patients during double-blind period	Efficacy population (ITT): • **Total patients: 95 patients** • **Satralizumab: 63 patients** • **Placebo: 32 patients** AQP4+ population : • **Total patients: 64 patients**

	• **Satralizumab: 41 patients** • **Placebo: 23 patients**
Dose and Regimen	• **Satralizumab (120 mg SC) at weeks 0, 2, 4, and Q4W thereafter** • **Placebo**
Endpoints	
	Primary: • Hazard ratio for time to first protocol-defined relapse (PDR). Time to first PDR was defined as the time from the date of randomization until the first occurrence of a PDR throughout the **double-blind period** (October 2018 data cut).
	Secondary: • **Pain**: change from baseline to week 24 in the VAS score, which is a subjective measure and consists of a 100 mm line with two endpoints representing 'no pain' to 'pain as bad as it could be'. Participants were asked to rate their pain by placing a mark on the line corresponding to their current level of pain. The distance along the line from the 'no pain' marker was then measured with a ruler, giving a pain score out of 10. • **Fatigue**: change from baseline to week 24 in the FACIT-F score, which includes 13 statements to measure fatigue/asthenia for participants with chronic, life-threatening illnesses. For each question, a participant rated his/her condition for the past week on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). A score was calculated by averaging the individual question scores, with lower scores indicative of less fatigue. • **Disability**: changes from baseline to week 24 on the EDSS score and visual acuity • **QoL**: changes from baseline to week 24 on the SF-36 and the EQ-5D scores. The SF-36 component scores range from 0 to 100. Higher scores indicate better QoL. The EQ-5D is a participant-answered questionnaire measuring 5 dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with 3 possible response categories: 1) no problems; 2) some problems; 3) severe problems. The EQ-5D index score is scored on a scale of –0.2 to 1; a higher score reflects a better health state. ○ **Safety**: incidence and severity of adverse events and serious adverse events.
Stratification factors	Prior therapy (B-cell depleting therapy or immunosuppressants/others) and the most recent attack in the last 1 year before screening (first attack or relapse)

6.1.1 Definition of protocol-defined relapse

A PDR was defined as the occurrence of new or worsening neurological symptoms attributable to NMOSD. Symptoms had to persist for more than 24 hours and were not attributable to confounding

clinical factors (e.g., fever, infection, injury, change in mood, adverse reactions to medications). New or worsening neurological symptoms that occur less than 31 days following the onset of a PDR were considered part of the same relapse (i.e., if two relapses had onset days that were 30 days of one another, they were counted only as one relapse), and the onset date used in the analysis was the onset date of the first relapse. The new or worsening neurological symptoms had to meet any of the following:

- An increase in score of at least 1.0 points on the EDSS, except for an increase to 1.0 or 1.5 from 0 (i.e., a 2.0-point increase on the EDSS is required if the baseline was 0).
- An increase of at least 2.0 points on one of the appropriate functional system scores (FSS).
- An increase of at least 1.0 points in two or more of the appropriate FSS if the baseline score was one or more.
- An increase of at least 1.0 points in single eye FSS when the baseline score in that eye is one or more.

The base of comparison for the increase was the score at the most recent EDSS/FS assessment visit. The appropriate FS change had to affect at least one of the following FS: pyramidal, cerebellar, brainstem, sensory, bowel/bladder, or visual (single eye). Sexual dysfunction and cerebral function did not suffice to establish a PDR.

Relapses regarded as a PDR by the Clinical Endpoint Committee (CEC), and followed by confirmation that EDSS/FSS assessment was performed within 7 days after the patient reported the symptoms to the site, were used for the primary analysis. Any potential relapses not evaluated within 7 days were censored from the primary analysis.

6.1.2 Measuring disease progression in NMOSD

The Expanded Disability Status Scale (EDSS) is used to characterize disability progression and relapse severity in NMOSD (see **section 6.1.1**). The EDSS was developed by the neurologist John Kurtzke in 1983 [11] to assess the level of disability in patients with MS, but it is also widely used in NMOSD to assess disease progression and relapse severity. The scale ranges from 0 to 10 in 0.5 increments, with increasing numbers representing higher levels of disability. Scoring is based on neurological examination; specifically, EDSS scores are based on measures of impairment in eight functional systems (FS) (see also **Figure 2**) which include:

- pyramidal – weakness or difficulty moving limbs
- cerebellar – ataxia, loss of coordination or tremor
- brainstem – problems with speech, swallowing, and nystagmus
- sensory – numbness or loss of sensations
- bowel and bladder function
- visual function
- cerebral (or mental) functions
- other.

Scores from 0 to 4.5 on the EDSS refer to people who can walk without impairment, whereas scores between 5.0 to 9.5 are defined by the impairment to walking. A score of 6 is considered an important milestone because it represents the need for a walking aid. The states represented by the EDSS are

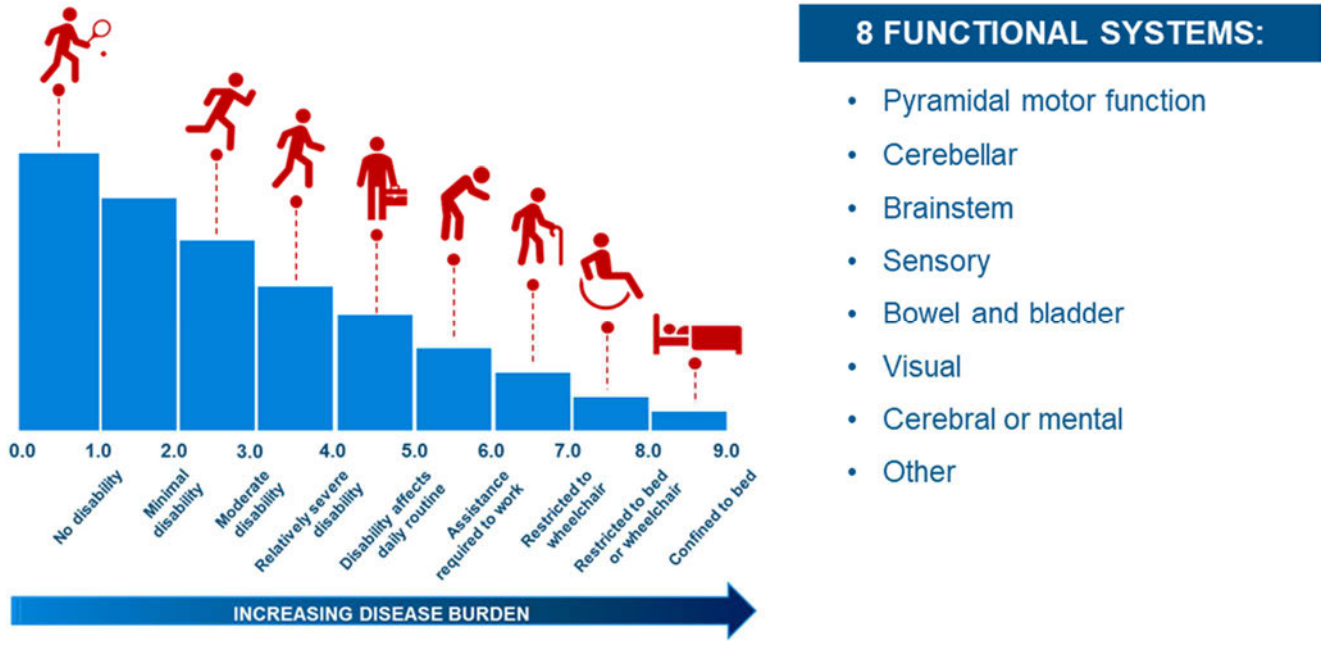
shown in **Table 2**, while a diagrammatic representation of the EDSS can be found in **Figure 2.**

Table 2 Description of EDSS states.

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. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4	Significant disability but self-sufficient, and up and about some 12 hours a day. Able to walk without aid or rest for 500 m
4.5	Significant disability but 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. Able to walk without aid or rest for 300 m
5	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200 m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100 m
6	Requires a walking aid – cane, crutch, etc. – to walk about 100 m with or without resting
6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20 m without resting
7	Unable to walk beyond approximately 5 m even with aid. Essentially restricted to wheelchair; though 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 and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day, and may require a motorized wheelchair
8	Essentially restricted to bed or chair or pushed in a wheelchair. 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	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10	Death

EDSS, Expanded Disability Status Scale; FS, functional system(s); m, meter(s).
Source: [11].

Figure 2 The Expanded Disability Status Scale.



Source: adapted from [11].

6.1.3 Patient population

Details regarding the key inclusion and exclusion criteria for trial participants in SAkuraStar are provided in **Table 3** below. In addition, a summary of the baseline demographics and characteristics are reported in **Table 4** below.

Table 3 Key efficacy-related inclusion and exclusion criteria.

Criteria
Inclusion
• Age 18 to 74 years • AQP4-IgG–seropositive or AQP4-IgG–seronegative NMO or NMOSD • ≥ 1 relapse in the 12 months before screening • EDSS score of 0 to 6.5
Exclusion
• Previous treatment with IL-6 inhibitory therapy, alemtuzumab, total body irradiation, or bone marrow transplantation at any time • Use of eculizumab, belimumab, or multiple sclerosis disease-modifying treatment within 6 months before baseline • Use of anti-CD4 agents, cladribine, or mitoxantrone within 2 years before baseline.

Table 4 Baseline demographics and characteristics.

Characteristics	ITT population		AQP4 IgG-seropositive population	
	Satralizumab (N=63)	Placebo (N=32)	Satralizumab (N=41)	Placebo (N=23)
Age - years	45.3 ± 12.0	40.5 ± 10.5	46.0 ± 12.0	40.1 ± 11.5
Age at clinical presentation - years	36.4 ± 10.7	39.3 ± 13.3	NR	NR
Sex – no. (%)				
Male	17 (27%)	1 (3%)	10 (24.4%)	1 (4.3%)
Female	46 (73%)	31 (97%)	31 (75.6%)	22 (95.7%)
Diagnosis - no. (%)*				
Neuromyelitis optica	47 (75%)	24 (75%)	26 (63.4%)	15 (65.2%)
Neuromyelitis optica spectrum disorder	16 (25%)	8 (25%)	15 (36.6%)	8 (34.8%)
AQP4-IgG seropositive - no. (%)	41 (65%)	23 (72%)	NA	NA
Annualised relapse rate	1.4 ± 0.6	1.5 ± 0.7	0.91 ± 0.50	1.02 ± 0.51

EDSS score§	3.9 ± 1.5	3.7 ± 1.6	4.02 ± 1.50	3.43 ± 1.55
VAS pain score¶				
Mean (SD)	31.7 ± 28.9	27.6 ± 30.8	NR	NR
Median (range)	25 (0-94)	9 (0-90)	NR	NR
FACIT-F score				
Mean (SD)	30.6 ± 11.7	29.7 ± 12.9	NR	NR
Median (range)	30 (6-52)	31 (5-48)	NR	NR
Race or ethnicity - no. (%)				
American Indian or Alaska Native	2 (3%)	0	2 (4.9%)	0
Asian (non-Japanese)	8 (13%)	6 (19%)	7 (17.1%)	6 (26.1%)
Black or African American	13 (21%)	3 (9%)	11 (26.8%)	3 (13.0%)
White	37 (59%)	22 (69%)	19 (46.3%)	13 (56.5%)
Other	3 (5%)	1 (3%)	2 (4.9%)	1 (4.3%)
Previous treatment - no. (%)				
B-cell-depleting therapy	8 (13%)	4 (13%)	5 (12.2%)	4 (17.4%)
Immunosuppressants or other	55 (87%)	28 (88%)	36 (87.8%)	19 (82.6%)
Disease duration - weeks	317.8 ± 340.9	214.7 ± 201.3	NR	NR
Type of most recent attack - no. (%)				
First attack	7 (11%)	4 (13%)	5 (12.2%)	4 (17.4%)
Relapse	56 (89%)	28 (88%)	36 (87.8%)	19 (82.6%)

Data are mean ± SD or n (%). * Patients either had neuromyelitis optica according to published criteria (seropositive or seronegative for antibodies against AQP4-IgG) or had neuromyelitis optica spectrum disorder (AQP4-IgG-seropositive status only) according to published criteria with idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral-segment spinal cord lesions on magnetic resonance imaging) or recurrent or simultaneous optic neuritis in both eyes. § Scores on the Expanded Disability Status Scale (EDSS) range from 0 (normal neurologic examination) to 10 (death). ¶ Scores on the visual analog scale (VAS) for the assessment of pain range from 0 to 100, with higher scores indicating more pain. Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) range from 0 to 52, with lower scores indicating more fatigue.

