Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende inebilizumab til behandling af neuromyelitis optica spektrum sygdom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. inebilizumab
2. Forhandlingsnotat fra Amgros vedr. inebilizumab
3. Ansøgers endelige ansøgning vedr. inebilizumab

Notat til vurderingsrapport: Inebilizumab til behandling af neuromyelitis optica spectrum sygdom

Først og fremmest vil vi gerne takke sekretariatet for en god proces. Alle tidslinjer blev overholdt, og vi havde rigeligt med tid til at adressere spørgsmålene i forbindelse med ansøgningen. Vi fandt spørgsmålene relevante og som udtryk for en grundig gennemgang.

Vi anerkender fuldt ud usikkerheden i den indirekte behandlingssammenligning (ITC) mellem inebilizumab og rituximab. Denne usikkerhed er forventelig, når man sammenligner on-label behandlinger med off-label behandlinger. Det er også derfor, at Amgen fremlagde en ITC mod placebo, som blev udeladt i evalueringsrapporten. Givet klinisk praksis ved NMOSD er vi enige i, at det ikke er tilstrækkeligt at basere en beslutning på en sammenligning mod placebo. Dog mener vi, at placeboanalysen kunne have bidraget til at informere en beslutning, relativt til den store usikkerhed i sammenligningen mod rituximab. Derudover finder vi det problematisk, at placeboanalysen blev fuldstændig udeladt fra rapporten, når det var et krav til os at inkludere den, jævnfør metodevejledningen. Der blev brugt meget plads på placeboanalysen, hvilket blev et problem i forhold til 100-siders grænsen for hovedteksten i ansøgningen, som vi ikke fik dispensation til at overskride. Denne plads kunne være blevet brugt til at beskrive yderligere detaljer om rituximabanalysen, men vi måtte i stedet prioritere kub at inkludere de mest nødvendige argumenter.

Vi finder det ligeledes kritisk, at sekretariatet konkluderer, at inebilizumab, testet i det største globale RCT i NMOSD til dato, har samme effekt og sikkerhedsprofil som rituximab, som kun er blevet testet i små, lokale studier.

Mere specifikt vil vi rette kritik mod valget om at inkludere RIN-1 og RIN-2 i effekt-sammenligningen, hvor det konkluderes, at der ikke er grund til at foretrække studiet af Kim et al. frem for RIN-studierne til vurdering af effekten af rituximab. Selvom vi anerkender begrænsningerne ved Kim et al.-studiet, blev dette studie valgt til vores ITC baseret på en systematisk tilgang med brug af statistiske metoder til at justere for forskellene. I vurderingsrapporten har sekretariatet valgt at sammenligne resultaterne af inebilizumab fra N-MOmentum med rituximab ved brug af RIN-1/RIN-2 uden at bruge en systematisk tilgang til at udføre sammenligningen. En sådan usystematisk og uigennemsigtig tilgang er stærkt tilbøjelig til bias og fejlfortolkning af behandlingseffekter, hvilket mindsker validiteten og pålideligheden af sammenligningerne.

Vi vil også gerne påpege, at RIN-studierne blev identificeret og inkluderet i Amgens systematiske litteratursøgning, men efter en yderligere vurdering blev de ikke inkluderet i ITC af flere årsager, beskrevet i ansøgningen. De vigtigste årsager var følgende:

I RIN-1 modtog patienter kombinationsbehandling med rituximab og steroider gennem hele studiet. Steroider blev givet i høje doser i de første otte uger og derefter reduceret til en lav daglig dosis gennem hele studiet. Det er sandsynligt, at dette har bidraget til en lavere attakhyppighed. Forfatterne til studiet påpeger også selv, at brugen af orale steroider kan have bidraget til en lavere attakhyppighed i både rituximab- og placeboarmene. I N-MOmentum modtog patienter kun inebilizumab og steroider samtidigt de første 21 dage efter et attak, for specifikt at evaluere effekten af inebilizumab i studiet. Denne forskel gør direkte sammenligninger af resultaterne mellem studierne meget upålidelige.
Derudover krævede man i RIN-1, at alle attakker blev bekræftet via MRI, hvilket betyder, at nogle attakker muligvis blev udelukket, hvis der ikke blev fundet læsioner (f.eks. hvis MRI blev taget for tidligt, eller hvis MRI af synsnerven ikke specifikt blev udført).

I RIN-studierne, i modsætning til i N-MOmentum, blev der heller ikke fundet nogen effekt på Expanded Disability Status Scale (EDSS)-score. EDSS er en vigtig parameter for at bestemme behandlingens

påvirkning på sygdomsprogression. At der forekommer forskel på EDSS i N-MOmentum men ikke i Rin 1-2 indikerer en forskel i effekt.

Det er problematisk, at sekretariatet vælger et studie (i dette tilfælde RIN-1/RIN-2), der er meget forskelligt fra N-MOmentum, og opdeler studiet for at finde en kort periode, som Sekretariatet anser for tilsvarende med en periode i N-MOmentum, hvilket derefter bruges som argument for konklusionen om ligestilling af effekt og sikkerhed mellem rituximab og inebilizumab. Denne metode til sammenligning af studier er ikke i overensstemmelse med Medicinrådets egne retningslinjer for indirekte sammenligninger, og ville sandsynligvis ikke være blevet accepteret, hvis den var blevet brugt som dokumentation fra en ansøger. Hvis sekretariatet havde brugt en systematisk tilgang til at identificere litteratur, kunne flere studier være blevet inkluderet i sammenligningen.Især da sammenligningen kun er narrativ. Nedenfor er en liste over studier, som med denne tilgang også kunne have belyst sagen. Studiet af Maral Seyed Ahadi et al. blev inkluderet i den indsendte SLR.

1. Efficacy and safety of rituximab in patients with refractory neuromyelitis optica spectrum disorders: A prospective observation in Iranian cases by Maral Seyed Ahadi et al. (1)
2. Anti-Rituximab antibody in patients with NMOSDs treated with low dose Rituximab by Ting Li et al. (2)
3. Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica by Maureen et al. (3)

Studiet af Maral Seyed Ahadi et al. rapporterede, at 8/18 patienter oplevede et attak. Studiet af Ting Li et al. rapporterede en årlig attakrate (ARR) på 0,4, Studiet af Maureen et al rapporterede ARR på 0.33, begge er signifikant højere end de 0,035, som Sekretariatet benytter i vurderingsrapporten. Baseret på dette, sammen med vores ITC baseret på Kim et al. Vises det at der er patienter, der ikke responderer godt på rituximabbehandling, og det er klart, at RIN 1-2 ikke er repræsentativ for alle NMOSD-patienter.

Flere studier indikerer, at raterne af rituximabsvigt er høje. Som nævnt i vores ansøgning er det kendt, at rituximab har begrænset effekt hos NMOSD-patienter, der er homozygote for en specifik F-allel-polymorfisme i Fc-receptor-genet FCGR3A (4). Denne polymorfisme findes hos ca. 48 % af NMOSD-patienterne. Denne polymorfisme påvirker ikke den kliniske effekt af inebilizumab; en post hoc-analyse af N-MOmentumstudiet fandt ingen sammenhæng mellem denne FCGR3A-polymorfisme og behandlingsrespons på inebilizumab.

Udover ovenførte argument stiller vi også spørgsmålstegn ved vurderingen af, at azathioprin og mycophenolatmofetil anses som ækvivalente alternativer, når der findes mere effektive, evidensbaserede on-label behandlinger. Dette understøttes også af NEMOS-gruppen, som har rangeret disse behandlinger efter MAbs (5).

Afslutningsvis håber vi, at der kan findes en løsning, så alle NMOSD-patienter kan få effektiv behandling. Rituximab anses som en effektiv behandling for mange patienter, men nogle patienter oplever tilbagefald. Der er et udækket behov for effektiv behandling til disse patienter.

Referanser

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5. https://link.springer.com/article/10.1007/s00415-023-11910-z

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

5/11/24

DBS/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	27.11.2024
Leverandør	Amgen
Lægemiddel	Uplizna (inebilizumab)
Ansøgt indikation	Monoterapi til behandling af voksne patienter med neuromyelitis opticaspektrumforstyrrelse (NMOSD), som er anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Uplizna (inebilizumab)

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Uplizna	100 mg	3 hætteglas	375.693	[redacted]	[redacted]

[redacted]

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, som gælder fra [redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2 viser lægemiddeludgiften for Uplizna,

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Uplizna	100 mg	3 hætteglas	300 mg uge 0 og uge 2 og herefter 300 mg hver 6. måned svarende til 3 pakninger pr. år. IV	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England*	Ikke anbefalet	Link til anbefaling

* Processen er anført som "discontinued"

Konklusion

[redacted]

Application for the assessment of Uplizna for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD)

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Color of highlighted text	**Definition of highlighted text**
	Confidential information
[Other]	**[Definition of color-code]**

Contact information

Contact information	
Name	**Jannick Burmester / Amgen Danmark**
Title	Health Economic Manager
Phone number	+45 2260 2686
E-mail	jburmest@amgen.com
Name (External representation)	**N/A**
Title	N/A
Phone number	N/A
E-mail	N/A

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Abbreviations

Abbreviation	Description
AAR	Annualized attack rate
AC	Adjudication Committee
ADCC	Antibody-dependent cellular cytolysis
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AIC	Akaike information criterion
AQP4	Aquaporin 4
AQP4+	Aquaporin 4-Immunoglobulin G-seropositive
AQP4-	Aquaporin 4-Immunoglobulin G-seronegative
ARR	Annualized relapse rate
BIC	Bayesian information criterion
CE	Cost-effectiveness
CLAD	Censored least absolute deviations
CNS	Central nervous system
CSR	Clinical study report
DMC	Danish Medicines Council
EQ-5D	EuroQol-5 Dimensions
EDSS	Expanded Disability Status Scale
FDA	U.S Food and Drug Administration
FSS	Functional system score
Gd	Gadolinium
GLS	Generalized least squares
HODaR	Health Outcomes Data Repository
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
IL	Interleukin
IPD	Individual patient data

IQR	Interquartile range
ITT	Intention-to-treat
LY	Life-year
mAB	Monoclonal antibody
MAE	Mean absolute error
MAIC	Matching adjusted indirect comparison
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MOGAD	Myelin-oligodendrocyte glycoprotein (MOG) antibody-associated disease
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSE	Mean squared error
NEMOS	Neuromyelitis Optica Study Group
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorder
OLP	Open-label extension period
OLS	Ordinary least squares
OWSA	One-way sensitivity analysis
PCS	Physical component summary
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PT	Preferred terms
PY	Patient-years
QALY	Quality-adjusted life year
QoL	Quality of life
RCP	Randomized controlled period
RCT	Randomized controlled trial
RR	Relative risk
SAT	Single arm trial
SD	Standard deviation
SIE	Severe infectious events
SOC	System organ class
SFP	Safety follow-up period
SLR	Systematic literature review
TEAE	Treatment-emergent adverse event

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Uplizna
Generic name	Inebilizumab
Therapeutic indication as defined by EMA	Uplizna is indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G-seropositive (AQP4+) (1)
Marketing authorization holder in Denmark	Amgen
ATC code	L04AA47
Combination therapy and/or co-medication	Not applicable
(Expected) Date of EC approval	25/04/2022
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic Assessment (JNHB)	No. No local or nordic guidelines exist for the the treatment of NMOSD, therefore it was not considered feasible.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Pack size of 3 vials Each vial contains 100 mg of inebilizumab in 10 mL at a concentration of 10 mg/mL. The final concentration after dilution is 1.0 mg/mL.

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Therapeutic indication relevant for the assessment	Uplizna is indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive (AQP4+).
Dosage regiment and administration	The recommended loading dose is 300 mg (3 vials of 100 mg) intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion. The recommended maintenance dose is 300 mg intravenous infusion every 6 months. Inebilizumab is for chronic treatment.
Choice of comparator	Rituximab Placebo
Prognosis with current treatment (comparator)	NMOSD is a severely disabling and potentially life-threatening condition, characterized by attacks of optic neuritis, myelitis, and certain brain and brainstem syndromes which often follow a relapsing course (2, 3). Most patients with NMOSD do not recover fully from the first attack (4, 5) and at least 90% will eventually have clinical relapses and accrue permanent disability(6). Studies of European patients, where the majority received immunosuppressive treatments, report a high degree of visual and motor disabilities within the first 10-12 years after disease onset (4, 7). The median life expectancy for Danish AQP4+ NMOSD patients was 19 years shorter than for the general population (64.08 years vs 83.07 years) (8). Causes of death in NMOSD include secondary infection, respiratory infection, respiratory failure, sepsis, and suicide (4, 9).
Type of evidence for the clinical evaluation	No head-to-head trials exist for inebilizumab (placebo-controlled). Indirect treatment comparison against rituximab.
Most important efficacy endpoints (Difference/gain compared to comparator)	Time to NMOSD attack: - [redacted] - Inebilizumab vs placebo: HR: 0.227; 95% CI: 0.121-0.423; p<0.0001 Worsening in EDSS score: - Inebilizumab vs rituximab: NR, data is applied from inebilizumab trial - Inebilizumab vs placebo: 14.9% vs 34.6%; OR: 0.352; 95% CI: 0.170-0.725; p=0.0047

Summary	
Most important serious adverse events for the intervention and comparator	Inebilizumab: Urinary tract infection - 2 (3.1%) (10) Rituximab: NR[a] Placebo: Urinary tract infection - 6 (12.8%) (10)
Impact on health-related quality of life	Clinical documentation: Mean (SD) change from baseline in SF-36 - Inebilizumab: 0.898 (9.505) in MCS, 0.752 (7.641) in PCS (10) - Rituximab: NR - Placebo: 3.092 (7.737) in MCS, 0.264 (6.645) in PCS (10) Health economic model: Better than comparator
Type of economic analysis that is submitted	A cost-utility analysis was conducted to assess the value of inebilizumab for NMOSD in terms of the cost per QALY. For the analysis, a Markov model has been developed in which patients transition each cycle between a defined set of health states associated with NMOSD.
Data sources used to model the clinical effects	Inebilizumab and placebo: N-Momentum trial (68) Rituximab: Kim et al. (11)
Data sources used to model the health-related quality of life	Based on N-Momentum trial for all treatments
Life-years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	[redacted]
Number of eligible patients in Denmark	Incidence: 2.9 Approx. 50-55 AQP4+ Patients

Summary	
Budget impact (in year 5)	[redacted]

[a]The included studies in the literature review did not report serious adverse events separately

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

A short description of the disease, its pathophysiology and clinical presentation are presented in Appendix O.

Prognosis

Following the first attack, a second attack is likely to occur within 1 year in 50–60% of patients, within 2 years in 70% of patients, and within 3 years in 90% of patients (4, 12). A recent Swedish study by Carlsson et al. assessed disease progression in 42 patients with NMOSD treated with rituximab (an anti-CD20 monoclonal antibody [mAb] increasingly used as a first-line maintenance therapy in Denmark; see section 3.3), of whom 24 (57%) were AQP4+. Among AQP4+ patients (92% women; mean follow-up time: 4.4 years), 37.5% relapsed during follow-up with a mean annual attack rate of 0.21 (interquartile rate [IQR]: 0–0.5) (13).

The severity of initial and subsequent attacks, and the number of subsequent attacks, are key prognostic factors in NMOSD. If patients are untreated, early and severe disability is common. Consequently, timely diagnosis and treatment are essential to improve prognosis (14, 15). Earlier disease recognition and treatment has improved the outlook for patients with NMOSD, but the prognosis is still poor compared with other neuroinflammatory conditions, such as MS (15). Other prognostic factors that affect NMOSD prognosis include genetic and clinical factors (4). For example, a longer length of myelitis lesions and the presence of symptomatic brain/brainstem lesions are associated with higher disability (16). Younger patients more frequently experience optic neuritis and have a higher risk of visual disability (17), while older patients have a higher risk of motor disability (4).

NMOSD can be life threatening and patients with NMOSD have an estimated 12-times higher mortality rate than patients with MS (18). Among the causes of death in NMOSD are secondary infection, including respiratory infection, respiratory failure, sepsis, and suicide (4, 9). Mortality rates depend on factors such as ethnicity, relapse rate, and age of onset (4, 19, 20).

In a recent population-based cohort follow-up study, Papp et al (8) assessed mortality among Danish patients with AQP4+ NMOSD identified between 2008 and 2020 from the Danish MS Registry and from Danish laboratories performing AQP4-antibody testing. The mean follow-up time was 103 months ([IQR 44–213) and approximately 90% of patients had received immunosuppressive therapies at some point. In total, 66 AQP4+ patients were identified, 15 of whom died during the follow-up. Among patients who died, 11 (73%) were treated with immunosuppressants (azathioprine, 4 [36%], rituximab, 3 [27%]). The standardized mortality ratio was 2.54 (95% confidence interval [CI]: 1.47-4.09) with a median life expectancy of 64.08 years (95% CI: 53.02-83.9) compared with 83.07 years for the general population. The disease-specific mortality rate was 0.020 (95% CI: 0.014-0.034) per 100,000 person-years with an excess mortality rate of 16.8 per 1,000 person-years. In 93% of deaths, the cause was directly related to NMOSD (defined as death occurring within 3 months after attack onset) and the most common cause of death was infection. Only age of onset was a predictive factor of death.

In the Swedish study by Carlsson et al., three deaths (13%) were reported over the study period, all of which occurred during hospitalization for severe infectious events (SIEs) (13). Another Swedish study of 92 patients with NMOSD (90% Caucasian; 44.6% and 38.0% treated with azathioprine and rituximab, respectively) between 1987 and 2006 reported a mortality rate of 3.3% (21).

Patients' functioning and health-related quality of life.
The consequences of NMOSD extend beyond the clinical setting, and include physical, functional, and psychological impacts that affect patients' quality of life (QoL) (22, 23). Mean EuroQol-5 Dimensions (EQ-5D) score in a study of 21 US patients with NMOSD was 0.74, which is lower that the US norm (0.867) and the world norm (0.902) (22).

Recovery from NMOSD attacks is often incomplete, leaving patients with neurodegeneration and disability, which worsens with each attack (24, 25). In some cases, even a single attack will be so severe that patients will not recover the ability to walk without assistance or will become functionally blind in at least 1 eye, despite rescue treatments (26). Common symptoms of NMOSD that can affect QoL include chronic pain, cognitive impairment, bowel/bladder dysfunction, fatigue, increased risk of anxiety and depression, and disability to vision-related symptoms (23).

3.2 Patient population

The patient population for this submission are adult patients with AQP4+ NMOSD. For testing of AQP4-IgG serostatus, cell-based serum assays (microscopy or flow cytometry-based detection) are recommended (27). Based on epidemiological data collected in Denmark or internationally evaluating disease onset and sex distribution in patients with AQP4+ NMOSD (summarized below), the majority of the patients are expected to be female and middle-aged or older. The most recent prevalence/incidence estimates for AQP4+ NMOSD were reported by the Danish Medicines Council (DMC) expert committee during the assessment process of satralizumab. The committee estimated the prevalence of patients with AQP4+ NMOSD in Denmark to be less than 50 and that five additional patients would be eligible for treatment each year (28). The numbers are confirmed by a Danish clinical expert who estimated that in Denmark there are around 4-5 new cases of

NMOSD per year and around 15-20 new patients over 5 years. Prevalence/incidence estimates, female/male ratio, and age at disease onset are reported from international and Danish studies, described below.

Prevalence/incidence estimates, female/male ratios and disease onset

Studies in Denmark

There are limited recent data on the prevalence/incidence of AQP4+ NMOSD in Denmark. A study by Papp et al. conducted between 2007 and 2014 estimated the prevalence to be 1.09 per 100,000 person-years and the incidence to be 0.07 per 100,000 person-years based on the 2015 criteria. The median age at disease onset was 35.5 years (range 5–76), 70% of the included patients were AQP4+ and the female/male ratio was 12:1 in the AQP4+ group (29). A study by Dale et al. conducted between 2012 and 2013 estimated the incidence of NMOSD for the central Denmark region to be 0.12 per 100,000 person-years based on the 2015 NMOSD criteria; however, only one of the patients was AQP4+ (30).

The estimates in Table 1 were calculated by using a prevalence of 1.09/100,000, an incidence of 0.07/100,000, and a global prevalence of 1.51/100,000 (8). The size of the Danish population was derived from Statistics Denmark 2019-2023 (31). The proportion of patients with AQP4+ NMOSD was assumed to be 70%.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	**2.8**	**2.9**	**2.9**	**2.9**	**2.9**
Prevalence in Denmark	**44.3**	**44.4**	**44.6**	**44.8**	**45.3**
Global prevalence *	**61.4**	**61.5**	**61.7**	**62.1**	**62.7**

* For small patient groups, also describe the worldwide prevalence.

Papp et al. (8) identified 51 Danish patients with NMOSD who were diagnosed and still alive in 2020, based on this estimate and the aforementioned incidence and prevalence estimates it is assumed that around 50-55 patients with AQP4+ NMOSD are eligible for treatment throughout year 1-5 (2024-2028) however, it should be noted that a Danish clinical expert has clarified that patients are not expected to switch treatment unless they experience break-through attacks. A summary of the number of all eligible patients per year is presented in Table 2.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	50-55	50-55	50-55	50-55	50-55

3.3 Current treatment options

The standard of care for acute attacks in both AQP4+ and AQP4- NMOSD are high-dose glucocorticoids and apheresis therapy. Low-dose oral glucocorticoids used for up to 3-6 months after an attack are also considered beneficial for preventing subsequent early attacks (32).

The primary treatment goal for NMOSD is to prevent future attacks and subsequent disability. This was also highlighted by a Danish clinical expert who emphasized that it is essential to use the highest efficacy treatment from the onset of disease to prevent relapses, because any relapse can cause severe disability. Up until recently, off-label use of immunosuppressants, such as azathioprine and mycophenolate mofetil, or the mAb rituximab, have been the main treatment options for patients with NMOSD. There is a lack of robust clinical evidence from large, prospective randomized controlled trials evaluating the efficacy and safety of these treatments in NMOSD. Additionally, off-label rituximab has safety warnings that require extensive monitoring and is associated with a risk of infections, with a Swedish study (n=42) reporting that 46% of patients receiving rituximab experienced severe infectious events (SIEs) (annual rate: 0.32, range: 0-3.3), including sepsis (21% of patients) (13). Furthermore, 46% of patients with NMOSD are homozygous for an F allele polymorphism in the FCGR3A gene (33), which is associated with a poor response to rituximab therapy (34).

There are currently no guidelines available in Denmark for the treatment of NMOSD. According to the DMC expert committee, which was convened during the assessment of satralizumab (28), there are treatments available that have shown some effect, such as rituximab, but there is no evidence with high certainty.

3.4 The intervention

An overview of inebilizumab, the intervention that is the focus of the current application, is presented in Table 3. Inebilizumab (UPLIZNA®) is a first-in-class humanized CD19 B-cell depleting mAb approved for the treatment of adult patients with AQP4+ NMOSD to reduce the risk of attacks and associated worsening of disability (35).

Mechanism of action

Inebilizumab binds specifically to CD19, a cell surface antigen present on pre-B and mature B cells, including plasmablasts and some plasma cells (36-39). Upon binding to B cells, inebilizumab provides rapid depletion of B lymphocytes via ADCC and antibody-dependent cellular phagocytosis (ADCP) (40). B cells are believed to play a central role in the pathogenesis of NMOSD (3).

Clinical value

In contrast to CD20-depleting mAbs, such as rituximab, inebilizumab acts on a broader range of B cells, potentially resulting in a more effective reduction in the production of pathogenic AQP4 autoantibodies and B-cell mediated inflammatory responses (41, 42). This broad and durable inebilizumab-mediated B-cell depletion has been shown to correlate with inebilizumab's statistically significant efficacy in clinically relevant outcomes, including reduced attack risk and disability progression, suggesting a potential disease-modifying effect (10). The pivotal phase 2/3, randomized, double-blind, placebo-controlled N-MOmentum trial, the largest clinical trial conducted in NMOSD to date across 25 countries (N=231), demonstrated that inebilizumab monotherapy significantly reduced the risk of an NMOSD attack by 77% in patients with AQP4+ NMOSD compared with placebo (hazard ratio [HR]: 0.227; 95% CI: 0.1214-0.4232; p<0.0001), which was maintained long-term (43). Inebilizumab is the only treatment shown to reduce the proportion of patients with disability worsening (measured by the EDSS), as described in Section 6.

A post-hoc analysis evaluated the impact of a highly prevalent FCGR3A mutation (V158F, by allelic status) (33) known to inhibit rituximab efficacy by 5.5 fold (158). This analysis included 142 patients (inebilizumab, n = 104; placebo, n = 38) who consented to *FCGR3A* polymorphism genotyping, of whom 14 (10%) were homozygous VV, 60 (42%) were heterozygous VF, and 68 (48%) were homozygous FF. There were no significant differences in the clinical metrics of NMOSD activity (AAR, relapse rate or EDSS) or B-cell depletion between V allele (VV and VF) and FF allele subgroups.

Finally, N-MOmentum also demonstrated that long-term treatment with inebilizumab is well tolerated (10).

Table 3 Overview of inebilizumab

Overview of intervention	
Therapeutic indication relevant for the assessment	Uplizna is indicated as monotherapy for the treatment of adult patients with euromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive (AQP4+).
Method of administration	Intravenous administration. Approximately 90 minutes with infusion pump.
Dosing	The recommended loading dose is 300 mg (3 vials of 100 mg) intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion. The recommended maintenance dose is 300 mg intravenous infusion every 6 months.
Dosing in the health economic model (including relative dose intensity)	Induction dose of 300 mg on days 1 and 15, followed by a maintenance dose 300 mg every 26 weeks.
Should the pharmaceutical be administered with other medicines?	Premedication with a corticosteroid (e.g. methylprednisolone 80-125 mg intravenous or equivalent) should be administered approximately 30 minutes prior to each inebilizumab infusion; and an antihistamine (e.g. diphenhydramine 25-50 mg orally

	or equivalent) and an anti-pyretic (e.g. paracetamol 500-650 mg orally or equivalent) approximately 30-60 minutes prior to each inebilizumab infusion.
Treatment duration / criteria for end of treatment	Inebilizumab is for chronic treatment
Necessary monitoring, both during administration and during the treatment period	**Infusion-related reactions:** The patient should be monitored for infusion reactions during the infusion and for at least 1 hour after the completion of the infusion. Infections: Inebilizumab causes reduction in peripheral blood lymphocyte count and Ig levels consistent with the mechanism of action of B-cell depletion. Reduction of neutrophil counts were also reported. Therefore, inebilizumab may increase the susceptibility to infections. A recent (i.e. within 6 months) complete blood cell count (CBC) including differentials and immunoglobulins should be obtained before initiation of inebilizumab. Assessments of CBC including differentials and immunoglobulins are also recommended periodically during treatment and after discontinuation of treatment until B-cell repletion. Prior to every infusion of inebilizumab, it should be determined whether there is a clinically significant infection. In case of infection, infusion of inebilizumab should be delayed until the infection resolves. Patients should be instructed to promptly report symptoms of infection to their physician. Treatment discontinuation should be considered if a patient develops a serious opportunistic infection or recurrent infections if Ig levels indicate immune compromise.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Testing for AQP4-IgG-seropositivity is standard practice in Denmark and therefore not specifically included in the model.
Package size(s)	Pack size of 3 vials, each vial containing 100 mg of inebilizumab in 10 mL at a concentration of 10 mg/mL.

Source: European Medicines Agency (44)

3.4.1 The intervention in relation to Danish clinical practice

Uplizna is indicated as monotherapy for the treatment of adult patients with euromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive (AQP4+). and is intended as an alternative to treatment with rituximab.

3.5 Choice of comparator(s)

Rituximab is the most relevant comparator to inebilizumab because, despite being off-label, it is the most widely used first-line treatment in patients with AQP4+ NMOSD (Table 4). This aligns with advice from clinical experts and previous documentation by the DMC (28).

Because the cost-effectiveness of rituximab (or any other treatment for NMOSD) has yet to be established in Danish clinical practice, inebilizumab will also be compared with placebo. This is aligned with methodological guidance and is agreed with the secretariat.

Table 4 Overview over rituximab

Overview of comparator	
Generic name	Rituximab
ATC code	L01FA01
Mechanism of action	Monoclonal antibody targeting CD20
Method of administration	Intravenous infusion. (Informed by Danish clinical expert and rituximab SmPC (45) Initial infusion of 1,000 mg: 4 h 45 mins Subsequent infusions of 1,000 mg: 2 h 50 mins.
Dosing	Fixed dose of 1,000 mg
Dosing in the health economic model (including relative dose intensity)	Induction dose of 1,000 mg at days 1, 8, 15, and 22, followed by a maintenance dose of 1,000 mg every 26 weeks
Should the pharmaceutical be administered with other medicines?	Premedication of an anti-pyretic, an antihistaminic, and glucocorticoids should be given before administration of rituximab.
Treatment duration/ criteria for end of treatment	Treatment is stopped due to lack of efficacy as assessed by clinician or when burden due to adverse events is considered too high.
Necessary monitoring, both during administration and during the treatment period	Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm, or hypoxia should have the infusion interrupted immediately. The infusion should not be restarted until complete resolution of all symptoms, and normalization of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis. Rituximab treatment comes with an increased risk of serious infections (including fatalities) and should not be administered to a patient with an active, severe infection. Infusion-related adverse reactions are common, severe infusion-related reactions with fatal outcomes have been reported. Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure, and/or myocardial infarction have occurred in patients treated with rituximab. Therefore, patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely. Cases of enteroviral meningoencephalitis including fatalities have been reported following use of rituximab.

Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	100 mg, 500 mg, 1,400 mg

Source: Rituximab Summar of Product Characteristics (SmPC) (45)

3.6 Cost-effectiveness of the comparator(s)

Rituximab is used off-label in patients with NMOSD and has not previously been assessed by the DMC in this indication.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The relevant efficacy outcomes are presented below in Table 5. Of note, annualized attack rate (AAR) and annualized relapse rate (ARR) are used synonymously; however, due to slightly differing definitions in the different publications between inebilizumab and rituximab, they are presented separately in the below table.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Time to attack (46)	Up to Day 197	Time from Day 1 to onset of an investigator-determined NMOSD attack on or before Day 197	Assessment visits were scheduled for each potential NMOSD attack during the trial
Change in EDSS score (46)	Up to Day 197	Worsening from baseline in EDSS at last visit during the randomized controlled period	The EDSS assessment was completed at screening, Day 1 of the randomized controlled period, at scheduled visits and at assessment visits

Abbreviations: AC: Adjudication committee; EDSS: Expanded Disability Status Scale
* Time point for data collection used in analysis (follow-up time for time-to-event measures)

Validity of outcomes

The validity of outcomes is discussed in Appendix P.

4. Health economic analysis

A cost-utility analysis was conducted because there are currently no treatments reimbursed for the NMOSD patient population in Denmark.

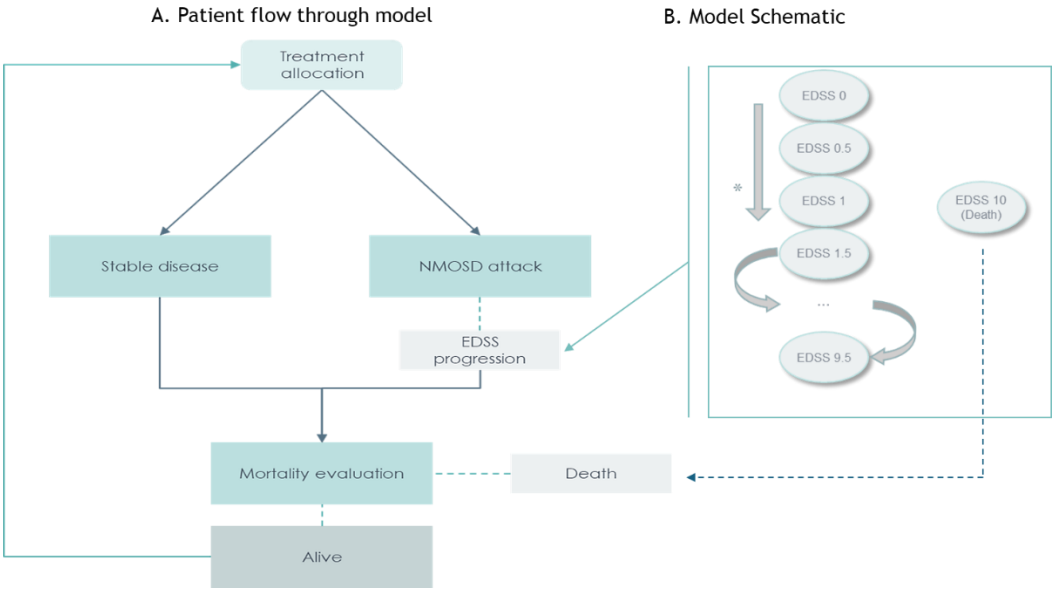
4.1 Model structure

A cost-utility analysis was conducted to assess the value of inebilizumab for NMOSD in terms of the cost per quality-adjusted life year (QALY). For the analysis, a Markov model was developed in which patients transitioned each cycle between a defined set of health states associated with NMOSD (see Figure 1).

Patients with NMOSD can experience attacks and NMOSD progression is highly linked to these attacks, which can cause persistent worsening of both symptoms and the disease (7). Persistent worsening of the disease can be defined as a change in EDSS, a method used to quantify worsening of disability and a measure of disease progression over time. The EDSS score ranges from 0 to 10, with 0 being full function and 10 being dead, i.e., as a patient's disease progresses with each attack the EDSS score increases, bringing the patient closer to death. Thus, when patients with NMOSD experience an attack, they risk a change in their EDSS score, which is reflected in the model structure: patients in the model transition between health states defined by EDSS scores (Figure 1B).

An EDSS state of 0.5 was implemented (which is not a defined EDSS score) to allow for model functionality (47). Patients can take a minimum EDSS step of 0.5 within the model, allowing for simple model implementation of EDSS state 0 transitions. In the model, patients can progress between the EDSS scores and by more than one score each time they make a transition. In addition to NMOSD mortality (EDSS 10), patients are at risk of dying due to any other cause (based on general population mortality) and can move to the death health state at any time during the simulation.

An illustration of the patient flow through the model is provided in Figure 1A. For more detailed information regarding the model structure please see Appendix Q.



Abbreviations: EDSS: Expanded Disability Status Scale
*All patients can transition to death from any state
**Patients can progress multiple EDSS points in a single cycle

Figure 1 (A) Patient flow through and (B) model schematic

4.2 Model features

Model features are summarized in Table 6 below.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients (>18 years old) with NMOSD who are AQP4+	As per the approved indication
Perspective	Limited societal perspective	According to DMC guidelines, see Appendix Q for further information
Time horizon	Lifetime (60 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at treatment start in the N-MOmentum trial (43 years). This was validated by a Danish clinical expert. Patients are modelled until they die or fill 100 years.
Cycle length	1 month	This cycle length is sufficiently short to capture NMOSD attacks and their consequences, see Appendix Q for further information.
Half-cycle correction	Yes	
Discount rate	3.5 % for years 0-35 2.5% for years 36-70 1.5% after 70 years	According to DMC method guideline version 1.3 discount rate should correspond to Danish Ministry of Finance (48) guidance.
Intervention	Inebilizumab (Uplizna®)	
Comparator(s)	Rituximab Placebo	According to Danish clinical experts because treatment guidelines are lacking. A comparison with placebo is included because there are no previously assessed treatments which have been approved and rituximab is being used off-label
Outcomes	Time to NMOSD attack EDSS progression Survival	The validity of the outcomes has been described in Appendix P, see also Appendix Q for further information.
Costs	Treatment costs, administration costs, patient transportation costs, patient costs, end-of-life costs, adverse event costs, healthcare resource use costs, associated with stable disease and NMOSD attack	Costs used in the analysis are described in section 0 and are in line with DMC guidelines
Methods of addressing uncertainty	Deterministic sensitivity analyses – one-way sensitivity analyses Deterministic scenario analysis	In line with DMC guidelines, please see Appendix Q for further information.

	Probabilistic sensitivity analyses	
Methods of valuing health effects	EQ-5D UK value set (49)	Quality of life was measured with the SF36 in the N-MOmentum trial and subsequently mapped to EQ-5D utility values (50) (see section 10).
Measuring health effects	SF-36	Quality of life was measured with the SF36 in the N-MOmentum trial and subsequently mapped to EQ-5D utility values (50) (see section 10).

Abbreviations: AQP4: Aquaporin-4; DMC, Danish Medicines Council: EDSS: Expanded Disability Status Scale; IgG: Immunoglobulin G; SF-36: 36-item Short Form Health Survey

5. Overview of literature

A list of ongoing inebilizumab and rituximab trials are found in Appendix K. documents the details of the SLR on real world evidence. It aimed to identify any studies on the clinical effectiveness and safety of inebilizumab and relevant comparators in NMOSD as identified in real-world evidence (RWE) studies.

5.1 Literature used for the clinical assessment

For the comparison of inebilizumab with placebo, no literature search was conducted because data from a placebo-controlled trial were available (10). For the comparison of inebilizumab with rituximab, a systematic literature review (SLR) was conducted. For details on this SLR, please refer to Appendix H.