6.1.4 Endpoints and assessments

The primary objective of the BN40900 (SAkuraStar) study was to evaluate the efficacy of ENSPRYNG® (satralizumab) against placebo in patients with NMOSD. Given that the AQP4-IgG status is a known prognostic factor in NMOSD, the proportion of patients who were negative for AQP4-IgG at the screening was capped per study protocol at approximately 30% of the total number of patients for the trial. **Table 5** lists the endpoints evaluated in the clinical trial.

Table 5 Key endpoints.

Endpoint	Definition

Primary	
PDR	Hazard ratio for time to first protocol-defined relapse (PDR). Time to first PDR was defined as the time from the date of randomization until the first occurrence of a PDR throughout the **double-blind period** (October 2018 data cut).
Secondary	
Pain	Change from baseline to week 24 in the VAS score, which is a subjective measure and consists of a 100 mm line with two endpoints representing 'no pain' to 'pain as bad as it could be'. Participants were asked to rate their pain by placing a mark on the line corresponding to their current level of pain. The distance along the line from the 'no pain' marker was then measured with a ruler, giving a pain score out of 10.
Fatigue	Change from baseline to week 24 in the FACIT-F score, which includes 13 statements to measure fatigue/asthenia for participants with chronic, life-threatening illnesses. For each question, a participant rated his/her condition for the past week on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). A score was calculated by averaging the individual question scores, with lower scores indicative of less fatigue.
Disability	Change from baseline to week 24 on the EDSS score and visual acuity.
QoL	**C**hange from baseline to week 24 on the SF-36 and the EQ-5D scores. The SF-36 component scores range from 0 to 100. Higher scores indicate better QoL. The EQ-5D is a participant-answered questionnaire measuring 5 dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with 3 possible response categories: 1) no problems; 2) some problems; 3) severe problems. The EQ-5D index score is scored on a scale of –0.2 to 1; a higher score reflects a better health state. o **Safety:** incidence and severity of adverse events and serious adverse events.

6.2 BN40900 (SAkuraStar) study results

2.2.1 Efficacy outcomes

SAkuraStar [12]: satralizumab monotherapy achieved a 55% reduction in the risk of relapses compared with placebo in the overall population (HR 0.45, 95% CI: 0.23–0.89; $p = 0.0184$). In the large (~67%) subgroup of patients seropositive for AQP4-IgG antibodies, the effect was higher with a 74% reduction in risk of relapses (HR 0.26, 95% CI: 0.11–0.63; $p = 0.0014$). In the overall satralizumab-treated population, 76.1% were relapse-free at 48 weeks and 72.1% were relapse-free at 96 weeks, compared with 61.9% and 51.2% with placebo, respectively. In the AQP4-IgG seropositive subgroup, 82.9% of patients were relapse-free at 48 weeks and 76.5% were relapse-free at 96 weeks when treated with satralizumab, compared to 55.4% and 41.1% with placebo, respectively.

No significant differences for the key secondary endpoints of pain (VAS) and fatigue (FACIT-F) were observed between the treatment arms, owing to failure in the hierarchical testing procedure.

Table 6 Overview of SAkuraStar trial outcomes (randomized double-blind period).

Clinical trial	SAkuraStar
Treatment and comparator arms	Satralizumab (SC) monotherapy (vs placebo)
Patient baseline characteristics	• N = 95 (2:1) • 67.4% AQP4+ NMO or NMOSD, ≥ 1 attack in last year, EDSS < 7 • 18–74 years
Efficacy, allcomers (ITT)	HR 0.45 (95% CI: 0.23–0.89) *p* = 0.0184
Efficacy, AQP4+ patients	HR 0.26 (95% CI: 0.11–0.63) *p* = 0.0014
Secondary outcome measures	No statistically significant evidence, due to failure in the hierarchical testing procedure
Safety	• 19.0% of patients had a SAE (vs 15.6% with placebo) • 17.36 SAEs per 100 PY (vs 14.78 per 100 PY with placebo) • No deaths

6.2.1 Safety outcomes

Satralizumab was generally well tolerated by patients with NMOSD. The safety profile was well-balanced across the treatment arms over the randomized double-blind period, except for a higher incidence of SAEs in the satralizumab group. The majority of AEs (65%) were reported mild to moderate. A similar rate of infections (including serious infections) was observed in patients treated with satralizumab compared with the placebo group. No deaths were reported.

Table 7 Summary of adverse events of all grades reported in > 10% of patients (during the randomized double-blind period).

Adverse events, N (%)	Satralizumab N = 63	Placebo N = 32
Urinary tract infection	11 (17.5)	8 (25.0)

Nausea	11 (17.5)	2 (6.3)
Arthralgia	10 (15.9)	1 (3.1)
Upper respiratory tract infection	10 (15.9)	6 (18.8)
Headache	10 (15.9)	4 (12.5)
Pain in extremity	9 (14.3)	3 (9.4)
Rash	9 (14.3)	1 (3.1)
Nasopharyngitis	9 (14.3)	1 (3.1)
Injection Related Reactions	8 (12.7)	5 (15.6)
Fatigue	7 (11.1)	2 (6.3)

7. Health economic model

7.1 Summary of model key features and assumptions

In the economic model, the incremental cost was estimated of satralizumab compared to placebo due to the clinical question from DMC. The key features and main parameters of the model are outlined in **Table 8**, whilst the main modeling assumptions are listed in **Table 9.**

Table 8 Key features of the analysis.

Feature	Input	Notes
Software	*Excel 2016*	
Model type	*Multi-state Markov model*	Appropriate for long-term chronic conditions and conditions featuring recurrent events, such as relapses. Allows for clear and reproducible model outcomes
Perspective	*Danish restricted societal perspective*	Following the DMC methodological guidelines [10]
Discount rate	*3.5% (efficacy and costs) 0-35 years* *2.5% (efficacy and costs) beyond year 35*	Discount rates referring to the guidelines from the Danish Ministry of Finance [13]
Time horizon	*Lifetime (50 years)*	Lifetime time horizon is important when modeling a chronic disease, such as NMOSD
Cycle length	*28 days (four-weeks))*	Appropriate for capturing individual relapse events in separate model cycles
Half-cycle correction	*Applied*	–
Included comparators and populations	*Satralizumab compared to:* • *Placebo (SAkuraStar AQP4+)* • *Placebo (SAkuraStar ITT)*	
Model outcomes	*Incremental cost*	
Treatment efficacy measure	Hazard ratio *(HR) for time to first PDR vs. placebo (for satralizumab)*	
TTOT assumption	*Actual treatment duration (capped at death)*	
TTOT parametric	*Satralizumab (SAkuraStar AQP4+) –*	

distribution	*Exponential* *Satralizumab (SAkuraStar allcomers) – Exponential*	
Mortality estimation	*Standardized mortality ratios (SMR) by EDSS state, increased by an acceleration factor.* [a]	
Drug dosing assumption	*Planned dose without vial sharing*	
Drug acquisition costs (DKK)	*Main treatment regimen costs*	
Administration costs (DKK)	*Yes, the first model cycle for satralizumab.*	
Adverse event management costs (DKK)	*Yes*	
Relapse management costs (DKK)	*Relapse costs can be broken down by individual cost items for treating a relapse (severe or mild/moderate).*	Definition of severe relapse from ECTRIMS online library. Levy M Oct 26, 2017; 200411[b]
Supportive care costs (DKK)	*Yes*	
Patient's costs (DKK)	*Yes*	As per the DMC methodological guidelines [10]
Travel costs (DKK)	*Yes*	

AQP4+, aquaporin-4 antibody seropositive; CSR, clinical study report; ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis; EDSS, Expanded Disability Status Scale; HR, hazard ratio; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LY, life-year; MS, multiple sclerosis; NHS, National Health Service; NMA, network meta-analysis; NMOSD, neuromyelitis optica spectrum disorder; PAS, patient access scheme; PDR, protocol-defined relapse; TTOT, time to off treatment; RCT, randomized controlled trial; SMR, standardized mortality ratio; STC, simulated treatment comparison.
[a] Taken from Pokorski *et al*, 1997 [1].
[b] https://onlinelibrary.ectrims-congress.eu/ectrims/2017/ACTRIMS-ECTRIMS2017/200411/michael.levy.point.of.no.return.outcomes.from.acute.relapses.of.neuromyelitis.html

Table 9 List of modelling assumptions.

Assumption	Justification
The populations of the SAkura trials are reflective of the Danish population	NMOSD is a rare and serious disorder. To achieve a sufficient sample size, the SAkuraSky trial was conducted as multi-center studies in several countries and are assumed to reasonably represent the NMOSD population in Denmark. Patient subgroups included in the model are 1) all NMOSD patients and 2) seropositive NMOSD patients (i.e., patients who tested positive for AQP4-Ab), to cover the labels in Denmark and comply with the protocol presented by the DMC [9]. See **section 7.4** (patient subgroups in the model).

Treatment is not assumed to impact the duration of relapses or recovery from a relapse	Risk/rate of relapse has demonstrably been influenced by treatment. While it is plausible that the effect of the treatment also impacts relapse duration or facilitates underlying recovery processes by preventing further relapses, available trial evidence is not sufficient to demonstrate such effects. Consequently, the model assumes that both relapse duration and recovery from a relapse are unaffected by the treatment, which could underestimate the clinical benefit of satralizumab.
Patients can progress or regress in EDSS	NMOSD is characterized by relapses and recoveries from relapses, and patient disability is a function of the number and severity of relapses [14-16]. The level of disability in NMOSD patients is preferentially measured using the EDSS scale. Although inter-rater variability has been flagged as an issue in MS (and potentially also in NMOSD), observations of improved EDSS scores have been widely reported in NMOSD literature, including publications of RCTs. Therefore, it is assumed that observations of improved EDSS scores do not represent measurement errors, but rather reflect recoveries from a relapse, which can vary in intensity. As such, linking relapses and recoveries to transitions to higher and lower EDSS states reflects the clinical reality.
Treatment effect is applied to EDSS progression but not regression	The goal of treatment in NMOSD is slowing down the rate of disability accumulation, i.e., reducing the risk and frequency of relapses. Treatment efficacy, as measured by the HR for time to first protocol-defined relapse (PDR), was modeled as a reduction in the risk of relapse (i.e., movement upon the EDSS scale) at any given point in time, as reflected by adjusting the probability of transitioning to a higher EDSS state.
EDSS transitions in 1 point rather than 0.5 point	The untransformed range of EDSS health states (spaced by 0.5 points) could theoretically offer improved discrimination between relapses of different severity. However, the number of patients included in the SAkura trials did not allow reliable estimates for all 20 EDSS states. Grouping wider ranges of EDSS scores would limit the model's ability to properly reflect the benefit of treatment, given that relapses increasing the EDSS score of two points or more are infrequent.
The likelihood of experiencing an optic neuritis attack is the same across the spectrum of EDSS states	Based on internal medical opinion, there is no clearly established relationship between visual impairment and EDSS in NMOSD, as patients may suffer from severe visual impairment (including blindness) at any EDSS level. Therefore, to better reflect the impact on patient QoL of potentially experiencing a unilateral or bilateral optic neuritis attack in higher EDSS states, a disutility for severe visual impairment was applied to EDSS health states 6 and above, assuming that the proportion of patients who suffer from severe visual impairment is the same for all EDSS states.
Link between risk of mortality and level of disability	A link between risk of mortality and level of disability was modeled by adjusting age-specific annual mortality rates in the general Canadian population by reported standardized mortality ratios (SMR) by EDSS states for MS patients, [1]. To reflect the fact that NMOSD is considered to be a more aggressive disease than MS, as patients may die from a relapse due to neurogenic respiratory failure, increased mortality risk in NMOSD compared to MS was accounted for by correcting the SMR by EDSS states by an inflation factor.
No direct treatment effect on mortality	No deaths were observed in the SAkuraStar trial and thus no direct treatment effect on mortality can be assumed. Therefore, the only effect on mortality for satralizumab considered in the cost model is indirect, through delaying disease

	progression.
Treatment effect is constant over time.	The base case scenario assumes that the treatment effect (i.e., the HR for time to first PDR) is constant over time. Time to first PDR could only be assessed in the double-blind period, as per trial protocol. Reductions in risk of relapse were assumed to be constant until treatment discontinuation. See **section 8.4.4** (treatment efficacy). ARR reduction data supports the assumption of a maintained treatment effect over a lifetime horizon.
Relapse definition	The model captures both mild/moderate and severe relapse based on the EDSS-progression of the patients. A mild/moderate relapse is defined as a progression on the EDSS-scale of 1 point, while a severe relapse is defined as a progression of more than 1 point on the EDSS-scale. The rate of progression is based on the natural history data and the applied treatment effect. This relapse definition is based on the definition of a protocol-defined relapse (see **section 6.1.1**).