Table 7 Relevant literature included in the assessment of efficacy and safety of inebilizumab and rituximab

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of
Data on file Unpublished data 2021: Inebilizumab Clinical Study Report. (10)	N-Momentum trial	NCT02200770	Start (date of first subject enrolled): 06 January 2015 Completion (date of final subject visit): 06 November 2020 Database lock final analysis: December 2020	Inebilizumab vs placebo Inebilizumab vs rituximab For AQP4+ NMOSD patients
Cabre P, Mejdoubi M, Jeannin S, Merle H, Plumelle Y, Cavillon G, et al. Treatment of neuromyelitis optica with rituximab: a 2-year prospective multicenter study. Journal of neurology. 2018;265(4):917–25. (51)	Not applicable	Not available	Start: Not reported Completion: Not reported	Inebilizumab vs rituximab For AQP4+ NMOSD patients

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of
Kim SH. Repeated Treatment With Rituximab Based on the Assessment of Peripheral Circulating Memory B Cells in Patients With Relapsing Neuromyelitis Optica Over 2 Years. Archives of Neurology. 2011;68(11):1412. (11)	Not applicable	Not available	Start: Not reported Completion: Not reported	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Maral Seyed Ahadi ANM, Nasrin Asgari, Mohammad Ali Sahraian. Efficacy and safety of rituximab in patients with refractory neuromyelitis optica spectrum disorders: A prospective observation in Iranian cases. Caspian J Intern Med. 2020;11(2):155-62. (52)	Not applicable	Not available	Start: August 2014 Completion: August 2016	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Uzunkopru C, Tutuncu M, Gunduz T, Gumus H, Sen S, Demir S, et al. The efficacy of rituximab in patients with neuromyelitis optica spectrum disorder: A real-world study from Turkey. Int J Clin Pract. 2021;75(7):e14158. (53),	Not applicable	Not available	Start: 2014 Completion: 2019	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Zhang M, Zhang C, Bai P, Xue H, Wang G. Effectiveness of low dose of rituximab compared with azathioprine in Chinese patients with neuromyelitis optica: an over 2-year follow-up study. Acta Neurol Belg. 2017;117(3):695-702. (54)	Not applicable	Not available	Start: February 1, 2009 Completion: September 30, 2016	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Kim S-H, Jeong IH, Hyun J-W, Joung A, Jo H-J, Hwang S-H, et al. Treatment Outcomes With Rituximab in 100 Patients With Neuromyelitis Optica: Influence of FCGR3A Polymorphisms on the Therapeutic Response to Rituximab. JAMA Neurology. 2015;72(9):989-95. (34)	Not applicable	Not available	Start: February 1, 2006 Completion: January 31, 2015	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Annovazzi P, Capobianco M, Moiola L, Patti F, Frau J, Uccelli A, et al. Rituximab in the treatment of Neuromyelitis optica: a multicentre Italian observational study. Journal of Neurology. 2016;263(9):1727-35.(55)	Not applicable	Not available	Not reported	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Correa-Diaz EP, Torres-Herran GE, Mino Zambrano JE, Paredes-Gonzalez V, Caiza-Zambrano FJ. Impact of Rituximab on relapse rate and disability in an	Not applicable	Not available	Start: January 2016 Completion: October 2019	Inebilizumab vs rituximab For AQP4+ NMOSD patients

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of
Ecuadorian cohort of patients with neuromyelitis optica spectrum disorders. Mult Scler Relat Disord. 2021;48:102683.(56)				
Gomez-Figueroa E, Noriega-Morales G, Casallas-Vanegas A, Zabala-Angeles I, Garcia-Estrada C, Neri D, et al. Effect of rituximab on disease activity in latin American patients with anti-aquaporin-4 (+) neuromyelitis optica spectrum disorder. Clin Neurol Neurosurg. 2020;196:106007. (57)	Not applicable	Not available	Not reported	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Lin J, Li X, Xue B, Tong Q, Chen Z, Zhu W, et al. Low-dosage of rituximab in Chinese patients with neuromyelitis optica spectrum disorder. J Neuroimmunol. 2018;317:1-4.(58)	Not applicable	Not available	Start: 2013 Completion: 2017	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Lu Q, Luo J, Hao H, Liu R, Jin H, Jin Y, et al. A long-term follow-up of rituximab treatment in 20 Chinese patients with neuromyelitis optica spectrum disorders. Mult Scler Relat Disord. 2020;40:101933.(59)	Not applicable	Not available	Start: January 2013 Completion: March 2019	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Xiao H, Zeng W, Li L, Li L, Cui Y, Wang J, et al. Retrospective Observation of Low-Dose Rituximab Treatment in Chinese Patients With Neuromyelitis Optica Spectrum Disorders in a Real-World Setting. Front Neurol. 2020;11:642.(60)	Not applicable	Not available	Start: January 2016 Completion: March 2020	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Shaygannejad V, Fayyazi E, Badihian S, Mirmosayyeb O, Manouchehri N, Ashtari F, et al. Long-term tolerability, safety and efficacy of rituximab in neuromyelitis optica spectrum disorder: a prospective study. J Neurol. 2019;266(3):642-50. (61)	Not applicable	Not available	Start: 2014 Completion: 2018	Inebilizumab vs rituximab For AQP4+ NMOSD patients
Bedi GS, Brown AD, Delgado SR, Usmani N, Lam BL, Sheremata WA. Impact of rituximab on relapse rate and disability in neuromyelitis optica. Mult Scler. 2011;17(10):1225-30. (62)	Not applicable	Not available	Start: January 1990 Completion: 2010	Inebilizumab vs rituximab For AQP4+ NMOSD patients

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of
Radaelli M, Moiola L, Sangalli F, Esposito F, Barcella V, Ferre L, et al. Neuromyelitis optica spectrum disorders: long-term safety and efficacy of rituximab in Caucasian patients. Mult Scler. 2016;22(4):511-9. (63)	Not applicable	Not available	Start: February 2006 Completion: September 2011	Inebilizumab vs rituximab For AQP4+ NMOSD patients

5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life was based on a head-to-head trial of inebilizumab compared with placebo (10). An SLR was conducted to identify alternative HSUVs, and the study conducted by Hümmert et al. (64) was included in the health economic model to facilitate a scenario analysis with alternative HSUVs.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 9.2)

Reference	Health state/Disutility	Reference to where in the application the data is described/applied
Hümmert MW, Schoppe LM, Bellmann-Strobl J, Siebert N, Paul F, Duchow A, et al. Costs and Health-Related Quality of Life in Patients With NMO Spectrum Disorders and MOG-Antibody-Associated Disease: CHANCE (NMO) Study. Neurology. 2022;98(11):e1184-e96 (64)	EDSS (0-3), EDSS (3-6), EDSS (6-9), EDSS (9-10)	Section 10.3

5.3 Literature used for inputs for the health economic model

Disutility for AEs were identified through pragmatic literature searches. Given the challenges in identifying these values, a practical approach over a strictly systematic one was chosen. The methodology included a thorough scan of various literature sources such as observational studies and health economic analyses. The search was expanded beyond traditional databases like PubMed, to include conference proceedings and policy documents. Without restricting the search to predefined eligibility criteria, a wide range of articles and studies was considered.

Table 9 Relevant literature used for input to the health economic model

Reference	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Luger TA, Barker J, Lambert J, Yang S, Robertson D, Foehl J, et al. Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis. J Eur Acad Dermatol Venereol. 2009;23(8):896-904. (65)	Disutility for AE: Arthralgia	Pragmatic literature search	Section 10.3.4 Table 33
Shiroiwa T, Noto S, Fukuda T. Japanese Population Norms of EQ-5D-5L and Health Utilities Index Mark 3: Disutility Catalog by Disease and Symptom in Community Settings. Value Health. 2021;24(8):1193-202 (66)	Disutility for AEs: Back pain, Cardiac complications, Depression, Dizziness, Fever, Thyroid complications	Pragmatic literature search	Section 10.3.4 Table 33
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84. (67)	Disutility for AEs: Hair loss, Leukopenia, Neutropenia, Pruritus, Vomiting/Nausea	Pragmatic literature search	Section 10.3.4 Table 33
Kristoffersen ES, Stavem K, Lundqvist C, Russell MB. Impact of chronic headache on workdays, unemployment and disutility in the general population. J Epidemiol Community Health. 2019;73(4):360-7. (68)	Disutility for AE: Headache	Pragmatic literature search	Section 10.3.4 Table 33
Wehler E SM, Kowal S, Campbell C, Boscoe A., editor A Health State Utility Model Estimating the Impact of Ivosidenib on Quality of Life in Patients with Relapsed/Refractory Acute Myeloid Leukemia. 23rd Congress of the European Hematology Association; 2018; Stockholm, Sweden. (69)	Disutility for AEs: Hepatoxicity, Hypotension, Pain	Pragmatic literature search	Section 10.3.4 Table 33
Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ. 2011;12(3):219-30. (70)	Disutility for AE: Administration-related reactions	Pragmatic literature search	Section 10.3.4 Table 33

Reference	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Matthews S, De Maria A, Passamonti M, Ristori G, Loiacono I, Puggina A, et al. The Economic Burden and Impact on Quality of Life of Herpes Zoster and Postherpetic Neuralgia in Individuals Aged 50 Years or Older in Italy. Open Forum Infect Dis. 2019;6(2):ofz007. (71)	Disutility for AE: Shingles	Pragmatic literature search	Section 10.3.4 Table 33
Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA Intern Med. 2013;173(12):1067-72. (72)	Disutility for AEs: Deep vein thrombosis, Pulmonary embolism	Pragmatic literature search	Section 10.3.4 Table 33
Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on health-related quality of life. BJU Int. 2012;110(11 Pt C):E830-6. (73)	Disutility for AE: Urinary tract infection	Pragmatic literature search	Section 10.3.4 Table 33
Sonnenberg FA, Burkman RT, Hagerty CG, Speroff L, Speroff T. Costs and net health effects of contraceptive methods. Contraception. 2004;69(6):447-59. (74)	Disutility for AE: Urinary tract infection	Pragmatic literature search	Section 10.3.4 Table 33
Hawe E, McBride D, Balp MM, Tian H, Halliday A, Stull DE. EQ-5D Utilities in Chronic Spontaneous/Idiopathic Urticaria. Pharmacoeconomics. 2016;34(5):521-7. (75)	Disutility for AE: Urticaria (mild, moderate, and severe)	Pragmatic literature search	Section 10.3.4 Table 33

Abbreviations: AE: Adverse event

6. Efficacy

As previously stated, this submission includes two comparisons, one of inebilizumab versus placebo (Section 6.1) and a second one of inebilizumab versus rituximab (Section 6.2).

6.1 Efficacy of inebilizumab compared with placebo in adult patients with NMOSD

6.1.1 Relevant studies

The final analysis of the N-MOmentum trial, which compared the efficacy and safety of inebilizumab with placebo in patients with NMOSD, forms the basis for the efficacy estimations for inebilizumab and placebo in this application (10). The AQP4+ population was a pre-defined subgroup of the intention-to-treat (ITT) population in the trial and is considered representative of the population in this application.

Table 10 Overview of study design for studies included in the comparison of inebilizumab vs placebo

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
N-MOmentum trial (NCT02200770) (10)	Multicenter, double-blind, randomized, placebo-controlled phase 2/3 trial with an OLP	The RCP for each participant was up to 197 days or until the occurrence of an adjudicated attack. All participants were followed-up for 12 months after the last dose as safety follow-up	Adult patients with active AQP4+ NMOSD	Inebilizumab (IV infusion), loading dose of 300 mg on Day 1 and Day 15, then 300 mg every 6 months	Placebo (IV infusion), given on Day 1 and Day 15, then every 6 months	**Primary** - Time to onset of an AC-determined NMOSD attack (on or before Day 197) **Key Secondary** - worsening of baseline EDSS stage (last visit during RCP), change from baseline in low-contrast visual acuity binocular score (last visit during RCP), cumulative total active MRI lesions (during RCP), number of NMO/NMOSD-related in-patient

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						hospitalizations (RCP+OLP) **Exploratory/Other** - AAR (RCP+OLP), assessment of NMOSD attack severity (RCP), NMOSD attack recovery (RCP), Modified Rankin Scale (RCP+OLP), Pain Numeric Rating Scale (RCP+OLP), SF-36 Health Survey (RCP+OLP), healthcare resource utilization (RCP+OLP), additional ophthalmology assessments (high-contrast visual acuity and RAPD) (RCP+OLP)

Abbreviations: AAR: Annualized attack rate; AC**:** adjudication committee; AQP4+**:** Aquaporin-4-Immunoglobulin G-seropositive; IV: Intravenous; NMOSD: Neuromyelitis optica spectrum disorder; MRI: Magnetic resonance imaging; OLP: Open-label extension period; RAPD: Relative afferent pupillary effect; RCP: Randomized controlled period.

6.1.2 Comparability of studies

Not applicable because only one placebo-controlled trial was conducted.

6.1.2.1 Comparability of patients across studies

The baseline characteristics of the AQP4+ population (a pre-defined subgroup of the ITT population) from N-MOmentum were broadly similar between treatment arms (Table 11).

Table 11 Baseline characteristics in N-MOmentum

	N-MOmentum trial	
	Placebo (n=52)	**Inebilizumab (n=161)**
Mean (SD) age, in years	42.4 (14.3)	43.2 (11.6)
Sex (female)	49 (94%)	151 (94%)
Race[a]		
White	24 (46%)	86 (53%)
Non-white	28 (54%)	74 (47%)
Multiple categories checked	0	1 (1%)
Mean (SD) disease duration, in years	2.9 (3.5)	2.5 (3.4)
Type of most recent attack		
Optic neuritis	19 (37%)	77 (48%)
Myelitis	32 (62%)	94 (58%)
Brain or brainstem	8 (15%)	6 (4%)
Previous treatment		
Any therapy[b]	51 (98%)	159 (99%)
Plasmapheresis	26 (50%)	58 (36%)
Intravenous immunoglobulin	3 (6%)	8 (5%)
Previous maintenance therapy		
Any previous immunosuppressive therapy	36 (69%)	112 (70%)
Corticosteroids	21 (40%)	74 (46%)
Nonbiological immunosuppression[c]	25 (48%)	77 (48%)
Biological agent[d]	5 (10%)	23 (14%)
No previous immunosuppressive therapy	16 (31%)	49 (30%)
Mean (SD) baseline gadolinium-enhancing lesions	0.8 (0.9)	1.2 (1.2)

	N-MOmentum trial	
	Placebo (n=52)	**Inebilizumab (n=161)**
Mean (SD) baseline EDSS score	4.4 (1.6)	3.8 (1.8)

Data are presented as n (%) if not specified otherwise. [a]Race was self-reported by patients; Non-white includes American Indian or Alaskan Naïve, Asian, Black or African American and Other (Mestizo, mixed, Arab, Hispanic, Vietnamese, Caucasian/Latino, and New Zealand Māori) [b]Any previous treatment for neuromyelitis optica, including rescue and maintenance therapy; some patients received more than one maintenance therapy. [c]All other non-biological, non-corticosteroid treatments, including azathioprine (40% placebo, 39% inebilizumab), cetirizine, ciclosporin, cyclophosphamide, fingolimod, methotrexate (0% placebo, 1% inebilizumab), mitoxantrone, mizoribine, mycophenolate mofetil (13% placebo, 16% inebilizumab), or pentoxifylline. [d]Including rituximab (10% placebo, 14% inebilizumab), interferon beta (2% placebo, 4% inebilizumab), natalizumab (0% placebo, 1% inebilizumab), glatiramer acetate (0% placebo, 1% inebilizumab)
Abbreviations: EDSS: Expanded Disability Status Scale: SD, Standard deviation
Source: CSR (10)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The N-MOmentum trial is the largest trial conducted in NMOSD patients to date. It provides data specifically on patients with AQP4+ NMOSD for whom reimbursement is sought. This population is considered reflective of the Danish patients expected to be treated with inebilizumab.

The most recent information available was published in a study by Papp et al., which compared mortality in patients with NMOSD compared to general public in Denmark. The study by Papp et al. specifically focuses on patients with AQP4+ NMOSD and is thus aligned with the patient population of this application. Among the 66 patients included in this study, the median age at disease onset was 48 years (8). This is older than that in the N-MOmentum trial, in which the median age at treatment initiation was 43 years (10). In the study by Papp et al., 89% of the population were female (8). This is similar to the N-MOmentum trial, in which 94% of the study participants were female (10). With regard to race, the proportion of non-white study participants was larger in the N-MOmentum trial compared with the Danish population in the study by Papp et al. (52% (10) vs 80% (8)); however, this can be expected in a multinational trial. The mean EDSS score in the study by Papp is higher (4.6) (8) than in the N-MOmentum trial (3.8) (10). This may be explained by the older population in the study by Papp et al., who have had more time to progress on the EDSS compared with the younger population in the N-MOmentum trial. In terms of phenotype, the two studies included a similar proportion of patients with NMOSD, yet there were more patients with neuromyelitis optica (NMO) in the N-MOmentum trial (85%) (10) than in the study by Papp et al. (39%) (8). Lastly, in both trials approximately half of patients had myelitis as first attack. In the N-MOmentum trial, more patients experienced optic neuritis as first attack than in the study by Papp et al. (50% (10) vs 24% (8)).

In summary, patients in the study by Papp et al. were older and had slightly worse disability than those in the N-MOmentum trial, as assessed using the EDSS.

Table 12 Characteristics of the relevant Danish population and the population in the health economic model

	Value in Danish population (8)	Value used in health economic model (10)
Median age, years	48[a]	43[b]
Gender (female)	89.4%	93.9%
Race		
Non-White[c]	NA	47.8%
White	80.3%	51.6%
Multiple categories checked	NA	0.5%
EDSS score, mean (SD)	4.6 (2.2)	3.94 (1.75)
Phenotype		
NMO	39.4%	85.0%
NMOSD	16.7%	15.0%
Other	43.9%[d]	NA
Type of first attack		
ON	24.2%	50.2%
Myelitis	54.5%[e]	52.1%
Other	21.2%[f]	12.2%[g]

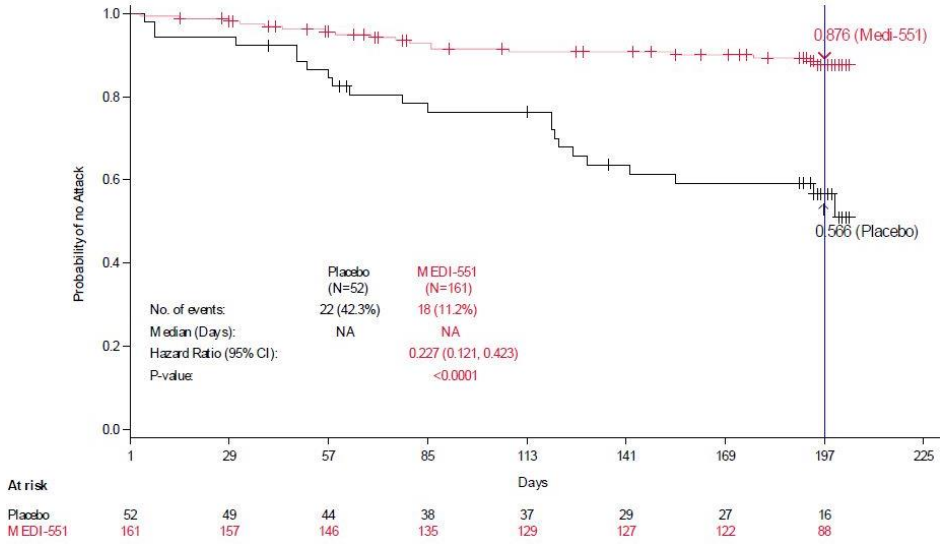
Abbreviations: EDSS: Expanded Disability Status Scale; NA: Not applicable; NMA: Neuromyelitis optica; NMOSD: Neuromyelitis optica spectrum disorder; ON: Optic neuritis; SD: Standard deviation
[a]Age at disease onset; [b]Age at start of treatment; [c]Includes American Indian or Alaskan Native, Asian, Black or African American and Other; [d]Includes patients with only optic neuritis and only transverse myelitis; [e]transverse myelitis; [f]Includes area postrema syndrome and brainstem syndrome; [g]includes brain/brainstem

6.1.4 Efficacy – results per N-MOmentum trial

6.1.4.1 Primary endpoint

The results of the primary analysis of the N-MOmentum trial (including all study participants who completed the randomized controlled period [RCP] with a database lock in December 2018) have been published (46). This section presents the results of the final analysis, which includes all study participants who completed the safety follow-up period or withdrew (database lock in December 2020) (10).

The primary endpoint, time to first AC-determined attack, was met. **In the AQP4+ population of the trial, 11% of the patients in the inebilizumab arm had an attack compared with 42% of patients in the placebo arm (HR: 0.227; 95% CI: 0.121-0.423; p<0.0001).** Figure 2 shows the Kaplan-Meier curve for this outcome.



Abbreviations: CI: Confidence interval; MEDI-551, Inebilizumab; NA: Not applicable
Source: N-MOmentum Clinical Study Report (10).

Figure 2 Kaplan-Meier estimates of time to onset of adjudicated attack

Across all demographic and clinical subgroups investigated in the AQP4+ population, inebilizumab consistently reduced the risk of AC-determined NMOSD attacks compared with placebo. The reduction in risk of NMOSD attacks with inebilizumab treatment was maintained (HR ≤ 0.4) and was statistically significant across the 9 sensitivity analyses conducted in the AQP4+ population (76).

Reasons for censoring

There were 22 subjects (out of 56 subjects) in placebo and 21 subjects (out of 174 subjects) in Ineb had AC-determined NMO attack as shown in the primary analysis.

The reasons for censoring for each treatment arm are presented in the following.

1) **1) Inebilizumab treatment arm**
Out of 153 censored subjects (171-21 = 153):

- - 5 subjects were censored due to “No-AC determined attack prior to discontinuing from RCP.
*NOTE: These 5 subjects are the same subjects displayed in Figure 1 without completing RCP in the Ineb group.

- - 148 subjects were censored due to “No-AC determined attack during RCP)
*NOTE: These 148 subjects who completed RCP but without any AC-determined attack during RCP

2) **2) Placebo treatment arm**
Out of 34 censored subjects (56-22 = 34):

- - All 34 were censored due to "No-AC determined attack during RCP)
*NOTE: These 34 subjects who completed RCP but without any AC-determined attack during RCP

6.1.4.2 Key Secondary endpoints

EDSS - A clinically meaningful worsening was defined as ≥2 points gained in EDSS score (a validated measure of disability in MS commonly used to measure disability in NMOSD) score for patients with a baseline score of 0; ≥1 point(s) for patients with a baseline score of 1 to 5; and ≥0.5 points for patients with a baseline score of ≥5.5 (10). **Significantly fewer patients receiving inebilizumab in the AQP4+ population experienced EDSS score worsening from baseline compared with patients receiving placebo (14.9% vs 34.6%; OR: 0.352; 95% CI: 0.170-0.725; p=0.0047).** During the open-label extension period (OLP), the proportion of patients who experienced EDSS score **worsening from baseline remained low** in patients originally randomized to inebilizumab, varying from 8.1% at Week 13 of the OLP to 10.8% at Week 104 of the OLP. In patients originally randomized to placebo but switched to inebilizumab in the OLP, the proportion experiencing worsening of EDSS generally decreased with time in the OLP, from 22.4% at Week 13 to 7.0% at Week 104. This indicates a **beneficial impact of inebilizumab on disability progression**. Of note, EDSS score for patients receiving inebilizumab remained stable throughout the 4 years or more after initiating inebilizumab; median change from baseline in EDSS score was 0.5 or less from the initiation of inebilizumab to throughout the follow-up period (43).

LCVAB - There was no difference between treatment arms in change of low-contrast visual acuity binocular score from baseline (difference -0.038; 95% CI: -2.312-2.236; p=0.97) (10). However, a sensitivity analysis of the primary endpoint (described in Section 6.1.4.1) found that patients in the inebilizumab arm were less likely to experience an optic neuritis attack than those in the placebo arm (HR: 0.222; 95% CI: 0.088-0.565, p=0.0016) (76).

Magnetic resonance imaging (MRI) - **Treatment with inebilizumab led to a statistically significant decrease in the cumulative number of active MRI lesions (rate ratio: 0.568; 95% CI: 0.385-0.836; p=0.0042)** (10). In patients with active MRI lesions, the inebilizumab group had a lower mean cumulative number of MRI lesions compared with the placebo group (1.7 vs 2.3 lesions).

NMOSD related Hospitalizations - In the RCP, **inebilizumab significantly reduced the number of inpatient hospitalizations** in the AQP4+ population **compared with placebo, with a rate ratio of 0.291 (95% CI: 0.1054-0.8017; p=0.0170)**. In the OLP, rate of NMOSD-related inpatient hospitalization was lower in the inebilizumab/inebilizumab group (15.2%) than in the placebo/inebilizumab group (19.6%) (10).

For results of exploratory and post-hoc analyses as well as a description of patient-reported outcomes, please see Appendix R.

6.1.4.3 End-of-study results

The recently published end-of-study results from the N-MOmentum trial, including results for 225 patients from the RCP and OLP (data cut-off from December 2020), showed the continued and sustained clinical efficacy of inebilizumab. In the AQP4+ population, 21% of patients experienced an attack (60 attacks in 44 patients. **The majority of patients treated with inebilizumab (77%) were attack-free at the end of four years. The AAR decreased over time, from 0.185 in year one to 0.022 in year four in the AQP4+ population.** The most common adverse events were urinary tract infection, nasopharyngitis and arthralgia. Infection rates did however not increase over four years (77).

6.1.5 Efficacy – results per [study name 2]

Not applicable as only one placebo-controlled trial was conducted.

6.2 Efficacy of inebilizumab compared to rituximab for adult patients with NMOSD

There are no relevant studies which directly compare inebilizumab with rituximab in adult patients with AQP4+. Therefore, an indirect treatment comparison (ITC) in form of an unanchored matching-adjusted indirect comparison (MAIC) based on individual patient data (IPD) has been conducted.

RIN-01, a randomized controlled trial in patients with AQP4+ NMOSD (78), was not considered eligible for inclusion for several reasons. Firstly, patients in RIN-01 received combination therapy with rituximab and concomitant steroids throughout the study. Steroids given for the first 8 weeks from visit 2 (randomization) to visit 4 and while they were gradually reduced after visit 4, this was only by 10% every visit and the dose was only reduced to 2 mg per day to the end of study (78). In contrast in N-MOmentum, patients only received concomitant steroids tapered to day 21. Further limitations are described in Appendix C.

The available efficacy evidence for inebilizumab has been presented in section 6.1. The following section will therefore focus solely on the presentation of the study included for rituximab.

6.2.1 Relevant studies

The studies included for the comparison with rituximab are summarized in Table 13.

Table 13 Overview of study design for studies included in the comparison of inebilizumab vs rituximab

Trial name, NCT number	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
Kim et al. (2011) (11)	Prospective, single-arm open-label study	2 years	Relapsing NMO or NMO spectrum disorder	Rituximab Half of the participants received an induction dose of 375mg/m^2 weekly for four weeks the other half received an induction dose of 1000mg twice two weeks apart Both groups received maintenance doses of 375mg/m^2 with a frequency depending on the CD27+B cell levels in the blood	NA	ARR (24 months), EDSS score (24 months), APQ4 antibody level (24 months), safety (24 months)

Abbreviations: ARR: Annual relapse rate; EDSS: Expanded disability status scale; NMOSD: Neuromyelitis optica spectrum disorder

6.2.2 Comparability of studies

As part of the feasibility analysis, Kim et al. (11) was compared with N-MOmentum (10). The eligibility criteria of both studies were broadly comparable, with both studies requiring patients to have had an attack prior to study initiation. Kim et al. required patients to have at least one attack in the year before the study initiation and N-MOmentum required patients to have had at least one attack in the year before study initiation or two attacks in the two years before. Both studies also only included adults; this was an inclusion criterion in N-MOmentum and in Kim et al., no patients aged under 18 years old were enrolled. Neither study allowed concomitant therapy use, with Kim et al. stating that all patients were required to have discontinued immunosuppressive therapy before starting rituximab treatment. This meant that both studies could isolate the outcomes for the treatment of interest. Baseline disease activity in both studies were broadly similar between the two studies, with a mean baseline AAR of 1.69 in N-MOmentum and 2.4 in Kim et al, and a mean EDSS score of 3.9 in N-MOmentum and mean EDSS score of 4.4 in Kim et al.. The duration of Kim et al. was up to 24 months, which was longer than the randomized controlled period from N-MOmentum (6 months)

but was similar to the open-label period of N-MOmentum (≥ 24 months) (10). There was no major difference in the study design.

It can therefore be assumed that, aside from the provided treatment, the studies are largely similar and are appropriate to compare in an indirect treatment comparison.

To date, there is no RCT comparing the treatment of rituximab with a placebo control group in the relevant patient group for this application. Therefore, an unanchored comparison of the time to attack of the N-MOmentum and the study by Kim et al. was conducted. This is a limitation, because the randomization into a treatment and a control group eliminates any bias in the selection of patients for treatment.

Selection bias is not only limited to the selection of patients for treatment, but also pertains to treatment discontinuation. During the N-MOmentum trial, almost no patients discontinued treatment, and any discontinuation was described in detail. The same level of scrutiny and monitoring cannot be expected in observational studies. Some observational studies also require a minimum follow-up period to include the patients in their analysis. If patients discontinue due to lack of efficacy, this might lead to overestimation of the effect of rituximab.

The included rituximab trial had a prospective design, which increases the validity of the studies. In the prospective design, the exposure (rituximab) is already defined, making it possible to indicate the temporal sequence between exposure and outcome, which reduces confounding factors and enhances causality. It is also possible to design the data collection for the specific purpose of the study, thus improving data quality.

Treatment heterogeneity may occur in different samples of patients with different characteristics who might not respond to the treatment in the same way. Therefore, the comparisons need to ensure comparability in baseline characteristics across trials to avoid cross-trial imbalances from different distributions of observed covariates. This can to some extent be alleviated in indirect comparisons using a MAIC. However, the MAIC analysis can only address balance issues of observed covariates, and any systematic relationship between unobserved covariates and the outcome resulting in treatment heterogeneity can lead to substantial bias in the indirect comparison. Even if the issue of unobserved covariates is disregarded, there still needs to be sufficient overlap in the baseline characteristics of the patients in the studies being compared to perform a MAIC analysis. In essence, a MAIC is unable to address and account for differences in study design and endpoint definition. Therefore, the results of such an analysis need to be interpreted with caution.

6.2.2.1 Comparability of patients across studies

The baseline characteristics of the rituximab trial by Kim et al. (9) is presented below in Table 14. For easier comparison, the baseline characteristics from the N-MOmentum (66) trial have been added to the table as well. The baseline characteristics for AQP4+ patients were broadly similar between the two studies regarding age and proportion female. Also baseline disease activity were broadly similar between the two studies, with

a mean baseline AAR of 1.63 in N-MOmentum and 2.4 in Kim et al, and a median EDSS score of 3.8 in N-MOmentum and mean EDSS score of 4.8 in Kim et al..

The baseline characteristics after matching are presented in Appendix C.

Table 14 Baseline characteristics of AQP4+ patients in studies included for the comparative analysis of efficacy and safety

	Kim et al.	N-Momentum trial
	Rituximab	**Inebilizumab**
Sample size (N)	21	161
Mean (SD) age in years	41.0 (10.3)	43.2 (11.6)
Gender (female), %	95.2%	94%
Baseline AAR, mean (SD)	1.9 (1.3)	1.63 (1.5)
Baseline EDSS, mean (SD)	4.8 (2.0)	3.8 (1.8)

Abbreviations: AAR: Annualizsed attack rate; AQP4: Aquaporin-4; EDSS: Expanded Disability Status Scale; NR: Not reported

6.2.3 Comparability of the study population(s) with Danish patients eligible for treatment

The population in the health economic model is based on the trial population of the N-MOmentum trial. This trial population is thus also used in the comparison of inebilizumab and rituximab. Therefore, the information on the comparison of the model population with the relevant Danish patients with NMOSD presented in the below Table 15 is the same as presented in section 6.1.3, Table 13.

Table 15 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (8)	Value used in health economic model (10)
Median age, years	48[a]	43[b]
Gender (female)	89.4%	93.9%
Race		
Non-White[c]	NA	47.8%
White	80.3%	51.6%
Multiple categories checked	NA	0.5%
EDSS score, mean (SD)	4.6 (2.2)	3.94 (1.75)

Phenotype		
NMO	39.4%	85.0%
NMOSD	16.7%	15.0%
Other	43.9%[d]	NA
Type of first attack		
ON	24.2%	50.2%
Myelitis	54.5%[e]	52.1%
Other	21.2%[f]	12.2%[g]

Abbreviations: EDSS: Expanded Disability Status Scale; NA: Not applicable; NMA: Neuromyelitis optica; NMOSD: Neuromyelitis optica spectrum disorder; ON: Optic neuritis; SD: Standard deviation
[a]Age at disease onset; [b]Age at start of treatment; [c]Includes American Indian or Alaskan Native, Asian, Black or African American and Other; [d]Includes patients with only optic neuritis and only transverse myelitis; [e]transverse myelitis; [f]Includes area postrema syndrome and brainstem syndrome; [g]includes brain/brainstem

6.2.4 Efficacy – results per Kim et al. (11)

The study by Kim et al. (11) enrolled 30 patients in total, of whom 21 had AQP4+ NMOSD. Over the follow-up period, the AQP4+ patients experienced a total of 11 attacks and had an AAR of 0.339. In total, 15 patients (71%) were attack-free during rituximab treatment.

When looking at the overall population (AQP4+ and AQP4-), the combined population experienced 14 attacks and the AAR was 0.292 over the mean follow-up of 1.60 years. In total, 21 patients (70%) were attack free during rituximab treatment. During treatment, the EDSS score improved in 24 patients and stabilized in one patient, with a decrease in mean EDSS score from 4.4 at baseline to 3.0 at the end of treatment. No patients died during the study.

7. Comparative analyses of efficacy

7.1 Comparison of inebilizumab with placebo

7.1.1 Differences in definitions of outcomes between studies

Not applicable because a placebo-controlled trial was conducted.

7.1.2 Method of synthesis

Not applicable because a placebo-controlled trial was conducted.

7.1.3 Results from the comparative analysis

Table 16 presents the results from the one placebo-controlled trial conducted.

Table 16 Results from the comparative analysis of inebilizumab vs placebo for adult AQP4+ NMOSD patients

Outcome measure	Inebilizumab (N=161)	Placebo (N=52)	Result
Time to first NMOSD attack from Day 1, up to Day 197	NA[a]	NA[a]	HR: 0.227 (95% CI: 0.121-0.423)
Change in EDSS score, Day 197	24/161 (15%)	18/52 (35%)	OR: 0.352 (95% CI: 0.170-0.725)
Annualized attack rate, 667.51 total person-years[b]	NA	NA	0.09

Abbreviations: EDSS, Expanded Disability Status Score; HR: Hazard ratio; NA: Not applicable; OR: Odds ratio
[a]This was conducted as a time-to-event analysis in the trial, and the median was never reached in the trial
[b]This endpoint was calculated over various lengths of exposure to inebilizumab and thus the time point is represented as the sum of the person-years for each study participant
Source: CSR (10)

Efficacy – results per [outcome measure]

Not applicable because a placebo-controlled trial was conducted.

7.2 Comparison of inebilizumab with rituximab

7.2.1 Differences in definitions of outcomes between studies

There are some differences in the definition of attack between the studies included in this comparison. In the inebilizumab trial (10, 46), an independent Adjudication Committee (AC) evaluated all possible NMOSD attacks. The AC members determined, by majority vote, whether an event met the definition of an NMOSD attack based on their judgment, clinical experience, the data provided and the protocol-defined criteria for an NMOSD attack (please see Appendix K for details on the criteria).

In the rituximab trials by Kim et al. (11), the equivalent to an attack was referred to as relapse. It was defined as objective worsening of new neurological symptoms lasting at least 24 hours that increased the EDSS score by at least half a step (0.5) or increased 1 point on 2 different functional systems of the EDSS or 2 points on 1 of the functional systems (excluding however bowel/bladder or cerebral functional systems).

All analyses for the indirect comparison used investigator-assessed attacks and not AC-assessed attacks from the N-MOmentum trial because Kim et al. did not report using an AC to evaluate attacks and therefore are more likely to have evaluated investigator-assessed attacks. Secondly, AC-determined attacks are not available for the OLP period

of N-MOmentum. Finally, investigator assessed attacks are more likely to reflect clinical practice.

7.2.2 Method of synthesis

To compare inebilizumab with rituximab, a MAIC based on an IPD analysis has been performed. A SLR was conducted to identify rituximab studies reporting IPD. This was to allow for a comparison with IPD on relevant efficacy endpoints for patients treated with inebilizumab from the N-MOmentum trial with IPD for patients treated with rituximab by matching baseline characteristics. The key outcome of interest was time to attack.

One study for rituximab by Kim et al. was identified and presented previously in this document (11) (please see section 6.2.1). For synthesis of the N-MOmentum trial and the study by Kim et al., an unanchored MAIC was conducted due to the lack of a common comparator arm in both trials. Propensity score weighting was used to reweight the IPD from N-MOmentum on patients receiving inebilizumab to achieve covariate balance with IPD for patients treated with rituximab retrieved from the study by Kim et al. allowing to fully adjust for observed patient differences across the trials. For the primary analysis, data from the inebilizumab arm from the blinded phase as well as data from the combined blinded and open-label phase of the N-MOmentum trial was used.

Details of the MAIC are presented in Appendix C.

7.2.3 Results from the comparative analysis

The results of the MAIC are presented in Table 17 below. Based on the hazard ratio presented, inebilizumab is estimated to be more effective in the prevention of attacks compared to rituximab. Details of the analysis are presented in the following section.

Table 17 Results from the comparative analysis of inebilizumab vs. rituximab for adult patients with AQP4+ NMOSD

Outcome measure	Inebilizumab[a]	Rituximab[a]	Result
Time to first attack (unweighted) – RCP only	NA	NA	[redacted]
Time to first attack (adjusted[c]) – RCP only	NA	NA	[redacted]
Time to first attack (unweighted) – RCP and OLP	NA	NA	[redacted]
Time to first attack (adjusted[b]) – RCP and OLP	NA	NA	[redacted]

Abbreviations: ESS: Effective sample size; HR: Hazard ratio OLP: Open-label period; p: p-value; RCP: Randomised controlled period; SE: Standard error

[a]For the analysis with RCP data only, the ESS for the weighted analysis was 161 and for the unweighted analysis 137. For the analysis with RCP and OLP data, the ESS for the weighted analysis was 176 and for the unweighted analysis 213. [b]Adjusted for age, ARR and sex (proportion male)

Efficacy – results for time to first attack

XXXXXX18 presents the results of the MAIC for time for first attack for the RCP only. The adjustment for age, ARR, and sex (proportion male) had limited impact on the estimated HR, lowering it from [redacted] in the unmatched scenario to [redacted] after matching. The distribution of weights and ESS were both found to be acceptable [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] present the results of the MAIC for time for first attack for the RCP and OLP. The adjustment for age, ARR, and sex (proportion male) had limited impact on the estimated HR, lowering it from [redacted] in the unmatched scenario to [redacted] after matching. The distribution of weights and ESS were both found to be acceptable. As the extrapolation of effect data in the economic model is based on data from the RCP and OLP, the HR corresponding to this is used in the model base case. The HR based on the RCP only is used in a scenario analysis.