7.2 Overview of the decision problem

For this health economic model, the DMC has presented one clinical question in the protocol:

- What value does *satralizumab* have compared to *placebo* in patients with Neuromyelitis Optica Spectrum Disease?

7.3 Modelling approach overview and rationale

7.3.1 Model structure

Characterization of disability and relapse severity in NMOSD is most commonly based on the Kurtzke EDSS scale [11], as detailed in **section 6.1.2.** This EDSS scale works in 0.5-point increments, on a scale from 0 to 10 (where 10 is defined as death). Accordingly, health states defined by the EDSS would result in 21 potential states. For the cost model, EDSS health states were collapsed to integer EDSS values for modeling tractability and consistency with EDSS health state utility values reported for MS. The cost model is thus based on 11 health states, ten states representing EDSS scores of 0 to 9, and an absorbing death state (**Figure 3**).

Patients enter the model in a baseline EDSS state distribution, reflecting the one observed in the SAkuraStar (described in **section 6.1.3**). The specific patient population analysed in the model are presented in **section 7.4**. The model time horizon base-case assumption was 50 years (lifetime).

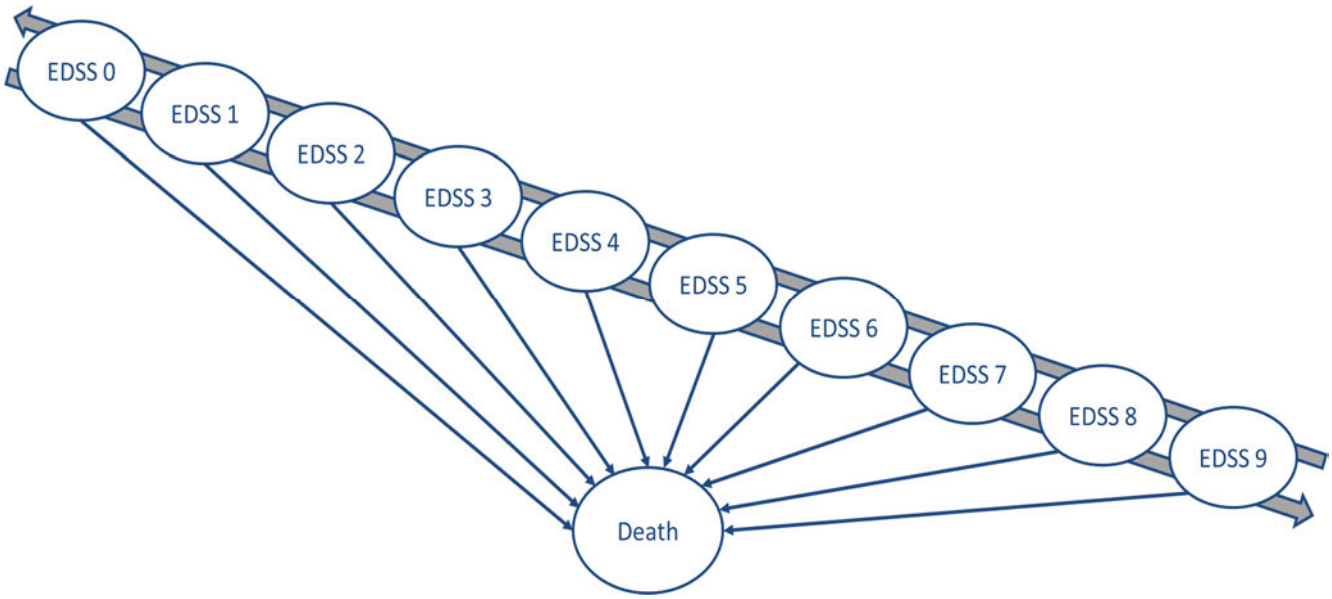
Disease course in NMOSD patients is essentially driven by relapses and recoveries from relapses, which is almost the totality of cases that result in changes in the EDSS score. Specifically, patients may experience a relapse (which is typically associated with a worsening/increase in the EDSS score), a recovery from relapse (which is typically associated with an improvement/decrease in the EDSS score), and death. As a consequence of that, during each model cycle patients are allowed to:

- Remain in the same EDSS state (reflecting a stable disease course)
- Move to a higher EDSS state (reflecting a relapse event)

- Move to a lower EDSS state (reflecting a recovery event)
- Go to “death” state

Transition probabilities for movement between each EDSS state are given in **section 8.4.2.**

Figure 3 Diagram of the model structure.



7.3.2 Clinical justification for the choice of model type and structure

4.3.2.1 Clinical justification for the choice of model structure

NMOSD is a relapse-driven disease. The number and severity of recurring relapses contribute directly to patient disability [14-16]. The overall level of disability in patients with NMOSD is preferentially measured using the EDSS scale system (see also **section 6.1.2**). For the vast majority of patients with NMOSD, relapses are associated with increases in the EDSS score whilst recoveries from relapses are associated with decreases in the EDSS score. Accordingly, it was deemed appropriate to model the disease course over time of NMOSD in the CE analysis by means of transitions among EDSS states. Given that relapses of any severity (resulting in transitions to higher EDSS states) as well as recoveries of different intensities (resulting in transitions to lower EDSS states) are possible, at least theoretically, transitions among all EDSS states were allowed.

4.3.2.2 Clinical justification for the choice of the modelling approach

Based on the current medical knowledge of NMOSD, disease courses cannot be easily predicted. Relapses can occur in clusters, i.e., as a sequence of relapse events closely spaced in time, and recoveries from relapses, either partial or total, might be relatively rapid, occur as a long series of small sequential improvements in disability interspersed with periods of stability, or may not occur at all. This implies that if a patient experienced a relapse, he/she can then experience another relapse (if the first relapse was part of a cluster), stabilize to a higher level of disability, or experience a subsequent clinical improvement. Similarly, if a patient with NMOSD has been stable for some time, he/she may continue remaining stable, experience another relapse or continue to clinically improve (if he/she was experiencing

a gradual recovery that was taking a long time to complete).

Markov models assume that a patient is always in one of a finite number of discrete health states and that the disease course can be represented by transitions from one state to another. This approach thus fits well with the model structure selected for this cost model. Furthermore, the ability of a Markov model to describe recurrent events, as well as its memoryless property, is consistent with the current knowledge about the disease course over time in patients with NMOSD, as described above.

It is worth pointing out that although other modeling approaches would have also been possible, they would all have been unfeasible/suboptimal compared to the one selected to evaluate the cost of satralizumab in patients with NMOSD:

- A partitioned survival model would not allow to model transitions to lower EDSS states (which are typically associated with the recovery from a relapse), as patients cannot go back to a lower health state in such models.
- More sophisticated approaches, e.g., discrete event simulations, could not be used due to their intensive data requirement; given that NMOSD is a rare disease, data availability is limited.

7.3.3 Disease course and health state transitions

In a near totality of cases, the disease course in NMOSD is associated with changes in the EDSS score, and thus with movements among EDSS states. To allow appropriate capturing of individual relapse events in separate model cycles, the model cycle length was selected to 28 days (four weeks). Such a short cycle length also allows reducing potential differences between actual and model-predicted transition times, provides a more accurate estimate of the length of time patients remain in a health state, and allows flexibility and accuracy in costing and dosing calculations [17].

In the cost model, baseline transition probabilities among EDSS states at every model cycle were estimated as follows:

1. yearly EDSS transition probabilities for each patient subgroup (see **section 8.4.2** for more details) were converted to yearly transition rates.
2. yearly rates were then converted to four-weekly rates.
3. four-weekly rates were finally converted to four-weekly transition probabilities.

Transitions among EDSS states for the placebo comparator were modeled using the baseline EDSS transition probabilities estimated as described above.

Transitions among EDSS states for the drug satralizumab was modeled based on the following procedure:

The proportion of patients alive receiving or having discontinued treatment with satralizumab at every model cycle was estimated based on time to off-treatment (TTOT) data (see **section 8.4.5** for more details)

For the proportion of patients alive receiving treatment with satralizumab, transitions among EDSS states were modeled using baseline EDSS transition probabilities adjusted for the treatment effect in the relevant patient subgroup (i.e., by applying the HR for time to first PDR to four-weekly rates for transitions to higher EDSS states).

For the proportion of patients having discontinued treatment with satralizumab, transitions among EDSS

states were modeled using baseline EDSS transition probabilities, i.e., following the same procedure used for the placebo comparators.

It was assumed that once patients had discontinued treatment, they would not be able to go back to an on-treatment status.

7.3.4 Half-cycle correction

It was assumed that transitions from one health state to another occur at the beginning of each cycle. In reality, however, state transitions are a continuous process, which may occur at any time during the cycle. The half-cycle correction was thus applied in the model to account for mid-cycle transitions. This assumes that state transitions occur, on average, halfway through the cycle. Due to the short cycle length of 28 days, the half-cycle correction was not expected to have a large impact on the results, but it was included in the model for completeness.

7.4 Comparators and patient populations

7.4.1 Patient population

The DMC protocol defined the patient population as: “Patients with NMOSD with an EDSS < 7, who have antibodies against AQP4 and have experienced at least one attack”. Therefore, to align with the DMC protocol for this assessment, the base-case analysis has been conducted with the AQP4-positive patient population of the SAkuraStar study. However, as this is a subpopulation of the ITT population in SAkuraStar, analysis with the ITT population is also possible within the model. The impact of conducting the analysis with the ITT population has been tested in a scenario analysis. To change the population within the model, please consult the ‘com’-cell in the ‘Model Inputs’-sheet.

7.4.2 Comparators

The model compares satralizumab to placebo, as defined in the DMC protocol.

8. Model inputs

8.1 Perspective

The perspective of the economic model is a restricted societal perspective, which includes costs related to drug acquisition, drug administration, monitoring, adverse events, patient time, and transportation. Indirect costs are not included as per the DMC’s guidelines [10].

8.2 Time horizon

For the base case scenario, a lifetime time horizon (50 years) was selected. This time horizon is expected to be sufficiently long to capture all-important differences in costs or clinical outcomes between the technologies being compared in a chronic disease such as NMOSD [18].

8.3 Discounting

In the base case, the annual discount rate for future costs was 3.5% for model year ≤35 and 2.5% for model year 35 to 70 in alignment with the Danish Ministry of Finance guidelines [13]. Discounting in the model is performed after the first year on a yearly basis.