[redacted]

[redacted]

[redacted]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

The model extrapolates the expected time to NMOSD attack, which is used to estimate the AAR. More details are provided in the following sections.

8.1.1.1 Extrapolation of time to first adjudicated attack

The primary outcome of the N-MOmentum trial was time to first adjudicated NMOSD attack. A constant risk of attack over time was assumed. This was based on a discussion with a Danish clinical expert and confirmed by a Norwegian clinical expert. Both experts advised that the attack risk in treated patients can be expected to be constant over time. Furthermore, a post-hoc analysis of the N-MOmentum trial showed that the AAR between 6 months and 2.5+ years was relatively similar with 0.07 between 6 months and 1.5 years, 0.06 between 1.5 years and 2.5 years, and 0.03 after 2.5 years (79). A similar

pattern was observed in a German registry study from 2023 (80). In the recently published end-of-study results from the N-MOmentum trial, a decrease in the AAR over time was observed (77). In the Markov model, the attack risk is therefore conservatively implemented as a probability of attack per 1-month cycle. To reflect this assumption and implementation, the exponential parametric function was considered a good fit. All other parametric functions considered did not reflect this assumption and were therefore excluded.

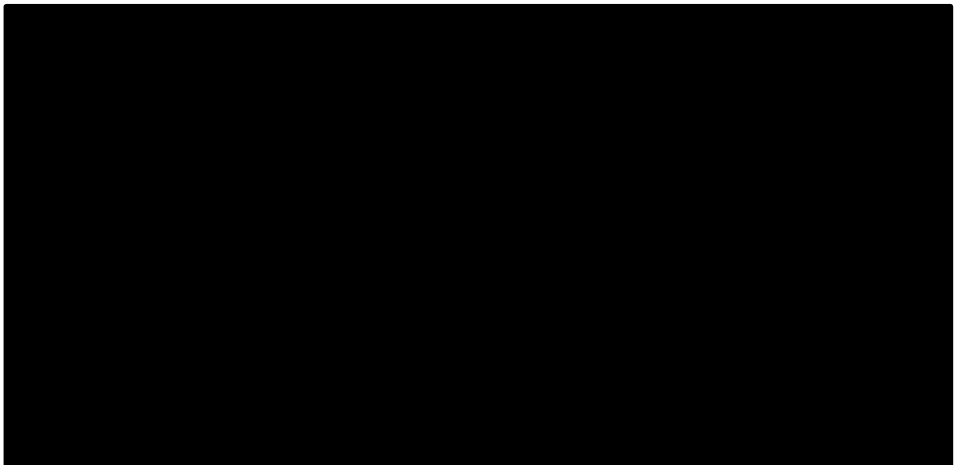
Table 20 Summary of assumptions associated with extrapolation of time to attack

Method/approach	Description/assumption
Data input	N-MOmentum trial Inebilizumab arm - blinded and open-label period Rituximab: Application of HR to inebilizumab data Placebo arm - blinded trial period only due to cross-over to inebilizumab in the open-label period; the data from the blinded period is used as proxy for the open-label period as well
Model	One model for extrapolation of efficacy: Exponential
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit*	Inebilizumab: Exponential Rituximab: Not applicable, as extrapolation is based on a HR compared to inebilizumab which was applied to extrapolations of inebilizumab Placebo: Exponential
Function with best BIC fit*	Inebilizumab: Exponential Rituximab: Not applicable, as extrapolation is based on a HR compared to inebilizumab which was applied to extrapolations of inebilizumab Placebo: Exponential
Function with best visual fit*	Inebilizumab: Exponential Rituximab: Not applicable, as extrapolation is based on a HR compared to inebilizumab which was applied to extrapolations of inebilizumab Placebo: Exponential
Function with best fit according to evaluation of smoothed hazard assumptions	Inebilizumab: Not applicable

Method/approach	Description/assumption
	Rituximab: Not applicable, as extrapolation is based on a HR compared to inebilizumab which was applied to extrapolations of inebilizumab Placebo: Not applicable
Validation of selected extrapolated curves (external evidence)	The modelled mortality based on the chosen extrapolation has been compared to the reported mortality of Danish NMOSD patients as well as the Danish general population. It could be observed that the modelled and the reported mortality were well aligned. For details please see Appendix Q.
Function with the best fit according to external evidence	Inebilizumab: Not applicable, as only the exponential function is included Rituximab: Not applicable Placebo: Not applicable, as only the exponential function is included
Selected parametric function in base case analysis	Inebilizumab: Exponential Rituximab: Not applicable Placebo: Exponential
Adjustment of background mortality with data from Statistics Denmark	No, background mortality was not explicitly accounted for in the analysis of time to NMOSD attack, as no patients died during the N-MOmentum trial. It is incorporated as a separate input in the health economic model.
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: AAR: annualized attack rate; NMOSD: Neuromyelitis optica spectrum disorder.
*An exponential function for time to first attack was the only appropriate model for estimating per-cycle probability of an attack.

The observed data (Kaplan-Meier curve) from the N-MOmentum trial is presented in [redacted], together with the extrapolated curves for inebilizumab and rituximab. The extrapolations are both based on the exponential distribution.



[redacted]

Extrapolation of [effect measure 2]

Not applicable. Time to first adjudicated attack was the only outcome which was extrapolated in the model.

8.1.2 Calculation of transition probabilities

When a patient experiences a NMOSD attack, the patient's EDSS score is at risk of changing. Changes in EDSS score associated with a NMOSD attack were based on a post-hoc analysis conducted in the patients with AQP4+ NMOSD from the N-MOmentum trial. Patients transition through the model across EDSS categories following an NMOSD attack. Patient transitions were modelled based on EDSS category prior to and following an NMOSD attack observed in the N-MOmentum trial. For a detailed description see Appendix Q.

Table 21 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
EDSS 0-10	EDSS 0-10	Post-hoc analysis of the AQP4+ population the of N-MOmentum trial based on EDSS category prior to the NMOSD attack	N-MOmentum trial (46), for detailed transitions see Table 113

Abbreviation: EDSS: expanded disability status scale.
Note: EDSS 10 corresponds to 'Death'.

Transitions in the model were also impacted by treatment discontinuation. For inebilizumab and rituximab, a discontinuation rate of [redacted] was applied, respectively (for details see Appendix Q). Patients on placebo are assumed to stay on this treatment indefinitely.

Lastly, the analysis took into account general population mortality as well as mortality related to NMOSD. For details please see Appendix Q.

8.2 Presentation of efficacy data from [additional documentation]

Not applicable, because no additional data source has been applied in the model.

8.3 Modeling effects of subsequent treatments

At treatment discontinuation, all patients are moved to the placebo treatment arm for the remainder of the model time horizon. For effects, see the description of placebo treatment arm in section 6.1.4.

8.4 Other assumptions regarding efficacy in the model

Not applicable, as all assumptions have been discussed previously.

8.5 Overview of modeled average treatment length and time in model health state

The average median time to attack for inebilizumab, rituximab and placebo estimated from the model is shown in [redacted]

[redacted]

	Modelled average time to attack (reference in Excel)	Modelled median time to attack (reference in Excel)	Observed median from relevant study
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: N/A: Not applicable
[a]Median time to attack was not reached in the clinical trial

The average time on treatment in years is presented below in [redacted]. Patients remain longer on treatment with inebilizumab, compared with rituximab and placebo. It can be observed that broken down by EDSS health state, patients on inebilizumab spent longer time in each of the EDSS health states, particularly in the EDSS health states 0 to 6.

[redacted]

Treatment	Treatment length (years)	EDSS 0-3.5 (years)	EDSS 3.5-6 (years)	EDSS 6-10 (years)
Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EDSS: Expanded Disability Status Scale

9. Safety

9.1 Comparison of inebilizumab versus placebo

9.1.1 Safety data from the clinical documentation

The safety data for inebilizumab and placebo was derived from the N-MOmentum trial (10). The safety follow-up period (SFP) started when a patient prematurely discontinued from the RCP or the OLP. The patient was then to be followed in the SFP until 52 weeks after the last dose of inebilizumab was given.

In the safety analyses, patients were included from the as-treated population. This population included all study participants who received treatment with inebilizumab and patients were grouped according to the treatment received, even if this was different to the treatment they were randomized to. AEs were coded to the corresponding system organ class (SOC) and preferred terms (PT) using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence, severity, and relationship to the investigational product were summarized. Specific AEs were counted once for each subject when calculating the percentage of patients who experienced an AE. If the same AE occurred multiple times within a subject, the highest severity and level of relationship observed were reported.

During the RCP, patients received two planned doses of inebilizumab or placebo. In the total as-treated population, 96.6% of subjects in the inebilizumab group and 94.6% of subjects in the placebo group received both planned doses. The mean dose of inebilizumab administered was 589.7 mg (standard deviation [SD] ±54.9). Because the number of subjects receiving only a single dose of inebilizumab was small (n = 9), a separate analysis of the efficacy and safety in this group was not performed.

Across the RCP and the OLP, 225 patients received at least 1 dose of inebilizumab (208 in the AQP4+ population) (10). As of May 2021, the total exposure in the AQP4+ population (‘any inebilizumab’, n = 208) was 667.51 person-years (10).

Median inebilizumab doses in the AQP4+ population was 8.0 (SD 2.7) (77, 81) 90·9% (n = 189) of these patients had > 1 year, 84·6% (n = 176) had > 2 years, 54·3% (n = 113) had > 3 years, and 34·6% (n = 72) had > 4 years of exposure to inebilizumab (81).

AEs that occurred in AQP4+ patients during the RCP are summarized in Table 24. AEs are reported as treatment-emergent adverse events (TEAEs) and adverse reactions are reported as product-related TEAEs, as reported in the clinical study report (CSR). There were no serious AEs with a frequency of ≥5% in the N-MOmentum trial reported for either of the study arms during the RCP **as such, the table originally labelled as “Table 17: Serious adverse events (Timepoint) has been removed.** Only adverse events which occurred during the RCP are presented in the main text as they are used in the economic model. A detailed listing of adverse events which occurred during the open-label period is presented in Appendix R In Table 118.

Table 24 Overview of safety events (RCP)

	Inebilizumab (N=161) (RCP, N-MOmentum trial)	Placebo (N=52) (N-MOmentum trial, RCP)	Difference, % (95 % CI)
Number of adverse events, n	479	169	NR
Number and proportion of patients with ≥1 adverse events, n (%)	119 (73.9%)	37 (71.2%)	NR
Number of serious adverse events*, n	11	8	NR
Number and proportion of patients with ≥1 serious adverse events*, n (%)	7 (4.3%)	6 (11.5%)	NR
Number of CTCAE grade ≥3 events, n	25	16	NR
Number and proportion of patients with ≥1 CTCAE grade ≥3 events§, n (%)	14 (8.7%)	7 (13.5%)	NR
Number of adverse reactions, n	82	28	NR
Number and proportion of patients with ≥1 adverse reactions, n (%)	14 (8.7%)	13 (25.0%)	NR
Number and proportion of patients who had a dose reduction, n (%)	0	0	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	4 (2.5%)	2 (3.9%)	NR
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	2 (1.2%)	0	NR

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; NR: Not reported; OLP: Open-label period; RCP: Randomized controlled period; *A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available.; Source: Clinical Study Report (10).

All AEs occurring in more than 5% of the patients for any model comparator (i.e. inebilizumab, rituximab, or placebo) were included in the health economic analysis to apply a common definition of AEs for all included comparators in the model.

Table 25 Adverse events used in the health economic model

Adverse events	Inebilizumab	Placebo		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)	N=161	N=52		
Arthralgia	17 (10.6%)	3 (5.8%)	CSR (10)	Alignment across all model comparators
Back pain	11 (6.8%)	2 (3.8%)	CSR (10)	
Cardiac complications[a]	1 (0.6%)	1 (1.9%)	CSR (10)	
Chills	2 (1.2%)	0	CSR (10)	
Depression	4 (2.5%)	5 (9.6%)	CSR (10)	
Diarrhea	7 (4.3%)	3 (5.8%)	CSR (10)	
Dizziness	3 (1.9%)	1 (1.9%)	CSR (10)	
Fever	2 (1.2%)	1 (1.9%)	CSR (10)	
Genital warts	0	0	CSR (10)	
Hair loss	1 (0.6%)	2 (3.8%)	CSR (10)	
Headache	14 (8.7%)	4 (7.7%)	CSR (10)	
Hepatotoxicity	0	0	CSR (10)	
Hypotension	0	1 (1.9%)	CSR (10)	
Influenza	4 (2.5%)	2 (3.8%)	CSR (10)	
Infusion-related reactions	15 (9.3%)	5 (9.6%)	CSR (10)	
Laboratory abnormalities	12 (7.5%)	4 (7.7%)	CSR (10)	
Leukopenia	1 (0.6%)	0	CSR (10)	
Myalgia	1 (0.6%)	2 (3.8%)	CSR (10)	
Nasopharyngitis	12 (7.5%)	6 (11.5%)	CSR (10)	
Neutropenia	4 (2.5%)	0	CSR (10)	
Oral herpes	2 (1.2%)	3 (5.8%)	CSR (10)	
Pain	1 (0.6%)	0		
Pain in extremity	9 (5.6%)	4 (7.7%)	CSR (10)	
Pruritus	2 (1.2%)	5 (9.6%)	CSR (10)	
Respiratory distress	0	0	CSR (10)	
Respiratory infection	9 (5.6%)	5 (9.6%)	CSR (10)	
Rigors	0	0	CSR (10)	
Shingles	0	1 (1.9%)	CSR (10)	
Throat Irritation	0	0	CSR (10)	
Thrombosis	0	0	CSR (10)	
Thyroid complications	0	0	CSR (10)	
Urinary tract infection	18 (11.2%)	5 (9.6%)	CSR (10)	
Urticaria	1 (0.6%)	1 (1.9%)	CSR (10)	
Vomiting	1 (0.6%)	4 (7.7%)	CSR (10)	
Weight loss	0	0	CSR (10)	

[a]Arrythmia

9.1.2 Safety data from external literature applied in the health economic model

Not applicable because no external literature data has been used for inebilizumab and placebo.

9.2 Comparison of inebilizumab versus rituximab

9.2.1 Safety data from the clinical documentation

Not applicable because data from the external literature has been used for rituximab AE rates.

9.2.2 Safety data from external literature applied in the health economic model

The risk of AEs associated with rituximab was extracted from studies identified in a SLR (see Appendix N). All studies describing AEs were included; however, reviews were scrutinized and the studies from each review were included instead of the reviews themselves if AEs were available. AEs were included in the health economic assessment if they were considered common (an incidence of ≥5%) in the respective treatment arms. The risk of AEs associated with rituximab was calculated as the weighted average of AEs reported in the identified studies, conditional on the studies' reporting the specific AE. The frequency per 100 PY was not reported in the studies identified in the SLR described. To compute the frequency per 100 PY for rituximab, it was assumed one event per patient experiencing an adverse event. Since one event per patient can be considered as a low assumption compared to a real-life situation, this can be considered as a conservative assumption. This assumption is tested in sensitivity analysis. The weighted AE rates used applied in the model are presented in Table 26 below.

Table 26 Adverse events that appear in more than 5% of patients treated with rituximab

Adverse events	Rituximab (N=variable*)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	**Number of adverse events**	**Frequency used in economic model for intervention**	**Number of patients with adverse events**	**Number of adverse events**	**Frequency used in economic model for comparator**	**Number of patients with adverse events**	**Number of adverse events**
Adverse event, n				N/A	N/A	N/A	N/A	N/A
Arthralgia	103	N/A	8.72%	N/A	N/A	N/A	N/A	N/A
Back pain	0	N/A	0	N/A	N/A	N/A	N/A	N/A
Cardiac complications	88	N/A	5.61%	N/A	N/A	N/A	N/A	N/A
Chills	88	N/A	12.15%	N/A	N/A	N/A	N/A	N/A
Depression	0	N/A	0	N/A	N/A	N/A	N/A	N/A
Diarrhea	18	N/A	5.50%	N/A	N/A	N/A	N/A	N/A
Dizziness	103	N/A	12.56%	N/A	N/A	N/A	N/A	N/A
Fever	112	N/A	6.79%	N/A	N/A	N/A	N/A	N/A
Genital wart	18	N/A	5.50%	N/A	N/A	N/A	N/A	N/A
Hair loss	18	N/A	11.10%	N/A	N/A	N/A	N/A	N/A
Headache	135	N/A	13.27%	N/A	N/A	N/A	N/A	N/A

Adverse events	Rituximab (N=variable*)			Comparator (N=x)			Difference, % (95 % CI)	
Hepatotoxicity	54	N/A	15.32%	N/A	N/A	N/A	N/A	N/A
Hypotension	127	N/A	10.32%	N/A	N/A	N/A	N/A	N/A
Influenza	85	N/A	5.80%	N/A	N/A	N/A	N/A	N/A
Infusion-related reactions	474	N/A	11.27%	N/A	N/A	N/A	N/A	N/A
Laboratory abnormalities	85	N/A	8.20%	N/A	N/A	N/A	N/A	N/A
Leukopenia	62	N/A	12.95%	N/A	N/A	N/A	N/A	N/A
Myalgia	191	N/A	8.72%	N/A	N/A	N/A	N/A	N/A
Nasopharyngitis	0	N/A	0	N/A	N/A	N/A	N/A	N/A
Neutropenia	54	N/A	11.94%	N/A	N/A	N/A	N/A	N/A
Oral herpes	0	N/A	0	N/A	N/A	N/A	N/A	N/A
Pain	18	N/A	5.50%	N/A	N/A	N/A	N/A	N/A
Pain in extremity	18	N/A	38.80%	N/A	N/A	N/A	N/A	N/A
Pruritus	18	N/A	5.50%	N/A	N/A	N/A	N/A	N/A
Respiratory distress	88	N/A	8.24%	N/A	N/A	N/A	N/A	N/A

Adverse events	Rituximab (N=variable*)			Comparator (N=x)			Difference, % (95 % CI)	
Respiratory infection	452	N/A	5.50%	N/A	N/A	N/A	N/A	N/A
Rigors	88	N/A	5.61%	N/A	N/A	N/A	N/A	N/A
Shingles	18	N/A	5.50%	N/A	N/A	N/A	N/A	N/A
Throat Irritation	18	N/A	16.60%	N/A	N/A	N/A	N/A	N/A
Thrombosis	18	N/A	11.10%	N/A	N/A	N/A	N/A	N/A
Thyroid complications	74	N/A	5.15%	N/A	N/A	N/A	N/A	N/A
Urinary tract infection	328	N/A	11.27%	N/A	N/A	N/A	N/A	N/A
Urticaria	18	N/A	11.10%	N/A	N/A	N/A	N/A	N/A
Vomiting	88	N/A	6.93%	N/A	N/A	N/A	N/A	N/A
Weight loss	18	N/A	11.10%	N/A	N/A	N/A	N/A	N/A

Sources: Uzunköprü et al. (53), Zhang et al. (54), Kim et al. (34), Annovazzi et al. (55), Cabre et al. (51), Bedi et al. (62), Seyed et al. (52), Correa-Diaz et al. (56), Gomez-Figueroa et al. (57), Lin et al. (58), Lu et al. (59), Xiao et al. (60), Radaelli et al. (63), Shaygannejad et al. (61),
*Depending on the number of studies included in the calculation of the average for each AE

10. Documentation of health-related quality of life (HRQoL)

Table 27 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
SF-36v2 Health Survey	N-MOmentum trial (10)	To compare the health-related quality of life of NMOSD patients treated with inebilizumab versus placebo. Is used to calculate health state utilities and a utility decrement for patients experiencing an attack.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

HRQoL data (SF-36 MCS/PCS) were collected as part of the N-MOmentum trial (described in section R.1.2).

The SF-36 health survey is a commonly used PRO instrument that asks 36 questions to measure functional health and well-being from the patient's point of view. The SF-36 is a generic PRO instrument and generates composite scores within eight health domains and two summary level scores: the PCS and MCS [49]. There is extensive literature evaluating the SF-36, with established general population norms and published studies providing potential benchmark values in most diseases or conditions [50].

The SF-36 is not a preference-based measure of HRQoL, and so cannot directly be used to generate the utility data required to calculate QALYs. To estimate QALYs using SF-36 HRQoL data, mapping methods are required to convert SF-36 responses/measurements into estimates of utilities. For this analysis, the data have been mapped to the EQ-5D (see section 10.2.1.1 for details).

The surveys had a 1-4 week recall period and were scheduled at different time points throughout the study period, as described in Section 10.1.2 Data collection.

When gathering data in a clinical trial, inherent biases may arise. This study design introduces several recognized sources of bias. The primary risks include the following.

- Recall bias: participants may have difficulty in accurately recalling and reporting their health-related experiences, which may impact the reliability of the data.
- Memory loss: Memory of health-related events tend to decay with time, which can lead to underestimation and overestimation of the true impact of the intervention on HRQoL.
- Variability in recall accuracy: Different individuals may recall experiences differently, leading to variability in the quality of the response.

- Event contamination: Events occurring outside of the 4-week period may influence perceptions, which can lead to bias.
- Selection bias: If participants in the trial are more motivated to improve their health, bias may be introduced.

10.1.2 Data collection

The N-MOmentum trial collected SF-36 data at 12-week intervals and immediately following the occurrence of an adjudicated NMOSD attack. Surveys with a 4-week recall were scheduled for completion by trial subjects at baseline, at Week 12, and on completion of the RCP. In addition, a survey with 1-week recall was used following the occurrence of an AC NMOSD attack. For patients continuing in the open-label extension study, surveys with a 4-week recall were scheduled for every 13 weeks.

In line with the population for this submission, only AQP4+ patients were included in the analysis. If a patient experienced an attack during the blinded RCP, they moved to the treatment arm in the OLP. Therefore, to avoid bias from including only treated patients from the OLP we restricted the sample to the RCP.

Information on completed and missing data are summarized in Table 28 (for full details please see Table 115 in Appendix Q). Baseline characteristics of patients with missing data are presented in Table 29.

Table 28 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data are missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Inebilizumab				
Baseline (RCP)	161	[redacted]	[redacted]	[redacted]
Week 12 (RCP)	161	[redacted]	[redacted]	[redacted]
Week 28 (RCP)	161	[redacted]	[redacted]	[redacted]
Baseline (OLP)*	154	[redacted]	[redacted]	[redacted]
Week 13 (OLP)	154	[redacted]	[redacted]	[redacted]
Week 26 (OLP)	154	[redacted]	[redacted]	[redacted]
Week 39 (OLP)	154	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 52 (OLP)	154	[redacted]	[redacted]	[redacted]
Placebo				
Baseline (RCP)	52	[redacted]	[redacted]	[redacted]
Week 12 (RCP)	52	[redacted]	[redacted]	[redacted]
Week 28 (RCP)	52	[redacted]	[redacted]	[redacted]
Baseline (OLP)*	47	[redacted]	[redacted]	[redacted]
Week 13 (OLP)	47	[redacted]	[redacted]	[redacted]
Week 26 (OLP)	47	[redacted]	[redacted]	[redacted]
Week 39 (OLP)	47	[redacted]	[redacted]	[redacted]
Week 52 (OLP)	47	[redacted]	[redacted]	[redacted]

Abbreviations: HRQoL: Health-related quality of life; OLP: Open-label period; RCP, Randomized controlled period.
*Baseline OLP corresponds to Day 197 of the RCP.

Table 29 Baseline characteristics of patients with missing data

	N-MOmentum trial	
	Placebo (n=39)	**Inebilizumab (n=89)**
Mean (SD) age, in years	39.7 (13.74)	42.9 (11.66)
Sex (female)	2 (5.1%)	8 (9.0%)
Race[a]		
White	17 (43.6%)	47 (52.8%)
Non-white	22 (56.3%)	41 (46.1%)
Multiple categories checked	0	1 (1.1%)
Ethnicity		
Hispanic or Latino	12 (30.8%)	16 (18.0%)
Mean (SD) disease duration, in years	3.20 (3.88)	2.55 (3.44)

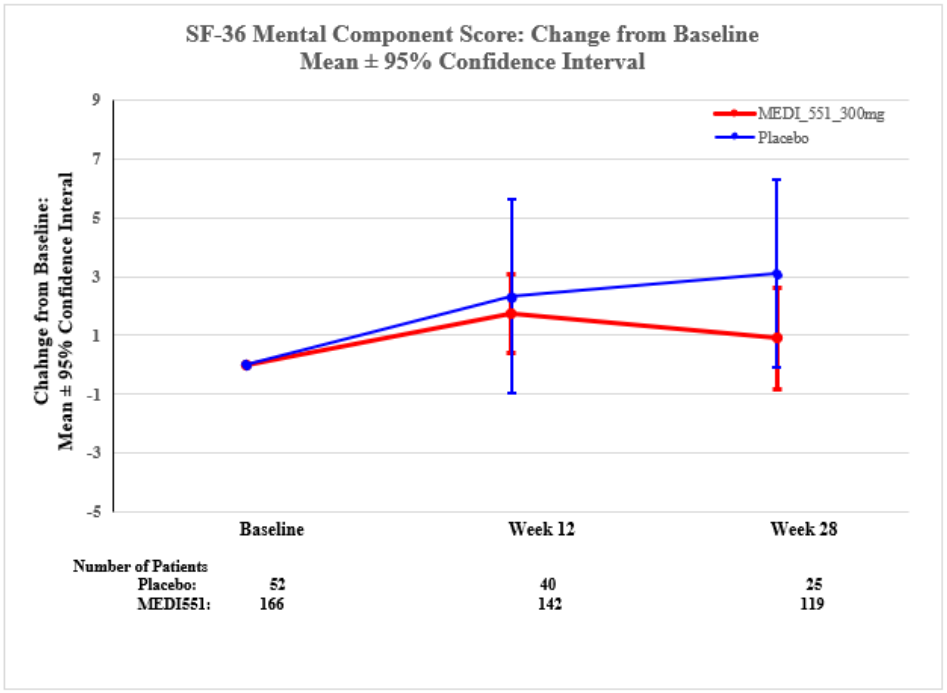
	N-MOmentum trial	
	Placebo (n=39)	**Inebilizumab (n=89)**
Type of most recent attack		
Optic neuritis	14 (35.9%)	48 (53.9%)
Myelitis	22 (56.4%)	48 (53.9%)
Brain or brainstem	7 (17.9%)	4 (4.5%)
Mean (SD) baseline gadolinium-enhancing lesions	0.9 (0.92)	1.3 (1.15)
Mean (SD) baseline EDSS score	4.32 (1.608)	3.78 (1.823)

Abbreviations: EDSS, Expanded Disability Status Score; SD, Standard deviation
Data are presented as n (%) if not specified otherwise.
[a]Race was self-reported by patients; Non-white refers to American Indian or Alaskan Native, Asian, Black or African American and Other (Mestizo, mixed, Arab, Hispanic, Vietnamese, Caucasian/Latino, and New Zealand Māori)
Source: Ad-hoc analysis of N-MOmentum trial data.

10.1.3 HRQoL results

The change from baseline for SF-36 scores in the N-MOmentum trial (10) is shown in Figure 6. Only data for the RCP are shown because patients crossed over to treatment with inebilizumab in the OLP.

Panel A



Panel B

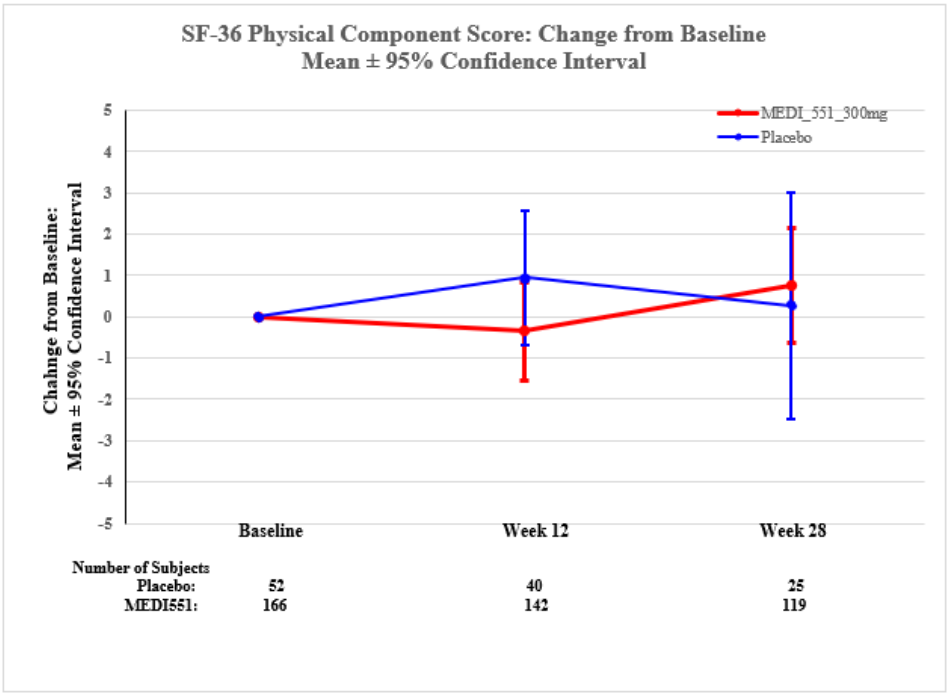


Figure 6 Change from baseline in SF-36 Mental component (Panel A) and Physical component (Panel B) in N-MOmentum (Randomized controlled period) APQ4+ population
Source: Ad-hoc analysis of N-MOmentum data

The results of the MCS and PCS of the SF-36 as measured in the AQP4+ patients are presented in Table 30. For full study period please see Table 116 in Appendix Q.

Table 30 SF-36 summary statistics

	Intervention		Comparator		Intervention vs comparator
	N	Mean (95%CI)	N	Mean (95%CI)	Difference (95% CI) p-value
Mental component, SF-36v2, ITT APQ4+ population					
Baseline RCP (absolute value)	[redacted]	[redacted]	[redacted]	[redacted]	
Week 12 RCP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28 RCP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline OLP	[redacted]	[redacted]	[redacted]	[redacted]	
Week 13 OLP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 26 OLP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 39 OLP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 OLP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 208 OLP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical component, SF-36v2, ITT APQ4 population					
Baseline RCP (absolute value)	[redacted]	[redacted]	[redacted]	[redacted]	
Week 12 RCP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28 RCP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline OLP	[redacted]	[redacted]	[redacted]	[redacted]	

	Intervention	Comparator	Intervention vs comparator
Week 13 OLP	[redacted]	[redacted]	[redacted]
Week 26 OLP	[redacted]	[redacted]	[redacted]
Week 39 OLP	[redacted]	[redacted]	[redacted]
Week 52 OLP	[redacted]	[redacted]	[redacted]
Week 208 OLP	[redacted]	[redacted]	[redacted]

CI = Confidence intervals. ITT = Intent-to-Treat. RCP = Random control period.

[a] Baseline indicates last assessment prior to first dose.

[b] Difference (95% CI) are estimated by mixed model for repeated measures including treatment as the major factor, visit as the repeated factor, and baseline measurement as the covariate.

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

Each score per individual that completed SF-36 was converted to a single health utility value using a mapping algorithm (please see section 10.2.1.1 for details). **This is used in the base case.**

Whilst the Rowen algorithm for calculating the HRQoL was used in the model base case given its greater sensitivity, directness, and mapping to the more common benchmark of EQ-5D utilities, there is an alternative option for utility weights available in the model. The model includes the option to apply utility values from a recent publication by Hümmert et al. evaluating the HRQoL using the EQ-5D-5L questionnaire and merged with clinical data from the NEMOS database (64).

Age-adjustments for QoL calculations are included in the model, as outlined in the DMC guidelines.

10.2.1.1 Mapping

To derive utility weights from the QoL data collected in the N-MOmentum trial, the mapping algorithm developed by Rowen et al (2009) was applied (50). In this study, the authors developed a mapping algorithm to convert SF-36 scores to EQ-5D utility values.

An alternative mapping algorithm was also tested, converting SF-36 scores to SF-6D utility values; however, this algorithm was only used as a scenario analysis due to the DMC's preferences for EQ-5D utilities.

The dataset from the Health Outcomes Data Repository (HODaR) (82) was used, which contains data from a prospectively collected survey of inpatients and outpatients in the UK. All adult patients (≥18 years) were included. Only individuals who are known to have died or who had a primary diagnosis upon admission of a psychological illness or learning disability were excluded. The survey is linked to routine health data. The response rate to the survey is around 50%. From the inpatient sample, 25,783 completed responses from 23,179 individuals who completed both the SF-36 and EQ-5D were included in the mapping exercise. From the outpatient sample, 9,081 completed responses from 8,610 individuals were included. In both samples, data were collected between mid-2002 and November 2004.

Given the wide range of conditions with varying severity included in the HODaR dataset, this population may be considered representative of patients included in the N-MOmentum trial.

For the mapping exercise, the UK time trade-off value set was used in the analysis (49) because a mapping algorithm to the Danish value set could not be identified and is not available, according to EuroQol. A regression analysis was used to study the relationship between SF-36 and EQ-5D in this study. Three different types of models were tested: a random effects model (set up as three different models for 1) all dimensions, 2) all dimensions and squared terms, and 3) all dimensions, squared terms and interactions), a tobit model, and a censored least absolute deviations (CLAD) model.

In terms of performance, the following mean squared error (MSE) and mean absolute error (MAE) were reported for the different models.

- Random effects generalized least squares (GLS) model 1 (full index): MSE 0.003; MAE 0.138
- Random effects GLS model 2 (full index): MSE 0.030; MAE 0.129
- Random effects GLS model 3 (full index): MSE 0.030; MAE 0.127
- Random effects tobit (full index): MSE 0.033; MAE 0.142
- CLAD (full index): MSE 0.033; MAE 0.133

The CLAD and tobit model did not improve the accuracy of the generated predictions (MSE and MAE did not get smaller). The most accurate predictions were based on the GLS model 3. Generally, the models predicted the milder health states well, but overpredicted the more severe EQ-5D states (true for all models). In comparison with existing algorithms (83, 84), the model by Rowen performs better in terms of a lower MSE and MAE.

10.2.2 Disutility calculation

Disutilities are applied in the health economic model for NMOSD attacks and AEs. Disutilities for experiencing an NMOSD attack were calculated using the SF-36v2 data collected in the N-MOmentum trial. Using the Rowen mapping algorithm (50), the

estimated change in utility was -0.1994 with an NMOSD attack and is applied in one model cycle per attack. Disutilities for experiencing an AE were applied given the negative impact AEs have on a patient's QoL. The applied utility decrements associated with AEs with an incidence of ≥5% were based on a targeted literature search of PubMed. The utility decrements applied in the model are presented in Table 33.

Table 31 Regression modelling of mapped utilities (Rowen algorithm)

Variable	Coefficient	SE	p-value
Inebilizumab (vs placebo)	[redacted]	[redacted]	[redacted]
EDSS group 3-5.5 (vs 0-2.5)	[redacted]	[redacted]	[redacted]
EDSS group 6+ (vs 0-2.5)	[redacted]	[redacted]	[redacted]
Constant (average utility for placebo, in EDSS <3, at mean age of around 42 years, etc.)	[redacted]	[redacted]	[redacted]

Abbreviations: EDSS: Expanded Disability Status Score; SE: Standard error

10.2.3 HSUV results

The utilities and disutilities applied in the economic model are summarized in Table 32 below.

Table 32 Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HRQoL by EDSS category (Rowen algorithm)				
EDSS [0,1)	[redacted]	EQ-5D-3L	UK (49)	Estimate is based on mean of both trial arms.
EDSS [1,2)	[redacted]	EQ-5D-3L	UK (49)	
EDSS [2,3)	[redacted]	EQ-5D-3L	UK (49)	
EDSS [3,4)	[redacted]	EQ-5D-3L	UK (49)	
EDSS [4,5)	[redacted]	EQ-5D-3L	UK (49)	
EDSS [5,6)	[redacted]	EQ-5D-3L	UK (49)	

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
EDSS [6,7)	[redacted]	EQ-5D-3L	UK (49)	
EDSS [7,8)	[redacted]	EQ-5D-3L	UK (49)	
EDSS [8,9)	[redacted]	EQ-5D-3L	UK (49)	
EDSS [9,10)	[redacted]	EQ-5D-3L	UK (49)	

Abbreviations: EDSS: Expanded Disability Status Score; HRQoL: health-related quality of life; HSUV: health state utility value

10.3 Presentation of the health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

An alternative set of HSUVs has been derived from the study by Hümmert et al. (64), which was identified from a SLR on QoL data in patients with NMOSD and is presented in the following section. **This study has been used in a scenario analysis.**

10.3.1 Study design

The study by Hümmert et al. (64) had a multicenter cross-sectional design and was conducted between April 2017 and April 2019 in Germany. Patients were included in the study if they were 18 years of age or older, were diagnosed with NMOSD according to 2015 International Panel for NMO Diagnosis criteria or MOG antibody-associated disease (MOGAD), lived in Germany and were not predominantly treated for a disease other than NMOSD/MOGAD.

10.3.2 Data collection

Patients were asked to complete the EQ-5D-5L questionnaire to evaluate their QoL. Of 275 available patients, 218 returned a completed questionnaire and 212 datasets were available for analysis.

Statistical significance of the parameters (index value, EuroQol Visual Analog Scale [EQ-VAS], and EQ-5D-5L) between disease duration subgroups (0-1 year vs >5 years and 0-5 years vs >5 years) was evaluated using the nonparametric Mann–Whitney U test. Additionally, the different serogroups were analyzed for differences. Subgroups of different disease severity (EDSS 0-3, EDSS 3.5-6, EDSS 6.5-8.5) were examined. To evaluate which factors influenced HRQoL as dependent variables, a variety of independent candidate variables were studied. Due to the skewed nature of the dependent variables, a generalized linear model was used, assuming that the dependent

variables follow a gamma distribution instead of a normal distribution. Independent variables were chosen based on their statistical significance in univariate regression analysis and information on at what point in the joint distribution the nonnormality matters, then analyzing them in two separate multiple linear regression models. The variables were then assessed for collinearity and interaction. Data from multiple regressions were then entered into two generalized linear models with the appropriate link functions to generate the usability of the data regardless of their distribution. Due to the explorative character of the study, multiple testing was not corrected for. Correlations between two nonparametric variables were tested with the Spearman test (ρ). Data are expressed as mean and 95% CI. Values of $p<0.05$ were considered statistically significant. Missing data resulted in different numbers of patients analyzed.