8.4 Clinical inputs

The base case analysis will be conducted with the AQP4-positive subpopulation. However, as described in section 7.4.1, the model includes both the AQP4-positive subpopulation as well as the ITT population of the SAkuraStar trial and clinical inputs are therefore presented for both populations in the following sections.

8.4.1 Patient population

The baseline characteristics for the patient population included in Sakura 309 trial are illustrated in **Table 8.4.1a**. The average body surface area has been calculated using the Dubois formula, using weight and heigh data from Sakura 309. All listed below are user definable within the model on the 'Model Inputs'-sheet.

Table 8.4.1a Proportion of EDSS scores at baseline for relevant population.

Parameter	Value	Reference
Average age of the cohort (years)	43.70	Sakura 309 trial AQP4-IgG positive population at baseline in the DB period [Data on file]
Body weight (kg)	73.00	
Height (cm)	164.21	
Body Surface Area (m^2)	1.80	Dubois formula
Proportion of males	18%	Sakura 309 trial AQP4-IgG positive population at baseline in the DB period [Data on file]

8.4.2 EDSS state distribution at baseline

The EDSS state distribution at the first model cycle for the different patient subgroups was assumed to reflect the one observed for each of these patient subgroups in the SAkuraStar trial (**Table 10**).

Table 10 Proportion of EDSS scores at baseline for relevant population.

	EDSS stage distribution at baseline (%)									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
AQP4+	0.00	9.38	14.06	31.25	21.88	4.69	18.74	0.00	0.00	0.00
Allcomers	0.00	8.42	16.84	27.37	24.21	3.16	20.00	0.00	0.00	0.00

8.4.3 Transition probabilities

NMOSD is a rare disease and, consequently, the SAkura trials could only enrol a limited number of patients with, to date, a limited follow-up. Therefore, to generate a set of baseline EDSS transition probabilities as clinically accurate as possible for the different patient subgroups included in the model, a global disease-specific registry (NMOBase) was utilized [19]. NMOBase is a web-based, global observational registry (a substudy of MSBase [msbase.org]) [20], designed for the clinical care and study of patients with NMOSD. No Danish patient registry for NMOSD patients was available. The global registry provides a broader characterization of the natural history of NMOSD than captured in clinical trials, and, as such, it was deemed to be the most appropriate and comparable data source for Danish

NMOSD patients for the cost model. The use of observational natural history data from a real-world setting in several countries increases the chance to have observations similar to the Danish patients. Furthermore, it is worth noting that the use of observational natural history data from a real-world setting has been accepted in previous NICE assessments (e.g., in MS).

In order to mimic as close as possible the baseline demographics and disease characteristics of the patient subgroups used in the cost model, a set of two patient cohorts was selected from the NMOBase dataset (see also **section 7.4**). This was necessary to obtain baseline EDSS transition probabilities matching as closely as possible the transition probabilities that would have been observed if they could be estimated in the patients on which treatment effect inputs were measured. The patient cohorts were the following:

- SAkuraStar AQP4+ like – DMT naïve (n=34)
- SAkuraStar ITT like – DMT naïve (n=87)

Although the base case scenario for the SAkuraStar like cohorts uses transition probabilities obtained from patients who were never exposed to relapse prevention therapy (i.e., DMT naïve), the model also allows to use of transition probabilities obtained from a mix of patients who were and was not exposed to relapse prevention therapy (i.e., SAkuraStarAQP4+ like [n=200] and SAkuraStar ITT like [n=366]).

Further details of this study (including the model fit statistics used to determine the best model for each of the transition probabilities) can be found in **Appendix C.** Baseline EDSS transition probabilities for the different patient subgroups used in the model are shown in **Table 11** and **Table 12**.

8.4.4 Mortality

It is generally considered that NMOSD is a more aggressive disease than MS, with patients potentially dying from relapse due to issues such as neurogenic respiratory failure. However, no deaths were recorded in the SAkuraStar trial up to the latest data cut-off dates (7 June 2019), making it impossible to use this source of information to inform NMOSD mortality rates. Furthermore, a review of the literature returned highly variable data in terms of mortality rates or death probabilities [4, 21-25], most likely owing to significant heterogeneity in patient baseline characteristics, prognostic factors, sample sizes, and follow-up times across studies. Such a high level of heterogeneity made it extremely difficult to generate any reliable estimates for death probabilities for NMOSD patients from the available literature.

In order to account for the fact that patients with higher levels of disability (as measured by the EDSS scale) are at a higher risk of death than the general population, the following approach to model mortality in NMOSD patients has been adopted. First, the age-and-gender-specific all-cause mortality rates by year in the general Danish population were obtained [26], and a weighted average of the general population all-cause mortality rate based upon the female to male ratio of NMOSD patients was calculated. Then, to account for an excess risk of mortality in patients with NMOSD relative to the general population (and relative to MS patients), such annual mortality rates were adjusted by means of standardized mortality ratios (SMR) for MS patients [1], which were in turn corrected to a 20% inflation factor. The base case value for the inflation factor was selected upon discussions with external experts. The SMRs per EDSS state used in the base-case scenario are shown in **Table 13**. Finally, age-specific annual probabilities of death by EDSS state were obtained by converting the adjusted age-specific annual mortality so obtained into annual probabilities.

Table 13 Standardized Mortality Ratios (SMRs) by EDSS state.

	EDSS state									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
MS[a]	1.0000	1.4320	1.6000	1.6370	1.6740	1.8420	2.2730	3.0970	4.4470	6.4540
NMOSD[b]	1.2000	1.7184	1.9200	1.9644	2.0088	2.2104	2.7276	3.7164	5.3364	7.7448

[a] Pokorski *et al*, 1997.
[b] NMOSD with 20% acceleration factor.
EDSS, Expanded Disability Status Scale, MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; SMR, standardized mortality ratio.

8.4.5 Treatment effect measures

The ultimate goal of therapy in patients suffering from a chronic debilitating disease such as NMOSD is to slow down the rate of disability accumulation. In NMOSD, slowing down the rate of relapses is believed to be highly correlated with slowing down the rate of disability accumulation. Therefore, the treatment effect was modelled as the efficacy of therapy on reducing the rate of relapses.

Accordingly, the treatment effects of satralizumab were applied to baseline EDSS transition rates, adjusted to a four-weekly cycle length. Specifically, this was achieved by applying the HR for time to first PDR (the primary endpoint from the SAkuraStar trial to the rate of transitioning to higher EDSS health states (i.e. to forward transitions only), to reflect the impact of treatment on reducing the risk of relapse at any point in time (see **section 8.4.2** for more details).

The HRs for time to first PDR were derived from the SAkuraStar trial during the double-blinded period (for satralizumab vs. placebo) and are reported in **Table 14**.

Table 14 Hazard ratios for time to first protocol-defined relapse. Data from the SakuraStar trial, observed during the double-blind period (October 2018 data cut).

Treatment effect	HR	LB	UB
Satralizumab Allcomers	0.450	0.230	0.890
Satralizumab AQP4+	0.260	0.110	0.630

The model also allows testing the impact of using a different treatment efficacy measure for satralizumab (i.e., the HR for time to first treated clinical relapse, where available) in sensitivity analyses. Note that the treatment efficacy measures come from the randomized double-blind phase of the SAkuraStar trial.

The base case scenario assumes that the treatment effect is constant over time, i.e., there is no treatment effect waning over time. Evidence from a pooled analysis of the SAkura trials supports this assumption. In fact, the annualized treated clinical relapse rate reduction versus placebo (adjusted by AQP4-IgG status and trial identifier) remained fairly constant at around 28% during the first four years of follow-up. The ARR reduction based on PDR could not be used for this assessment, as PDRs were only assessed in the double-blind period. However, the model still allows users to test scenarios where the treatment effect fades out over time. No deaths were observed in the SAkuraStar and thus no direct treatment effect on mortality can be assumed. Therefore, the only effect on mortality for satralizumab in the model is indirect,

through delaying disease progression.

8.4.6 Treatment discontinuation

In the cost model, treatment discontinuation was modelled for satralizumab.

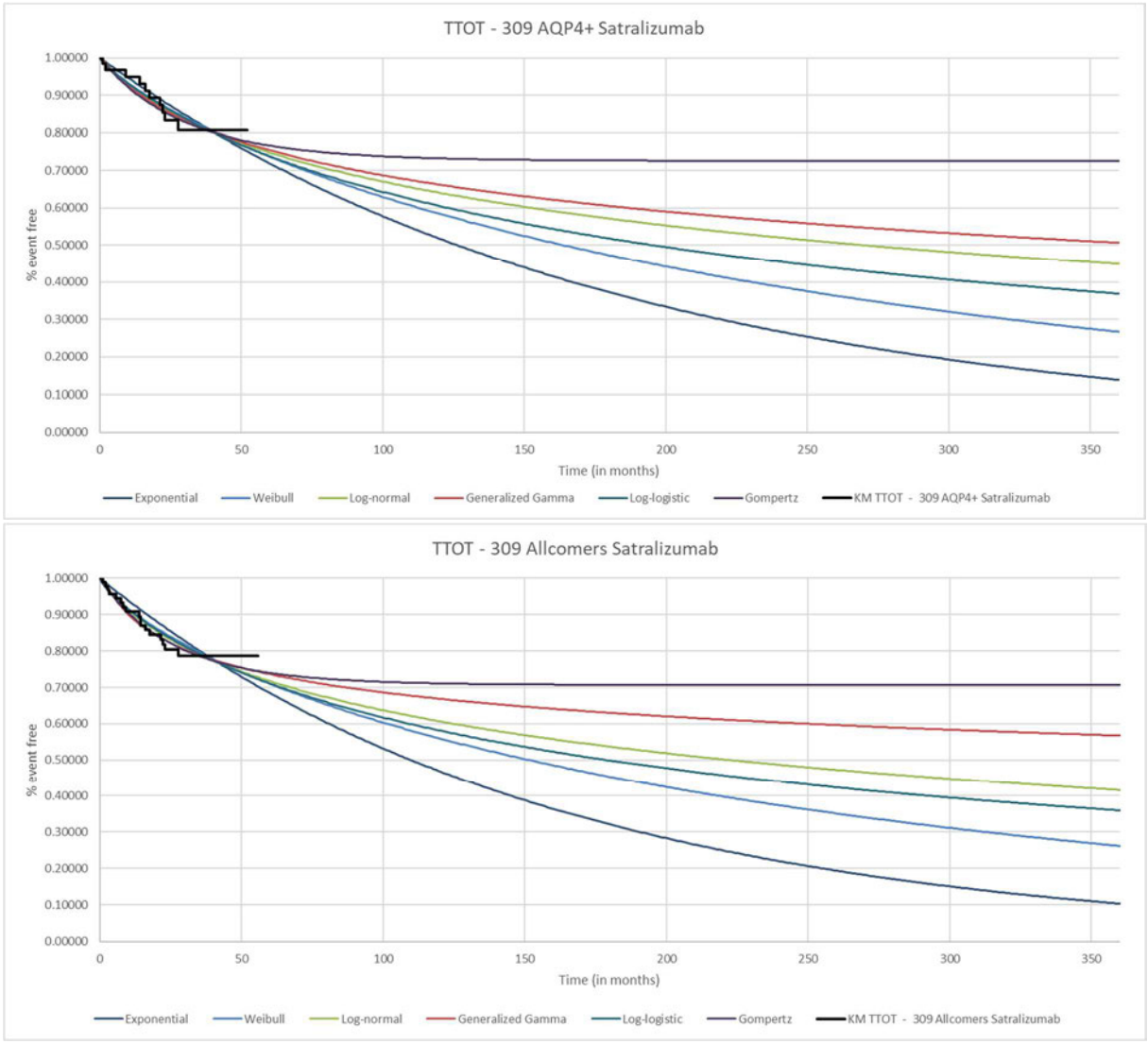
5.2.6.1 Treatment discontinuation for main comparator therapy

At each model cycle, the proportion of patients alive discontinuing treatment with the main comparator therapy was estimated by means of time to treatment discontinuation (hereafter referred to as time to off-treatment [TTOT]) data for satralizumab obtained from the SAkuraStar (February 2020 data cut). For each patient subgroup included in the model, a set of parametric distributions (i.e., exponential, Weibull, lognormal, loglogistic, Gompertz and generalized gamma were fitted [all in SAS] onto Kaplan Meier curves for TTOT for satralizumab in the corresponding subgroup from the SAkuraStar trial. These distributions were used to model treatment discontinuation, both during and beyond the trial period. Criteria for selecting the best parametric distribution were best model fit statistics overall (AIC/BIC and log-likelihood, with emphasis on AIC). In cases where selection of the best parametric distribution based exclusively on best model fit statistics was difficult, the best visual fit was also used as additional criteria for model selection. Model fit statistics are shown in **Appendix B.**

5.2.6.2 At every time *t* in the cost model, the probability of discontinuing satralizumab was calculated as the value of the parametric function at time t_x divided by the value of the parametric function at time t_{x-1}. In order to not estimate treatment cost for patients who are not alive, the TTOT curves are at any time capped by the proportion of patients alive. No stopping rule was applied for satralizumab. Time to treatment discontinuation inputs

Base case TTOT parametric model estimates are provided in **Table 15,** whilst the final TTOT parametric distributions for satralizumab in each patient subgroup used in the model, fitted to their respective Kaplan-Meier plots, are displayed in **Figure 4.** Further details of fitted parameters and fit statistics for all distributions fitted to each treatment arm can be found in **Appendix B**.

Figure 4 Time to off-treatment, model parametric distributions for 309 AQP4+ satralizumab and 309 Allcomers satralizumab



AQP4+, aquaporin-4 IgG seropositive; KM, Kaplan-Meier; TTOT, time to off-treatment.

8.5 Health resource use and costs

The approach to understanding the costs associated with NMOSD patients on treatment with either satralizumab or placebo involved consulting a Danish clinical expert in the treatment of NMOSD patients [27]. The clinical expert gave input to the resource use associated with NMOSD patients.

The direct treatment-related costs for satralizumab were based on internal Roche Data, while costs related to placebo are based on clinical expert inputs [27] and DRG tariffs.

All costs reported here are in Danish kroner (DKK).

8.5.1 Drug acquisition costs

Satralizumab comes in single-dose prefilled syringes readily available for subcutaneous (SC) injection which a patient can administer at home if the treating physician determines that it is appropriate, and that the patient can perform the injection technique. The prefilled syringes do not allow dose modification, hence all patient treated with satralizumab will be treated with a fixed dose syringe. It is therefore not possible to modify the dose, therefore no wastage is assumed for patients treated with satralizumab.

For each treatment, expected drug costs per patient were calculated based on the list price per dosage unit, the dosing and administration schedule used in clinical trials, whenever available, (**Table 16**), and treatment discontinuation data based on TTOT curves (see **8.4.5**). For the main comparator therapies, a distinction was made in the model between the cost for loading doses and the cost for maintenance doses.

Table 16 Drug dose and administration schedule.

			Dose				
Regimen	**Drug**	**Dosing**	**Loading**	**# of loading doses**	**Maintenance**	**Treatment cycle length (in days)**	**# of model cycles per treatment cycle**
Satralizumab	Satralizumab	Fixed	360	1	120	28.00	1.00

#, number.

Drug costs for satralizumab were calculated based on the average dose in the treated population according to the selected dosing scenario and the prices of the available vials, as shown in **Table 17**.

DKK, Danish Kroner; mg, milligram.

Drug costs per model cycle were then calculated and the total drug costs per treatment cycle are shown in **Table 18**.

[redacted]

8.5.2 Drug administration costs

Administration costs accounted for in the model include administration costs per treatment cycle. The administration cost is based on the Danish DRG tariffs and was only applied in the satralizumab arm. A distinction was made in the model between costs for the first treatment cycle and costs for subsequent treatment cycles. Based on the feedback from the Danish clinical expert, patients treated with satralizumab would go to the hospital for the first two administrations due to both administration and training in self-administration of satralizumab. The loading period of satralizumab contains administration on days 0, 14, and 28, followed by maintenance every four weeks. Based on the Danish clinical expert's feedback it was assumed that patients would have the first two administrations of satralizumab at the hospital, therefore, the cost associated with administration of satralizumab was only applied in the first model cycle reported in **Table 19**.

Table 19 Administration cost.

	Satralizumab		
	% of patients	**Costs (DKK)**	**References**
Administration cost first treatment cycle	100%	6,704	DRG 2021 - 01MA98, MDC01 1-dagsgruppe, pat. mindst 7 år, diagnosis: DG360, Neuromyelitis optica, procedure: BWAA31, Medicingivning ved subkutan injektion, two administration within the first cycle
Cost per treatment cycle		**6,704**	
Administration cost subsequent treatment cycles	100%	0	
Cost per treatment cycle		**0**	

AE, adverse event; DKK, Danish Kroner.

8.5.3 Adverse events

Only treatment-related AEs with a severity grade of 3 or higher and SAEs were considered in the analysis (whenever such information was available) (**Table 20**) and the associated unit costs of these AEs based on the Danish DRG tariffs (**Table 21**). AEs for satralizumab were from the February 2020 data cut, whilst those for placebo were limited to the double-blind period of the SAkuraStar study. Where feasible, the rates of treatment-related grade 3 or higher or SAEs were calculated separately for every treatment using the number of events and total time at risk for the AQP4+ population, where available. Otherwise, AE rates were calculated by assuming that the number of AEs experienced was equal to the number of patients experiencing an AE and/or that the time at risk was the same as that for the cohort of patients used for the respective satralizumab arm selected for the comparison. From the individual AE rates

calculated as described above, a 4-weekly probability of experiencing a specific AE was calculated and used to derive 4-weekly AE costs.

Table 20 Incidence of grade 3 or higher adverse event or serious adverse events for satralizumab and relevant comparators used in the model.

	AQP4+		ITT	
	SAkuraStar (monotherapy)		**SAkuraStar (monotherapy)**	
	Satralizumab	**Placebo**	**Satralizumab**	**Placebo**
AE term (MeDRA)	**Number of AEs/patients experiencing an grade 3 or higher AE**			
Back pain	1		1	
Dermatitis			1	
Diarrhea			1	
Eye pain	1		1	
Gastrointestinal viral infection			1	
Influenza	1		1	
Neutropenia	1		1	
Pain in extremity			1	
Pneumonia			1	
Pulmonary sepsis	1		1	
Tooth abscess		1		1
Upper respiratory tract infection	1		1	
Urinary tract infection				2
Vertigo	2		2	

Table 21 Adverse event costs.

Adverse event [a]	Unit cost (DKK)	References
Back pain	1,617	DRG 2021 - 08MA98, MDC08 1-dagsgruppe, pat. mindst 7 år, diagnosis: DM549, Rygsmerter UNS
Dermatitis	1,735	DRG 2021 - 09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år, diagnosis: DL251, Dermatitis UNS forårsaget af hudkontakt med lægemiddel
Diarrhea	5,130	DRG 2021 - 06MA11, Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Eye pain	964	DRG 2021 - 02MA01, Øvrige indlæggelser eller besøg ved øjensygdomme, diagnosis: DH571, Øjensmerter
Gastrointestinal viral infection	5,130	DRG 2021 - 06MA11, Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DA084: Tarminfektion forårsaget af virus UNS
Influenza	1,862	DRG 2021 - 03MA98, MDC03 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DJ091: Influenza med påvist influenzavirus A
Neutropenia	3,114	DRG 2021 - 16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år, diagnosis: DI109, Neutropenia
Pain in extremity	1,024	DRG 2021 - 70OP99, Ikke gruppérbar pga. manglende oplysninger, diagnosis: FB28014, Smerter i overekstremitet
Pneumonia	1,732	DRG 2021 - 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år, diagnosis: DJ189, Pneumoni UNS
Pulmonary sepsis	2,676	DRG 2021 - 18MA98, MDC18 1-dagsgruppe, pat. mindst 7 år, diagnosis: DA419, Sepsis UNS
Tooth abscess	1,862	DRG 2021 - 03MA98, MDC03 1-dagsgruppe, pat. mindst 7 år, diagnosis: DK047, Periapikal tandabsces uden fistel
Upper respiratory tract infection	1,862	DRG 2021, 03MA98: MDC03 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DJ069: Akut øvre luftsvejsinfektion UNS
Urinary tract infection	1,906	DRG 2021, 11MA98, MDC11 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DN390: Urinvejsinfektion uden angivelse af lokalisation
Vertigo	5,091	DRG 2021, 03MA02, Svimmelhed, Diagnosis: DH814: Central vertigo

[a] Grade 3, 4, or SAE
AE, adverse event; DKK, Danish Kroner; SAE, serious adverse event.

8.5.4 Supportive care costs

NMOSD is characterized by relapses that frequently require hospitalization, outpatient care, and treatment. For patients who experience a relapse, costs associated with relapses may be more than four times higher compared with patients who do not [28]. Compared to non-NMOSD controls, patients with highly active NMOSD have a greater comorbidity burden, greater proportions of hospitalization, and more emergency department visits [29].

Supportive care costs for NMOSD patients in Denmark were based on inputs from the Danish clinical

expert estimating a consultation at a neurologist every six months independent of EDSS score [27]. Thus, the supportive care cost has been included as a cycle cost in the model based on the Danish DRG tariffs (**Table 22**).

Table 22 Supportive care costs.

Activity	Annual number of visits	Cost per unit (DKK)	References
Neurologist consultation	2	3,353	DRG 2021 - 01MA98, MDC01 1-dagsgruppe, pat. mindst 7 år, diagnosis: DG360, Neuromyelitis optica, procedure: ZZ0149AI, Neurologisk undersøgelse
Total annual cost (DKK)		**6,706**	
Cycle cost applied in the model (DKK)		**514**	

DKK, Danish Kroner
EDSS, Expanded Disability Status Scale.

The Danish clinical expert estimated that patients with relapse would have inpatients' visits for 5 days [27]. It was assumed that 50% of the mild/moderate attack would result in an inpatient visit, similar to the expert committee's estimate for the assessment of Soliris® by the DMC [30]. The costs related to an inpatient visit were estimated based on the Danish DRG tariffs reported in **Table 23.**

Patients who experience a severe relapse would all have an inpatient visit during an attack in line with the clinical expert opinion [27]. The Danish clinical expert reported treatment of a mild/moderate relapse would consist of IV steroids for five days for inpatients and a severe relapse IV methylprednisolone and plasma exchange during the five days inpatient stay. The dose of IV steroids and IV methylprednisolone would be 1g per day according to the study by Kimbrough et al. [31] and the price of the drugs was found on Medicinpriser.dk (**Table 24**). The cost of plasma exchange and intravenous injection was assumed to be included in the tariff of an inpatient visit to avoid double-counting. Due to the previous assumption that 50% of mild/moderate attacks would result in an inpatient visit, the other 50% would result in an outpatient's visit to a neurologist. For this reason the relapse management cost of a mild/moderate relapse is less than a severe relapse. The total cost of relapse management included in the model is reported in **Table 25**.

Table 23 Inpatient visit and outpatient visit cost relapse management.

Relapse management inpatient visit and outpatient visit cost	Cost per unit (DKK)	References
Inpatient visit	40,774	DRG 2021 - 01MA07, Dissemineret sklerose og cerebellar ataxi, diagnosis: DG360, Neuromyelitis optica, procedure: DG359, Dissemineret sklerose UNS
Outpatient visit	3,353	DRG 2021 - 01MA98, MDC01 1-dagsgruppe, pat. mindst 7 år, diagnosis: DG360, Neuromyelitis optica, ZZ0149AI, Neurologisk undersøgelse

Table 24 Drug cost relapse management.