10.3.3 HRQoL Results

Details on the collected EQ-5D data were not provided in the publication. Results were presented only in form of aggregated utility weights. These are presented in the next section.

10.3.4 HSUV and disutility results

The utility weights reported by Hümmert et al. (64) and the disutility weights derived for adverse events from the literature are presented in Table 33.

Table 33 Overview of health state utility values and disutilities

	Results	Instrument	Tariff (value set) used	Comments
HRQoL by EDSS category				
EDSS [0,3)	0.8450 95% CI 0.82–0.88	EQ-5D-5L	German value set	Hümmert et al. 2022 (64)
EDSS [3,6)	0.7050 95% CI 0.66–0.75	EQ-5D-5L	German value set	Hümmert et al. 2022 (64)
EDSS [6,9)	0.1950 95% CI 0.13–0.28	EQ-5D-5L	German value set	Hümmert et al. 2022 (64)
EDSS [9,10)	0.1950	EQ-5D-5L	German value set	Hümmert et al. 2022 (64) Assumed to be the same as utility for EDSS score 8.5.

	Results	Instrument	Tariff (value set) used	Comments
	95% CI 0.13–0.28			
Disutilities				
Arthralgia	0.2	EQ-5D	NR	Luger et al. 2009 (65)
Back pain	0.117	EQ-5D-5L	Japanese value set	Shiroiwa et al. 2021 (66)
Cardiac complications	0.054	EQ-5D-5L	Japanese value set	Shiroiwa et al. 2021 (66)
Chills	0	NA	NA	Assumption
Depression	0.184	EQ-5D-5L	Japanese value set	Shiroiwa et al. 2021 (66)
Diarrhea	0.047	Standard gamble	NA	Nafees et al. 2008 (67)
Dizziness	0.098	EQ-5D-5L	Japanese value set	Shiroiwa et al. 2021 (66)
Fever	0.078	EQ-5D-5L	Japanese value set	Shiroiwa et al. 2021 (66)
Genital warts	0.001	NA	NA	Assumed the same as mild infection
Hair loss	0.045	Standard gamble	NA	Nafees et al. 2008 (67)
Headache	0.41	SF-6D	UK value set	Kristoffersen et al. 2019 (68)
Hepatotoxicity	0.218	NR	NR	Wehler et al. 2018 (69)
Hypotension	0.02	NR	NR	Wehler et al. 2018 (69)
Infusion-related reactions	0.011	Standard gamble	NA	Boye et al. 2011 (70)
Laboratory abnormalities	0	NA	NA	Assumption
Leukopenia	0.09	Standard gamble	NA	Nafees et al. 2008 (67)

	Results	Instrument	Tariff (value set) used	Comments
Myalgia	0.117	NA	NA	Assumed same as back pain
Nasopharyngitis	0.032	EQ-5D-5L	Japanese value set	Shiroiwa et al. 2021 (66)
Neutropenia	0.09	Standard gamble	NA	Nafees et al. 2008 (67)
Oral herpes	0.001	NA	NA	Assume same as mild infection
Pain	0.105	NR	NR	Wehler et al. 2018 (69)
Pain in extremity	0.117	NA	NA	Assumed same as back pain
Pruritus	0.020	NA	NA	Nafees et al. 2008
Respiratory distress	0.025	NA	NA	Shiroiwa et al. 2021
Respiratory infection	0.083	EQ-5D-5L	Japanese value set	Shiroiwa et al. 2021 (66)
Rigors	0.000	NA	NA	Assumption
Shingles	0.134	EQ-5D	Italian value set	Matthews et al. 2019 (71)
Throat Irritation	0.000685	NA	NA	Assumed equal to mild infection
Thrombosis	0.22	NA	NA	Mean of deep vein thrombosis and pulmonary embolism
Deep vein thrombosis	0.19	Standard gamble	NA	Hogg et al. 2018 (72)
Pulmonary embolism	0.25	Standard gamble	NA	Hogg et al. 2018 (72)
Thyroid complications	0.006	EQ-5D-5L	Japanese value set	Shiroiwa et al. 2021 (66)
Urinary tract infection	0.01	NR	NR	Bermingham et al. 2012 (73), Sonnenberg et al. 2004 (74)
Urticaria	0.21	NA	NA	Mean of mild, moderate and severe

	Results	Instrument	Tariff (value set) used	Comments
mild	0.162	EQ-5D-3L	UK value set	Hawe et al. 2016 (75)
moderate	0.205	EQ-5D-3L	UK value set	Hawe et al. 2016 (75)
severe	0.265	EQ-5D-3L	UK value set	Hawe et al. 2016 (75)
Vomiting/Nausea	0.049	Standard gamble	NA	Nafees et al. 2008 (67)
Weight loss	0	NA	NA	Assumption

Abbreviations: EDSS, Expanded Disability Status Score; HRQoL, Health-related quality of life; NA: Not applicable; NR, Not reported

11. Resource use and associated costs

11.1 Pharmaceutical costs - intervention and comparator

The pharmaceutical costs for inebilizumab were provided by Amgen. Information on pharmaceutical costs for rituximab were derived from the Danish Medicines Agency (85). Rituximab 100 mg and 500 mg are provided by Sandoz (Rixathon) and 1,400 mg by Roche (note, the 100 mg and 1,400 mg strengths are not used in the model analysis as a fixed dose of 1,000 mg is applied). All costs are presented in Table 34 below. Patients receiving placebo are assumed not to accrue any pharmaceutical costs.

Table 34 Pharmaceutical costs used in the model

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]
Inebilizumab	100 mg	3	[redacted]
Rituximab	500 mg	1	6,687.00

11.2 Pharmaceutical costs – co-administration

Not applicable.

11.3 Administration costs

Inebilizumab and rituximab are both administered as intravenous infusions. Thus, a cost is applied for each administration of these medicines. The unit cost was derived from the Danish DRG catalogue and is presented below in Table 35.

Table 35 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Intravenous infusion	With every administration of inebilizumab and rituximab	1,941.00	DRG01MA98	DRG 2024

11.4 Disease management costs

Data on disease management of patients with NMOSD were derived from patient-level data from the N-MOmentum trial (10), and validated and updated to reflect the Danish clinical setting by a Danish clinical expert. Data are reported as resource use per EDSS category during stable disease periods and resource use per attack.

In a post-hoc analysis, the healthcare resource uses associated with ambulance transport, home visits from nurse, home visits from physician, other healthcare visits, primary care physician, emergency room visits, and hospitalization days for both general and intensive care were estimated as the number of healthcare resource uses per year and per attack during stable periods and attack periods, respectively. For hospitalizations, the expected length of each hospitalization was also measured. To better reflect the Danish clinical practice, and advised by Danish clinical expert, an average of four treatments of plasmaphereses and Methylprednisolon IV each are added per patient per attack.

The analysis estimated resource use for stable disease periods and NMOSD attacks, respectively. Attack periods were defined as the period from the prior observed visit until the date of an adjudicated attack. Stable periods were defined as the periods outside the attack periods. The analysis was performed in the N-MOmentum subpopulation of the ITT population who were AQP4+. Healthcare resource use was estimated as the mean resource utilization within a given resource category among patients in the given EDSS category and from attack assessment visits for stable periods and attacks, respectively.

Table 36 presents the results on the average healthcare resource use per year during the stable periods. The healthcare resource use per year generally increased with EDSS intervals. Table 37 presents the mean length of hospitalizations during the stable periods as advised by Danish clinical expert.

Table 36 Healthcare resource use per year during stable disease periods

Healthcare resource	EDSS 0-3.5	EDSS 3.5-6	EDSS 6-10
Ambulance transport	[redacted]	[redacted]	[redacted]
Home visits from nurse	[redacted]	[redacted]	[redacted]
Home visits from physician	[redacted]	[redacted]	[redacted]
Other healthcare visits	[redacted]	[redacted]	[redacted]
Primary care physician	[redacted]	[redacted]	[redacted]
Emergency room	[redacted]	[redacted]	[redacted]
Hospitalization days (general care)	[redacted]	[redacted]	[redacted]
Hospitalization days (intensive care)	[redacted]	[redacted]	[redacted]

Abbreviations: EDSS: Expanded Disability Status Score
Source: Post hoc analysis of data from N-MOmentum, Danish clinical expert
Note: Bootstrap standard errors are reported in parentheses.

Table 37 Mean number of days hospitalized per hospitalization during the stable periods

Healthcare resource	EDSS 0-3.5	EDSS 3.5-6	EDSS 6-10
Hospitalization length, general care, days	2.000 (NA)	4.000 (NA)	4.000 (NA)
Hospitalization length, intensive care, days	0.000 (NA)	1.000 (NA)	2.000 (NA)

Abbreviations: EDSS: Expanded Disability Status Score; NA: Not available
Source: Post hoc analysis of data from N-MOmentum, Danish clinical expert

Table 38 presents the results on the mean healthcare resource use during attack periods, and Table 39 presents the results on the mean length of hospitalizations during attack periods.

Table 38 Healthcare resource use per attack

Healthcare resource	Mean use
Ambulance transport	[redacted]
Other healthcare visits	[redacted]
Primary care physician	[redacted]
Emergency room	[redacted]
Hospitalization, general care,)	[redacted]
Hospitalization, intensive care	[redacted]
Plasmaphereses	[redacted]
Methylprednisolon IV	[redacted]

Abbreviations: NA: Not available; IV, Intravenous
Source: Post hoc analysis of data from N-MOmentum, Danish clinical expert
Note: Bootstrap standard errors are reported in parentheses.

Table 39 Mean number of days hospitalized per hospitalization during attacks

Healthcare resource	Mean length (days)
Hospitalization length, general care	7.667 (1.526)
Hospitalization length, intensive care	6.000 (NA)

Abbreviations: NA: Not available, Source: Post hoc analysis of data from N-MOmentum, Danish clinical expert,
Note: Bootstrap standard errors are reported in parentheses.

Unit costs linked to the estimated use of specific healthcare resources (Table 36-Table 39) associated with stable disease and attacks are presented in Table 40. Unit costs are presented for the cost year 2024, and have been updated to this year where applicable using the consumer price index for Denmark (86).

Table 40 Disease management costs used in the model

Healthcare resource	Frequency	Unit cost, DKK	Reference
Ambulance transport	See table 36 - 38	1,731.80	Jervelund et al. (87)
Home visits from nurse	See table 36 – 38	504.34	The Municipalities' and Regions' Salary Data Office (KRL) (88)
Home visits from physician	See table 36 – 38	1,181.63	Practicing Physician's Organisation (PLO) (89)
Other healthcare visits	See table 36 – 38	488.19	The Municipalities' and Regions' Salary Data Office (KRL) (88)
Primary care physician	See table 36 – 38	160.72	Practicing Physician's Organisation (PLO) (89)
Emergency room	See table 36 – 38	1,941	DRG 2024 - 01MA98
Hospitalization, general care	See table 36 and 38	42,170	DRG 2024 - 01MA07
Hospitalization, intensive care, per day	See table 36 – 38	27,024.29	Lindholt and Sørensen 2010 (90); assumed length of stay according to Table 37 and Table 39.
Plasmaphereses, per infusion	See table 36 – 38	47,943.00	DRG 2024 – 01MP10. 4 infusions per attack assumed.
Methylprednisolon IV, per infusion	See table 36 – 38	2,509.09	Solu-Medrol Pfizer (85).plus IV infusion (DRG 2024 - DRG01MA98). 4 infusions per attack assumed.

11.5 Costs associated with management of adverse events

All AEs are assumed to be treated at the hospital. Costs associated with AEs were based on 2024 DRGs and are presented in Table 41.

Table 41 Costs associated with the management of adverse events

	DRG code	Unit cost/DRG tariff
Arthralgia	DRG 10MA98	2,364.00
Back pain	DRG 23PR01	1,626.00

	DRG code	Unit cost/DRG tariff
Cardiac complications	DRG 05MA07	19,623.00
Chills	NA	0.00[a]
Depression	DRG 19MA02	24,122.00
Diarrhea	DRG 06MA98	1,561.00
Dizziness	DRG 03MA02	8,171.00
Fever	DRG 21MA98	1,684.00
Genital wart	DRG 13MA98	1,314.00
Hair loss	NA	0.00[a]
Headache	DRG 03MA98	2,107.00
Hepatotoxicity	DRG 07MA98	1,947.00
Hypotension	DRG 05MA98	1,183.00
Influenza	DRG 03MA98	2,107.00
Infusion-related reactions	DRG 10MA98	1,847.00
Laboratory abnormalities	NA	0.00[a]
Leukopenia	DRG 16MA03	37,129.00
Myalgia	DRG 08MA98	1,626.00
Nasopharyngitis	DRG 03MA98	2,107.00
Neutropenia	DRG 16MA03	37,129.00
Oral herpes	DRG 18MA98	2,570.00
Pain	DRG 23MA03	5,103.00
Pain in extremity	DRG 23PR01	2,364.00
Pruritus	DRG 09MA98	1,625.00
Respiratory distress	DRG 04MA98	1,311.00
Respiratory infection	DRG 04MA06	60,209.00
Rigors	NA	0.00[a]
Shingles	DRG 18MA98	2,570.00

	DRG code	Unit cost/DRG tariff
Throat Irritation	DRG 03MA98	2,107.00
Thrombosis		
Deep vein thrombosis	DRG 16MA10	27,121.00
Pulmonary embolism	DRG 16MA10	27,121.00
Thyroid complications	DRG 10MA98	1,847.00
Urinary tract infection	DRG 11MA98	1,550.00
Urticaria		
mild	DRG 09MA98	1,625.00
moderate	DRG 09MA98	1,625.00
severe	DRG 09MA04	34,816.00
Vomiting/nausea	DRG06MA98	1,561.00
Weight loss	NA	0.00[a]

[a]Assumed to have negligible costs, [b]includes infusion-related reactions for inebilizumab and injection-related reactions for rituximab

11.6 Subsequent treatment costs

Subsequent treatment costs have not been included in the analysis. There are several off-label treatments available. However, owing to a lack of uniform guidelines, scarcity of data, and not to introduce additional uncertainty, it was not considered feasible to model subsequent treatments. This can be considered as a conservative approach because additional costs would have been added to both treatment arms.

11.7 Patient costs

Costs for patient time spent on treatment and healthcare are included in the analysis. Based on the DMC's unit cost catalogue and inflated to the cost year 2024, using the consumer price index for Denmark (January to April 2024) (86)., a patient hour is valued with 204.86 DKK per hour (91). Transport costs of 141.28 DKK for a roundtrip were applied, based on the DMC's unit cost catalogue (91). Transportation costs are associated with each of the activities listed in Table 42. Time spend in each activity are validated by Danish clinical expert.

Table 42 Patient costs used in the model

Activity	Time spent (hours)
Inpatient hospitalization	
EDSS 0-3.5	[redacted]
EDSS 3.5+6	[redacted]
EDSS 6-10	[redacted]
Attack	[redacted]
Intensive care unit	
EDSS 0-3.5	[redacted]
EDSS 3.5-6	[redacted]
EDSS 6-10	[redacted]
Attack	[redacted]
Emergency room visit	[redacted]
Primary care visit	[redacted]
Other healthcare visits	[redacted]
Home visits	
Nurse	[redacted]
Physician	[redacted]
Treatment administration	
Inebilizumab	[redacted]
Rituximab	[redacted]

Source: Post hoc analysis of data from N-MOmentum, Danish clinical expert

11.8 Other costs (e.g. costs for home care nurses, outpatient rehabilitation and palliative care cost)

End-of-life costs or terminal care costs are included in the model. In each cycle, patients face a risk of death due to general mortality risk and NMOSD-related mortality risk. End-of-life costs are applied as a one-off cost upon progression to death and include costs for supporting patients in the terminal stage by providing them with needed comfort. Costs were derived from the 2024 Danish DRG catalogue, applying a unit cost of 4,511 DKK (DRG 26MP45).

Direct non-medical costs and investments and indirect costs as derived from the German study by Hümmert et al. (64) are available in the model but not included in the base case per DMC guidance. They can however be included when chosen via a check-box.

12. Results

12.1 Base case overview

Table 43 Base case overview

Feature	Description	
Comparator	Rituximab	Placebo
Type of model	Markov model	
Mean age at start	43 years	
Time horizon	60 years (lifetime)	
Treatment line	1st line. At discontinuation, patients move to placebo.	
Measurement and valuation of health effects	Health-related quality of life measured with SF-36 in N-MOmentum (10). UK population weights were used to estimate health state utility values	
Costs included	Pharmaceutical costs, Administration costs, Health care resource use costs, Costs of adverse events, Patient costs, End of life costs	
Dosage of pharmaceutical	Fixed dosing for inebilizumab and rituximab	Fixed dosing for inebilizumab.
Average time on treatment	[redacted]	[redacted]
Parametric function for TTFA	[redacted]	[redacted]
Inclusion of waste	[redacted]	
Average time in model health state	[redacted]	[redacted]

Feature	Description	
	[redacted]	[redacted]

[a] Includes treatment on inebilizumab and placebo. Average time on inebilizumab equals 15.6 years
[b] Includes treatment on rituximab and placebo. Average time on rituximab equals 8.7 years

12.1.1 Base case results

In the base case for inebilizumab vs. rituximab, the ICER was [redacted] per QALY gained. Table 44 summarises the base case results.

The ICER is not only driven by the pharmaceutical costs, but also the longer average treatment period for inebilizumab ([redacted] with inebilizumab and rituximab). Nearly 50% of the inebilizumab cost is incurred due to the increased time on treatment due to better treatment effect of inebilizumab leading to a longer survival for patients in this group as well as the higher discontinuation of patients on rituximab treatment leading to shorter treatment duration in this group. Although total costs in all categories are higher for inebilizumab, it can also be noted that costs for attacks are consistently lower with inebilizumab ([redacted] for inebilizumab vs [redacted] for rituximab), reflecting that patients experience fewer attacks while on treatment with inebilizumab.

Table 44 Base case results, discounted estimates, inebilizumab vs. rituximab

	Inebilizumab	Rituximab	Difference
Pharmaceutical costs	[redacted]	[redacted]	[redacted]
Pharmaceutical costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life-years gained (EDSS [0-3.5))	[redacted]	[redacted]	[redacted]
Life-years gained (EDSS [3.5-6))	[redacted]	[redacted]	[redacted]

	Inebilizumab	Rituximab	Difference
Life-years gained (EDSS [6, 10))	[redacted]	[redacted]	[redacted]
Total life-years	[redacted]	[redacted]	[redacted]
QALYs ((EDSS [0-3.5))	[redacted]	[redacted]	[redacted]
QALYs (EDSS [3.5-6))	[redacted]	[redacted]	[redacted]
QALYs (EDSS [6, 10))	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)*	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life-year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

Abbreviations: NA, Not applicable; NR, Not reported
* Not reported separately in model calculations. Included in QALYs per health state

In the base case for inebilizumab vs. placebo, the ICER was DKK [redacted] per QALY gained. Table 45 summarises the base case results.

It can be observed that although total costs in all categories are higher for inebilizumab due to the extended survival, it can also be noted that costs for attacks are consistently lower with inebilizumab ([redacted] for inebilizumab vs DKK [redacted] for placebo), reflecting that patients experience fewer attacks while on treatment with inebilizumab.

Table 45 Base case results, discounted estimates, inebilizumab vs. placebo

	Inebilizumab	Placebo	Difference
Pharmaceutical costs	[redacted]	[redacted]	[redacted]
Pharmaceutical costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]

	Inebilizumab	Placebo	Difference
Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life-years gained (EDSS [0-3.5))	[redacted]	[redacted]	[redacted]
Life-years gained (EDSS [3.5-6))	[redacted]	[redacted]	[redacted]
Life-years gained (EDSS [6, 10))	[redacted]	[redacted]	[redacted]
Total life-years	[redacted]	[redacted]	[redacted]
QALYs ((EDSS [0-3.5))	[redacted]	[redacted]	[redacted]
QALYs (EDSS [3.5-6))	[redacted]	[redacted]	[redacted]
QALYs (EDSS [6, 10))	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)*	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life-year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

Abbreviations: NA, Not applicable; NR, Not reported
* Not reported separately in model calculations. Included in QALYs per health state

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

12.2.1.1 Deterministic sensitivity analyses, inebilizumab vs. rituximab

The results of the different sensitivity analyses for inebilizumab vs. rituximab are presented in Table 46 and

Figure 7. The parameters with the largest impact on the ICER were the ones on the HR, different discount rates, the number of events per patient assumed in the calculation of AEs for rituximab, inebilizumab treatment costs as well as discontinuation rates for both

inebilizumab and rituximab. In the remaining scenario analyses the results remained generally consistent with the base case.

Table 46 One-way sensitivity analyses results, inebilizumab vs rituximab

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)	% change
Base case						
Discount rate						
Start age						
Time horizon						
Half-cycle correction						
AE assumption, number of events per person (rituximab)						
QALY weights						

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)	% change
EDSS decrement associated with an NMOSD attack						
Extrapolation of NMOSD attacks						
Analysis method of change in EDSS score associated with an NMOSD attack						
HR						
Utility decrement associated with attack						
EDSS decrement associated with attack						
Treatment discontinuation						
Health care resource use						

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)	% change
associated with stable disease	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use associated with NMOSD attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Adverse events,	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

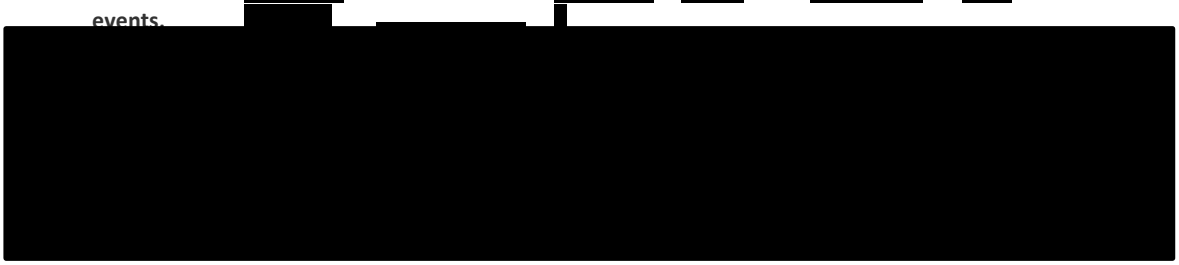


Figure 7. Tornado diagram one-way sensitivity analysis, inebilizumab vs. rituximab

The below Table 47 presents the pricing analysis of inebilizumab compared to rituximab.

Table 47 Inebilizumab price's impact on the ICER, inebilizumab vs rituximab

Inebilizumab Price (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (DKK/QALY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12.2.1.2 Deterministic sensitivity analyses, inebilizumab vs. placebo

The results of the different sensitivity analyses for inebilizumab vs. placebo are presented in Table 48 and

Figure 8. The scenarios with largest variation are the scenarios on discount rates, extrapolation of NMOSD attacks and inebilizumab treatment costs. In the remaining scenario analyses the results remained generally consistent with the base case.

Regarding the extrapolation of NMOSD attacks, this refers to the choice of underlying data (i.e. 6-month RCP only vs up to 4.5 years for RCP and OLP combined which is used in the base case). Since most of the attacks occur in the initial period after treatment start, it takes time for the effect of inebilizumab to be shown. At the same time, the longer follow-up time in the OLP lowers the uncertainty in the estimates for inebilizumab. Since there is only one way of estimating the outcome of placebo, using the RCP (due to the cross-over from placebo to inebilizumab in the OLP), the effect of inebilizumab becomes more evident when using the OLP, thus explaining the difference between including data from the RCP only compared to RCP combined with OLP.

Table 48 One-way sensitivity analyses results, inebilizumab vs placebo

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)	% change
Base case						
Discount rate						
Start age						
Time horizon						

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)	% change
Half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY weights	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EDSS decrement associated with an NMOSD attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolation of NMOSD attacks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis method of change in EDSS score associated with an NMOSD attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility decrement associated with attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
EDSS decrement associated with attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)	% change
Health care resource use associated with stable disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The figure presents the effect of changing individual key model parameters on the estimated ICER.

Figure 8. Tornado diagram one-way sensitivity analysis, inebilizumab vs. placebo

Table 49 Inebilizumab price's impact on the ICER, inebilizumab vs placebo

Inebilizumab Price (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (DKK/QALY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12.2.2 Probabilistic sensitivity analyses

12.2.2.1 Probabilistic sensitivity analyses, inebilizumab vs. rituximab

The PSA was run with 1,000 iterations. XXXXXXX9 presents the total discounted costs and QALY outcomes associated with inebilizumab and rituximab. The cloud is mainly located in the north-east quadrant, where incremental costs and QALYs are positive, with a few iterations located in the north-west quadrant (27 iterations) where rituximab is

dominant. XXXXXXX10 presents the decision uncertainty associated with the decision between inebilizumab and rituximab over the range of WTP values in the form of a cost-effectiveness acceptability curve (CEAC). The curve illustrates the probability of a treatment being cost-effective at any given WTP threshold. Rituximab has the highest probability of being cost-effective with a WTP value of around DKK 4,050,000. At WTPs above DKK 4,050,000 inebilizumab has the highest probability of being cost-effective.

The PSA convergence is presented in

[redacted] and [redacted] in Appendix Q.

[redacted]

[redacted]

[redacted]

[redacted]

12.2.2.2 Probabilistic sensitivity analyses, inebilizumab vs. placebo

The PSA was run with 1,000 iterations. XXXXXXX11 presents the total discounted costs and QALY outcomes associated with inebilizumab and placebo. The cloud is evenly distributed in the north-east quadrant, where incremental costs and QALYs are positive. XX

[redacted] presents the CEAC between inebilizumab and placebo, where placebo has the highest probability of being cost-effective with a WTP value of around DKK 1,550,000. At WTPs above DKK 1,550,000 inebilizumab has the highest probability of being cost-effective.

The PSA convergence is presented in

[redacted]

[redacted]

[redacted]

13. Budget impact analysis

13.1 Number of patients (including assumptions of market share)

It is challenging to make a prognosis of the dynamics of the therapeutic area given that there is no experience with inebilizumab. Based on feedback from a Danish clinical expert, it was assumed that there would be 15 new patients in 5 years, and in case of market approval for inebilizumab, the expert assumed that inebilizumab would have a market uptake of 5-10 new patients (in 5 years). Additionally, 1-2 patients on off-label treatment are assumed to switch treatment to inebilizumab each year due to insufficient treatment effect. In case of inebilizumab not being approved, all patients will be treated with either of the comparator (rituximab or placebo) depending on setting. This is aligned with previous assessments by DMC (28, 92). The budget impact is calculated as the difference between the two assumptions (i.e. inebilizumab is introduced vs is not introduced). Table 50 summarizes the cumulative market uptake with and without a recommendation.

Table 50 Number of new patients expected to be treated over the next five-year period if the pharmaceutical is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Inebilizumab	2	4	4	4	1
Comparator*	3	1	1	1	4
			Non-recommendation		
Inebilizumab	0	0	0	0	0
Comparator*	5	5	5	5	5

*Rituximab or placebo, depending on choice of comparator

13.2 Budget impact

Pharmaceuticals (using AIP prices), healthcare and end-of-life costs are included in the expenditure per patient per year and are taken from the CEM using the same inputs and assumptions as described in section 11. All costs are undiscounted.

Table 51 Expected budget impact of recommending the pharmaceutical for the indication, inebilizumab vs. rituximab

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52 Expected budget impact of recommending the pharmaceutical for the indication, inebilizumab vs. placebo

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

Prof. Zsolt Illes MD, PhD, DSc. Department Of Neurology, Odense University Hospital

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Appendix A. Main characteristics of studies included

Table 53 Main characteristics of studies included – N-MOmentum trial

Trial name: N-MOmentum trial (10)	NCT number: NCT02200770
Objective	The aim of the N-MOmentum study was to assess the efficacy and safety of B-cell depletion with inebilizumab as a monotherapy in reducing the risk of attacks and disability in NMOSD.
Publications – title, author, journal, year	Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Cree BAC, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk DM, Fujihara K, Paul F, Cutter GR, Marignier R, Green AJ, Aktas O, Hartung HP, Lublin FD, Drappa J, Barron G, Madani S, Ratchford JN, She D, Cimbora D, Katz E; N-MOmentum study investigators. Lancet. 2019 Efficacy and safety of inebilizumab in Asian participants with neuromyelitis optica spectrum disorder: Subgroup analyses of the N-MOmentum study. Fujihara K, Kim HJ, Saida T, Misu T, Nagano Y, Totsuka N, Iizuka M, Kido S, Terata R, Okumura K, Hirota S, Cree BAC.. Mult Scler Relat Disord. 2023 Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum Study. Flanagan EP, Levy M, Katz E, Cimbora D, Drappa J, Mealy MA, She D, Cree BAC. Mult Scler Relat Disord. 2022 Disability Outcomes in the N-MOmentum Trial of Inebilizumab in Neuromyelitis Optica Spectrum Disorder. Marignier R, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk D, Fujihara K, Paul F, Cutter GR, Green AJ, Aktas O, Hartung HP, Lublin FD, Williams IM, Drappa J, She D, Cimbora D, Rees W, Smith M, Ratchford JN, Katz E, Cree BAC; N-MOmentum Study Investigators. Neurol Neuroimmunol Neuroinflamm. 2021 Sensitivity analysis of the primary endpoint from the N-Momentum study of inebilizumab in NMOSD. Cree BA, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk D, Fujihara K, Paul F, Cutter GR, Marignier R, Green AJ, Aktas O, Hartung HP, Williams IM, Drappa J, She D, Cimbora D, Rees W, Ratchford JN, Katz E. Mult Scler. 2021
Study type and design	Multicenter, double-blind, randomized controlled phase 2/3 trial with an open-label extension period. Enrolled patients were randomly allocated 3:1 via a central interactive voice system and interactive web response system, and a permuted block randomization scheme. The participants, investigators, sponsor, adjudication committee, and staff involved in patient treatment and clinical evaluation, including the person who assigned EDSS scores, were masked to the treatment

Trial name: N-MOmentum trial (10)	NCT number: NCT02200770
	received. Cross-over from the placebo to the inebilizumab arm was allowed at the start of the open-label period.
Sample size (n)	230 in total, 213 (93%) were AQP4+
Main inclusion criteria	- Adults (18 years and older) with an EDSS score ≤7.5 (≤8.0 if the Investigator and medical monitor agreed that the subject was reasonably able to participate in the study) - A diagnosis of NMOSD at the time of screening - A documented history of ≥1 NMOSD attacks that required rescue therapy in the previous year or ≥2 NMOSD attacks that required rescue therapy in the preceding 2 years - Subjects who had a relapse immediately prior to screening must have had at least 4 weeks in which their relapse symptoms were stable or improving prior to randomization - AQP4+ and AQP4- subjects (as tested and verified by the central laboratory only) were enrolled in the study, with the aim to reflect the ratio of AQP4+ to AQP4- represented in the literature (approximately 80% subjects who are AQP4- and 20% of subjects who are AQP4-). Subjects who are AQP4-, where the diagnosis of NMOSD is less clear, needed to meet the clinical criteria for NMOSD according to Wingerchuk et al 2006 (93) by the determination of independent Eligibility Committee.
Main exclusion criteria	- Use of background immunosuppressive therapy while on trial was not permitted - Concomitant or previous therapy (rituximab or any experimental B-cell depleting agent within last 6 months, alemtuzumab, total lymphoid irradiation, bone marrow transplant, T-cell vaccination therapy, intravenous immune globulin, natalizumab, cyclosporin, methotrexate, mitoxantrone, cyclophosphamide, tocilizumab, eculizumab) - Drug or food allergy - Autoimmune diseases - Any concomitant disease that required steroid treatment within the 6 months prior to screening - AQP4- subjects with a brain MRI abnormality that met the diagnostic criteria for multiple sclerosis - Receipt of any of the following: a) Any live or attenuated vaccine within 3 weeks prior to Day 1 (administration of killed vaccines was acceptable, the Sponsor recommended that Investigators ensure all subjects were up to date on required vaccinations prior to study entry); b) Bacillus of Calmette and Guérin vaccine within one year of signing the ICF; c) Blood transfusion within 4 weeks prior to signing the ICF. - Immunodeficiency status - Clinically significant serious active or chronic viral or bacterial infection - Malignancy risk - General safety

Trial name: N-MOmentum trial (10)	NCT number: NCT02200770
	- Laboratory criteria - B cell counts - D19+ B-cell counts below the lower limit of normal according to the central laboratory
Intervention	During RCP, a fixed dose of 300 mg inebilizumab was given on Day 1 and Day 15. During the OLP, a fixed dose of 300 mg inebilizumab administered on OLP Day 1 and then every 26 weeks was predicted to fully deplete peripheral blood B cells to undetectable levels and maintain B-cell suppression for the dose interval of the OLP. To maintain masking, a placebo dose was given on Day 15. In total, 175 participants were randomized to the intervention arm. Of these patients, 169 completed the RCP.
Comparator(s)	A placebo-comparator treatment arm was chosen for the conduct of this study and, like the intervention, was given on Day 1 and Day 15. For those randomly allocated to placebo, 300 mg inebilizumab was administered on open-label Days 1 and 15 to establish B-cell depletion. Subsequently, all participants in the OLP received 300 mg inebilizumab every 26 weeks to maintain B-cell depletion. In total, 56 participants were assigned to the placebo arm of the trial and 54 completed RCP.
Follow-up time	The RCP was 197 days. The OLP duration was a minimum of 2 years for all participants. The OLP ended and the study is completed. The total inebilizumab exposure was 730.36 person-years.
Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was time to NMOSD attack, assessed by an adjudication committee based on pre-defined criteria. Secondary endpoints were worsening in EDSS score, annualized attack rate, health-related quality of life as assessed by SF-36, and safety. **Other endpoints:** Change from baseline in low-contrast visual acuity binocular score, cumulative total active MRI lesions, number of NMO/NMOSD-related in-patient hospitalizations, Modified Rankin Scale, Pain Numeric Rating Scale and healthcare resource utilization were also secondary endpoints in the study, but results are not included in this application.
Method of analysis	All efficacy analyses were intention-to-treat analyses. Safety endpoints were assessed in the as-treated population.

Trial name: N-MOmentum trial (10)	NCT number: NCT02200770
	The primary endpoint was assessed by survival analysis, with Cox proportional hazards regression with placebo as the reference group, and treatment and serotype as explanatory factors. For worsening in EDSS score from baseline at last visit, the odds ratio was calculated using a logistic regression model with treatment, serostatus, and baseline score as explanatory variables and non-responder imputation (with missing values considered as worsening). Treatment-emergent adverse events were summarized by system organ class and preferred terms using Medical Dictionary for Regulatory Activities version 21.0 and were reported descriptively. More detailed information is available in the supplementary data of the trial publication (46).
Subgroup analyses	The following prespecified subgroup analyses of the primary and key secondary endpoints were all conducted in the ITT population: - sex (male vs female) - baseline EDSS score (<5 vs ≥5) - number of prior NMOSD relapses (<2 vs ≥2) - disease duration category (<5 years vs ≥5 years) - AQP4-IgG serostatus (positive vs negative) as determined at screening The nominal p-value and 95% CIs of treatment effect were provided for each subgroup analysis. Forest plots were generated to visually present the consistency of treatment effect in different subgroups with overall treatment effect. Regarding the safety analysis, analysis by AQP4-IgG serostatus (positive versus negative) was planned. In addition, TEAEs (by system organ class and preferred term) during the RCP were summarized by sex (male versus female). Per the FDA's request, subgroup analyses by race, site region, and previous treatment for the prevention of NMO attacks on the primary endpoint and overall summary of TEAEs during the RCP were performed.
Other relevant information	This trial was conducted in the USA, Australia, Bulgaria, Canada, Colombia, Czechia, Estonia, Germany, Hong Kong, Hungary, Israel, Japan, Republic of Korea, Mexico, Republic of Moldova, New Zealand, Peru, Poland, Russian Federation, Serbia, South Africa, Spain, Taiwan, Thailand, and Turkey.

Abbreviations: AQP4-IgG: Aquaporin 4-Immunoglobulin G; EDSS: Expanded disability status scale; FDA: U.S. Food and Drug Administration; ITT: Intention-to-treat; MRI: Magnetic resonance imaging; NMOSD: Neuromyelitis optica spectrum disorder; OLP: Open-label extension period; RCP: Randomized controlled period; TEAE: treatment-emergent adverse event

Table 54 Main characteristic of studies included – Kim et al.

Trial name: Kim et al. 2011 (11)	NCT number: NA
Objective	To evaluate the efficacy and safety of repeated rituximab treatment based on the assessment of peripheral circulating memory B cells over 24 months in patients with relapsing NMO
Publications – title, author, journal, year	Kim SH, Kim W, Li XF, Jung IJ, Kim HJ. Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. Arch Neurol. 2011;68(11):1412-20.
Study type and design	Prospective open-label study
Sample size (n)	30 in total, 21 (70%) were AQP4+
Main inclusion criteria	Patients were included if they had relapsing NMO according to the 2006 diagnostic criteria or NMO spectrum disorders and had at least 1 relapse which had occurred during the 12 months prior to starting rituximab treatment.
Main exclusion criteria	Patients were excluded if they had cardiac dysfunction, hepatic or renal disease, a history of cancer and chronic infection, or abnormal complete blood cell count, were pregnant, and if of reproductive age who were not willing to use contraception.
Intervention	Rituximab Induction dose: 1) 375 mg/m^2 once per week for 4 weeks or 2) 1000 mg twice a week with a 2-week interval Maintenance dose: 375 mg/m^2 whenever frequency of memory B cells was 0.05% or more in peripheral blood mononuclear cells
Comparator(s)	Not applicable, as no comparator arm was included
Follow-up time	Patients were followed over 24 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Annual relapse rate and changes in EDSS score. **Other endpoints:** AQP4 antibody levels and safety.
Method of analysis	The annualized relapse rate, EDSS score, and serum anti–AQP4-antibody levels were compared before and after 24 months of

Trial name: Kim et al. 2011 (11)	NCT number: NA
	rituximab treatment using the Wilcoxon signed-rank test and the 2-sided sign test.
Subgroup analyses	Not applicable
Other relevant information	The trial was conducted in Korea.