Relapse management drug costs	Cost per unit (DKK)	References
Methylprednisolone 40mg/ml of a 2 ml vial	60.11	Medicinpriser.dk (DATE: 27/07/2021)

Table 25 Total relapse management costs.

Total relapse management	Patient proportion %	Cost per unit (DKK)	References
Mild/Moderate			DRG 2021 - 01MA07, Dissemineret sklerose og cerebellar ataxi, diagnosis: DG360, Neuromyelitis optica, procedure: DG359, Dissemineret sklerose UNS Medicinpriser.dk (DATE: 27/07/2021) [27, 30]
Inpatient visit	50%		
Outpatient visit	50%		
Total cost per unit (DKK)		23,942	
Severe			
Inpatient visit	100%		
Outpatient visit	0%		
Total cost per unit (DKK)		44,531	

8.5.5 Patient and transportation cost

Patient costs are included in the model in line with the DMC method guidelines [10]. The unit cost per hour is assumed to be DKK 179 in line with the DMC guidelines [32]. Satralizumab is subcutaneously self-administered. Based on the feedback from the clinical expert, it has been assumed that patients will have training in the hospital for the first and second self-administration of satralizumab. The clinical expert estimated the patient time for the first training to be 45 minutes and the second to 15 minutes. The third administration will be done at home by the patient while talking to a nurse on the phone for 15 minutes. The Danish clinical expert estimated that patients would spend 5 minutes at home for each subsequent self-administration [27]. The estimated patient cost associated with the administration of satralizumab has been reported in **Table 26**. As no treatment was given in the placebo arm, no patient cost or transportation cost associated with administration of therapy was estimated.

Table 26 Patient costs associated with administration of satralizumab.

Activity	Hours per visit	Total cost (DKK)
Administration of satralizumab 1st visit	0.75 hours	134
Administration of satralizumab 2nd visit	0.25 Hours	45
Administration of satralizumab 3rd administration	0.25 Hours	45
Administration of satralizumab subsequent cycles	0.08 Hours	15

Patient cost associated with monitoring was estimated based on the time usage estimates provided by the Danish clinical expert [27]. The monitoring did not differ between the different health states, for this reason, the same monitoring costs were applied to all health states in the model. The estimated patient cost associated with monitoring is reported in **Table 27**.

Table 27 Patient cost associated with monitoring of NMOSD patients.

Activity	Hours per visit	Annual number of visits	Total annual cost (DKK)
Neurologist consultation	0.75 hours	2	269

Based on consultation with a Danish clinical expert[27], 5 days of admission to the hospital was to be expected for a relapse. In the Soliris® HE assessment by the DMC, the time usage of a relapse was estimated to be 30 hours [30]. As the estimate of 30 hours closely aligns with the estimate of 5 admission days provided by our Danish clinical expert[27], 30 hours of patient time have been applied for all inpatient admission. However, as it is assumed that 50% of mild/moderate relapses result in an inpatient admission, the patient time estimated for these relapses corresponds to the assumption made. This estimate is similar to the estimates used in the Soliris® application, therefore, we believe it to be reasonable to use the estimates from the Soliris® assessment by DMC [27].

The Danish clinical expert consulted estimated an outpatients visit of 20 minutes concerning relapses. For that reason, the other 50% of mild/moderate relapses resulted in an outpatient visit [27]. The patient costs associated with relapses are reported in **Table 28**.

Table 28 Patient cost associated with a relapse.

Relapse	Hours per relapse	Total cost per relapse (DKK)
Mild/moderate	15.2	2,721
Severe	30	5,370

Satralizumab is dispensed at the hospital. The Danish clinical expert estimated that four annual dispensations of satralizumab would be required [27]. Two of the dispensing visits are assumed to occur

at supportive care visits, the remaining two will occur between supportive care visits. The patient cost associated with dispensing of satralizumab outside of the supportive care visits is reported in **Table 29**.

Table 29 Patient cost associated with dispensing of satralizumab outside of the supportive care visits.

Activity	Hours per visit	Annual number of visits	Total annual cost (DKK)
Dispensing of satralizumab	0.5	2	179

Transportation costs are included in the model in line with DMC guidelines [10] and were applied in the model. A rate of DKK 100 per visit was applied in the model. As training at the hospital occurs at the first and second administration of satralizumab, transportation cost has been applied in the first model cycle. See **Table 30** for the applied transportation cost associated with administration of satralizumab at the hospital.

Table 30 Transportation costs associated with administration of satralizumab.

Activity	Transportation cost per administration (DKK)
Administration of satralizumab 1st model cycle	200
Administration of satralizumab subsequent model cycles	0

Transportation cost associated with monitoring was estimated based on input from a Danish clinical expert [27]. The estimated transportation cost associated with monitoring is reported in **Table 31**.

Table 31 Transportation cost associated with monitoring of NMOSD patients.

Activity	Annual number of visits	Total annual cost (DKK)
Neurologist consultation	2	200

Transportation cost associated with relapse was based on the Danish clinical expert input that patients either would have an outpatient- or inpatient visit in connection with relapse [27]. Thus, it was assumed that patients only would have transportation costs associated with one hospital visit as reported in **Table 32**.

Table 32 Transportation cost associated with relapse.

Activity	Transportation cost per relapse (DKK)
Transportation concerning relapse	100

As satralizumab is dispensed at the hospital twice annually outside of the regular monitoring visits, the transportation cost associated with the dispensing visits of satralizumab is reported in **Table 33.**

Table 33 Transportation cost associated with dispensing of satralizumab.

Activity	Annual number of visits	Total annual cost (DKK)
Dispensing of satralizumab	2	200

9. Results

9.1 Base case results

Results of the base case analysis are present below in **Table 34**. The analysis estimated an incremental cost of satralizumab compared to placebo of [redacted] over a lifetime horizon. The incremental cost is due to the drug cost of satralizumab. The analysis showed that the treatment with satralizumab was associated with fewer costs regarding relapse management and AE management when having a treatment duration of 157.2 months.

Table 34 Base case analysis.

	Satralizumab (DKK)	Placebo (DKK)	Satralizumab vs. placebo (DKK)
Drug cost	[redacted]	[redacted]	[redacted]
Treatment administration cost	6,704	0	*6,704*
AE management	7,544,929	0	*7,544,929*
Relapse management (mild/moderate)	1,136	887	*249*
Relapse management (severe)	77,448	105,603	*-28,155*
Supportive care	55,840	81,347	*-25,507*
Patient costs	131,223	86,753	*44,470*
Travel costs	22,829	17,984	*4,845*
Total	[redacted]	[redacted]	[redacted]
	Satralizumab	**Placebo**	**Satralizumab vs. placebo**
Treatment duration in months	[redacted]	[redacted]	[redacted]
Number of relapse on tx - moderate/mild	1.1	0.0	1.1
Number of relapse off tx - moderate/mild	5.0	7.6	-2.6
Number of relapse on tx - severe	0.4	0.0	0.4
Number of relapse off tx - severe	2.0	3.1	-1.1
Total number of relapses	8.4	10.7	-2.2

9.2 Scenario analysis

The results of the different scenario analyses are presented below in **Table 35.** Overall, the different scenario analyses show a robust result except for the scenario where the parameter "Treatment duration assumption" is chosen to the value "Lifetime (capped at death)" resulting in an incremental cost of [redacted] This scenario seems, however, unrealistic to assume that none of the patients would go off-treatment at some point.

Table 35 Scenario analysis

Number	Parameter	Value	Inc cost, satralizumab vs. placebo
Base case			[redacted]
1	Treatment duration assumption	Actual treatment duration (capped at death)	
2	Treatment duration assumption	Lifetime (capped at death)	
3	Distributions for TTOT	Exponential	
4	Distributions for TTOT	Weibull	
5	Distributions for TTOT	Log-normal	
6	Distributions for TTOT	Generalized Gamma	
7	Distributions for TTOT	Log-logistic	
8	Distributions for TTOT	Gompertz	
9	Distributions for TTOT	Gamma	
10	Distributions for TTOT	KM with Exponential tail	
11	Distributions for TTOT	KM with Weibull tail	
12	Distributions for TTOT	KM with Log-normal tail	
13	Distributions for TTOT	KM with Gen. Gamma tail	
14	Distributions for TTOT	KM with Log-logistic tail	
15	Distributions for TTOT	KM with Gompertz tail	
16	Distributions for TTOT	KM with Gamma tail	
17	Distributions for TTOT	Piecewise exponential	
18	Treatment effect waning assumption	Effect is maintained over time	
19	Treatment effect waning assumption	Effect is limited in time	
20	EDSS backward transitions assumption	Yes	
21	EDSS backward transitions assumption	No	
22	Patient population for the comparison in the SAkuraStar cohorts (all vs. DMT naïve only patients)	DMT naïve	
23	Patient population for the comparison in the SAkuraStarcohorts (all vs. DMT naïve only patients)	All	
24	Time horizon	35	
25	Time horizon	40	
26	Time horizon	45	
27	Time horizon	50	

28	Time horizon	55	[redacted]
29	Time horizon	60	
30	NMOSD mortality acceleration factor	1	
31	NMOSD mortality acceleration factor	1,125	
32	NMOSD mortality acceleration factor	1,25	
33	NMOSD mortality acceleration factor	1,375	
34	NMOSD mortality acceleration factor	1,5	

10. Budget impact analysis

10.1 Methods

The budget impact model was developed to estimate the expected budget impact of recommending satralizumab as a possible standard treatment in Denmark for NMOSD AQP4-IgG seropositive patients presented in the DMC protocol [9]. The budget impact was estimated per year for the first 5 years after the introduction of satralizumab in Denmark.

The cost per patient model was partially nested within the budget impact model, and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the population in the cost per patient model.

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where satralizumab is recommended as a standard treatment and the scenario where satralizumab is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

10.1.1 Prevalence and incidence of patients

Roche intern analysis estimated prevalence and incidence of patients was very similar to the numbers used in the application of Soliris®. For this reason, it was decided to adopt the same assumptions in terms of market uptake as in the Soliris® assessment, as well as the market uptake of the new drug with or without a recommendation.

In the Soliris® application, a prevalent population of 43 NMOSD patients was assumed, and a yearly incidence of new patients to be approx. five patients each year [30]. These numbers of prevalent and incident patients with NMOSD have been applied in the model, please see **Table 36** for a tabulated overview.

Table 36 Prevalence and incidence of NMOSD patients applied in the budget impact model

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients	43	5	5	5	5
Total number of patients	43	48	53	58	63

Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. Regardless, the estimates will be associated with uncertainty. The potential market share for satralizumab with or without a recommendation was aligned with the assumptions made in the application of Soliris® [30], where 2 patients of the prevalent population will start satralizumab treatment in year 1 and a total of 15 patients will be on treatment with satralizumab in year 5. See **Table 37** for tabulated patient numbers for the budget impact analysis.

Table 37 Yearly number of incident patients on satralizumab or placebo, with and without a recommendation

	No recommendation for satralizumab						Recommendation for satralizumab				
Treatment	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**		**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Satralizumab	0	0	0	0	0		2	4	4	4	1
Placebo	43	5	5	5	5		41	1	1	1	4
Total patients	43	48	53	58	63		43	48	53	58	63
Total patients on satralizumab	**0**	**0**	**0**	**0**	**0**		**2**	**6**	**10**	**14**	**15**

10.1.2 Costs

Included costs in the budget impact model were drug costs, administration costs, relapse management costs, supportive care costs, and adverse event management costs. Patient- and transportation costs were not included as these are not part of the regional budgets. Discounting was not used in the budget impact model in line with DMC's methods guidelines [10]. The undiscounted cost output of the cost per patient model was used directly to inform the cost per year per patient in the budget impact model for satralizumab and placebo.