Abbreviations: AQP4: Aquaporin 4; ARR: Annualized relapse rate; EDSS: Expanded disability status scale; NMO: Neuromyelitis optica

Appendix B. Efficacy results per study

Results per study

Table 55 Results per N-MOmentum trial

Results of N-MOmentum trial (NCT02200770)											
				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**		
Median time (days) to adjudication committee-determined NMOSD attack	Inebilizumab	161	N/A[a]	NR	NR	NR	HR: 0.227	0.121-0.423	<0.0001	Subjects in the ITT AQP4+ population with new or worsening symptom(s) of a potential AC-determined NMOSD attack were evaluated at an Assessment Visit at the clinical site by the Investigator as soon as possible, but within 72 hours of the report.	CSR (10)
	Placebo	52	N/A[a]								CSR (10)
Worsening from baseline in EDSS score	Inebilizumab	161	26 (14.9%)	NR	NR	NR	OR: 0.352	0.1704-0.7252	0.0047	Worsening in EDSS score from baseline to last visit of the RCP (ITT AQP4+ population). Trained and certified neurologists (EDSS raters), who were independent of study	CSR (10)
	Placebo	52	19 (33.9%)								CSR (10)

										Investigators and subjects, conducted the assessments.	
Annualized attack rate	Inebilizumab	60	0.09	N/A	N/A	N/A	N/A	N/A	N/A	A descriptive summary of AC-determined NMOSD attack rate over various lengths of exposure to inebilizumab was chosen as an endpoint to provide an approximate rate of attacks on an annualized basis.	CSR (10)
	Placebo	N/A	N/A[b]								N/A

Abbreviations: AC: Adjudication committee; AQP4+: Aquaporin 4-Immunoglobulin G-seropositive; CSR: Clinical study report; EDSS: Expanded disability status scale; HR: Hazard ratio; ITT: Intention-to-treat; N/A: Not applicable; NMOSD: Neuromyelitis optica spectrum disorder; NR: Not reported

[a]The median was never reached in the trial.

[b]An annualized attack rate for the placebo treatment period cannot be calculated because subjects are removed from the placebo-controlled portion of the study after an AC-adjudicated attack

Table 56 Results per Kim et al.

Results of Kim et al. (NA)											
				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**		
ARR – total population	Rituximab	30	0.292 (NR)	NR	NR	NR	NR	NR	NR	ARR was compared before and after 24 months of rituximab treatment using the Wilcoxon signed-rank test and the 2-sided sign test.	Kim et al. (11)

ARR – AQP4+ population	Rituximab	21	0.339 (NR)	NR	NR	NR	NR	NR	NR	ARR was compared before and after 24 months of rituximab treatment using the Wilcoxon signed-rank test and the 2-sided sign test.	Kim et al. (11)
Change in EDSS score – total population	Rituximab	30	3.0 (NR)	NR	NR	NR	NR	NR	NR	EDSS score was compared before and after 24 months of rituximab treatment using the Wilcoxon signed-rank test and the 2-sided sign test.	Kim et al. (11)

Abbreviations: ARR: Annualized relapse rate; EDSS: Expanded Disability Status Scale; NR: Not reported

Appendix C. Comparative analysis of efficacy

Table 57 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Background

A SLR was conducted in 2023 and updated in 2024 to identify relevant clinical studies evaluating inebilizumab and rituximab in patients with NMOSD (see Appendix H). This identified eight studies evaluating rituximab (11, 78, 94-99). Of these studies evaluating rituximab, no studies in an exclusively AQP4+ population were deemed appropriate to include in a feasibility analysis, including RIN-01, a RCT evaluating rituximab (78).

When evaluating all rituximab studies regardless of AQP4 status, two studies were identified (11, 97). The study by Kim et al. was found to report detailed information on individual patients and their attacks, which could be extracted and digitized to allow an estimation of baseline and on-treatment annual attack rate (AAR), time to first attack, and disease duration specifically for the AQP4+ subpopulation of interest (11). In contrast, the study reported by Nikoo et al., (which had a higher proportion of patients on rituximab with AQP4- NMOSD [57%]) did not report sufficient individual patients details to isolate/analyse the AQP4+population (97). Patients with AQP4-NMOSD have different disease characteristics, prognosis and response to therapy than those with AQP4+ NMOSD (100-102) and consequently, it was not appropriate to evaluate studies that do not report data separately for AQP4+ and AQP4- patients. Therefore, only Kim et al. was included in this analysis to allow us to specifically evaluate patients with AQP4+ NMOSD (11).

This analysis used data from the AQP4+ population in Kim et al. (11) and the AQP4+ population from N-MOmentum (10) and evaluated time to first attack as the primary analysis.

Scope for Analysis and study eligibility

The scope of this analysis in form of the PICO is presented below in Table 58

Table 58 Scope of the ITC

	Description
Population	Adults (aged > 18 years) with AQP4+ NMOSD
Intervention	Inebilizumab
Comparator	Rituximab
Outcome	Unanchored MAIC analysis: time to first attack and AAR for inebilizumab vs rituximab
Study design	RCP, RCP and OLE (all patients treated with inebilizumab)
Other	Identification of prognostic variables and effect modifiers using N-MOmentum IPD Generation of clinically credible matching scenarios for the MAIC analyses Application of a 'base case' matching scenario to the inebilizumab global CEM

Abbreviations: AAR, annualized attack rate; AQP4+, aquaporin seropositive; CEM, cost-effectiveness model; IPD, individual patient data; MAIC, matching adjusted indirect treatment comparison; OLE, open label extension; RCP, randomized controlled period; RCT, randomized controlled trial.

by the SLR that evaluated inebilizumab monotherapy and rituximab in patients with AQP4+ NMOSD were included in the feasibility assessment.

Studies were included in the feasibility assessment if they:

- Meet the SLR eligibility criteria presented in Table 59
    - Randomized controlled trials (RCTs) or single-arm trials evaluated against clinical SLR eligibility criteria
- Are full publications
    - It was assumed these would not contain sufficient detail to fully evaluate the study
- Report rituximab treatment arm separately to other treatments
- Report data from only AQP4+ patient populations only

No studies were identified that reported data from AQP4+ only patient populations and met the eligibility criteria for inclusion in the MAIC. Studies reporting a mixed AQP4 population were then evaluated, resulting in the identification of two studies (11, 97). Table 2 and figure 1 in Kim et al. 2011 can be extracted and digitized to allow recreation of sufficient IPD to allow separation of the AQP4+ subpopulation, allowing estimation of the baseline AAR and disease duration for this AQP4+ subpopulation. However, Nikoo et al. only reported outcomes for the combined population, and it was not possible to isolate the AQP4+ population and consequently this study was not included in the ITC.

Table 59 Eligibility criteria for includsion in MAIC

Criteria	Assessment
Reports potential prognostic/predictive variables[a]	Reports the following baseline variables: • Age • Duration of NMOSD • Ancestry/ethnicity • AQP4 status • Prior treatment • AAR/attack history • EDSS score
Eligibility criteria similar to N-MOmentum[b]	Inclusion criteria • Adults aged ≥ 18 years • Documented history of either ≥ 1 attack requiring rescue therapy in the prior year or ≥ 2 attacks requiring rescue therapy in the previous 2 years • EDSS score of ≤ 7.5 at randomization (patients with an EDSS score of 8.0 were potentially eligible if the patient was assessed by the investigator and medical monitor as able to participate) • AQP4-IgG-seropositive NMOSD with documented history of either ≥ 1 attack requiring rescue therapy in the prior year or ≥ 2 attacks requiring rescue therapy in the previous 2 years • Subjects who had a relapse immediately prior to screening must have had ≥4 weeks in which their relapse symptoms were stable or improving prior to randomization Exclusion criteria • Receipt of any of the following within 3 months prior to randomization: natalizumab (Tysabri®); cyclosporin; methotrexate; mitoxantrone; cyclophosphamide; tocilizumab; eculizumab • Any concomitant disease other than NMOSD that required treatment with oral or intravenous steroids at doses > 20 mg/day for > 21 days

Concomitant treatment similar to N-MOmentum	• All patients also received oral corticosteroids (prednisone 20 mg/day or equivalent) between Days 1 and 14, tapered to Day 21, to minimize the risk of an attack immediately following the first inebilizumab treatment • No other use of immunosuppressants was permitted during the RCP		
Baseline disease activity similar to N-MOmentum OLE AQP4+ population		**Inebilizumab**	**Placebo**
	Baseline attack rate, AAR	1.682 (ITT: 1.726)	1.456 (ITT: 1.567)
	EDSS score Mean (SD)	3.8 (1.8)	4.4 (1.6)
	Median (range)	3.5 (0 to 8.0)	4.0 (1.0 to 8.0)
	≥ 4 prior attacks	47%	45%
	Time from first attack to first IP administration, years Mean (SD)	5.19 (5.90)	5.19 (5.69)
	Median (range)	3.01 (0.2, 27.4)	(0.1, 26.3)
	Disease duration (from diagnosis), years Mean (SD)	2.5 (3.4)	2.9 (3.5)
	Median (range)	1.1 (0.1 to 22.2)	1.7 (0.2 to 16.9)
	Median age (range), years	43 (18 to 73)	43 (18 to 74)
Rituximab dosing similar between rituximab studies	Similar between rituximab studies – if studies report very different doses, possibility to group by dose (rituximab not approved for use in NMOSD so unclear what the dose is typically used in clinical practice)		

Endpoint definitions similar to N-MOmentum	Time to first NMOSD attack
	• Time (in days) to the onset of an NMOSD attack, defined as the presence of a new symptom(s) or worsening of an existing symptom(s) related to NMOSD upon neurological evaluation that met at least one of 18 protocol-defined criteria (see CSR)
	  ○ Confirmed by an independent AC
	  ○ Based off investigator-assessment alone
	• If hazard ratio for time to first attack vs placebo is directly reported, this will be used
	• If no placebo arm available, hazard rate or KM plot of sufficient quality to digitize will be required (note: this is an essential requirement to be able to conduct an unanchored MAIC)
	  ○ If individual-level time to first attack data is otherwise reported or can be digitized from figures, will be estimated
	  ○ Time to NMOSD attack may be back-calculated from studies reporting annualized attack rate, if these studies report point estimates and variance indicators
	• Timeframe: up to 5 years		

Annualized Attack Rate

- Annualized attack rate is defined in N-MOmentum as total number of attacks divided by total person years at risk
  - If AAR is directly reported, this will be used
  - If IPD is reported in tabular format, AAR will be calculated
  - If a KM plot of risk of NMOSD attack is published, AAR can be approximated based on digitized time to event data
  - If other plots or tables describing the number of experienced attacks duration of observation are present, these will be digitized for estimation of baseline and on-treatment AAR
- Timeframe: up to 5 years

Percentage of patients with worsening in EDSS score or similar

- A participant was considered to have a worsening in overall EDSS score of at least 2 if baseline EDSS score was 0, or at least 1 point if baseline EDSS score is 1 to 5, or at least 0.5 point if baseline EDSS score is 5.5 or more
- Timeframe: up to 5 years

Abbreviations: AAR, annualized attack rate; AQP4+, aquaporin seropositive; matching adjusted indirect treatment comparison; NMOSD, Neuromyelitis optica spectrum disorder; OLE, open label extension; RCT, randomized controlled trial.

aThese have been identified from the literature reported in the Global Value Dossier. The indirect treatment comparison will identify prognostic and effect modifiers using N-MOmentum data and based on the variables identified, the studies that meet the inclusion criteria might change slightly.

bIf studies report a stricter eligibility criteria than N-MOmentum, it might be feasible to conduct an indirect treatment comparison with a subset of the N-MOmentum inebilizumab population that reflects this stricter eligibility criteria.

Comparison of N-MOmentum and Kim et al.

As part of the feasibility analysis, Kim et al. (11) was compared with N-MOmentum (10) (Table 60). The eligibility criteria of both studies were broadly comparable, with both studies requiring patients requiring patients to have had an attack prior to study initiation. Kim et al. required patients to have at least one attack in the year before the study initiation and N-MOmentum required patients to have had at least one attack in the year before study initiation or two attacks in the two years before. Both studies also only included adults; this was an inclusion criterion in N-MOmentum and in Kim et al., no patients aged under 18 years old were enrolled. Neither study allowed concomitant therapy use, with Kim et al. stating that all patients were required to have discontinued immunosuppressive therapy before starting rituximab treatment. This meant that both studies could isolate the outcomes for the treatment of interest. Baseline disease activity in both studies were broadly similar between the two studies, with a mean baseline AAR of 1.69 in N-MOmentum and 2.4 in Kim et al, and a mean EDSS score of 3.9 in N-MOmentum and mean EDSS score of 4.4 in Kim et al. The duration of Kim et al. was up to 24 months, which was longer than the randomized controlled period from N-MOmentum (6 months) but was similar to the open-label period of N-MOmentum (≥ 24 months).

We can therefore assume that, aside from the provided treatment, the study populations are largely similar and are appropriate to compare in an indirect treatment comparison.

Table 60 Comparison of N-MOmentum and Kim et al.

	N-MOmentum	Kim et al. (11)

Participants, N	230 (174 inebilizumab vs 56 placebo)	30
AQP4+ population	213 (93%; 161 inebilizumab vs 52 placebo)	21 (70%)
Key Inclusion Criteria	Adults (≥ 18 years) ≥ 1 relapse in previous year or 2 relapses in previous 2 years EDSS ≤ 7.5 (patients with EDSS of 8.0 may be eligible if the investigator and medical monitor assess that the patient is reasonable able to participate in the study)	≥ 1 relapse had occurred during the 12 months before the start of rituximab therapy
Key Exclusion Criteria	Active hepatitis B, C and/or TB ALT/AST >2X ULN	Taking any other immunosuppressant or other type of medication (including herbal drugs) without permission of the physician during the study
Baseline variables reported	IPD available	Age, age at onset, duration of NMOSD, prior treatment, AAR, EDSS score, sex
Baseline disease activity	AAR, mean (SD): 1.69 (1.51) EDSS, mean: : 3.9 (range: 0–8.0)	AAR, mean: 2.4 EDSS, mean 4.4 (range: 1.0–8.5)
Study Design	Randomized, placebo-controlled, monotherapy	Single-arm (prospective open-label study)
Duration of RCP	28 Weeks (6 months)	Efficacy 24 months after intervention
Duration of OLE	≥ 104 Weeks (24 months)	
Dose Regimen	300 mg IV at Weeks 0 and 2, then Q26W	Induction: 375 mg/m^2 (approx. 500g) infused once per week for 4 weeks (n = 16) or 1000 mg infused twice, with a 2-week interval (n = 14). Maintenance: Whenever the frequency of memory B cells was 0.05% or more in PBMCs, patients were given 1 additional infusion of rituximab (375 mg/m^2).
Primary Endpoint	Time to first AC-determined attack (IPD available)	AAR
Components of Attack Definition for Primary Endpoint	New or worsening NMOSD symptoms Visual exam changes Change in EDSS MRI lesions	Attacks were defined as objective worsening of new neurological symptoms lasting at least 24 hours that increased the EDSS score by at least half a step (0.5) or increased 1 point on 2 different functional systems of the EDSS or 2 points on 1 of the functional systems (excluding bowel/bladder or cerebral functional systems)

ARR, annualized relapse rate; AC, adjudication committee; EDSS, Expanded Disability Status Scale; IPD, individual patient data; MRI, magnetic resonance imaging; NMOSD, Neuromyelitis optica spectrum disorder; OLE, open label extension; SC, subcutaneous; SD, standard deviation.

Kim et al. was a prospective, single-center, open-label study that evaluated the efficacy and safety of rituximab in patients with NMOSD over up to 2 years. In total, 30 patients were enrolled, of whom 21 had AQP4+ NMOSD (Table 61). The mean age of the AQP4+ population was 41 years and 95% were female. Over the follow-up period, the AQP4+ patients experienced a total of 11 attacks and had an AAR of 0.339. In total, 15 patients (71%) were attack-free during rituximab treatment.

When looking at the overall population (AQP4+ and AQP4-), the mean age was 38 years and 90% were female. Over the mean follow-up of 1.60 years, the combined population experienced 14 attacks and the AAR was 0.292. In total, 21 patients (70%) were attack free during rituximab treatment. During treatment, the EDSS score improved in 24 patients and stabilized in 1 patient, with a decrease in mean EDSS score from 4.4 at baseline to 3.0 at the end of treatment. No patients died during the study.

Table 61 Baseline characteristics from Kim et al.

Characteristic	Total population (N = 30)	AQP4+ population (n = 21)
Age (years), mean (SD)	38.4 (10.5)	41.0 (10.3)
EDSS score, mean (SD)	4.4 (2.1)	4.8 (2.0)
Female, n (%)	27 (90.0)	20 (95.2)
No. of attacks in 1 y prior to study entry, mean (SD)	2.9 (1.3)	1.3 (1.2)
AAR, mean (SD)	2.4 (1.74)	1.9 (1.3)
Time since first attack (years), mean (SD)	4.8 (4.2)	5.2 (4.2)

AAR, annualized attack rate; AQP4+, aquaporin-4 positive; EDSS, Expanded Disability Status Scale; SD, standard deviation.

Objective

The objective of this indirect treatment comparison (ITC) was to compare the efficacy of inebilizumab and rituximab in patients with AQP4+ NMOSD using matching-adjusted indirect comparison (MAIC). The ITC evaluated the clinical outcome 'time to first attack' between inebilizumab and rituximab in patients with NMOSD.

Methods

Overview and recommendations

MAIC is a method for population-adjusted indirect comparison designed to adjust for differences in distribution of effect modifiers between different trials and thereby allow estimation of the relative treatment effects between two interventions that have not been directly compared in a randomized controlled trial. Briefly, propensity score weighting is used over known or expected effect modifiers to such that individual level patient data (IPD) from one clinical trial are adjusted to match corresponding reported aggregate statistics for another study population. Applying these weights, the outcome statistics of interest should, under ideal circumstances, reflect the counterfactual situation in which the trial population for which IPD is available were the same as the comparator trial population for the variables in question. Thus, MAIC may be used to reduce bias in naïve comparison stemming from differences in the distribution of effect modifiers.

MAIC can be conducted in two notably different situations: anchored comparison, where the included trials include common study arms, e.g. placebo, that can be used for indirect relative treatment effect estimation. This relies on an assumption of transitivity through the common study arm, as in comparison using Bucher's approach or network meta-analysis.

The other MAIC approach, unanchored comparison, is used in the absence of a common study arm between trials, or where the common study arms are deemed incomparable for other reasons, such as differences in the study populations, differences in the standard of care, etc. Importantly, in unanchored MAIC, adjustment should be done both for unevenness in prognostic factors *and* effect modifiers, while anchored MAIC relies on adjustment to effect modifiers only; unevenness in the distribution of prognostic factors should be accounted for through comparison of the common study arms.

MAIC was the ITC technique chosen because it minimizes the potential selection bias caused by differences in patient characteristics between studies by assigning weights to the population with available IPD so that it matches the aggregated baseline data of the population with which it will be compared *(Phillippo et al, 2016; Signorovitch et al, 2010)*. To increase the robustness of the analysis, studies evaluating rituximab were evaluated both separately and as a total rituximab population, which was combined using meta-analysis.

In the primary comparison between inebilizumab, as measured in the N-MOmentum trial (10), and rituximab, as measured in the trial described by Kim et al. (11), an unanchored MAIC was used for time to event, specified as first NMOSD attack following active treatment in the AQP4+ NMOSD subgroup of patients, measured as hazard ratio (HR). In the primary analysis, the RCP of the N-MOmentum trial was used for comparison. AAR was not compared for the RCP, as the period of observation was too short for meaningful comparison.

In line with current best practice, guidelines produced by the UK National Institute for health and Care Excellence (NICE) were followed, which can be found in NICE technical support document 18: "methods for population-adjusted indirect comparisons in submissions to NICE" (104).

As part of the feasibility analysis, Kim et al. (11) was compared with N-MOmentum (10) (Table 60). The eligibility criteria of both studies were broadly comparable, with both studies requiring patients requiring patients to have had an attack prior to study initiation. Kim et al. required patients to have at least one attack in the year before the study initiation and N-MOmentum required patients to have had at least one attack in the year before study initiation or two attacks in the two years before. Both studies also only included adults; this was an inclusion criterion in N-MOmentum and in Kim et al., no patients aged under 18 years old were enrolled. Neither study allowed concomitant therapy use, with Kim et al. stating that all patients were required to have discontinued immunosuppressive therapy before starting rituximab treatment. This meant that both studies could isolate the outcomes for the treatment of interest. Baseline disease activity in both studies were broadly similar between the two studies, with a mean baseline AAR of 1.69 in N-MOmentum and 2.4 in Kim et al, and a mean EDSS score of 3.9 in N-MOmentum and mean EDSS score of 4.4 in Kim et al. The duration of Kim et al. was up to 24 months, which was longer than the randomized controlled period from N-MOmentum (up to 197 days) but was similar to the open-label period of N-MOmentum (≥ 24 months) (77). There was no major difference in the study design.

It can therefore be assumed that, aside from the provided treatment, the studies are largely similar and are appropriate to compare in an indirect treatment comparison.

Prognostic factors and effect modifiers

MAIC relies on appropriate weighting for relevant baseline characteristics. In this study, we utilize unanchored MAIC, which is applicable when there is any overlapping placebo arm. Consequently, our adjustment focuses on both likely prognostic factors (PF) and effect modifiers (EM).

The subset of variables available as potential candidates for weighting will by necessity be limited by what is reported in terms of aggregate data for Kim et al. (11).

Selection of relevant prognostic factors and effect modifiers will be informed by and analysis of IPD from the population from the N-MOmentum trial (10).

IPD from the N-MOmentum trial (10) was employed to investigate candidate variables as PF and/or EM. As the outcome of interest is time to event (specifically, time to investigator-determined NMOSD attack, we use Cox proportional hazards (Cox PH) models to investigate covariate functioning as PH and/or EM. For each candidate covariate, a separate model was fitted, with

independent variables being treatment allocation (active treatment vs placebo), the covariate of interest, and their interaction. A supplementary analysis was also conducted using the negative binomial model to ensure all relevant variables were captured. Comparatively low p values for baseline score × treatment allocation interaction coefficients would indicate potential EM, while comparatively low baseline score *p* values would indicate likely PF.

The pool of variables to investigate is limited to variables available both in the N-MOmentum IPD (10) and reported in Kim et al. (11).

Propensity score weighting (MAIC)

Propensity score weighting was done in R using an approach mathematically equivalent (though theoretically more precise and efficient) to the one recommended by NICE DSU.

First, a centred matrix was generated, with one column per covariate and statistic to be included in the matching.

If v_o is a vector of observed values for a covariate, and *tv* is the corresponding aggregate target value, mean values (and proportions) were populated by $v_c = v_o - t_v$. For standard deviations with target SD t_{sd}, the corresponding column was populated with $vc = (v_o - t_v)^2 - t_{sd}^2$

If the centred matrix is denoted *X,* and the vector of coefficients equal to the number of columns of *X* is β_X, we used the Broyden–Fletcher–Goldfarb–Shanno algorithm to minimize the following expression:

$$\sum e^{X \times \beta_x}$$

With the fitted coefficients β_x , a vector w of individual propensity score weights can be calculated as $e^{X \times \beta_X}$, and the effective sample size as $\frac{(\sum w)^2}{\sum (w^2)}$.

Outcome and statistics modelling

All analyses used investigator-assessed attacks and not AC-assessed attacks because Kim et al. did not report using an AC to evaluate attacks and therefore are more likely to have evaluated investigator-assessed attacks. Secondly, AC-determined attacks are not available for the OLP period of N-MOmentum. Finally, investigator assessed attacks are more likely to reflect clinical practice. The primary analysis used data from the RCP of N-MOmentum. However, the RCP is considerably shorter than the duration of the Kim et al. study, whereas the N-MOmentum OLP period and Kim et al. are more similar in length; therefore, additional analyses used data from the OLP as well as the RCP and included all individuals treated with inebilizumab.

The outcome of interest was HR for time to first NMOSD attack, as estimated using weighted Cox PH models. As the linear scale of a Cox PH regression model is the natural logarithm of the HR, calculations for comparisons were made on this scale.

As Kim et al. reports on individual patients in such a way as to allow digitization of IPD, the comparison was done directly on time to first NMOSD attack for the relevant active treatment group from the N-MOmentum trial (RCP active treatment arm or combined RCP and OLP, including all individuals exposed to inebilizumab), and the patients treated with rituximab in Kim et al.

If *t* denotes treatment allocation, the model took on the form:

$$TTAA = \beta_t t$$

All included patients from Kim et al. were assigned a weight of 1, while for the N-MOmentum IPD, separate models were fitted for each propensity score weighting scenario, applying their respective participant-level weights in the Cox PH model.

Conducted analysis

The following analyses were conducted:

1) Time to first investigator-determined NMOSD attack in the AQP4+ populations from N-MOmentum and Kim et al., with N-MOmentum data from the RCP. This was done by employing digitized IPD from the trial described by Kim et al., combined with reweighted IPD from the N-MOmentum trial in a single Cox PH model.
2) 2) Time to first investigator-determined NMOSD attack in the AQP4+ populations from N-MOmentum and Kim et al., with N-MOmentum data from all individuals exposed to inebilizumab (combined RCP and OLE).

Digitization of data from Kim et al.

Information on the individual patients included in the trial is reported in Figure 2 and Table 2 in the study by Kim et al (11). Data from Kim et al. Table 2 were extracted using the tesseract and magick packages in R, followed by manual comparison of extracted data to the published table. Data from the plot of attacks from Kim et al. Figure 2 were digitized using the DigitizeIt software. These data on attacks in Figure 2 were sufficient to estimate individual level disease duration from first attack, baseline ARR from first attack, ARR following treatment, and time to first attack in the rituximab population in Kim et al (11).

The reported disease duration for N-MOmentum and Kim et al. (11) are both shorter than the time from first attack, suggesting that these are based on diagnosis time rather than first attack time. It is not possible to recreate individual time of diagnosis from the figure and table in Kim et al. Instead, in this analysis, duration will be defined as the time from first attack to initiation of active treatment, as this can be identified from the figure in Kim et al. and the N-MOmentum IPD.

In accordance with the description in the paper, 21 patients were identified as AQP4+ defined as having an optical density of > 0.170 for anti-AQP4-Ab. These were used in the comparison to the AQP4+ subpopulation from N-MOmentum.

Sensitivity analyses and base case selection

Once the relevant PFs and EMs were identified, several baseline characteristic matching combinations were used. The most clinically plausible combination, ideally based on clinician input as well as having a suitable effective sample size (ESS) and distribution of weights, formed the base case.

Results

Empirical investigation of potential PFs and Ems

Table 62 Table 63 show the empirical investigation of potential PFs and EMs using Cox PH model and negative binomial model, respectively. The dependent variable in Table 62 is the time to first investigator determined attack or censoring. The dependent variable in Table 63the number of observed attacks, offset by the natural logarithm of observational time in years. That data set was too small to result in significant p values and therefore additional judgement was required to determine PFs and EMs. As sex was a binary variable in this analysis (male or female), sex was evaluated by using the variable ‘male’. The analysis using the negative binomial model found that males have a smaller benefit from treatment than females.

Table 62 Potential PFs and EMs using Cox PH model

Covariate	PF			EM			Interpretation**
	Estimate	SE	p	Estimate	SE	p	
Age	[redacted]						
Log duration							
Log AAR							
White							
Asian							
Black							
Male							
EDSS							
AQP4+							
Previous azathioprine							

*Owing to the small number of AQP4- patients, the analysis did not provide meaningful results (near asymptotic).

AQP4+, aquaporin-4 positive; ARR, annualised relapse rate; EDSS, expanded disability status scale; EM, effect modifier; PF, prognostic factor; SE, standard error.

** The interpretation is based on relative p values, and thresholds are set as likely < 0.1 < possible < 0.3 < unlikely

[redacted]Table 63 Potential PFs and EMs using negative binomial model

Covariate	PF			EM			Interpretation**
	Estimate	SE	p	Estimate	SE	p	
Age	[redacted]						
Log duration							
Log AAR							

White	[redacted]						
Asian	[redacted]						
Black	[redacted]						
Male	[redacted]						
EDSS	[redacted]						
AQP4+	[redacted]						
Previous azathioprine	[redacted]						

*Owing to the small number of AQP4- patients, the analysis did not provide meaningful results (near asymptotic).

AQP4+, aquaporin-4 positive; ARR, annualised relapse rate; EDSS, expanded disability status scale; EM, effect modifier; PF, prognostic factor; SE, standard error.

** The interpretation is based on relative p values, and thresholds are set as likely < 0.1 < possible < 0.3 < unlikely

[redacted]Variables for matching of baseline characteristics

Table 64 shows the variables considered in the matching.

Table 64 Variables considered for matching

Covariate	AQP4+ subgroup (N = 21)		All patients (N = 30)	
	Mean	(SD)	Mean	(SD)
Age	[redacted]			
Onset age	[redacted]			
Log duration	[redacted]			
Expanded Disability Status Scale score	[redacted]			
Log AAR prior to treatment	[redacted]			
	[redacted]			
Proportion male	[redacted]			

Proportion with AQP4+ NMOSD	[redacted]	[redacted]	[redacted]	[redacted]
Proportion received prior azathioprine	[redacted]	[redacted]	[redacted]	[redacted]

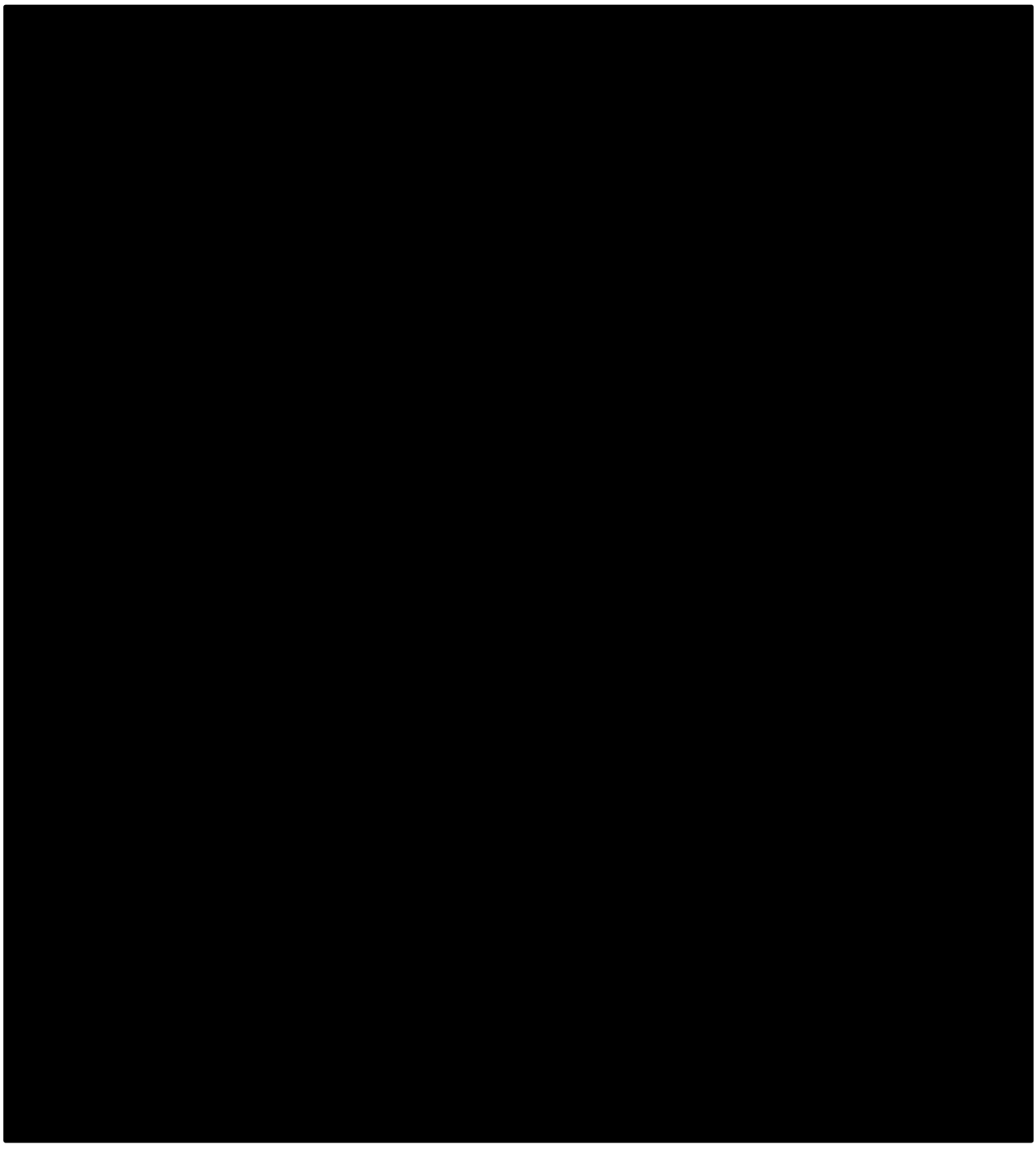
AQP4+, aquaporin-4 positive; ARR, annualised relapse rate; EDSS, expanded disability status scale.

Scenarios and base case selection

Table 65 reports the scenarios with combinations of covariates that were tested. Based on a combination of feedback from clinical experts, judgments of resulting ESS and distribution of resulting weights, the scenario with age, ARR, and sex (self-reporting as being male or female) was selected as the base case scenario. The inclusion of (log) duration was found to result in very skewed distribution of weights, particularly when combined with age and ARR and was therefore not included in the base case analysis.

Based on ESS, distribution of weights, and clinical expertise, the scenario adjusting for age, logARR, and sex (proportion male/female) was selected as the base case scenario.

Table 65 Matching scenarios

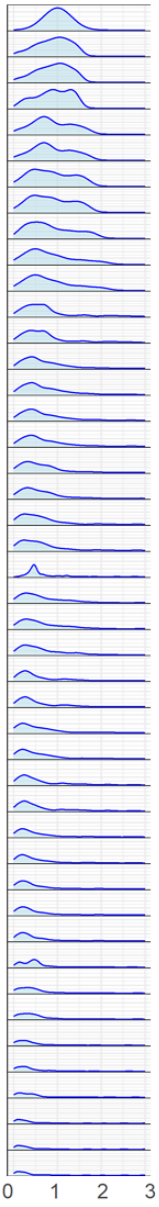


Note: AQP4+ included as a covariate in analyses of combined AQP4+ and AQP4- populations. ARR refers to ARR at baseline. AQP4+, aquaporin-4 positive; ARR, annualised relapse rate; Aza, azathioprine; EDSS, expanded disability status scale.

Following covariate matching, the ESS and weight distribution for the following populations are shown in Table 66 and Table 67.Based on ESS, distribution of weights, and clinical expertise, the scenario adjusting for age, log(ARR), and sex (proportion male/female) was selected as the base case scenario.

Table 66 Covariate matching, ESS, and weight distribution for AQP4+ population (RCP only)

	AQP4+	Age		log(ARR)		Male	Onset age		Asian	EDSS		log(Duration)		zathioprir	eSS		Weight density
Scenario	%	Mean	SD	Mean	SD	%	Mean	SD	%	Mean	SD	Mean	SD	%	n	%	
naive	**100.0%**	**43.2**	**11.6**	**0.19**	**0.84**	**6.2%**	**41.2**	**12.1**	**23.0%**	**3.84**	**1.78**	**1.02**	**1.23**	**39.1%**	**161.0**	**100.0%**	
Age, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.5%	39.3	10.9	23.4%	3.76	1.73	0.77	1.14	36.6%	136.7	84.9%	
Age, Sex, log(ARR)	**100.0%**	**41.0**	**10.3**	**0.44**	**0.67**	**4.8%**	**39.3**	**10.9**	**23.5%**	**3.76**	**1.72**	**0.77**	**1.14**	**36.6%**	**136.6**	**84.9%**	
Age, log(Duration)	100.0%	41.0	10.3	0.08	0.72	5.6%	38.8	10.9	23.1%	3.86	1.73	1.28	0.96	42.6%	135.3	84.0%	
Age, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	4.5%	39.5	10.8	19.0%	3.74	1.71	0.74	1.15	23.8%	127.5	79.2%	
Age, Sex, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	4.8%	39.5	10.8	19.1%	3.74	1.71	0.74	1.15	23.8%	127.4	79.1%	
Onset age, log(ARR)	100.0%	37.8	10.4	0.44	0.67	4.6%	35.8	10.9	22.2%	3.69	1.72	0.84	1.12	38.0%	123.3	76.6%	
Onset age, Sex, log(ARR)	100.0%	37.8	10.4	0.44	0.67	4.8%	35.8	10.9	22.2%	3.69	1.72	0.84	1.12	38.0%	123.3	76.6%	
Age, log(Duration), Azathioprine	100.0%	41.0	10.3	0.09	0.73	5.2%	39.0	10.8	17.0%	3.86	1.71	1.28	0.96	23.8%	117.5	73.0%	
Onset age, Sex, log(ARR), Azathioprine	100.0%	37.6	10.6	0.44	0.67	4.8%	35.8	10.9	17.4%	3.68	1.70	0.81	1.12	23.8%	112.7	70.0%	
Onset age, log(ARR), Azathioprine	100.0%	37.6	10.6	0.44	0.67	4.8%	35.8	10.9	17.4%	3.68	1.70	0.81	1.12	23.8%	112.7	70.0%	
Age, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	3.4%	39.1	10.9	19.7%	4.83	2.03	1.00	1.18	39.1%	85.6	53.2%	
Age, Sex, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	39.1	10.9	20.0%	4.83	2.03	1.00	1.19	38.9%	85.3	53.0%	
log(Duration), log(ARR)	100.0%	41.1	11.3	0.44	0.67	5.5%	38.4	11.8	26.9%	4.22	1.71	1.28	0.96	41.8%	81.7	50.8%	
log(Duration), Sex, log(ARR)	100.0%	41.1	11.3	0.44	0.67	4.8%	38.3	11.8	26.7%	4.23	1.71	1.28	0.96	41.7%	81.6	50.7%	
Age, log(Duration), log(ARR)	100.0%	41.0	10.3	0.44	0.67	5.2%	38.3	10.9	27.1%	4.20	1.71	1.28	0.96	41.3%	80.9	50.2%	
Age, log(Duration), Sex, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	38.3	10.9	27.0%	4.20	1.71	1.28	0.96	41.2%	80.7	50.1%	
Age, EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	3.6%	39.3	10.8	15.5%	4.83	2.03	0.97	1.19	23.8%	77.1	47.9%	
Age, Sex, EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	4.8%	39.3	10.8	15.9%	4.83	2.03	0.97	1.20	23.8%	77.0	47.8%	
Onset age, EDSS, log(ARR)	100.0%	38.2	10.4	0.44	0.67	3.3%	35.8	10.9	19.4%	4.83	2.03	1.08	1.17	41.1%	75.6	46.9%	
Onset age, Sex, EDSS, log(ARR)	100.0%	38.2	10.4	0.44	0.67	4.8%	35.8	10.9	19.9%	4.83	2.03	1.08	1.17	40.9%	75.2	46.7%	
Age, Onset age	100.0%	41.0	10.3	0.01	0.82	5.6%	35.8	10.9	30.3%	3.98	1.87	1.54	1.19	50.5%	73.7	45.8%	
log(Duration), log(ARR), Azathioprine	100.0%	41.1	11.1	0.44	0.67	4.9%	38.5	11.4	21.6%	4.22	1.70	1.28	0.96	23.8%	68.9	42.8%	
log(Duration), Sex, log(ARR), Azathioprine	100.0%	41.1	11.1	0.44	0.67	4.8%	38.5	11.4	21.5%	4.22	1.70	1.28	0.96	23.8%	68.9	42.8%	
Age, log(Duration), Sex, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	4.8%	38.5	10.7	21.7%	4.20	1.70	1.28	0.96	23.8%	68.6	42.6%	
log(Duration), Sex, EDSS, log(ARR)	100.0%	42.1	11.6	0.44	0.67	4.8%	39.6	12.0	22.7%	4.83	2.03	1.28	0.96	42.5%	68.2	42.4%	
log(Duration), EDSS, log(ARR)	100.0%	42.1	11.6	0.44	0.67	3.9%	39.5	12.0	22.6%	4.83	2.03	1.28	0.96	42.4%	68.2	42.4%	
Onset age, EDSS, log(ARR), Azathioprine	100.0%	38.0	10.6	0.44	0.67	3.5%	35.8	10.9	14.8%	4.83	2.03	1.05	1.17	23.8%	67.5	42.0%	
Onset age, Sex, EDSS, log(ARR), Azathioprine	100.0%	38.0	10.6	0.44	0.67	4.8%	35.8	10.9	15.3%	4.83	2.03	1.05	1.18	23.8%	67.5	41.9%	
Age, log(Duration), EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	3.6%	38.6	10.8	21.8%	4.83	2.03	1.28	0.96	42.2%	66.2	41.1%	
Age, log(Duration), Sex, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	38.6	10.8	22.0%	4.83	2.03	1.28	0.96	42.3%	66.2	41.1%	
log(Duration), EDSS, log(ARR), Azathioprine	100.0%	42.3	11.3	0.44	0.67	3.5%	39.9	11.7	18.1%	4.83	2.03	1.28	0.96	23.8%	58.0	36.0%	
log(Duration), Sex, EDSS, log(ARR), Azathioprine	100.0%	42.3	11.4	0.44	0.67	4.8%	39.9	11.7	18.5%	4.83	2.03	1.28	0.96	23.8%	58.0	36.0%	
Age, log(Duration), EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	3.5%	38.7	10.6	17.1%	4.83	2.03	1.28	0.96	23.8%	57.8	35.9%	
Age, log(Duration), EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	3.5%	38.7	10.6	17.1%	4.83	2.03	1.28	0.96	23.8%	57.8	35.9%	
Age, log(Duration), Sex, EDSS, log(ARR), Azathiopr	100.0%	41.0	10.3	0.44	0.67	4.8%	38.7	10.6	17.6%	4.83	2.03	1.28	0.96	23.8%	57.7	35.9%	
Age, Onset age, Azathioprine	100.0%	41.0	10.3	0.06	0.83	4.2%	35.8	10.9	25.8%	3.81	1.83	1.51	1.23	23.8%	54.1	33.6%	
Age, Onset age, Sex, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	35.8	10.9	40.0%	4.20	1.79	1.40	1.16	44.6%	39.7	24.6%	
Age, Onset age, log(ARR)	100.0%	41.1	10.3	0.44	0.68	3.6%	35.8	10.9	39.8%	4.20	1.79	1.40	1.17	44.5%	39.5	24.5%	
Age, Onset age, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	2.6%	35.8	10.9	36.4%	4.83	2.03	1.48	1.16	44.6%	33.3	20.7%	
Age, Onset age, Sex, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	35.8	10.9	36.8%	4.83	2.03	1.49	1.16	44.7%	33.3	20.7%	
Age, Onset age, Sex, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	4.8%	35.8	10.9	36.3%	4.16	1.80	1.41	1.19	23.8%	31.2	19.4%	
Age, Onset age, EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	2.4%	35.8	10.9	32.4%	4.83	2.03	1.50	1.18	23.8%	27.0	16.8%	
Age, Onset age, EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	2.4%	35.8	10.9	32.4%	4.83	2.03	1.50	1.18	23.8%	27.0	16.8%	
Age, Onset age, Sex, EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.68	4.8%	35.8	10.9	33.3%	4.83	2.03	1.50	1.18	23.8%	27.0	16.8%	

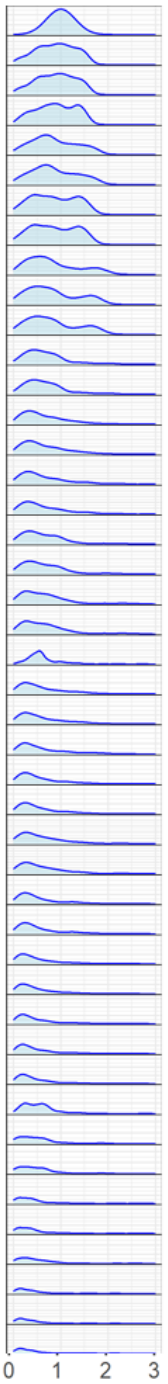


Note: ARR refers to ARR at baseline.

AQP4+, aquaporin-4 positive; ARR, annualised attack rate; Aza, azathioprine; EDSS, expanded disability status scale.

Table 67 Covariate matching, ESS, and weight distribution for AQP4+ population (RCP and OLE)

	AQP4+	Age		log(ARR)		Male	Onset age		Asian	EDSS		log(Duration)		zathioprin	eSS		Weight density
Scenario	%	Mean	SD	Mean	SD	%	Mean	SD	%	Mean	SD	Mean	SD	%	n	%	
naïve	100.0%	43.0	12.3	0.17	0.81	6.1%	40.9	12.8	21.1%	3.96	1.75	1.05	1.22	39.4%	213.0	100.0%	
Age, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.9%	39.2	11.0	22.3%	3.88	1.73	0.77	1.17	36.7%	176.1	82.7%	
Age, Sex, log(ARR)	**100.0%**	**41.0**	**10.3**	**0.44**	**0.67**	**4.8%**	**39.2**	**11.0**	**22.3%**	**3.88**	**1.73**	**0.77**	**1.17**	**36.7%**	**176.1**	**82.7%**	
Age, log(Duration)	100.0%	41.0	10.3	0.08	0.70	5.9%	38.7	11.0	21.9%	3.99	1.75	1.28	0.96	43.8%	175.4	82.3%	
Age, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	5.0%	39.3	11.0	18.9%	3.87	1.71	0.74	1.19	23.8%	164.3	77.1%	
Age, Sex, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	4.8%	39.3	11.0	18.9%	3.87	1.71	0.74	1.19	23.8%	164.3	77.1%	
Onsetage, log(ARR)	100.0%	37.9	10.4	0.44	0.67	4.8%	35.8	10.9	22.2%	3.82	1.73	0.84	1.14	37.9%	164.6	77.3%	
Onsetage, Sex, log(ARR)	100.0%	37.9	10.4	0.44	0.67	4.8%	35.8	10.9	22.2%	3.82	1.73	0.84	1.14	37.9%	164.6	77.3%	
Age, log(Duration), Azathioprine	100.0%	41.0	10.3	0.10	0.70	5.6%	38.9	10.9	16.9%	4.02	1.72	1.28	0.96	23.8%	149.7	70.3%	
Onsetage, Sex, log(ARR), Azathioprine	100.0%	37.8	10.4	0.44	0.67	4.8%	35.8	10.9	18.8%	3.82	1.71	0.82	1.16	23.8%	151.3	71.0%	
Onsetage, log(ARR), Azathioprine	100.0%	37.8	10.4	0.44	0.67	5.0%	35.8	10.9	18.9%	3.82	1.71	0.82	1.16	23.8%	151.3	71.0%	
Age, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	39.0	11.0	18.8%	4.83	2.03	0.96	1.18	38.5%	118.6	55.7%	
Age, Sex, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	39.0	11.0	18.8%	4.83	2.03	0.96	1.18	38.5%	118.6	55.7%	
log(Duration), log(ARR)	100.0%	40.3	11.8	0.44	0.67	5.4%	37.4	12.3	26.0%	4.33	1.70	1.28	0.96	42.0%	109.4	51.3%	
log(Duration), Sex, log(ARR)	100.0%	40.2	11.7	0.44	0.67	4.8%	37.4	12.3	25.9%	4.33	1.71	1.28	0.96	42.0%	109.3	51.3%	
Age, log(Duration), log(ARR)	100.0%	41.0	10.3	0.44	0.67	5.5%	38.2	11.0	26.3%	4.33	1.72	1.28	0.96	41.5%	103.8	48.7%	
Age, log(Duration), Sex, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	38.2	11.0	26.2%	4.34	1.72	1.28	0.96	41.5%	103.6	48.6%	
Age, EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	5.5%	39.2	10.9	15.7%	4.83	2.03	0.94	1.20	23.8%	107.1	50.3%	
Age, Sex, EDSS, log(ARR), Azathioprine	100.0%	41.0	10.3	0.44	0.67	4.8%	39.1	11.0	15.6%	4.83	2.03	0.94	1.20	23.8%	106.8	50.1%	
Onsetage, EDSS, log(ARR)	100.0%	38.2	10.4	0.44	0.67	4.6%	35.8	10.9	19.0%	4.83	2.03	1.04	1.15	39.5%	107.4	50.4%	
Onsetage, Sex, EDSS, log(ARR)	100.0%	38.2	10.4	0.44	0.67	4.8%	35.8	10.9	19.0%	4.83	2.03	1.04	1.15	39.5%	107.4	50.4%	
Age, Onset age	100.0%	41.0	10.3	0.02	0.81	5.9%	35.8	10.9	28.8%	4.06	1.80	1.54	1.19	46.0%	101.4	47.6%	
log(Duration), log(ARR), Azathioprine	100.0%	40.2	11.6	0.44	0.67	5.1%	37.5	12.1	21.6%	4.34	1.68	1.28	0.96	23.8%	93.2	43.7%	
log(Duration), Sex, log(ARR), Azathioprin	100.0%	40.2	11.6	0.44	0.67	4.8%	37.5	12.1	21.5%	4.34	1.69	1.28	0.96	23.8%	93.1	43.7%	
Age, log(Duration), Sex, log(ARR), Azathi	100.0%	41.0	10.3	0.44	0.67	4.8%	38.4	10.9	21.3%	4.34	1.70	1.28	0.96	23.8%	88.7	41.7%	
log(Duration), Sex, EDSS, log(ARR)	100.0%	40.9	11.8	0.44	0.67	4.8%	38.2	12.2	22.3%	4.83	2.03	1.28	0.96	42.8%	93.0	43.6%	
log(Duration), EDSS, log(ARR)	100.0%	40.9	11.8	0.44	0.67	4.6%	38.2	12.2	22.3%	4.83	2.03	1.28	0.96	42.8%	92.9	43.6%	
Onsetage, EDSS, log(ARR), Azathioprine	100.0%	38.0	10.4	0.44	0.67	5.3%	35.8	10.9	16.1%	4.83	2.03	1.02	1.17	23.8%	93.8	44.0%	
Onsetage, Sex, EDSS, log(ARR), Azathio	100.0%	38.0	10.4	0.44	0.67	4.8%	35.8	10.9	16.0%	4.83	2.03	1.02	1.17	23.8%	93.5	43.9%	
Age, log(Duration), EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	38.4	10.8	22.3%	4.83	2.03	1.28	0.96	42.6%	88.9	41.7%	
Age, log(Duration), Sex, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.8%	38.4	10.8	22.3%	4.83	2.03	1.28	0.96	42.6%	88.9	41.7%	
log(Duration), EDSS, log(ARR), Azathiopr	100.0%	40.8	11.7	0.44	0.67	4.7%	38.3	12.1	18.2%	4.83	2.03	1.28	0.96	23.8%	78.3	36.7%	
log(Duration), Sex, EDSS, log(ARR), Azath	100.0%	40.8	11.7	0.44	0.67	4.8%	38.3	12.1	18.2%	4.83	2.03	1.28	0.96	23.8%	78.3	36.8%	
Age, log(Duration), EDSS, log(ARR), Azat	100.0%	41.0	10.3	0.44	0.67	4.9%	38.5	10.7	17.9%	4.83	2.03	1.28	0.96	23.8%	76.4	35.9%	
Age, log(Duration), EDSS, log(ARR), Azat	100.0%	41.0	10.3	0.44	0.67	4.9%	38.5	10.7	17.9%	4.83	2.03	1.28	0.96	23.8%	76.4	35.9%	
Age, log(Duration), Sex, EDSS, log(ARR),	100.0%	41.0	10.3	0.44	0.67	4.8%	38.5	10.7	17.9%	4.83	2.03	1.28	0.96	23.8%	76.4	35.9%	
Age, Onset age, Azathioprine	100.0%	41.0	10.3	0.08	0.83	5.2%	35.8	10.9	25.5%	3.99	1.75	1.49	1.26	23.8%	83.6	39.2%	
Age, Onset age, Sex, log(ARR)	100.0%	41.1	10.3	0.44	0.68	4.8%	35.8	10.9	36.2%	4.25	1.74	1.35	1.22	39.1%	56.5	26.5%	
Age, Onset age, log(ARR)	100.0%	41.0	10.3	0.44	0.67	4.0%	35.8	10.9	36.1%	4.25	1.74	1.35	1.22	39.0%	56.4	26.5%	
Age, Onset age, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.68	3.4%	35.8	10.9	33.6%	4.83	2.03	1.42	1.19	41.1%	48.4	22.7%	
Age, Onset age, Sex, EDSS, log(ARR)	100.0%	41.0	10.3	0.44	0.68	4.8%	35.8	10.9	33.7%	4.83	2.03	1.43	1.19	41.0%	48.4	22.7%	
Age, Onset age, Sex, log(ARR), Azathiopr	100.0%	41.0	10.3	0.44	0.67	4.8%	35.8	10.9	33.0%	4.23	1.72	1.34	1.25	23.8%	47.7	22.4%	
Age, Onset age, EDSS, log(ARR), Azathio	100.0%	41.0	10.3	0.44	0.67	3.5%	35.8	10.9	30.9%	4.83	2.03	1.44	1.22	23.8%	40.5	19.0%	
Age, Onset age, EDSS, log(ARR), Azathio	100.0%	41.0	10.3	0.44	0.67	3.5%	35.8	10.9	30.9%	4.83	2.03	1.44	1.22	23.8%	40.5	19.0%	
Age, Onset age, Sex, EDSS, log(ARR), Aza	100.0%	41.0	10.3	0.44	0.67	4.8%	35.8	10.9	31.1%	4.83	2.03	1.44	1.22	23.8%	40.6	19.0%	



Note: ARR refers to ARR at baseline.

AQP4+, aquaporin-4 positive; ARR, annualised attack rate; Aza, azathioprine; EDSS, expanded disability status scale.

Primary analysis results

HR for time to first NMOSD attack in the AQP4+ population (RCP only)

The adjustment for age, ARR, and sex (proportion male) had limited impact on the estimated HR, lowering it from [redacted] in the unmatched scenario to [redacted] after matching. The distribution of weights and ESS were both found to be acceptable (Table 68 and XXXXXXX13).

Table 68 HR for time to first NMOSD attack in the AQP4+ population (RCP only)

[redacted]

HR for time to first NMOSD attack in the AQP4+ population (combined RCP and OLE)

The adjustment for age, ARR, and sex (proportion male) had limited impact on the estimated HR, lowering it from [redacted] in the unmatched scenario to [redacted] after matching. The distribution of weights and ESS were both found to be acceptable (see XXXXXX69 and XXXXXXX14).

[redacted]

Discussion

In the primary analysis in AQP4+ patients using the RCP, inebilizumab demonstrated a reduction in the HR for time to first NMOSD attack versus rituximab both before (HR [redacted]) and after weighting (HR [redacted]). These results were confirmed by the analysis in AQP4+ patients using all inebilizumab treated patients in the combined RCP and OLE (before weighting HR [redacted]; after weighting HR [redacted]). Owing to the limitations of the number of patients, the results did not reach statistical significance; however, they do give an indication of the potential benefit that inebilizumab provides compared with rituximab in an AQP4+ population, which should be evaluated in confirmatory studies.

The method for identifying relevant studies evaluating inebilizumab and rituximab was robust as the studies were identified by SLR, the preferred means of evidence identification. However, there was a lack of large, high quality studies evaluating rituximab and the study identified is small in size with few AQP4+ patients (n = 21). The small sample size of the rituximab study is a major limitation of the analysis, and the results should therefore be interpreted with caution and be viewed as hypothesis-generating.

Other limitations of the analysis are that it is:

- Limited to variables/outcomes reported by Kim et al., which has published a restricted set
- The definition of attack is not identical in both studies
- The MAIC cannot control for unobserved covariates
- There may be differences in the schedule and frequency of assessments between the N-MOmentum and the rituximab trials; this is not reported in rituximab trials so the extent of the difference and the impact it may have on the results is unclear

RIN-01, a randomized controlled trial in patients with AQP4+ NMOSD, was not considered eligible for inclusion for several reasons. Firstly, patients in RIN-01 received combination therapy with rituximab and concomitant steroids throughout the study. Steroids given for the first 8 weeks from visit 2 (randomization) to visit 4 and while they were gradually reduced after visit 4, this was only by 10% every visit and the dose was only reduced to 2 mg per day to the end of study (78). In contrast in N-MOmentum, patients only received concomitant steroids tapered to day 21. This was to ensure that the trial was specifically evaluating the efficacy of inebilizumab. The use of steroids in RIN-01 may explain why the rate of attacks was so low in the study, including in the placebo arm, in which the annualized attack rate decreased from 0.7 before the study to 0.32 during the study period. The authors of RIN-01 agree that the use of oral steroids could have accounted for the reduction in attacks in both study group. Consequently, this is highly likely to impact the outcomes and means an analysis cannot be conducted comparing RIN-01/RIN-02 with N-MOmentum.

Secondly, in RIN-01, an attack was defined as any symptoms reported by the patient or any new signs that were consistent with CNS lesions and were associated with objective abnormalities (new lesions on T2 or Gd-enhanced images on magnetic resonance imaging [MRI]) (78). In N-MOmentum, attacks that had severe clinical symptoms did not require verification with MRI, only attacks with less severe clinical symptoms required the presence of lesions shown on MRI. There is a risk that not all clinical attacks present with lesions that can be easily identified on MRI, especially those on the optic nerve if a specific MRI of the optic nerve was conducted. Furthermore, if the MRI was conducted too close to the attack, they may not yet have been able to see the corresponding lesion. This means that some attacks in RIN-01 may have been missed.

Finally, RIN-01 was conducted in an exclusively Asian population and there is evidence that these patients have slightly different characteristics to patients from other ethnicities that may preclude comparison with a non-Asian population. NMOSD is more common in Asian patients, with a 4-fold higher prevalence of NMOSD in East Asian populations compared with Caucasian populations

(105); however, these patients may have a less severe phenotype and in a post hoc analysis of N-MOmentum, Asian patients were found to have a lower baseline AAR (106).

Appendix D. Extrapolation

D.1 Extrapolation of time to first adjudicated attack

The primary model transition is the patient's risk of experiencing an NMOSD attack. Parametric modelling was used to determine the risk of an NMOSD attack from the start of the model, which is a common approach when the analysis needs to be extended beyond the clinical trial observation period. The analysis assumed that the parametric model was applied for the full duration of the economic model, including the time of the analysis where clinical trial data are available. This allows for a more robust representation of uncertainty from the trial results and a formal exploration via probabilistic sensitivity analysis (PSA).

D.1.1 Data input

In the model base case, time to first NMOSD attack for patients treated with inebilizumab was extrapolated to patients' lifetime from the time-to-event data from N-MOmentum including data from the open-label period. As an alternative option, the model includes the possibility to extrapolate time to first NMOSD attack for patients treated with inebilizumab based on data from the randomized controlled period only.

Similarly, time to first NMOSD attack for patients receiving placebo as comparator was separately extrapolated to patients' lifetime applying time-to-event data from N-MOmentum. Since patients in the placebo arm of the N-MOmentum trial would cross over to receiving inebilizumab in the open-label period, the extrapolations for placebo are always based on data from the randomized, controlled period.

Similar data were not available for the primary comparator of the model, i.e. rituximab. For patients receiving this treatment in the model, the estimated relative risk from the MAIC (hazard ratio for the time to first attack of rituximab compared with inebilizumab) was applied to obtain comparable estimates on the risk of experiencing an NMOSD attack.

D.1.2 Model

From the N-MOmentum trial, time-to-first-attack Kaplan Meier data were available for the open label period in the intervention arm, and the blinded-treatment period for both the intervention and placebo arms. All parametric functions fit to the data show a decreasing risk of first attack per unit time, except for the exponential function where the risk of the first attack per unit time is constant.

When assessing the suitability of survival models, Latimer (107) discusses several criteria, including the good model fit to the observed data, visual inspection and the clinical plausibility of the extrapolated portion. Models that meet only one of these criteria are likely to be inappropriate.

When the exponential function is applied within the Markov model, a constant rate of attack is applied per cycle (month) for the duration of the model time horizon. This is clinically plausible assuming that the rate of subsequent attacks is equal to that of the first. Otherwise applying the time-to-first-attack functions without a constant attack rate is not a rational decision, given that the model is designed to also capture subsequent attacks experienced by the model cohort over a lifetime horizon.

Not only is the application of the other functions beside the exponential one for time-to-first-attack curves irrational, but it is also clinically implausible. These functions apply a decreasing attack rate over time – because they model time to first attack. KOLs have reported that a decreasing rate of subsequent attacks over time is not clinically realistic and that it rather remains constant. The literature also indicates a constant attack rate (79, 80).

Furthermore, as a follow-up to Latimer, Bagust and Beale (108) argue that an exponential distribution should be the default parametric function for long-term projection and that clear evidence should be required before other options are considered. Other curves may be applied when evidence indicate accelerating event rates, as with background mortality risk with age over the long term for example, or other circumstances where deviations from exponential functions are likely. None of these assumptions are valid for inebilizumab treatment in NMOSD.

Considering 1) that applying non-exponential functions of time-to-first attack to model subsequent attacks is not rational, 2) a reasonable visual fit of the exponential function, 3) the validation of modelled survival compared to the Danish NMOSD population (see Appendix Q), 4) the assumed clinical plausibility of a constant risk of attack (an assumption only fulfilled by the exponential function), and (5) all other functions likely overestimate the effect of inebilizumab, the exponential function is considered to be the only appropriate option for this analysis.

The model was fitted using the ‘flexsurv’ package in R (data analysis and statistics software). The distribution rate parameter was estimated for both the blinded trial period only and the open-label period for patients randomized into treatment with inebilizumab and for the blinded trial period only for patients receiving placebo.

Extrapolations with additional parametric functions are included in the following sections for comparison.

D.1.3 Proportional hazards

A test of the proportional hazard assumption was not included.

D.1.4 Evaluation of statistical fit (AIC and BIC)

Goodness of fit was assessed using Akaike information criterion (AIC) and the Bayesian information criterion (BIC) statistical criteria. In general, when comparing across parametric models fit to the same data, the lowest AIC and BIC values represent the best-fit parametric model. The magnitude of the absolute AIC and BIC values is not

meaningful because these values depend on the set of data. However, relative differences are meaningful.

The lifetime extrapolation rate parameter and goodness-of-fit estimates for the OLP for inebilizumab are depicted in Table 70.

Table 70 Rate parameter and goodness-of-fit estimates for extrapolation of time to first NMOSD attack for inebilizumab, including open-label period

	Exponential	Weibull	Gompertz	Log-normal	Log-logistic	Gamma	Generalised gamma
Rate	[redacted]		[redacted]			[redacted]	
Shape		[redacted]	[redacted]		[redacted]	[redacted]	
Scale		[redacted]			[redacted]	[redacted]	
Meanlog				[redacted]			
Sdlog				[redacted]			
Mu							[redacted]
Sigma							[redacted]
Q							[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

Source: Post hoc analysis of data from N-MOmentum trial

D.1.5 Evaluation of visual fit

XXXXXXX15 shows the inebilizumab Kaplan-Meier (KM) curve from the N-MOmentum trial plotted over the extrapolated survival curve.

XXXXXXX16 depicts the inebilizumab Kaplan-Meier curve from the N-MOmentum trial (including only the RCP) plotted over the extrapolated survival curve.
XXXXXXX17 presents the placebo Kaplan-Meier curve from the N-MOmentum trial plotted over the extrapolated survival curve.

It should be noted that AC-determined NMOSD attack data from N-MOmentum was used to set up the inebilizumab parametric TTAA extrapolation curve (XXXXXXX15), whilst investigator attack data was used to generate the comparative HR for inebilizumab vs rituximab (Appendix C) that was subsequently applied to this curve to generate the rituximab long-term extrapolation (XXXXXXX5). This decision was dictated by the following parameters:

- N-MOmentum AC-determined attack data were initially chosen in the model set up to provide a robust data source for parametric extrapolation of life-time efficacy; however, no adjudicated attack data are available for the rituximab trial used in the MAIC (11), thus a comparison of inebilizumab to rituximab using AC determined attack data was not possible
- Nevertheless, the high concordance rate between adjudicated and investigator attack reporting in N-MOmentum strongly suggests that using investigator attack data would generate a similar parametric extrapolation curve

[redacted] presents all extrapolated curves for inebilizumab.

From the below curves it can be observed that the exponential function is likely to be the most conservative function to use and the only one reflective of a constant risk of attack.

[redacted]

[redacted]

D.1.6 Evaluation of hazard functions

The selection of hazard functions was based on the visual fit presented in D.1.5 and clinical plausibility. Statistical fit is presented in Table 70.

D.1.7 Validation and discussion of extrapolated curve

The extrapolation for time to first attack has been presented and discussed with clinical experts. The non-exponential functions apply a decreasing risk of attack over time – because they model time to first attack. KOLs have reported that a decreasing risk of subsequent attacks over time is not clinically realistic and that it rather remains constant. The literature also indicates a constant risk of attack (79, 80). The recently published end-of-study results from the N-MOmentum trial even indicate a decreasing trend over time (77). Therefore this assumption may be considered conservative.

D.1.8 Adjustment of background mortality

Background mortality was not explicitly accounted for in the analysis of time to NMOSD attack, because no patients died during the N-MOmentum trial. This is instead incorporated as a separate input in the health economic model.

D.1.9 Adjustment for treatment switching/cross-over

A cross-over analysis was not performed.

Waning effect

No waning effect is assumed for any product included in the model.

Cure point

No cure point was considered in the model as NMOSD is a chronic disease.

D.2 Extrapolation of [effect measure 2]

Not applicable as no additional effect measures were extrapolated.

Appendix E. Serious adverse events

Table 71 Serious adverse events for AQP4+ patients (RCP and OLP)

Adverse events	Inebilizumab (N=161), RCP	Placebo (N=52), RCP	Inebilizumab/Inebilizumab (N = 154), OLP	Placebo/Inebilizumab (N = 47), OLP
Adrenal insufficiency	1 (0.6%)	0	0	0
Arthralgia	1 (0.6%)	0	1 (0.6%)	0
Atypical pneumonia	1 (0.6%)	0	0	0
Burns, third degree	1 (0.6%)	0	0	0
Cholangitis acute	1 (0.6%)	0	0	0
Cholecystitis acute	1 (0.6%)	0	0	1 (2.1%)
Diarrhea	1 (0.6%)	0	0	0
Hepatic function abnormal	1 (0.6%)	0	0	0
Ileus	1 (0.6%)	0	0	0

Adverse events	Inebilizumab (N=161), RCP	Placebo (N=52), RCP	Inebilizumab/Inebilizumab (N = 154), OLP	Placebo/Inebilizumab (N = 47), OLP
Myelitis transverse	1 (0.6%)	0	0	0
NMOSD	1 (0.6%)	0	1 (0.6%)	1 (2.1%)
Shock	1 (0.6%)	0	0	0
Breast cancer female	0	1 (1.9%)	0	0
Chest pain	0	1 (1.9%)	0	0
Dyspnea	0	1 (1.9%)	0	0
Hypoglycemia	0	1 (1.9%)	0	0
Meningitis viral	0	1 (1.9%)	0	0
Migraine	0	1 (1.9%)	0	0
Pneumonia	0	1 (1.9%)	3 (1.9%)	1 (2.1%)
Septic shock	0	1 (1.9%)	0	0

Adverse events	Inebilizumab (N=161), RCP	Placebo (N=52), RCP	Inebilizumab/Inebilizumab (N = 154), OLP	Placebo/Inebilizumab (N = 47), OLP
Visual acuity reduced	0	1 (1.9%)	0	0
Urinary tract infection	0	0	2 (1.3%)	6 (12.8%)
Abdominal pain upper	0	0	1 (0.6%)	0
Appendicitis	0	0	1 (0.6%)	0
Back pain	0	0	1 (0.6%)	0
Bacteremia	0	0	1 (0.6%)	0
COVID-19	0	0	1 (0.6%)	0
COVID-19 pneumonia	0	0	1 (0.6%)	0
Calculus bladder	0	0	1 (0.6%)	0
Cataract	0	0	1 (0.6%)	0
Cellulitis	0	0	1 (0.6%)	0

Adverse events	Inebilizumab (N=161), RCP	Placebo (N=52), RCP	Inebilizumab/Inebilizumab (N = 154), OLP	Placebo/Inebilizumab (N = 47), OLP
Central nervous system infection	0	0	1 (0.6%)	0
Chorioretinitis	0	0	1 (0.6%)	0
Colon cancer	0	0	1 (0.6%)	0
Connective tissue disorder	0	0	1 (0.6%)	0
Deafness	0	0	1 (0.6%)	0
Foot fracture	0	0	1 (0.6%)	0
Herpes zoster	0	0	1 (0.6%)	0
Influenza	0	0	1 (0.6%)	0
Infusion-related reaction	0	0	1 (0.6%)	0
International normalized ratio increased	0	0	1 (0.6%)	0
Neutropenia	0	0	1 (0.6%)	0

Adverse events	Inebilizumab (N=161), RCP	Placebo (N=52), RCP	Inebilizumab/Inebilizumab (N = 154), OLP	Placebo/Inebilizumab (N = 47), OLP
Peripheral nerve palsy	0	0	1 (0.6%)	0
Pneumonia bacterial	0	0	1 (0.6%)	0
Post cardiac arrest syndrome	0	0	1 (0.6%)	0
Progressive multifocal leukoencephalopathy	0	0	1 (0.6%)	0
Pyrexia	0	0	1 (0.6%)	0
Renal abscess	0	0	1 (0.6%)	0
Respiratory failure	0	0	1 (0.6%)	0
Steroid withdrawal syndrome	0	0	1 (0.6%)	0
Umbilical hernia	0	0	1 (0.6%)	0
Weight decreased	0	0	1 (0.6%)	0

Adverse events	Inebilizumab (N=161), RCP	Placebo (N=52), RCP	Inebilizumab/Inebilizumab (N = 154), OLP	Placebo/Inebilizumab (N = 47), OLP
Wrist fracture	0	0	1 (0.6%)	0
Acute kidney injury	0	0	0	2 (4.3%)
Acute respiratory failure	0	0	0	1 (2.1%)
Appendicitis perforated	0	0	0	1 (2.1%)
Bronchiolitis	0	0	0	1 (2.1%)
Constipation	0	0	0	1 (2.1%)
Delirium	0	0	0	1 (2.1%)
Depression	0	0	0	1 (2.1%)
Drug reaction with eosinophilia and systemic symptoms	0	0	0	1 (2.1%)
Gastroesophageal reflux disease	0	0	0	1 (2.1%)

Adverse events	Inebilizumab (N=161), RCP	Placebo (N=52), RCP	Inebilizumab/Inebilizumab (N = 154), OLP	Placebo/Inebilizumab (N = 47), OLP
Hepatic failure	0	0	0	1 (2.1%)
Hepatitis A	0	0	0	1 (2.1%)
Hyponatremia	0	0	0	1 (2.1%)
Lumbosacral radiculopathy	0	0	0	1 (2.1%)
Neuroborreliosis	0	0	0	1 (2.1%)
Osteomyelitis	0	0	0	1 (2.1%)
Pickwickian syndrome	0	0	0	1 (2.1%)
Pyelonephritis chronic	0	0	0	1 (2.1%)
Rhabdomyolysis	0	0	0	1 (2.1%)
Seizure	0	0	0	1 (2.1%)
Sinusitis	0	0	0	1 (2.1%)

Adverse events	Inebilizumab (N=161), RCP	Placebo (N=52), RCP	Inebilizumab/Inebilizumab (N = 154), OLP	Placebo/Inebilizumab (N = 47), OLP
Sleep apnea syndrome	0	0	0	1 (2.1%)
Subcutaneous abscess	0	0	0	1 (2.1%)
Uremic encephalopathy	0	0	0	1 (2.1%)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Note: Numbers are presented as n (%)
Abbreviations: RCP: Randomized controlled period, OLP: Open-label period

Appendix F. Health-related quality of life

Not applicable.

Appendix G. Probabilistic sensitivity analyses

Please see below a list of parameters included in the sensitivity analyses.

Table 72. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Treatment-related parameters				
Time to first NMOSD attack	Cholesky decomposition based on variance-covariance matrix			Multivariate normal
Hazard ratio - rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation – inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation – rituximab	[redacted]	[redacted]	[redacted]	[redacted]
HSUV				
First attack EDSS 0-1 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]
First attack EDSS 1-2 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]
First attack EDSS 2-3 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]
First attack EDSS 3-4 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]
First attack EDSS 4-5 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]
First attack EDSS 5-6 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]
First attack EDSS 6-7 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]

First attack EDSS 7-8 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]
First attack EDSS 8-9 - Blinded treatment	[redacted]	[redacted]	[redacted]	[redacted]
Utility decrement associated with an attack	[redacted]	[redacted]	[redacted]	[redacted]
Healthcare resource use associated with stable disease				
General inpatient hospitalization – EDSS 0-3.5	[redacted]	[redacted]	[redacted]	[redacted]
General inpatient hospitalization – EDSS 3.5-6	[redacted]	[redacted]	[redacted]	[redacted]
General inpatient hospitalization – EDSS 6-10	[redacted]	[redacted]	[redacted]	[redacted]
Intensive care unit - EDSS 0-3.5	[redacted]	[redacted]	[redacted]	[redacted]
Intensive care unit - EDSS 3.5-6	[redacted]	[redacted]	[redacted]	[redacted]
Intensive care unit - EDSS 6-10	[redacted]	[redacted]	[redacted]	[redacted]
Emergency room visit - EDSS 0-3.5	[redacted]	[redacted]	[redacted]	[redacted]
Emergency room visit - EDSS 3.5-6	[redacted]	[redacted]	[redacted]	[redacted]
Emergency room visit - EDSS 6-10	[redacted]	[redacted]	[redacted]	[redacted]
Ambulance use – EDSS 0-3.5	[redacted]	[redacted]	[redacted]	[redacted]
Ambulance use – EDSS 3.5-6	[redacted]	[redacted]	[redacted]	[redacted]

Ambulance use – EDSS 6-10	[redacted]	[redacted]	[redacted]	[redacted]
Primary care visits – EDSS 0-3.5	[redacted]	[redacted]	[redacted]	[redacted]
Primary care visits – EDSS 3.5-6	[redacted]	[redacted]	[redacted]	[redacted]
Primary care visits – EDSS 6-10	[redacted]	[redacted]	[redacted]	[redacted]
Other healthcare visits – EDSS 0-3.5	[redacted]	[redacted]	[redacted]	[redacted]
Other healthcare visits – EDSS 3.5-6	[redacted]	[redacted]	[redacted]	[redacted]
Other healthcare visits – EDSS 6-10	[redacted]	[redacted]	[redacted]	[redacted]
Nurse home visits – EDSS 0-3.5	[redacted]	[redacted]	[redacted]	[redacted]
Nurse home visits – EDSS 3.5-6	[redacted]	[redacted]	[redacted]	[redacted]
Nurse home visits – EDSS 6-10	[redacted]	[redacted]	[redacted]	[redacted]
Physician home visits – EDSS 0-3.5	[redacted]	[redacted]	[redacted]	[redacted]
Physician home visits – EDSS 3.5-6	[redacted]	[redacted]	[redacted]	[redacted]
Physician home visits – EDSS 6-10	[redacted]	[redacted]	[redacted]	[redacted]
Healthcare resource use associated with NMOSD attack				
General inpatient hospitalization	[redacted]	[redacted]	[redacted]	[redacted]
Intensive care unit	[redacted]	[redacted]	[redacted]	[redacted]
Emergency room visit	[redacted]	[redacted]	[redacted]	[redacted]

Ambulance use	[redacted]	[redacted]	[redacted]	[redacted]
Primary care visits	[redacted]	[redacted]	[redacted]	[redacted]
Other healthcare visits	[redacted]	[redacted]	[redacted]	[redacted]
Home visits nurse	[redacted]	[redacted]	[redacted]	[redacted]
Home visits physician	[redacted]	[redacted]	[redacted]	[redacted]
Plasmaphereses	[redacted]	[redacted]	[redacted]	[redacted]
Methylprednisolon IV	[redacted]	[redacted]	[redacted]	[redacted]
MRU time use				
Number of treatments, plasmaphereses	[redacted]	[redacted]	[redacted]	[redacted]
Number of treatments, Methylprednisolon IV	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event probabilities				
Urinary tract infection - Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Administration-related reactions – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Back pain – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Headache – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/Vomiting – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes – Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Depression – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Fever – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory infection – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia - Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory abnormalities – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Influenza – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Hair loss – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Genital wart – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Throat Irritation – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Thrombosis – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Chills – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Shingles – Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Respiratory distress – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Rigors – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac complications – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid complications – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Pain - Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection - Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Administration-related reactions – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Back pain – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Headache – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/Vomiting – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Depression – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Fever – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]

Respiratory infection – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia - Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory abnormalities – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Influenza – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Hair loss – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Genital wart – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Throat Irritation – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Thrombosis – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Chills – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Shingles - Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]

Rigors – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac complications – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid complications – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pain - Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Administration-related reactions - Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Headache – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Hair loss – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Throat Irritation – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Thrombosis – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Chills – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]

Influenza – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory abnormalities – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia - Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory infection – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/vomiting – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Fever – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Genital wart – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Shingles – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Pain – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Rigors – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac complications – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid complications – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Back pain – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Depression - Rituximab	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events per 100 PY				
Urinary tract infection - Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Administration-related reactions – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Back pain – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Headache – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/Vomiting – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Depression – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Fever – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory infection – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia - Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory abnormalities – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Influenza – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia – Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Hair loss – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Genital wart – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Throat Irritation – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Thrombosis – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Chills – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Shingles – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Rigors – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac complications – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid complications – Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Pain - Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection - Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Administration-related reactions – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Back pain – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]

Headache – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/Vomiting – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Depression – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Fever – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory infection – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia - Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory abnormalities – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Influenza – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Hair loss – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]

Hypotension – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Genital wart – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Throat Irritation – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Thrombosis – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Chills – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Shingles - Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Rigors – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac complications – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid complications – Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pain - Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Administration-related reactions - Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Headache – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Hair loss – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]

Hepatotoxicity – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Throat Irritation – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Thrombosis – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Chills – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Influenza – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory abnormalities – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia - Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory infection – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/vomiting – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Fever – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Genital wart – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Shingles – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]

Pruritus – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Pain – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Rigors – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac complications – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid complications – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Back pain – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes – Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Depression - Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Time-use				
Time-use, IP hospitalization,(0,3.5]	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, IP hospitalization,(3.5,6]	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, IP hospitalization,(6,10]	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, IP hospitalization,Attack	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, ICU,(0,3.5]	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, ICU,(3.5,6]	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, ICU,(6,10]	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, ICU,Attack	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, ER visits	[redacted]	[redacted]	[redacted]	[redacted]

Time-use, Primary care visits	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, Other healthcare visits	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, Home vists, Nurse	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, Home visits, Physician	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, Treatment administration, Inebilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, Treatment administration, Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Time-use, Treatment administration, Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Appendix H. Literature searches for the clinical assessment

Efficacy and safety of the intervention and comparator(s)

The objective of this systematic literature review (SLR) was to identify studies documenting the efficacy and safety as of inebilizumab and relevant comparators in NMOSD as reported in clinical trials. The initial SLR was conducted in 2023, and updated in 2024. This appendix reports the details of the clinical SLR. This SLR was aimed at to identifying studies documenting the efficacy and safety as of inebilizumab and relevant comparators in NMOSD as reported in clinical trials.