10.2 Results

10.2.1 Base case result

Based on the base case assumptions, the estimated budget impact of recommending satralizumab as a possible standard treatment in Denmark for the population described in the clinical question was [redacted] shown in **Table 38**.

Table 38 Budget impact

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Not recommended	[redacted]				
Recommended					
Total budget impact					

11. Discussion and conclusion

The analysis of the model estimated that treatment of NMOSD patients with satralizumab resulted in an incremental cost of [redacted] versus placebo. As the treatment arm with placebo does not accrue any drug cost, the placebo arm will naturally have a lower total cost compared to the satralizumab arm, where the patients are treated with a therapy. The drug cost drives the total cost of the satralizumab arm, where patients on average are on treatment for 157.2 months (≈13 years). The analysis showed that the cost associated with relapse management was less for the satralizumab arm compared to the placebo arm, as treatment with satralizumab prolonged time to disease progression for the patients.

The base case analysis was made on the subgroup of NMOSD AQP4+ patients from the SakuraStar trial to align with the proposed population defined in the protocol by the DMC. The scenario analysis indicated that the incremental cost did not differ significantly when using either the ITT group or the subgroup of AQP4+ patients. The use of the subgroup of AQP4+ patients is therefore expected to have a minor impact on the results of the model.

An increased incremental cost will naturally lead to an increased budget impact, especially when considering that patients will go from having no treatment to being on treatment. The budget impact analysis suggested that a recommendation of satralizumab would result in an increased budget impact of [redacted] at year 5.

The clinical question requires comparison to placebo. Patients with AQP4 positive NMOSD will be offered various treatments at neurology departments today. These treatments are off-label and not recommended in guidelines, but there are costs connected to these. In addition to this there are costs and resource use connected to NMOSD patients that are not efficiently treated. Neither of these shows in this analysis because comparator is placebo.

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13. APPENDICES

A. SAkuraStar trial inclusion/exclusion criteria

Table 39 Key efficacy-related inclusion and exclusion criteria (SAkuraStar trial).

SAkuraStar
Inclusion
• Age 18 to 74 years • AQP4-IgG–seropositive or AQP4-IgG–seronegative NMO or NMOSD • ≥ 1 relapse in the 12 months before screening • EDSS score of 0 to 6.5
Exclusion
• Previous treatment with IL-6 inhibitory therapy, alemtuzumab, total body irradiation, or bone marrow transplantation at any time • Use of eculizumab, belimumab, or multiple sclerosis disease-modifying treatment within 6 months before baseline • Use of anti-CD4 agents, cladribine, or mitoxantrone within 2 years before baseline.

AQP4, Anti–aquaporin-4; CD4, cluster of differentiation 4; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; IL-6, interleukin-6; NMOSD, neuromyelitis optica spectrum disorder.

B. TTOT methodology

Criteria for the selection of the parametric distribution were best model fist statistics overall (AIC/BIC log-likelihood, with a major focus on AIC). In cases where selection of the best parametric distribution based exclusively on best model fit statistics was difficult, the best visual fit was also added as an additional criterion for model selection.

Table 40 Regression coefficients and AIC values and ranking for TTOT parametric distributions.

			Regression Coefficients						
Population	**Treatment arm**	**Distribution**	**1**	**2**	**3**	**AIC**	**Rank**	**BIC**	**Rank**
309 AQP4+	Satralizumab	EXPONENTIAL	5.204660			92.64	1	94.77	1
309 AQP4+	Satralizumab	WEIBULL	5.544850	1.221069		94.05	5	98.31	5
309 AQP4+	Satralizumab	LNORMAL	5.595838	2.247899		93.36	3	97.61	3
309 AQP4+	Satralizumab	GEN GAMMA	5.448568	2.727204	-0.514402	95.28	6	101.66	6
309 AQP4+	Satralizumab	LLOGISTIC	5.273494	1.137962		93.78	4	98.03	4
309 AQP4+	Satralizumab	GOMPERTZ	4.663415			92.82	2	97.07	2
309 Allcomers	Satralizumab	EXPONENTIAL	5.064722			151.44	5	153.96	1
309 Allcomers	Satralizumab	WEIBULL	5.500906	1.312299		151.57	6	156.59	5
309 Allcomers	Satralizumab	LNORMAL	5.403430	2.279122		149.57	2	154.59	3
309 Allcomers	Satralizumab	GEN GAMMA	4.057873	3.109300	-1.958453	150.26	3	157.79	6
309 Allcomers	Satralizumab	LLOGISTIC	5.185804	1.214867		151.01	4	156.03	4
309 Allcomers	Satralizumab	GOMPERTZ	4.449496			149.40	1	154.42	2

C. NMOBase study

▪ F.1. Study cohorts

The overall cohort based on which all SAkura like cohorts were selected was defined based on the following criteria:

- clinical diagnosis of NMOSD as per Wingerchuk 2015, diagnostic criteria (including retrospective diagnoses)
- availability of the minimum dataset (MS center details, patient year of birth, sex, date of disease onset, clinical relapses, and at least 2 clinic visits with recorded expanded disability status scores (EDSS).
- any serostatus included and any patients with a diagnosis of 'definite MS' or myelin oligodendrocyte glycoprotein (MOG)-IgG positive were excluded (n = 389).

▪ F.2. Methodology

To generate transition probabilities, the following methodology was used [33]:

- The assessment was based on all subjects included in the MSBase registry (NMOBase sub-registry) until October 9th, 2019, who met the study requirements (listed above).
- Transition probabilities were generated using a continuous multi-state model (MSM), using the R msm package [34]. For the transition count matrices associated with each transition probability matrix, please refer to the CE model excel file. Please see appendix E for description of the msm package and the statistical analysis protocol for this analysis.
- Covariates used were age, sex, and a binary covariate representing the ever/never exposure to immunosuppressants for relapse prevention (there were not enough data for other covariates).

Based on preliminary analyses of the NMOBase datasets, an imbalance between the total number of visits where a decrease in the EDSS score was recorded compared to the preceding visit (i.e., recovery visits) and the total number of visits where an increase in the EDSS score was recorded compared to the preceding visit (i.e., relapse visits) was observed. In the attempt to reduce such an imbalance, the following two-step filtering procedure was used, before proceeding with the estimation of EDSS transition probabilities:

- visits that were temporally close to each other (i.e., visits performed within 90 days from the preceding one) were identified in the NMOBase dataset, for each patient cohort

- visits that were performed within 90 days from their preceding visit and that were found to be in the middle of a sequence of three visits featuring consecutive EDSS increases/decreases (based on a 0.5 point spaced EDSS scale) from their respective preceding visits were excluded from the analysis dataset used for each patient cohort

The 90-day threshold for temporally close visits was selected in accordance with the NMOBase team.

The rationale behind this approach was that of treating subsequent relapses within a cluster, as well as a series of subsequent recovery visits temporally close to each other, as one single relapse/recovery event

where the EDSS change was the greatest increase/decrease observed in the sequence of visits. This also allowed to limit the number of visits discarded (and any potential convergence issue associated with it), while at the same time minimizing the loss of potentially informative visits (e.g., EDSS increases separated by relatively long-time span with no visits in between, which may potentially represent two independent relapses).

Results

Fit statistics used to determine the best model fit for each of the transitional probabilities are shown in **Table 41**.

Table 41 Goodness of fit of EDSS transition matrics for SAkura 309 AQP4+ like cohort.

Model	AIC	df	LR Test	df	*p*-value
Unadjusted	4,620.75	19	Comparator reference model		
Age	4,556.92	38	101.84	19	$2.49*10^{-13}$
Sex	4,622.01	38	36.75	19	0.01
DMT	4,631.86	38	26.90	19	0.11
Age + Sex + DMT	4,545.67	76	189.09	57	$4.44*10^{-16}$

AIC, Akaike information criterion; df, Dickey-Fuller test; DMT, disease-modifying treatment; LR test, likelihood-ratio test

Table 42 Goodness of fit of EDSS transition matrices for SAkura 309 ITT like cohort

Model	AIC	df	LR Test	df	*p*-value
Unadjusted	7,847.40	19	Comparator reference model		
Age	7,738.03	38	147.37	19	0
Sex	7,839.85	38	45.55	19	0.00
DMT	7,855.17	38	30.24	19	0.05
Age + Sex + DMT	7,701.76	76	259.65	57	0

AIC, Akaike information criterion; df, Dickey-Fuller test; DMT, disease-modifying treatment; LR test, likelihood-ratio test

D. Classification of visual impairment status

Table 43 Severe visual impairment classification.

Patients with severe visual impairment	
Patients with severe visual impairment in just one eye (i.e., the worst-seeing eye) encompassed:	Patients with severe visual impairment in both the worse- and best- seeing eyes encompassed:

• Patients with severe visual impairment in the worst-seeing eye and no visual impairment in the best-seeing eye • Patients with severe visual impairment in the worst-seeing eye and mild visual impairment in the best-seeing eye • Patients with blindness in the worst-seeing eye and no visual impairment in the best-seeing eye • Patients with blindness in the worst-seeing eye and mild visual impairment in the best-seeing eye	• Patients with severe visual impairment in both the worst- and best-seeing eyes • Patients with blindness in the worst-seeing eye and severe visual impairment in the best-seeing eye • Patients with blindness in both the worst-and best-seeing eyes

E. msm R package and statistical analysis protocol of NMOBase data

The msm package for R allows a general multi-state model to be fitted to longitudinal data (often consisting of observations of the process at arbitrary times, so that the exact times when the state changes are unobserved). Multi-state Markov models are a useful way of describing a process in which an individual moves through a series of states in continuous time. For a given multi-state model, the next state to which an individual moves, and the time of the change, is governed by a set of transition intensities $q_{rs}(t, z(t))$ for each pair of states r and s. The intensities may also depend on the time of the process t, or more generally a set of individual-specific or time-varying explanatory 1 variables z(t). The intensity represents the instantaneous risk of moving from state r to state s:

$$q_{rs}(t, z(t)) = \lim_{\delta t \to 0} P(S(t + \delta t) = s | S(t) = r)/\delta t$$

The intensities form a matrix Q whose rows sum to zero, so that the diagonal entries are defined by:

$$q_{rr} = -\sum_{s \neq r} q_{rs}.$$

To fit a multi-state model to data, the msm package estimates such a transition intensity matrix. In a time-homogeneous continuous-time Markov model, a single period of occupancy (or sojourn time) in state r has an exponential distribution, with rate given by $-q_{rr}$, (or mean $-1/q_{rr}$). The remaining elements of the rth row of Q are proportional to the probabilities governing the next state after r to which the individual makes a transition. The probability that the individual's next move from state r is to state s is $-q_{rs}/q_{rr}$.

The msm function itself implements maximum-likelihood estimation for general multi-state Markov or hidden Markov models in continuous time (Kalbfleisch and Lawless[1] and later Kay [2]), applicable to any form of transition matrix. The likelihood is calculated from the transition probability matrix P(t).

For a time-homogeneous process, the (r, s) entry of P(t), $p_{rs}(t)$, is the probability of being in state s at a time t + u in the future, given the state at time u is r. P(t) can be calculated by taking the matrix exponential of the scaled transition intensity matrix (see, for example, Cox and Miller [3]).

$$P(t) = \mathrm{Exp}(tQ)$$

For simpler models, it is feasible to calculate an analytic expression for each element of P(t) in terms of Q. The msm package calculates P(t) analytically for selected 2, 3, 4 and 5-state models. For other models, which can have any transition structure on any number of states in principle, P(t) is determined from the matrix exponential. This is calculated using eigensystem decomposition (if eigenvalues are distinct) or a method based on Padé approximants with scaling and squaring [4] (if there are repeated eigenvalues).

Please find the statistical analysis protocol embedded below:

Prot SG41416 satralizumab v2.pdf

Reference list:

[1] J.D. Kalbfleisch and J.F. Lawless. The analysis of panel data under a Markov assumption. Journal of the American Statistical Association, 80(392):863–871, 1985.

[2] R. Kay. A Markov model for analysing cancer markers and disease states in survival studies. Biometrics, 42:855–865, 1986.

[3] D. R. Cox and H. D. Miller. The Theory of Stochastic Processes. Chapman and Hall, London, 1965

[4] C. Moler and C. van Loan. Nineteen dubious ways to compute the exponential of a matrix, twenty-five years later. SIAM Review, 45(1):3–49, 2003

Medicinrådet

Medicinrådets protokol for vurdering vedrørende satralizumab til behandling af neuromyelitis optica spektrum sygdom

Version 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

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

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

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

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1. Begreber og forkortelser

AQP4	Aquaporin-4
CDP	*Confirmed Disability Progression*
EDSS	*Expanded Disability Status Scale*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention-to-treat*
MKRF:	Mindste klinisk relevante forskel
NMOSD	Neuromyelitis optica spektrum sygdom
MS	Multipel sklerose
MSQOL-54	*Multiple Sclerosis Quality of Life-54*
NICE:	*The National Institute for Health and Care Excellence*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PP:	*Per Protocol*
RR:	Relativ risiko
SD	Standardderivation
SMD:	*Standardized Mean Difference*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Roche, som ønsker, at Medicinrådet vurderer satralizumab til neuromyelitis optica spektrum sygdom. Medicinrådet modtog den foreløbige ansøgning den 15. september 2020.

2.1 Neuromyelitis optica spektrum 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 et år efter 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 komplementprotein i relation til læsionerne [5].

For patienter med NMOSD er den væsentligste sygdomsprogression forbundet med attakker.

Fagudvalget finder, at det er vanskeligt at give et præcist estimat af antallet af nye patienter med NMOSD. Medicinrådet 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 [6]. Der foreligger ikke danske data efter 2014. På den baggrund antager fagudvalget, at antallet af patienter, der er kandidater til behandling med satralizumab, sandsynligvis ligger under 50 patienter, og at 5 nye patienter årligt vil være kandidater til behandlingen. Dette estimat er forbundet med stor usikkerhed.

2.2 Satralizumab

IL-6 er et signalstof, der har en central rolle i den sygdomsdrevne aktivering af immunforsvaret ved NMOSD. Ved høj sygdomsaktivitet er niveauet af IL-6 højt i cerebrospinalvæsken, og dette er (formentlig) en drivende faktor for inflammationen, der fører til tab af oligodendrocytter og demyelisering hos patienter med NMOSD [7,8]. IL-6-medieret aktivering er bl.a. vigtigt for dannelsen af antistoffer med AQP4 [9]. Satralizumab er et monoklonalt antistof, der binder til IL-6-receptoren [10] og dermed hindrer/sænker inflammationstilstanden i cerebrospinalvæsken .
120 mg satralizumab skal administreres subkutant ved behandlingsstart, efter to uger og efter fire uger i en opstartsfase. Derefter skal 120 mg satralizumab administreres subkutant hver fjerde uge.
Behandlingen har til formål at mindske antallet af attakker og forsinke sygdomsudviklingen. Det er relevant, da hvert attak kan medføre vedvarende skade.

Satralizumab fik positive opinon af Det Europæiske Lægemiddelagentur (EMA) i april 2021. Satralizumab forventes at få følgende indikation:

"Behandling af neuromyelitis optica spektrum forstyrrelser hos voksne og unge over 12 år med NMOSD som er AQP-4-antistof positive"

2.3 Nuværende behandling

Målet med den nuværende behandling er at forsinke/hindre attakker, hindre varig funktionsnedsættelse og forbedre livskvaliteten.
Selvom der ikke er andre anbefalede 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 foreligger evidens af høj kvalitet.

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.

Medicinrådet vurderer lægemidlet eculizumab til samme indikation som satralizumab og forventer at tage stilling til en eventuel anbefaling i juni 2021.

3. Kliniske spørgsmål

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

Valg af komparator
Valget af komparator er vanskeligt, da der ikke er andre godkendte lægemidler til indikationen. Medicinrådet har derfor valgt at sammenligne med placebo. Medicinrådet vil i vurderingen af satralizumab tage 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. Medicinrådet vil tage dette i betragtning, så vurderingen af satralizumab giver et så retvisende indtryk af effekten af satralizumab i forhold til klinisk praksis som muligt. Medicinrådet vil vurdere effekten af den nuværende behandling og hvis muligt sammenligne effekten af satralizumab med nuværende behandling.

Population
Populationen i det kliniske spørgsmål omfatter patienter med en Expanded Disability Status Scale (EDSS; se afsnit 3.2.1) < 7, fordi patienter med mere fremskreden sygdom i dansk klinisk praksis ikke ville blive tilbudt sygdomsmodificerende behandling.

3.1 Klinisk spørgsmål 1

Hvilken værdi har satralizumab sammenlignet med placebo for patienter med neuromyelitis optica spektrum sygdom?

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

Intervention
120 mg satralizumab s.c. ved dag 0, efter to uger og fire uger, efterfulgt af 120 mg satralizumab s.c. hver fjerde uge, evt. i kombination med anden immunsupprimerende terapi.

Komparator
Placebo

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Effektmål

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

Medicinrådet har valgt at benytte samme effektmål og MKRF som i vurderingen af eculizumab af hensyn til konsistens mellem de to vurderinger.

Tabel 1. Oversigt over valgte 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
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 visuel funktion (0-6 point)	Forskel på 0,2 point på et år
Livskvalitet	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring på SF-36	Forskel på 0,5 SD

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
**Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
EDSS: Expanded Disability Status Scale, SD: Standard Deviation.

3.2.1 Kritiske effektmål

Årlig attakrate

Den årlige attakrate beskriver antal bekræftede attakker pr. patient om året. Medicinrådet betragter dette effektmål som kritisk, da patienter med NMOSD ofte kan have relativt mange attakker, og hvert attak 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 [11,12].
Medicinrådet vurderer, at den mindste klinisk relevante forskel er 0,2 attakker pr. patient om året.

Forebyggelse af attakker er mere væsentligt for patienter med NMOSD end for patienter med attakvis MS, fordi attakkerne ofte er mere invaliderende. Medicinrådet 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. Medicinrådet vurderer, at attakker er en mere væsentlig del af sygdomsforløbet for patienter med NMOSD, og at attakker optræder hyppigere hos disse patienter. I et dansk kohortestudie var den årlige attakrate 0,55. Derfor er effektmålet kritisk i denne protokol, og den mindste klinisk relevante forskel er defineret anderledes end i protokoller for attakvis MS.

Bivirkninger
Bivirkninger er et kritisk effektmål, da det belyser, hvor godt patienterne tolererer satralizumab sammenlignet med komparator. Medicinrådet ønsker data på nedenstående måleenheder og med længst mulig opfølgningstid:

Alvorlige bivirkninger
Medicinrådet 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 Medicinrådet ikke, at det acceptabelt, at en ny behandling medfører markant flere bivirkninger. Medicinrådet vurderer derfor, at den mindste klinisk relevante forskel i andelen af patienter, der får alvorlige bivirkninger, er 5 %-point.

Gennemgang af bivirkningsprofil
Medicinrådet ønsker en gennemgang af satralizumabs 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 satralizumab.

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.
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 og 3,5 defineres ved patienter, der er i stand til at gå min. 500 m uden nogen hjælp; scorer mellem 3,5 og 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.
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 [13].
Dette effektmål er kritisk, da et centralt mål med behandlingen er at forsinke progression af de funktionelle symptomer på sygdommen.
Effektmålet ønskes opgjort som gennemsnitlig ændring i EDSS-scoren. Den mindste klinisk relevante forskel mellem satralizumab og placebo vurderes af Medicinrådet at være en score på 0,2. Medicinrådet 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 Medicinrådet valgt, at synsskarphed er et vigtigt effektmål. Synsskarphed måles på en Snellen-tavle, og Medicinrådet 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. Medicinrådet er opmærksom på, at der derved er en vis redundans mellem de to 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 satralizumab og placebo vurderes af Medicinrådet at være en forskel i den gennemsnitlige ændring på 0,2 point i løbet af et år. Medicinrådet 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
Medicinrådet ønsker effektmålet opgjort med det generiske instrument SF-36. Medicinrådet har tidligere benyttet Multiple Sclerosis Quality of Life-54 (MSQOL-54) til vurderinger af lægemidler til behandling af MS, da det er et sygdomsspecifikt og valideret mål for livskvalitet, der inkluderer selvrapporterede subjektive indikatorer for fysisk, emotionel og social funktionalitet og trivsel [14,15]. MSQOL-54 bygger på SF-36, og da det ikke er valideret i NMOSD, har Medicinrådet valgt det generiske instrument. For helbredsrelateret livskvalitet anvendes ofte en mindste klinisk relevant forskel på 0,5 standarddeviationer (SD), og Medicinrådet 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 Medicinrådet data fra et andet valideret instrument, som er relevant for patienter med NMOSD, eksempelvis det generiske EQ-5D.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Medicinrådet kan også inddrage upublicerede og eventuelt fortrolige data – se Medicinrådets principper for anvendelse af upublicerede data.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie, hvor satralizumab er sammenlignet direkte med placebo. Studiet er rapporteret i følgende publikation(er):

- **SAkuraStar:** Traboulsee, A. et. al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder- a randomized double-blind, multicenter placebo-controlled phase 3 trial. Lancet, 2020, 19:402-412, incl. supplementary material. NCT: NCT02073279

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere data, men skal konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator.

5. Den endelige ansøgning

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

Studier og resultater

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

Statistiske analyser

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

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

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.
- Narrative analyser.
- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

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

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

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

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

6. Evidensens kvalitet

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

7. Andre overvejelser

Medicinrådet pointerer, at sammenligningen med placebo ikke er retvisende, da patienter i Danmark behandles med forskellige aktive behandlinger. Dette forhold vil indgå i Medicinrådets vurdering af satralizumab. Medicinrådet vil vurdere effekten af den nuværende behandling og hvis muligt sammenligne effekten af satralizumab med nuværende behandling.

Medicinrådet er opmærksom på, at EMA har angivet, at satralizumab kan benyttes både som monoterapi og i kombination med immunsupprimerende behandlinger. Medicinrådet ønsker, at ansøger redegør for kombinationsbehandling i det kliniske studie og beskriver overvejelser i relation til dansk klinisk praksis.

Medinrådet ønsker derudover, at ansøger redegør for, i hvor høj grad satralizumab ligner lægemidlerne tocilizumab og sarilumab, som ligeledes er interleukin 6-hæmmere. Ansøger bedes redegøre for virkningsmekanisme, indikationer og bivirkningsprofiler.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og Medicinrådet vil derfor ikke tage stilling til en foreløbig placering af lægemidlet. Medicinrådet er imidlertid i gang med at vurdere eculizumab til samme indikation og vil derfor i forbindelse med vurderingen af satralizumab sammenligne de to lægemidler i et bilag til vurderingsrapporten.

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10. 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 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
Jeppe Romme Christensen *Afdelingslæge*	Region Hovedstaden
Hilde Omestad *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Elisabeth Penninga *Overlæge*	Dansk Selskab for Klinisk Farmakologi
Kan ikke opfylde Medicinrådets habilitetskrav	Sclerosebehandlingsregistret
Kan ikke opfylde Medicinrådets habilitetskrav	Dansk Neurologisk Selskab
Marie Lynning *Patient/patientrepræsentant*	Danske Patienter
Malene Krüger *Patient/patientrepræsentant*	Danske Patienter

Sammensætning af fagudvalg	
Preben Borring Andersen *Overlæge*	Inviteret af formanden
Matthias Kant *Overlæge*	Inviteret af formanden

Medicinrådets sekretariat

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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.1	29. juni 2021	En fejl i indikationsteksten for satralizumab er rettet.
1.0	10. juni 2021	Godkendt af Medicinrådet.