The initial SLR and its update were conducted based on the reporting standards of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (109) and general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions (110) and key HTA bodies, such as the National Institute for Health and Care Excellence (NICE) (110) Canadian Agency for Drugs and Technologies in Health (CADTH) (111, 112), and Institute for Quality and Efficiency in Health Care (IQWiG) (113). By following the methodologies of these HTA bodies, the global SLR package complied with general SLR requirements of most other HTA bodies.

Electronic database searches for the initial SLR were carried out in May 2023. The SLR update was performed because of the requirement to include recent single-arm, non-randomized clinical trials as evidence for subsequent ITC analysis. These studies were excluded during the original SLR. Additionally, the SLR update aimed at identifying any randomised controlled trials (RCTs) or single arm trials (SATs) published since 2023. The update only covers clinical evidence, that will be used for the indirect treatment comparison (ITC) and subsequent cost-effectiveness modelling.

Electronic searches for both the initial SLR and SLR updated were conducted in Embase, Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic reviews (CDSR) as well as the Database of Abstracts and Reviews of Effects (DARE). The searches of the updated SLR were conducted for the complete Cochrane library, and therefore also included the American College of Physicians (ACP) journal club, the NHS Economic Evaluations Database (NHS EED), the Cochrane Methodology Register (CMR) and the Health Technology Assessment Database (HTA).

The SLR update included the following steps:

- Electronic searches to identify clinical evidence published since 2023, these searches were carried out on 13 March 2024 and identified both RCTs and single arm trials (SATs).
- Re-assessment of studies from the initial SLR (clinical efficacy) that were previously excluded with the exclusion reason “study design”. During the initial SLR studies were excluded with this reason if the study design was other than

RCT. Articles from original SLR that were excluded at title/abstract screening and FTR stage were re-screened/re-assessed.

Electronic searches for the SLR update were performed on 13 March 2024 on OVID platform.

Table 73 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	1974 – 12.03.2024	Initial search: 23.05.2023 Updated search: 12.03.2024
Medline	Ovid	1946 – 12.03.2024	Initial search: 23.05.2023 Updated search: 12.03.2024
Cochrane Central Register of Controlled Trials (CENTRAL)	Ovid	1991 to February 2024	Initial search: 23.05.2023 Updated search: February 2024
Cochrane Database of Systematic reviews (CDSR)	Ovid	2005 to 06.03.2024	Initial search: 23.05.2023 Updated search: 06.03.2024
Database of Abstracts and Reviews of Effects (DARE)*	Ovid	1991 to 2015	Initial search: 23.05.2023 Updated search 13.03.2024
American College of Physicians (ACP) journal club	Ovid	1991 to February 2024	Initial search: not searched Updated search: February 2024
NHS Economic Evaluations Database (NHS EED)*	Ovid	1995 to 2015	Initial search: not searched Updated search: 13.03.2024

Database	Platform/source	Relevant period for the search	Date of search completion
Cochrane Methodology Register (CMR)*	Ovid	1995 - 2012	Initial search: not searched Updated search: 13.03.2024
Health Technology Assessment Database (HTA)*	Ovid	2001 to 2016	Initial search: not searched Updated search: 13.03.2024

*DARE, NHS EED, CMR and HTA databases were discontinued and only the archived versions are available

Table 74 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov		"Neuromyelitis Optica" OR "Neuromyelitis Optica Spectrum Disorder" OR "NMOSD"	Initial search: 05.06.2023-28.08.2023 Updated search: 03.04.2024
WHO ICTRP		"Neuromyelitis Optica" OR "Neuromyelitis Optica Spectrum Disorder" OR "NMOSD"	Initial search: 05.06.2023-28.08.2023 Updated search: 03.04.2024
EU Clinial Trials Rregister		"Neuromyelitis Optica" OR "Neuromyelitis Optica Spectrum Disorder" OR "NMOSD"	Initial search: 05.06.2023-28.08.2023 Updated search: 03.04.2024
Health Canada's Clinical Trials Database		"Neuromyelitis Optica"	Initial search: 05.06.2023-28.08.2023 Updated search: 03.04.2024

Congress abstracts that were indexed in Embase were identified during electronic searches either in the original SLR (and re-assessment) or SLR update. Additional manual searches were performed for congresses that were not indexed in Embase and included years 2020 to 2024.

Table 75 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
AMCP	2020-2022: indexed in Embase 2023: not indexed in Embase	2020 to 2022: no manual searches performed 2023: PDF booklet available (https://www.jmcp.org/), manual search performed	"Neuromyelitis ", “NMOSD”	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024
ACTRIMS	2020-2021 and 2023: indexed in Embase 2022: not indexed in Embase	2020-2021 and 2023: no manual searches performed 2022: PDF booklet available (https://journals.sagepub.com/doi/full/10.1177/13524585221094745), manual search performed	"Neuromyelitis ", “NMOSD”	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024
CMSC	2020-2023: not indexed in Embase	2020-2023: PDF booklets available on IJMSC (International journal of MS care: https://meridian.allenpress.com/ijmsc/issue/browse-by-year), manual search performed	"Neuromyelitis ", “NMOSD”	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024
CONy	2020-2023: not indexed in Embase	2020-2021: abstracts unavailable 2023 and 2024: manual search performed	"Neuromyelitis ", “NMOSD”	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024
ECTRIMS	2020-2023: indexed in Embase	2020-2023: no manual searches performed	Not applicable	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024
JNLF	2021-2023: not indexed in Embase	Abstract available in French only (https://mediatheque.jnlf.fr), no manual searches performed	Not applicable	Initial search: 23.05.2023-01.06.2023 Updated search:

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
				27.03.2024
NANOS	2021-2023: not indexed in Embase	2021-2023: manual search performed in the database NOVEL – NANOS Annual Meeting (ehsl_novel_nam) (https://collections.lib.utah.edu/search?facet_setname_s=ehsl_novel_nam	"Neuromyelitis", “NMOSD”	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024
AAN	2020-2023: indexed in Embase	No manual searches performed	Not applicable	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024
EAN	2020-2022: indexed in Embase 2023: not indexed in Embase	2020-2022: no manual searches performed 2023: PDF booklets available, manual search performed	"Neuromyelitis", “NMOSD”	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024
DGKN	2020-2023: indexed in Embase 2024: indexed in Embase after electronic search	2020-2023: no manual searches performed 2024: manual search performed	"Neuromyelitis", “NMOSD”	Initial search: 23.05.2023-01.06.2023 Updated search: 27.03.2024

Abbreviations: AAN, Meetings of the American Academy of Neurology; ACTRIMS, Congress of the American Committee for Treatment and Research in Multiple Sclerosis; AMCP, Academy of Managed Care Pharmacy; CMSC, Consortium of Multiple Sclerosis Centers Annual Meeting; CONy, World Congress on Controversies in Neurology; DGKN, Congress for Clinical Neuroscience with Advanced Training Academy of the German Society for Clinical Neurophysiology and Functional Neuroimaging; EAN, Meetings of the European Academy of Neurology; ECTRIMS, Congress of the European Committee for Treatment and Research in Multiple Sclerosis; JNLF, Journees de Neurologie de Langue Francaise; NANOS, North American Neuro-Ophthalmology Society Annual Meeting;

H.1.1 Search strategies

The search strategies include a combination of free-text and controlled vocabulary terms specific to each database (e.g., Emtree terms for Embase or Medical Subject Headings in MEDLINE). The search strings are presented in Table 104, Table 105, Table 106, Table 107 and Table 108.

Available (validated) search filters are available from key HTA bodies for study design and outcomes, not for population terms. Internal search terms were used to identify relevant literature. These have been cross-checked with key publications to ensure search identifies most relevant studies. Relevant interventions were identified through reviews and clinicaltrials.gov screening (114-119). Search strategies for RCTs, non-randomised clinical trials and single arm trials were based on SIGN and NICE. Language restrictions were based on standard limits in Ovid.

Table 76 of search strategy table for Medline

No.	Query	Results initial search	Results updated search
#1	exp neuromyelitis optica/	4248	4526
#2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	6263	6719
#3	or/1-2	6263	6719
#4	immunosuppressive agents/	104299	105764
#5	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn.	721391	750049
#6	exp mycophenolate mofetil/ or (mycophenolic acid mofetil or mycophenolate mofetil or "cell cept" or cellcept or cellmune or cellsept or munoloc or myclausen or myfenax).ti,ab,kw,kf,rn.	14566	15099
#7	exp methotrexate/ or (methotrexat* or methopterine* or abitextrate* or adx 2191 or adx2191 or amethopterin* or ametopterine* or antifolan* or biotrexate* or brimexate* or canceren* or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate* or emthexat* or farmitrexat* or farmitrexate* or farmotrex* or folex* or ifamet* or imeth* or jylamvo* or lantarel* or ledertrexate* or lumexon* or maxtrex* or metatrexan* or methoblastin* or methotrate* or metoject* or metotrexat* or mexate* or mpi 2505 or mpi2505 or neotrexate* or nordimet* or novatrex* or nsc 740 or nsc740 or otrexup* or r 9985 or r9985 or rasuvo* or reditrex* or reumatrex* or rheumatrex* or texate* or tremetex* or trexall* or trexeron* or wr 19039 or wr19039 or xaken* or xatmep* or zexate* or zlatal*).ti,ab,kw,kf,rn.	60657	62011
#8	exp cyclophosphamide/ or (cyclophosphamid*2 or alkyroxan or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo-cell or cycloblastin*2 or "cyclofos amide " or cyclofosfamid#2 or cyclophar or cyclophosphan*2 or cylostin or cycloxan or cyrevia or cytophosphan*2 or cytoxan or endoxan*2 or endocyclo or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid).ti,ab,kw,kf,rn.	84447	86065

No.	Query	Results initial search	Results updated search
#9	exp mitoxantrone/ or (mitoxantron*2 or "cl 232,315 " or "cl 232315 " or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxantrona or mitoxgen or mitozantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or "now 85 34 " or "now 8534 " or now8534 or "nsc 279836 " or "nsc 301739 " or "nsc 301739d " or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ravenova).ti,ab,kw,kf,rn.	6781	6879
#10	exp rituximab/ or (rituximab or "abp 798 " or apb798 or blitzima or "ct p10 " or ctp10 or "gp 2013 " or gp2013 or halpryza or "hlx 01 " or hlx01 or "ibi 301 " or ibi301 or "idec 102 " or "idec c2b8 " or idec102 or idecc2b8 or mabthera or "mk 8808 " or mk8808 or "pf 05280586 " or "pf 5280586 " or pf05280586 or pf5280586 or "r 105 " or r105 or reditux or "rg 105 " or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294 " or ro452294 or "rtxm 83 " or rtxm83 or ruxience or truxima or "tuxella ").ti,ab,kw,kf,rn.	30576	32306
#11	(eculizumab or abp 959 or abp959 or bcd 148 or bcd148 or elizaria or soliris).ti,ab,kw,kf,rn.	2529	2723
#12	(inebilizumab or "medi 551 " or medi551 or "mt 0551 " or mt0551 or uplizna or "vib 0551 " or vib0551).ti,ab,kw,kf,rn.	92	112
#13	(toclizumab or actemra or atlizumab or "bat 1806 " or bat1806 or lusinex or "msb 11456 " or msb11456 or "r 1569 " or r1569 or "rg 1569 " or rg1569 or "ro 4877533 " or ro4877533 or roactemra).ti,ab,kw,kf,rn.	121	133
#14	(satralizumab or enspryng or "rg 6168 " or rg6168 or "ro 5333787 " or ro533787 or "sa 237 " or sa237 or sapelizumab).ti,ab,kw,kf,rn.	100	113
#15	(orelabrutinib or "icp 022" or icp022 or innobruka).ti,ab,kw,kf,rn.	25	40
#16	(Ublituximab or Briumvi or "emab 6" or emab6 or "lfb r 604" or "lfb r603" or lfbr603 or "tg 1101" or tg1101 or "tgtx 1101" or tgtx1101 or utuxin).ti,ab,kw,kf,rn.	66	79
#17	(NBP-01 or NBP01).ti,ab,kw,kf,rn.	6	6
#18	(telitacicept or RC18 or RC-18).ti,ab,kw,kf,rn.	48	79
#19	(belimumab or benlysta or "gsk 1550188" or gsk1550188 or "hgs 1006" or hgs1006).ti,ab,kw,kf,rn.	1004	1131
#20	(daratumumab or dalinvi or darasarex or darzalex or "hlx 15" or hlx15 or "jnj 54767414" or jnj54767414).ti,ab,kw,kf,rn.	1472	1676
#21	(ravulizumab or "alxn 1210" or "alxn 1810" or alxn1210 or alxn1810 or ultomiris).ti,ab,kw,kf,rn.	153	202
#22	(ofatumumab or arzerra or "gsk 1841157" or gsk1841157 or HuMaxCD20 or kesimpta or "omb 157" or omb157).ti,ab,kw,kf,rn.	754	818
#23	(zanubrutinib or "bgb 3111" or bgb3111 or brukinsa).ti,ab,kw,kf,rn.	259	346
#24	("hbm 9161" or hbm9161 or "hl 161" or "hl 161 bkn" or "hl 161bkn" or "hl 61" or "hl161 hl161 bkn" or hl161bkn or hl61 or "imvt 1401" or "imvt1401" or "rvt 1401" or rvt1401).ti,ab,kw,kf,rn.	10	9
#25	(edralbrutinib or "ebi 1459" or ebi1459 or "shr 1459" or shr1459 or "tg 1701" or tg1701).ti,ab,kw,kf,rn.	2	2

No.	Query	Results initial search	Results updated search
#26	mil62.ti,ab,kw,kf,rn.	0	0
#27	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw,kf,rn.	343187	352298
#28	Prednisone/ or Prednisolone/ or Methylprednisolone/ or Betamethasone/ or (prednisone or prednisolone or meprednisone or methylprednisone or methylprednisolone or betamethasone).ti,ab,kw,kf,rn.	134930	137665
#29	Prednisone/ or Prednisolone/ or Methylprednisolone/ or Betamethasone/ or (prednisone or prednisolone or meprednisone or methylprednisone or methylprednisolone or betamethasone).ti,ab,kw,kf,rn.	134930	137665
#30	(ocrelizumab or "pro 70769" or pro70769 or ocrevus or "pr 070769" or "r 1594" or r1594 or "rg 1594" or rg1594 or "rhumab 2H7" or "ro 4964913" or ro4964913).ti,ab,kw,kf,rn.	860	1007
#31	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw,kf,rn.	290736	301452
#32	exp tacrolimus/ or (tacrolimus or advagraf or astagraf or envarsus or "fk 506" or fk506 or "fr 900506" or fr900506 or fugimycin or graceptor or hecoria or "l 679934" or l679934 or "mld 987" or mld987 or modigraf or "mtd 2019" or mtd219 or "mustopic oint" or prograf or prograft or protopic or protopy or "rtu 007" or rtu007 or tac-lac or tacforius or tsukubaenolide).ti,ab,kw,kf,rn.	28748	29649
#33	BAT4406F.ti,ab,kw,kf,rn.	0	0
#34	Immunoglobulins/ or immunoglobulin G.ti,ab,kw,kf,rn.	188880	191799
#35	Plasmapheresis/ or Plasma Exchange/ or (plasmapheresis or (plasma adj exchange)).ti,ab,kw,kf,rn.	24280	25049
#36	or/4-35	1709527	1766342
#37	3 and 36	2271	2463
#38	exp Randomized Controlled Trial/ or exp Random Allocation/	683908	700819
#39	exp Double-Blind Method/ or exp Single-Blind Method/	206888	209963
#40	exp clinical trial/ or exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp controlled clinical trial/	970864	990773
#41	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt.	80508	83332
#42	exp controlled clinical trials as topic/ or exp Randomized Controlled Trials as Topic/ or exp clinical trials as topic/	382288	388824

No.	Query	Results initial search	Results updated search
#43	exp Multicenter Study/	334049	344077
#44	exp Placebos/	39464	39600
#45	exp Cross-Over Studies/	55118	56313
#46	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or dumm* or mask*)).tw,ti,ab,hw,kf.	269475	277102
#47	randomized controlled trial.pt.	593290	610010
#48	controlled clinical trial.pt.	95312	95582
#49	random*.ti,ab,kw. or randomi?ed controlled trial*.tw. or rct.tw.	1425879	1507386
#50	(random* adj2 allocat*).tw.	43461	45845
#51	blind*.ti,ab,kw.	346763	360095
#52	(placebo* or assign* or allocat* or volunteer* or sham).ti,ab,kw.	1018668	1061551
#53	prospective studies/	659188	682215
#54	(parallel* or factorial* or crossover* or cross over*).ti,ab,kw.	488045	505360
#55	trial.ti.	285696	304886
#56	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	160835	168324
#57	(nonrandom* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	54277	57314
#58	('double-blind' or 'double-blinded').tw,af. or (open label or open-label).af.	272439	281531
#59	(single arm or single group).ti,ab,hw,kf.	17548	19666
#60	(basket adj2 trial*).ti,ab,hw,kf.	334	384
#61	observational study/	142095	153157
#62	observational studies as topic/	8751	9546
#63	clinical studies as topic/	783	821
#64	controlled before-after studies/	724	753
#65	cross-sectional studies/	466978	495632
#66	historically controlled study/	227	232
#67	interrupted time series analysis/	1826	2004
#68	cohort studies/	328533	338746
#69	longitudinal studies/	165035	170145
#70	prospective studies/	659188	682215
#71	retrospective studies/	1118854	1186940
#72	follow-up studies/	691542	696048
#73	case-control studies/	327840	332482
#74	single-case studies as topic/	98	100
#75	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	218004	239241
#76	cohort*.ti,ab,kf.	850373	926077
#77	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	529912	559075

No.	Query	Results initial search	Results updated search
#78	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	168727	177422
#79	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	343864	365954
#80	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	674788	732263
#81	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	158585	166392
#82	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	637	641
#83	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	231712	245682
#84	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	108379	117978
#85	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	4906	5255
#86	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	431778	472991
#87	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3258	3603
#88	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	20159	22123
#89	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	1695	1789
#90	((uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic* or noninterventional or non interventional or pragmatic) adj1 (study or studies)).ti,ab,kf.	110105	114246
#91	or/38-90	6838757	7166815
#92	37 and 91	929	1018
#93	case reports/	2336806	2390091
#94	(animal* not human*).sh,hw.	5079797	5158120
#95	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	5038793	5200788
#96	or/93-95	9980459	10218166
#97	92 not 96	821	909
#98	limit 97 to english language	783	871
#99	Initial search: (conference or congress).pt.	67273	-
	Updated search: limit 98 to yr="2023 -Current"	-	129
#100	Initial search: limit 99 to yr="1860 - 2019"	66241	-
	Updated search: remove duplicates from 99	-	127
#101	Initial search: 98 not 100	783	-

No.	Query	Results initial search	Results updated search
	Updated search: -	-	-

Table 77 of search strategy table for Embase

No.	Query	Results initial search	Results updated search
#1	exp myelooptic neuropathy/	12307	13123
#2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	11376	12047
#3	1 or 2	13593	14523
#4	immunosuppressive agent/	86704	89880
#5	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn.	951978	984854
#6	exp mycophenolate mofetil/ or (mycophenolic acid mofetil or mycophenolate mofetil or "cell cept" or cellcept or cellmune or cellsept or munoloc or myclausen or myfenax).ti,ab,kw,kf,rn.	45421	49847
#7	exp methotrexate/ or (methotrexat* or methopterine* or abitextrate* or adx 2191 or adx2191 or amethopterin* or ametopterine* or antifolan* or biotrexate* or brimexate* or canceren* or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate* or emthexat* or farmitrexat* or farmitrexate* or farmotrex* or folex* or ifamet* or imeth* or jylamvo* or lantarel* or ledertrexate* or lumexon* or maxtrex* or metatrexan* or methoblastin* or methotrate* or metoject* or metotrexat* or mexate* or mpi 2505 or mpi2505 or neotrexate* or nordimet* or novatrex* or nsc 740 or nsc740 or otrexup* or r 9985 or r9985 or rasuvo* or reditrex* or reumatrex* or rheumatrex* or texate* or tremetex* or trexall* or trexeron* or wr 19039 or wr19039 or xaken* or xatmep* or zexate* or zlatal*).ti,ab,kw,kf,rn.	213687	222561
#8	exp cyclophosphamide/ or (cyclophosphamid*2 or alkyroxan or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo-cell or cycloblastin*2 or "cyclofos amide " or cyclofosfamid#2 or cyclophar or cyclophosphan*2 or cylostin or cycloxan or cyrevia or cytophosphan*2 or cytoxan or endoxan*2 or endocyclo or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid).ti,ab,kw,kf,rn.	270481	280635
#9	exp mitoxantrone/ or (mitoxantron*2 or "cl 232,315 " or "cl 232315 " or cl232,315 or cl232315 or dhad or dhaq or	26453	27179

No.	Query	Results initial search	Results updated search
	domitrone or elsep or formyxan or genefadrone or misostol or mitoxantrona or mitoxgen or mitozantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or "now 85 34 " or "now 8534 " or now8534 or "nsc 279836 " or "nsc 301739 " or "nsc 301739d " or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ravenova).ti,ab,kw,kf,rn.		
#10	exp rituximab/ or (rituximab or "abp 798 " or apb798 or blitzima or "ct p10 " or ctp10 or "gp 2013 " or gp2013 or halpryza or "hlx 01 " or hlx01 or "ibi 301 " or ibi301 or "idec 102 " or "idec c2b8 " or idec102 or idecc2b8 or mabthera or "mk 8808 " or mk8808 or "pf 05280586 " or "pf 5280586 " or pf05280586 or pf5280586 or "r 105 " or r105 or reditux or "rg 105 " or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294 " or ro452294 or "rtxm 83 " or rtxm83 or ruxience or truxima or "tuxella ").ti,ab,kw,kf,rn.	110539	117983
#11	exp eculizumab/ or (eculizumab or abp 959 or abp959 or bcd 148 or bcd148 or elizaria or soliris).ti,ab,kw,kf,rn.	9423	10228
#12	exp inebilizumab/ or (inebilizumab or "medi 551 " or medi551 or "mt 0551 " or mt0551 or uplizna or "vib 0551 " or vib0551).ti,ab,kw,kf,rn.	394	459
#13	exp tocilizumab/ or (toclizumab or actemra or atlizumab or "bat 1806 " or bat1806 or lusinex or "msb 11456 " or msb11456 or "r 1569 " or r1569 or "rg 1569 " or rg1569 or "ro 4877533 " or ro4877533 or roactemra).ti,ab,kw,kf,rn.	26601	29057
#14	exp satralizumab/ or (satralizumab or enspryng or "rg 6168 " or rg6168 or "ro 5333787 " or ro533787 or "sa 237 " or sa237 or sapelizumab).ti,ab,kw,kf,rn.	322	397
#15	exp orelabrutinib/ or (orelabrutinib or "icp 022" or icp022 or innobruka).ti,ab,kw,kf,rn.	107	192
#16	exp Ublituximab/ or (Ublituximab or Briumvi or "emab 6" or emab6 or "lfb r 604" or "lfb r603" or lfbr603 or "tg 1101" or tg1101 or "tgtx 1101" or tgtx1101 or utuxin).ti,ab,kw,kf,rn.	399	470
#17	(NBP-01 or NBP01).ti,ab,kw,kf,rn.	7	7
#18	(telitacicept or RC18 or RC-18).ti,ab,kw,kf,rn.	89	135
#19	exp Belimumab/ or (belimumab or benlysta or "gsk 1550188" or gsk1550188 or "hgs 1006" or hgs1006).ti,ab,kw,kf,rn.	3999	4454
#20	exp daratumumab/ or (daratumumab or dalinvi or darasarex or darzalex or "hlx 15" or hlx15 or "jnj 54767414" or jnj54767414).ti,ab,kw,kf,rn.	6312	7571
#21	exp Ravulizumab/ or (ravulizumab or "alxn 1210" or "alxn 1810" or alxn1210 or alxn1810 or ultomiris).ti,ab,kw,kf,rn.	636	850
#22	exp ofatumumab/ or (ofatumumab or arzerra or "gsk 1841157" or gsk1841157 or HuMaxCD20 or kesimpta or "omb 157" or omb157).ti,ab,kw,kf,rn.	4041	4387
#23	exp zanubrutinib/ or (zanubrutinib or "bgb 3111" or bgb3111 or brukinsa).ti,ab,kw,kf,rn.	910	1356
#24	exp batoclimab/ or ("hbm 9161" or hbm9161 or "hl 161" or "hl 161 bkn" or "hl 161bkn" or "hl 61" or "hl161 hl161 bkn" or hl161bkn or hl61 or "imvt 1401" or "imvt1401" or "rvt 1401" or rvt1401).ti,ab,kw,kf,rn.	48	75
#25	exp edralbrutinib/ or (edralbrutinib or "ebi 1459" or ebi1459 or "shr 1459" or shr1459 or "tg 1701" or tg1701).ti,ab,kw,kf,rn.	24	27

No.	Query	Results initial search	Results updated search
#26	mil62.ti,ab,kw,kf,rn.	4	8
#27	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw,kf,rn.	983044	1024450
#28	prednisone/ or prednisolone/ or meprednisone/ or methylprednisolone/ or betamethasone/ or (prednisone or prednisolone or meprednisone or methylprednisone or methylprednisolone or betamethasone).ti,ab,kw,kf,rn.	436453	455837
#29	exp ocrelizumab/ or (ocrelizumab or "pro 70769" or pro70769 or ocrevus or "pr 070769" or "r 1594" or r1594 or "rg 1594" or rg1594 or "rhumab 2H7" or "ro 4964913" or ro4964913).ti,ab,kw,kf,rn.	4083	4762
#30	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw,kf,rn.	512962	526596
#31	exp tacrolimus/ or (tacrolimus or advagraf or astagraf or envarsus or "fk 506" or fk506 or "fr 900506" or fr900506 or fugimycin or graceptor or hecoria or "l 679934" or l679934 or "mld 987" or mld987 or modigraf or "mtd 2019" or mtd219 or "mustopic oint" or prograf or prograft or protopic or protopy or "rtu 007" or rtu007 or tac-lac or tacforius or tsukubaenolide).ti,ab,kw,kf,rn.	102240	107310
#32	BAT4406F.ti,ab,kw,kf,rn.	0	0
#33	immunoglobulin G/ or "immunoglobulin G".ti,ab,kw,kf,rn.	221359	229413
#34	plasmapheresis/ or plasma exchange/ or (plasmapheresis or (plasma adj exchange)).ti,ab,kw,kf,rn.	55448	58208
#35	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	2825510	2925641
#36	3 and 35	7330	7936
#37	exp Randomized Controlled Trial/ or exp randomization/	860131	886995
#38	exp double blind procedure/ or exp single blind procedure/	259986	268332
#39	exp clinical trial/ or exp controlled clinical trial/ or exp phase 4 clinical trial/ or exp phase 3 clinical trial/ or exp phase 2 clinical trial/	1846871	1888457
#40	exp Multicenter Study/	377820	386987
#41	exp placebo/	403321	410157
#42	exp crossover procedure/	75221	77257

No.	Query	Results initial search	Results updated search
#43	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or dumm* or mask*)).tw,ti,ab,hw,kf.	366225	376443
#44	exp "controlled clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/	441619	457554
#45	random*.ti,ab,kw. or randomi?ed controlled trial*.tw. or rct.tw.	1984478	2060938
#46	(random* adj2 allocat*).tw.	54689	56716
#47	blind*.ti,ab,kw.	506134	518915
#48	(placebo* or assign* or allocat* or volunteer* or sham).ti,ab,kw.	1387932	1428082
#49	prospective study/	877274	908567
#50	(parallel* or factorial* or crossover* or cross over*).ti,ab,kw.	595315	609831
#51	trial.ti.	402863	417710
#52	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	351235	455366
#53	(nonrandom* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	70267	72945
#54	('double-blind' or 'double-blinded').tw,af. or (open label or open-label).af.	395787	407914
#55	Initial search: (single arm or single group).ti,ab,hw,kf.	33904	-
	Updated search: (single arm or single-arm or single group or single-group or non comparative or noncomparative or non-comparative).ti,ab,hw,kf,tw.	-	44040
#56	(basket adj2 trial*).ti,ab,hw,kf.	768	862
#57	observational study/	328404	362955
#58	cross-sectional study/	563468	619686
#59	cohort analysis/	1037107	1130901
#60	longitudinal study/	193609	208450
#61	prospective study/	877274	908567
#62	retrospective study/	1469001	1582187
#63	follow up/	2050765	2156256
#64	exp case control study/	224500	232835
#65	quasi experimental study/	11286	12250
#66	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	349164	371410
#67	cohort*.ti,ab,kf.	1476111	1554683
#68	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	816003	847670
#69	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	271051	281032
#70	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	495791	516602
#71	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	1151543	1215466
#72	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	214583	220616
#73	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	704	710

No.	Query	Results initial search	Results updated search
#74	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	354035	369492
#75	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	166037	178416
#76	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	5816	6100
#77	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	575621	615898
#78	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3609	3844
#79	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	25337	27070
#80	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	2373	2463
#81	((uncontrolled or non randomi#ed or nonrandomi#ed or pragmatic) adj1 (study or studies)).ti,ab,kf.	16763	17568
#82	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81	9811833	10253263
#83	36 and 82	3520	3908
#84	case report/	2904053	2975259
#85	(animal* not human*).sh,hw.	4844367	4929872
#86	(book or chapter or conference review or editorial or erratum or letter or note or short survey or tombstone).pt.	3749414	3851329
#87	84 or 85 or 86	11067395	11313585
#88	83 not 87	2803	3116
#89	limit 88 to english language	2738	3047
#90	Initial search: abstract.pt.	4769353	-
	Updated search: limit 89 to yr="2023 -Current"	-	418
#91	Initial search: limit 90 to yr="1883 - 2019"	3841769	-
	Updated search: remove duplicates from 90	-	411
#92	Initial search: 89 not 91	1993	-
	Updated search: -	-	-

Table 78 of search strategy table for CENTRAL

No.	Query	Results initial search	Results updated search*
#1	exp neuromyelitis optica/	75	94
#2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	454	543

No.	Query	Results initial search	Results updated search*
#3	or/1-2	454	543
#4	immunosuppressive agents/	5863	6839
#5	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw.	44233	46965
#6	exp mycophenolate mofetil/ or (mycophenolic acid mofetil or mycophenolate mofetil or "cell cept" or cellcept or cellmune or cellsept or munoloc or myclausen or myfenax).ti,ab,kw.	3395	3637
#7	exp methotrexate/ or (methotrexat* or methopterine* or abitextrate* or adx 2191 or adx2191 or amethopterin* or ametopterine* or antifolan* or biotrexate* or brimexate* or canceren* or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate* or emthexat* or farmitrexat* or farmitrexate* or farmotrex* or folex* or ifamet* or imeth* or jylamvo* or lantarel* or ledertrexate* or lumexon* or maxtrex* or metatrexan* or methoblastin* or methotrate* or metoject* or metotrexat* or mexate* or mpi 2505 or mpi2505 or neotrexate* or nordimet* or novatrex* or nsc 740 or nsc740 or otrexup* or r 9985 or r9985 or rasuvo* or reditrex* or reumatrex* or rheumatrex* or texate* or tremetex* or trexall* or trexeron* or wr 19039 or wr19039 or xaken* or xatmep* or zexate* or zlatal*).ti,ab,kw.	12209	12564
#8	exp cyclophosphamide/ or (cyclophosphamid*2 or alkyroxan or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo-cell or cycloblastin*2 or "cyclofos amide " or cyclofosfamid#2 or cyclophar or cyclophosphan*2 or cylostin or cycloxan or cyrevia or cytophosphan*2 or cytoxan or endoxan*2 or endocyclo or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid).ti,ab,kw.	13167	13663
#9	exp mitoxantrone/ or (mitoxantron*2 or "cl 232,315 " or "cl 232315 " or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxantrona or mitoxgen or mitozantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or "now 85 34 " or "now 8534 " or now8534 or "nsc 279836 " or "nsc 301739 " or "nsc 301739d " or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ravenova).ti,ab,kw.	1437	1484
#10	exp rituximab/ or (rituximab or "abp 798 " or apb798 or blitzima or "ct p10 " or ctp10 or "gp 2013 " or gp2013 or halpryza or "hlx 01 " or hlx01 or "ibi 301 " or ibi301 or "idec 102 " or "idec c2b8 " or idec102 or idecc2b8 or mabthera or "mk 8808 " or mk8808 or "pf 05280586 " or "pf 5280586 " or pf05280586 or pf5280586 or "r 105 " or r105 or reditux or "rg 105 " or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or	5644	6035

No.	Query	Results initial search	Results updated search*
	rixathon or riximyo or "ro 452294 " or ro452294 or "rtxm 83 " or rtxm83 or ruxience or truxima or "tuxella ").ti,ab,kw.		
#11	(eculizumab or abp 959 or abp959 or bcd 148 or bcd148 or elizaria or soliris).ti,ab,kw.	437	506
#12	(inebilizumab or "medi 551 " or medi551 or "mt 0551 " or mt0551 or uplizna or "vib 0551 " or vib0551).ti,ab,kw.	85	99
#13	(toclizumab or actemra or atlizumab or "bat 1806 " or bat1806 or lusinex or "msb 11456 " or msb11456 or "r 1569 " or r1569 or "rg 1569 " or rg1569 or "ro 4877533 " or ro4877533 or roactemra).ti,ab,kw.	183	203
#14	(satralizumab or enspryng or "rg 6168 " or rg6168 or "ro 5333787 " or ro533787 or "sa 237 " or sa237 or sapelizumab).ti,ab,kw.	75	84
#15	(orelabrutinib or "icp 022" or icp022 or innobruka).ti,ab,kw.	13	20
#16	(Ublituximab or Briumvi or "emab 6" or emab6 or "lfb r 604" or "lfb r603" or lfbr603 or "tg 1101" or tg1101 or "tgtx 1101" or tgtx1101 or utuxin).ti,ab,kw.	54	55
#17	(NBP-01 or NBP01).ti,ab,kw.	0	0
#18	(telitacicept or RC18 or RC-18).ti,ab,kw.	33	47
#19	(belimumab or benlysta or "gsk 1550188" or gsk1550188 or "hgs 1006" or hgs1006).ti,ab,kw.	332	365
#20	(daratumumab or dalinvi or darasarex or darzalex or "hlx 15" or hlx15 or "jnj 54767414" or jnj54767414).ti,ab,kw.	552	644
#21	(ravulizumab or "alxn 1210" or "alxn 1810" or alxn1210 or alxn1810 or ultomiris).ti,ab,kw.	150	193
#22	(ofatumumab or arzerra or "gsk 1841157" or gsk1841157 or HuMaxCD20 or kesimpta or "omb 157" or omb157).ti,ab,kw.	306	335
#23	(zanubrutinib or "bgb 3111" or bgb3111 or brukinsa).ti,ab,kw.	100	125
#24	("hbm 9161" or hbm9161 or "hl 161" or "hl 161 bkn" or "hl 161bkn" or "hl 61" or "hl161 hl161 bkn" or hl161bkn or hl61 or "imvt 1401" or "imvt1401" or "rvt 1401" or rvt1401).ti,ab,kw.	17	20
#25	(edralbrutinib or "ebi 1459" or ebi1459 or "shr 1459" or shr1459 or "tg 1701" or tg1701).ti,ab,kw.	6	6
#26	mil62.ti,ab,kw.	3	7
#27	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw.	44535	48298
#28	Prednisone/ or Prednisolone/ or Methylprednisolone/ or Betamethasone/ or (prednisone or prednisolone or meprednisone or methylprednisone or methylprednisolone or betamethasone).ti,ab,kw.	22666	23779
#29	(ocrelizumab or "pro 70769" or pro70769 or ocrevus or "pr 070769" or "r 1594" or r1594 or "rg 1594" or rg1594 or "rhumab 2H7" or "ro 4964913" or ro4964913).ti,ab,kw.	302	344
#30	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088"	29165	31143

No.	Query	Results initial search	Results updated search*
	or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw.		
#31	exp tacrolimus/ or (tacrolimus or advagraf or astagraf or envarsus or "fk 506" or fk506 or "fr 900506" or fr900506 or fugimycin or graceptor or hecoria or "l 679934" or l679934 or "mld 987" or mld987 or modigraf or "mtd 2019" or mtd219 or "mustopic oint" or prograf or prograft or protopic or protopy or "rtu 007" or rtu007 or tac-lac or tacforius or tsukubaenolide).ti,ab,kw.	5410	5738
#32	Initial search: or/4-31	146634	-
	Updated search: BAT4406F.ti,ab,kw.	-	1
#33	Initial search: 3 and 32	273	-
	Updated search: Immunoglobulins/ or immunoglobulin G.ti,ab,kw.	-	2858
#34	Initial search: (animal* not human*).sh,hw.	2741	-
	Updated search: Plasmapheresis/ or Plasma Exchange/ or (plasmapheresis or (plasma adj exchange)).ti,ab,kw.	-	1603
#35	Initial search: (address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	21421	-
	Updated search: or/4-34	-	159872
#36	Initial search: 34 or 35	24153	-
	Updated search: 3 and 35	-	321
#37	Initial search: 33 not 36	271	-
	Updated search: (animal* not human*).sh,hw.	-	3345
#38	Initial search: limit 37 to english language	267	-
	Updated search: (address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	-	19998
#39	Initial search: -	-	-
	Updated search: 37 or 38	-	23333

No.	Query	Results initial search	Results updated search*
#40	Initial search: -	-	-
	Updated search: 36 not 39	-	319
#41	Initial search: -	-	-
	Updated search: limit 40 to english language [Limit not valid in DARE,CLCMR,ACP Journal Club,CDSR; records were retained]	-	315
#42	Initial search: -	-	-
	Updated search: limit 41 to yr="2023 -Current" [Limit not valid in DARE; records were retained]	-	33

Table 79 of search strategy table for Cochrane Database of Systematic Reviews

No.	Query	Results initial search	Results updated search
#1	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).ti,ab,kw.	0	See Table 78

Table 80 of search strategy table for Database of Abstracts of Reviews of Effects

No.	Query	Results initial search	Results updated search
#1	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	0	See Table 78

H.1.2 Systematic selection of studies

The Population, Intervention, Comparator, Outcomes, and Study design (PICOS) eligibility criteria are outlined in Table 109. Selection of studies was guided by the PICOS criteria and followed a 2-stage process: (1) title and abstract screening, and (2) full text review. All records were screened by two independent reviewers, with conflicts resolved by a third, independent reviewer. Following the article selection process, a list of included and excluded studies (with reasons for exclusion) for each step was generated.

In some instances, studies included a broader patient population than the target population of these SLRs. Based on guidance from the Institute for Quality and Efficiency in Health Care (IQWiG) (120), studies were included if at least 80% of the study

population met the PICOS criteria outlined below or if relevant subgroup data were available.

Neither geographic nor time limit restrictions were applied in the initial search. The SLR update was limited to studies published since the initial search for the inclusion of any new studies. Records were not extracted if they only reported on subgroups that were not of interest.

Title/Abstract review

All records were screened at the title/abstract level by two independent reviewers with disagreements resolved by a third, independent researcher. All papers included by the reviewers at the end of this stage were retained for Step 2. Papers excluded at this level were disregarded and the rejection reason was recorded for use in the PRISMA flow diagram.

In the SLR update, citations for title and abstract screening were retrieved from two sources:

1. SLR update: Citations identified during electronic searches were downloaded using EndNote (at which point most duplicates were identified and removed) into a Microsoft Excel spreadsheet.

2. Re-screening: Citations that were not RCTs and were excluded at title and abstract screening with the exclusion category “study design” during original SLR were eligible for re-screening. Included citations from both screenings were cross-checked for duplicates.

Full-text review

The publications included after abstract review were obtained for a full review of the text. Two independent reviewers screened all citations and full-text articles and any discrepancies in their decisions were resolved by a third, independent reviewer. All papers included after the full-text review were retained for data extraction. A record was kept of papers excluded at this stage along with a clear justification for their exclusion; this was reported in table format in the Excel report as per the NICE guidance (121). The details for the inclusion/exclusion criteria were consulted throughout this step to assist with data collection. This ensured that all decisions regarding the inclusion and exclusion of studies were consistent throughout the review process. Specific exclusion reasons as per the PICOS criteria were recorded at the full-text screening stage. The study selection process was reported in a PRISMA flow diagram.

In the SLR update, similarly to title and abstract screening articles were retrieved from two sources:

1. Full texts of publications included during screening were included for full text review.
2. Re-assessment: In addition to publications included during re-screening, publications excluded at full text review in the original SLR (exclusion category: “study design”) were included for full text review.

Data extraction

Once the list of SLRs for inclusion was finalized, data extraction was carried out using a pre-defined Microsoft Excel®-based data extraction template (DET), ensuring that data were extracted uniformly and that the extracted data were comparable across studies. Data were extracted by two independent reviewers and independently checked by a third, senior reviewer in accordance with CRD guidance (122). In the event of a discrepancy, a consensus-based discussion or a third reviewer was consulted to make the final decision.

In the updated SLR, data from the included studies were extracted into the DET from the initial SLR to capture publication, study, patient, and treatment characteristics, as well as outcome data of interest. The DET was slightly modified during the SLR update (i.e., additional columns were added to capture e.g., age at onset).

The following subgroups were defined as subgroups of interest:

- AQP4+ population
- EDSS score at baseline
- Subgroups by prior therapy
    - Prior immunosuppressant (e.g., AZA, MMF)
    - Prior B-cell depleting therapy (e.g., rituximab)
    - Treatment-naïve population
- Regional/ethnical subgroups
- Age (added during SLR update)
- Age on onset (added during SLR update)

An additional assessment was performed on publications that met the PICOS inclusion/exclusion criteria before proceeding to data extraction. During the additional assessment data cross-check for publications reporting results from studies already identified in the original SLR was performed. Publications were not selected for extraction if: (1) data were already present in the original DET; (2) more recent data were already present in the original DET; (3) data were reported only for subgroups that were not listed as subgroup of interest; (4) no outcomes of interest were presented.

The data were extracted by one reviewer, and a second reviewer assessed the entries to ensure consistency and accuracy against the source article as a validation step.

Relevant SLRs, network meta-analyses (NMAs), and indirect treatment comparisons (ITCs) reporting study types of interest included, but not submitted for data extraction. Instead, their reference lists were reviewed for relevant articles that had not been identified through the above searches. The citations were retrieved with citationschaser from Lens.org (123) and the titles were screened for relevant articles using keywords “neuromyelitis” or “NMOSD” or “NMO”.

Table 81 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with NMOSD	• Disease other than NMOSD • Non-human • Healthy volunteers
Intervention	Monoclonal antibodies • B-cell depleting agents • Inebilizumab (anti-CD19) • Rituximab (anti-CD20) • Ublituximab (anti-CD20) • Belimumab (BAFF inhibitor) • Daratumumab (anti-CD38) • Ofatumumab (anti-CD20) • Ocrelizumab (anti-CD20) • Mil62 (anti-CD20) • BAT4406F (anti-CD20) Interleukin-6 signaling blocking agents • Satralizumab • Tocilizumab Complement blocking agents • Eculizumab • Ravulizumab • FcRn inhibitors • Batoclimab (HBM9161) Bruton's tyrosine kinase inhibitors • Orelabrutinib • Zanubrutininb • Edralbrutinib (SHR1459) Other immunosuppressants • Azathioprine • Mycophenolate mofetil • Cyclophosphamide • Tacrolimus • Telitacicept (RC18) • Glucocorticoids • Methotrexate • Cyclosporin A • Mitoxantrone Others • NPB-01 (Human immunoglobulin G) • Intravenous immunoglobulin G • Plasmapheresis	Studies not including at least one of the interventions listed in the inclusion criteria
Comparators	• Any included intervention • Any non-included intervention	None
Outcomes	• Time to NMOSD attack/relapse • NMOSD attack/relapse rate • Changes in disability scores (i.e., EDSS) • Change visual acuity scores • Number of active MRI lesions • Number of patients with positive anti-drug antibodies (ADAs) • Safety outcomes	No limitations

	• Disease-related PROs (i.e., MSIS-29) • Disease-related HRQoL	
Study design/publication type	• Randomized controlled trials (RCTs) • Systematic reviews and meta-analyses (for cross-checking only) • Single-arm trials, i.e. phase 1 and 2 (criterion added during SLR update)	• Non-human, pre-clinical studies • Reviews, Editorials, Notes, Comments, Letters • Phase 1 Dose finding study or PK study (criterion removed for SLR update) • Case reports/case series • RWE studies (prospective observational studies, retrospective studies, cross-sectional studies, database and registry analyses)
Language restrictions	English language	Full-text articles not published in English

In the initial SLR, the database search returned 3,054 records, of which 1,994 were excluded during title and abstract screening. Of the 173 full texts assessed, 74 reports were excluded. Reasons for exclusion at the full-text review stage included PICOS categories outcomes (n = 13), study design (n = 60), and duplicates (n = 1). Following the grey literature search, 13 relevant reports from the congress review, five from the bibliographic search, and 91 from the trial registries met review inclusion criteria. In total, 117 reports from 13 unique studies were included in the SLR. For data extraction, 104 publications on 13 unique studies were prioritized. The remaining 13 reports were excluded from data extraction due to their focus on subgroup population not of interest (subpopulation with no concomitant immunosuppressants (n=4); with relapse (n=3); AQP4-negative NMOSD (n=2); adolescent (n=2); steroid tapering (n=1); concomitant autoimmune disease (n=1)). The flow of literature is presented as a PRISMA diagram in Figure 19.

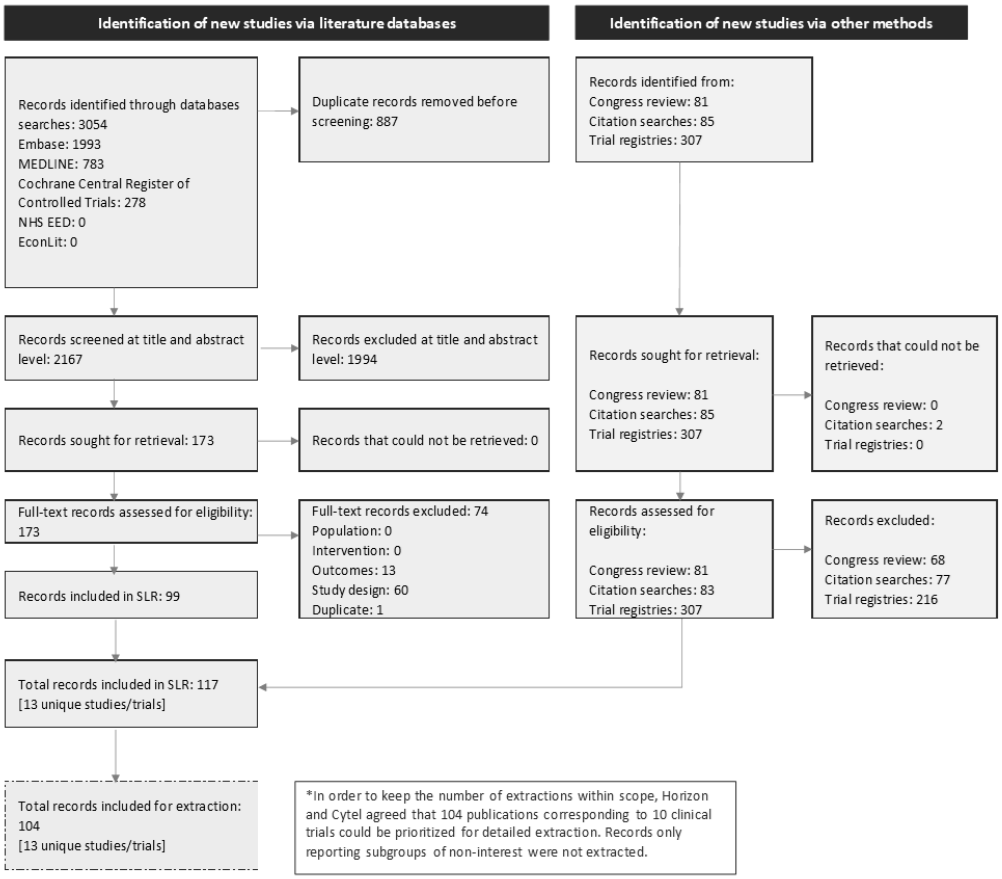


Figure 19 PRISMA flow diagramme for initial clinical SLR

During the SLR update, electronic searches identified 571 publications (Embase 411, MEDLINE 127, Cochrane library 33) of which 81 were removed as duplicates and 490 were submitted for the title and abstract screening stage. Following the screening 442 publications were excluded and 48 were included for the full text review stage. During the re-screening, 1431 publications that were excluded during the original SLR with the reason “study design” (only RCTs were included in the original SLR) were submitted for title and abstract rescreening. During this step 1385 were excluded and 46 were selected for the full text review. Before full text review publications from both screenings were crosschecked and 7 duplicates were removed. In addition, 8 publications from the original SLR (excluded at full text review with “study design”) were included for reassessment. Altogether, 95 publications were submitted to full text review and 37 were excluded.

Five publications were categorized as SLR, NMA or ITC and were submitted for reference checks to identify any relevant publications that were not captured during the electronic search and rescreening; 2 additional references were identified during this step.

Initially, 53 publications were included for data extraction, however following crosschecking with the data already extracted during the original SLR 44 publications

were excluded. Congress search identified 9 abstracts that were included for data extraction, therefore 31 studies were extracted and included in the summary report.

The results of the updated clinical SLR are presented in Figure 20.

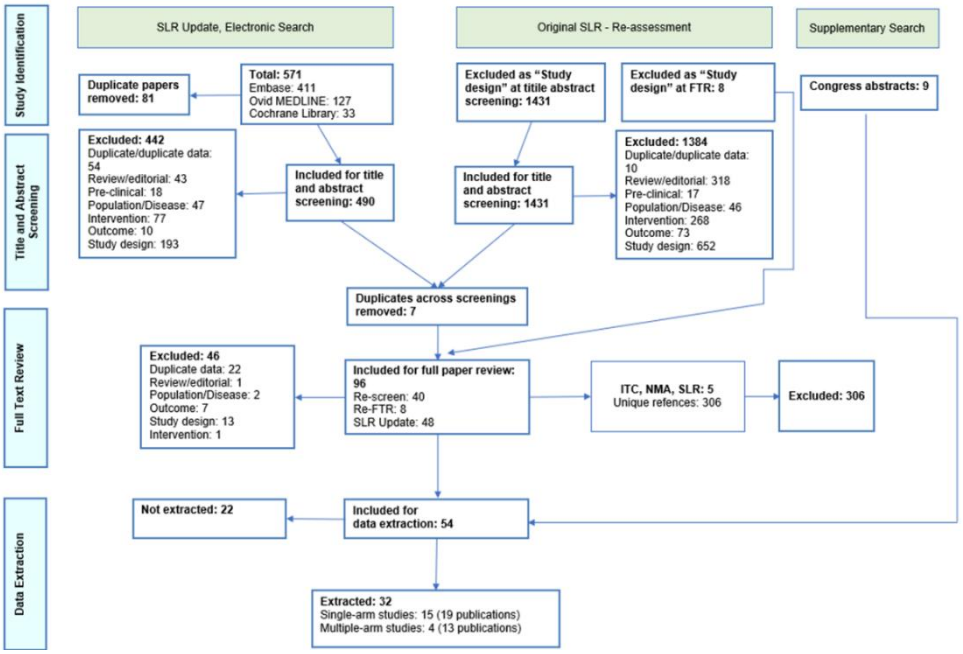


Figure 20 PRISMA flow diagramme for updated clinical SLR

Table 82 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
N-MOmentum (NCT 02200770)	To assess the efficacy and safety of inebilizumab in reducing the risk of attacks and disability in NMOSD	Phase 2/3 double blind RCT	NMOSD	Inebilizumab (n=174) Comparator (n=56)	Time (in days) from day 1 to the onset of an NMOSD attack (as determined by the adjudication committee), on or before day 197	Worsening of EDSS score from baseline (increase of ≥2 from baseline of 0, increase of ≥1 from baseline of 1–5, or increase of ≥0·5 from baseline of ≥5·5); change from

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						baseline in low-contrast visual acuity binocular score (by low-contrast Landolt C broken ring chart); cumulative total number of active MRI lesions (new gadolinium-enhancing lesions, or new or enlarging T2 lesions, measured across the optic nerve, brain, brainstem, and spinal cord); and number of NMOSD-related inpatient hospitalisations, longer than an overnight stay.

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Kim et al.	To evaluate the efficacy and safety of repeated rituximab treatment based on the assessment of peripheral circulating memory B cells over 24 months in patients with relapsing NMO	Prospective open-label study	NMOSD	Rituximab (n=30) Induction dose: 1) 375 mg/m2 once per week for 4 weeks or 2) 1000 mg twice a week with a 2-week interval Maintenance dose: 375 mg/m2 whenever frequency of memory B cells was 0.05% or more in peripheral blood mononuclear cells	Annual relapse rate Follow-up period: 24 months	Changes in EDSS score, AQP4 antibody levels and safety Follow-up period: 24 months

H.1.3 Quality assessment

Both the initial and updated SLRs were undertaken utilizing a rigorous methodology to minimize potential limitations, adhering to established guidelines by leading organizations such as the Centre for Reviews and Dissemination and the Cochrane Collaboration Handbook (110), and key HTA organizations (110, 112, 113), and was designed to satisfy the requirements of the majority of HTA organizations. The SLRs encompassed multiple databases and grey literature searches to ensure robust inclusion of publications containing evidence for NMOSD. The PICOS approach allowed for strict criteria to identify included studies. Two reviewers were involved at every stage of the SLRs (title/abstract review, full-text review, data extraction, and analysis) to ensure quality. Specific studies were identified that focused on NMOSD through a search strategy that was well balanced for specificity and sensitivity. The SLRs followed a transparent search strategy whereby the results can be reproduced using the same search terms and databases. There was no

restriction on the timeframe for the clinical efficacy and effectiveness SLRs ensuring that all studies on NMOSD could be captured since database inception.

However, this SLR is not without limitations. Conclusions of the SLR were based on the included publications only. Some data were reported exclusively in conference abstracts, providing a limited context for interpretation. Sources of confounding within the dataset included, but were not limited to, country differences, sample size, treatment, severity of disease, and comorbidities. Moreover, publication bias is an inherent limitation to every SLR and cannot be avoided, despite a rigorous methodology. It may happen when pertinent studies, either ongoing or completed, remain unpublished. Studies included in these SLRs were limited by outcomes of interest at the data extraction phase; studies without relevant outcomes of interest were excluded. Included studies may be biased toward achieving a positive result. Differences between the study characteristics of the included studies were observed and may introduce bias into the conclusions of these studies, and therefore the conclusions of these SLRs. Additionally, despite implementing vigorous and accepted systematic review methods to mitigate bias the outcomes of SLRs, including this one, are restricted by the quality and quantity of evidence derived from the incorporated studies. A significant limitation of the available evidence from SATs studies is the inclusion of small numbers of patients in many studies. Furthermore, the search strings were limited to treatments of interest, increasing the risk of overlooking relevant evidence if treatment was not indexed or mentioned in the title or abstract. Finally, in the SLR update, only studies excluded based on "study design" were reassessed, potentially omitting relevant single-arm trials that were misclassified.

A list of excluded full text studies is embedded below.

NMOSD_Clinical SLR_List of rejected

SOURCE	AUTHORS	TITLE	ABSTRACT	REASON FOR REJECTION
Neurology. 64(7):1270-2, 2005 Apr 12.	Cree BA Lamb S Morgan K Chen A Waubant E Genain C	An open label study of the effects of rituximab in neuromyelitis optica	Eight patients with worsening neuromyelitis optica were treated with rituximab to achieve B cell depletion. Treatment was well tolerated. Six of eight patients were relapse free and median attack rate declined from 2.6 attacks/patient/year to 0 attacks/patient/year (p = 0.0078). Seven of eight patients experienced substantial recovery of neurologic function over 1 year of average follow-up. The pretreatment median Expanded Disability Status Scale score was 7.5, and at follow-up examination was 5.5 (p = 0.013).	STUDY DESIGN
International journal of MS care. Vol.22(S2):77-76p, 2020.	Greenberg BM de Seze J Fox E Saiz A Takashi Yamamura Marcillat C Xiujing Kou Weber K	(RTH01) Safety of Satralizumab Based on Pooled Data from Phase 3 Studies in Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)2020 Virtual Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 26-29, 2020	Background: Interleukin-6 (IL-6) is implicated in the immunopathology of neuromyelitis optica spectrum disorder (NMOSD). Satralizumab, a humanized recycling monoclonal antibody that binds to the IL-6 receptor, demonstrated a reduction in NMOSD relapse risk in two phase 3 studies: SAkuraSky (satralizumab in combination with baseline immunosuppressants; trial registration: NCT02028884), and SAkuraStar (satralizumab monotherapy; NCT02073279). Objectives: To evaluate the safety of satralizumab vs placebo in a pooled population of patients with NMOSD from the SAkura studies, using the latest data from their open-label extension (OLE) periods. Methods: SAkuraStar and SAkuraSky are randomized studies comprising a double-blind (DB) period (satralizumab 120 mg every 4 weeks vs placebo) followed by an OLE period (satralizumab only). The combined DB and extension period was defined as the overall satralizumab treatment (OST) period (cutoff June 7, 2019). Safety was evaluated in the DB and OST periods and reported as adverse event (AE) rates per 100 patient-years (PYs). Results: The pooled DB population	STUDY DESIGN

	Weinshenker BG		included 178 patients (satralizumab, n = 104; placebo, n = 74), and a total of 166 patients received satralizumab in the OLE. Mean and median satralizumab exposures in the OST period were 133.3 and 128.6 weeks. Rates of AEs and serious AEs were comparable between satralizumab and placebo groups in the DB period (AEs: 478.49 vs 506.51 events/100 PYs, respectively; serious AEs: 14.97 vs 17.98 events/100 PYs, respectively), and were consistent in the OST period. In the DB period, 4 patients (3.8%) in the satralizumab group and 6 (8.1%) in the placebo group withdrew from study due to an AE. Infection rates were lower with satralizumab vs placebo in the DB period (113.04 vs 154.85 events/100 PYs), with no increased risk of opportunistic infections. Infection rates with satralizumab were similar between the DB and OST periods. The injection-related reaction rate was higher with satralizumab vs placebo in the DB period (17.03 vs 8.99 events/100 PYs); injectionrelated reactions were mostly mild-to-moderate and did not lead to treatment discontinuation. No deaths or anaphylactic reactions were reported. Conclusions: In patients with NMOSD, satralizumab was well tolerated and showed a favorable safety profile. Results from the overall satralizumab treatment period, which expanded on the DB periods by adding data from the ongoing OLE periods, were consistent with the DB period results.	
Neurology. Vol.92(15): 2019-05-04 to 2019-05-10. 71st Annual Meeting of the American Academy of Neurology, AAN 2019. Philadelphia, PA. United States. Netherlands Lippincott Williams and Wilkins	Cree B Bennett J Kim HJ Weinshenker B Pittock S Wingerchuk D Fujihara K	A double-masked, placebo-controlled study with open-label period to evaluate the efficacy and safety of inebilizumab in adult subjects with neuromyelitis optica spectrum disorders-top line efficacy and safety results	Objective: To evaluate the safety and efficacy on relapse prevention, of inebilizumab, an anti-CD19, B-cell depleting monoclonal antibody in neuromyelitis optica spectrum disorder (NMOSD). Background: Currently there are no approved therapies for NMOSD. Empiric experience suggests that depleting B-cells may have therapeutic benefit in attack prevention. Design/Methods: N-MOmentum is a phase III, double-masked, randomized, placebocontrolled trial of inebilizumab (MEDI-551) in NMOSD. A three-member eligibility committee confirmed entry criteria for AQP4-IgG seronegative subjects. Participants were randomized 3:1 to either treatment with inebilizumab or placebo. Concurrent treatment with other immune suppressants was prohibited. The placebo-controlled period was limited to 6.5 months in duration. The primary outcome measure was time to first adjudicated attack. Clinical criteria for NMOSD attacks were developed and implemented. A three-member committee adjudicated all investigator-reported attacks. Patients who either experienced an adjudicated attack or completed the	OUTCOMES

	Paul F Cutter G Marignier R Green A Aktas O Hartung H-P Drappa J Barron G Madhani S Ratchford J She D Katz E		controlled phase of the study were offered treatment with inebilizumab in an open label extension study. Acute attacks were treated with the investigator's choice of therapy. Results: On September 7, 2018, the external data safety monitoring committee (DSMC) concluded that continued enrollment with potential exposure to placebo was no longer ethical due to demonstrated efficacy and safety. The DSMC recommended that all participants in the randomized controlled period be moved to active treatment with inebilizumab and that all study participants continue in the open label extension protocol for ongoing safety assessments. 230 subjects from 24 countries were randomized and dosed (planned sample size: 252). 212 were seropositive and 18 were seronegative for anti-AQP4 antibodies. 42 adjudicated attacks occurred in the controlled period. The study remains masked and data lock will occur in December 2018 after which analysis of the primary and secondary endpoints and safety will occur. Conclusions: Top-line data on inebilizumab's efficacy and safety in NMOSD will be presented.	
Multiple sclerosis journal. Vol.23(3):990-991p, 2017-10-25 to 2017-10-28. 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. Paris. France. Netherlands SAGE Publications Ltd	Badihian S Nikoo Z Shaygannejad V Asgari N Ashtari F	Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: a randomized clinical trial	Background: Neuromyelitis Optica spectrum disorder (NMOSD) often follows a relapsing course. As disability in NMOSD is attack-related, effective treatments are needed. We aimed to compare the efficacy of azathioprine (AZA) and rituximab (RIT) as maintenance therapy in NMOSD patients. Methods: An open, randomized clinical trial conducted during September 2015 to December 2016, in Isfahan, Iran. Initially 100 NMOSD patients were approached, 86 entered the study and 68 cases completed the trial. All patients had a relapsing-remitting course with expanded disability extended scale (EDSS) ⩽7 (median 2.75, range=0-7). Patients were randomized into two groups, which did not differ according to age, gender distribution and disease duration. In the AZA group 35 patients (20 aquaporin- 4 (AQP4)-IgG positive) were started on 50 mg/day oral	STUDY DESIGN

			AZA, increased to 2-3 mg/kg/day (with oral prednisolone as adjunctive therapy). In the RIT group 33 patients (13 aquaporin- 4-IgG positive), received 1 g intravenous rituximab, repeated two weeks later, and then every six months. Annualized relapse rate (ARR) was measured as the primary outcome, and EDSS as the secondary outcome after 12 months of intervention. Results: The mean ARR (standard deviation [SD]) in the AZA group decreased from 1 (0.38) to 0.51 (0.55) (P-value< 0.001) and in the RIT group decreased from 1.30 (0.68) to 0.21 (0.42) (P-value< 0.001). ARR after intervention minus ARR before intervention (mean [SD]) was 1.09 (0.72) in RIT group and 0.49 (0.59) in AZA group (P-value< 0.001). EDSS after intervention minus EDSS before intervention (mean [SD]) was 0.98 (1.14) in RIT group and 0.44 (0.54) in AZA group (P-value< 0.001). Nineteen patients (54.3%) in AZA group and 26 patients (78.8%) in RIT group became relapse-free after intervention (P-value=0.033). Conclusion: AZA and RIT can both effectively decrease ARR and EDSS in NMOSD patients. RIT was significantly more effective than AZA treatment.	
Multiple sclerosis journal. Vol.25, pp.137-138, 2019-09-11 to 2019-09-13. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2019. Stockholm. Sweden. Netherlands SAGE Publications Ltd	Weinshenker B Wingerchuk D Green A Bennett J Kim HJ Pittock S Fujihara K Paul F Cutter G Marignier R	Diagnosis, severity, and recovery of attacks in the N-MOmentum study of inebilizumab in Neuromyelitis optica spectrum disorder	Introduction: The N-MOmentum study compared the effects of inebilizumab vs. placebo (3:1 randomization, without background immunosuppressive therapy) on risk of neuromyelitis optica spectrum disorder (NMOSD) attack in 230 subjects. The primary endpoint was time to first adjudicated NMOSD attack. Objective: Discuss process and implications of rigorous attack diagnosis in NMOSD clinical trial Methods: A set of 18 attack criteria were developed in collaboration with NMOSD experts. Potential attacks were evaluated by both investigators and an independent adjudication committee (AC) of 3 NMOSD experts to ensure reliable and consistent application of the criteria. Attack diagnosis required new/worsening NMOSD symptoms, ophthalmologic and/or EDSS changes that met at least one criterion, and supportive MRI findings in cases where clinical criteria were indeterminate. The attack criteria cover optic neuritis (ON), myelitis, and brain/brainstem. Attack severity was graded according to a predefined scale based on domain-specific neurological changes since the last assessment. Attack recovery was graded on the degree of domain-specific neurological improvement 30 days after the attack assessment. Results: Of the 64 potential attacks, protocol criteria were met for 51 (80%) as determined by investigators and 43 (67%) as determined by the AC. 54/64 (84%) decisions by the AC were unanimous, indicating a high degree of inter-member agreement. Of the 43 AC-determined	OUTCOMES

	Aktas O Hartung H-P Drappa J Barron G Madani S Ratchford J Shi D Cimbora D Katz E Cree B		attacks, 27 were myelitis, 20 ON, and 2 brainstem, with 6 affecting more than one domain. MRI-requiring criteria were deemed to have been met 16/43 times by the AC. Of attacks in the placebo group, 45% were graded as major and 55% as minor, compared to 29% major and 71% minor attacks in the inebilizumab-treated group. Among the 17 attacks with follow-up data in the placebo group, 53% exhibited no recovery and 47% had at least partial recovery. In the 13 inebilizumab group attacks, 46% exhibited no recovery and 54% had at least partial recovery. Conclusion: By implementing consistent processes for the diagnosis and adjudication of NMOSD attacks, the N-MOmentum study provides information regarding attack severity and recovery in response to inebilizumab. Furthermore, this study helps establish provisional criteria for attack diagnosis for clinical and research application, and highlights the diagnostic challenges, the supportive role of neuroimaging, and the importance of independent expert review.	
Multiple Sclerosis Journal. Conference: 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2021. Virtual. 27(2 SUPPL) (pp 151), 2021. Date of Publication: October 2021.	Royston M. Kielhorn A. Tanvir I. Sabatella G.	Disease outcomes in the absence of a relapse in patients with neuromyelitis optica spectrum disorder	Introduction: Aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD) is characterized by unpredictable relapses that can lead to severe impairment through vision loss, neurological disability, and poor health-related quality of life (HRQoL). Current therapeutic strategies focus on preventing relapses. However, it is unclear if any disease worsening occurs in the absence of a relapse. Objective(s): To investigate changes in disability and HRQoL outcomes in the absence of an adjudicated relapse in patients with AQP4+ NMOSD. Method(s): Analyses were based on data collected from the phase 3 PREVENT study and its open label extension (OLE). Key outcome measures for these post hoc analyses included: Expanded Disability Status Scale for general disability progression, Hauser Ambulation Index for mobility, Modified Rankin Score for dependence in daily activities, and the European Quality of Life 5-Dimension questionnaire and the 36-Item Short Form Survey for HRQoL. Four different subsets of patient data were used, none of which included relapse events	OUTCOMES

			irrespective of the treatment arm: all patients who were enrolled until an adjudicated on-trial relapse or end of the study; patients who did not experience any on-trial relapse; all patients who reached the 1-year mark in PREVENT; and all patients from the OLE (up to 222 weeks). Result(s): For all patient data sets analyzed, no significant worsening was observed in the absence of a relapse across all outcomes. These findings were consistent for all assessment timepoints over the 120-week study period for all patients enrolled in PREVENT and for the subset of non-relapsing patients. Similar findings were observed across the 48-week period for the patient population (n = 82) who completed at least 1 year of the study, suggesting these analyses were not influenced by the number of patients completing the study. Also, in the absence of a relapse, no disease worsening was observed on key outcomes at the 19 assessment timepoints in the PREVENT extended study timeframe. Conclusion(s): Studies have shown that patients worsen after NMOSD relapses. Here, we show that in the absence of relapses and regardless of the analytical approach, current disease outcome measures could not detect a clinically meaningful worsening of disability or HRQoL. These findings reinforce the critical importance of a therapeutic approach aimed at preventing relapses in patients with AQP4+ NMOSD to avoid disability worsening.	
The New England journal of medicine. (no pagination), 2019. Date of Publication: 03 May 2019.	Pittock S.J. Berthele A. Fujihara K. Kim H.J. Levy M. Palace J. Nakashima I. Terzi M.	Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder	BACKGROUND: Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing, autoimmune, inflammatory disorder that typically affects the optic nerves and spinal cord. At least two thirds of cases are associated with aquaporin-4 antibodies (AQP4-IgG) and complement-mediated damage to the central nervous system. In a previous small, open-label study involving patients with AQP4-IgG-positive disease, eculizumab, a terminal complement inhibitor, was shown to reduce the frequency of relapse. METHOD(S): In this randomized, double-blind, time-to-event trial, 143 adults were randomly assigned in a 2:1 ratio to receive either intravenous eculizumab (at a dose of 900 mg weekly for the first four doses starting on day 1, followed by 1200 mg every 2 weeks starting at week 4) or matched placebo. The continued use of stable-dose immunosuppressive therapy was permitted. The primary end point was the first adjudicated relapse. Secondary outcomes included the adjudicated annualized relapse rate, quality-of-life measures, and the score on the Expanded Disability Status Scale (EDSS), which ranges from 0 (no disability) to 10 (death). RESULT(S): The trial was stopped after	DUPLICATE

	Totolyan N. Viswanathan S. Wang K.-C. Pace A. Fujita K.P. Armstrong R. Wingerchuk D.M.		23 of the 24 prespecified adjudicated relapses, given the uncertainty in estimating when the final event would occur. The mean (+/-SD) annualized relapse rate in the 24 months before enrollment was 1.99+/-0.94; 76% of the patients continued to receive their previous immunosuppressive therapy during the trial. Adjudicated relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in the placebo group (hazard ratio, 0.06; 95% confidence interval [CI], 0.02 to 0.20; P<0.001). The adjudicated annualized relapse rate was 0.02 in the eculizumab group and 0.35 in the placebo group (rate ratio, 0.04; 95% CI, 0.01 to 0.15; P<0.001). The mean change in the EDSS score was -0.18 in the eculizumab group and 0.12 in the placebo group (least-squares mean difference, -0.29; 95% CI, -0.59 to 0.01). Upper respiratory tract infections and headaches were more common in the eculizumab group. There was one death from pulmonary empyema in the eculizumab group. CONCLUSION(S): Among patients with AQP4-IgG-positive NMOSD, those who received eculizumab had a significantly lower risk of relapse than those who received placebo. There was no significant between-group difference in measures of disability progression. (Funded by Alexion Pharmaceuticals; PREVENT ClinicalTrials.gov number, NCT01892345; EudraCT number, 2013-001150-10.).Copyright ? 2019 Massachusetts Medical Society.	
Clinical Neurology. Conference: 62nd Annual Meeting of the Japanese Society of Neurology. Kyoto Japan. 61(Supplement 1) (pp S366), 2021. Date of Publication: 2021.	Yamamura T. Araki M. Okuno T. Misu T. Guo Y.-C. Hemingway C. Matsushima J. Sugaya N.	Exploring steroid tapering in NMOSD patients treated with satralizumab in SAkuraSky: A case series	Background Oral steroid maintenance therapy is widely used in patients with neuromyelitis optica spectrum disorder (NMOSD) despite side effects with long-term use. In SAkuraSky, a double-blind, phase 3 study, satralizumab added to baseline immunosuppressive treatment reduced relapse risk with a favourable safety profile vs placebo in NMOSD patients. Objective To review a case series of 16 patients undergoing steroid tapering during the open-label extension (OLE) of SAkuraSky. Design/Methods During the double-blind period (DBP), patients were randomized to satralizumab (120 mg s.c.) or placebo administered at Weeks 0, 2, 4, and Q4W thereafter. During the OLE, oral steroid doses could be tapered at the investigator's discretion. Results 36 patients receiving baseline oral steroids entered the OLE. Steroids were tapered in 16 of these patients (clinical cut-off date, CCOD, 18 Feb 2020). In this subgroup, the mean satralizumab exposure during the OLE was 163.6 weeks. The median dose (range) of oral steroid was 10 mg (5-25 mg) at OLE baseline, and 2.75 mg (0-15 mg) at CCOD. Before DBP, the mean annual relapse rate (ARR) was 1.13. During DBP, the mean ARR of those	STUDY DESIGN

	Yamashita M. Von Budingen H.-C. Miyamoto K.		randomized to satralizumab vs placebo was 0.32 vs 0.48. During the OLE, the ARR was 0.06. 2 of 16 patients experienced clinical relapse during the OLE and continued satralizumab. The safety profiles were comparable with Phase 3 outcomes. Conclusions During the OLE of SAkuraSky, 16 patients tapered steroid and the ARR did not increase from the DBP. Patient numbers limit interpretation.	
Journal of Clinical Apheresis. 37(1):70-81, 2022 Feb.	Boedecker SC Luessi F Engel S Kraus D Klimpke P Holtz S Meinek M Marczynski P Weinmann A Weinmann-Menke J	Immunoadsorption and plasma exchange-Efficient treatment options for neurological autoimmune diseases	BACKGROUND: Therapeutic plasma exchange (TPE) and immunoadsorption (IA) are first or second line treatment options in patients with neurological autoimmune diseases, including multiple sclerosis, neuromyelitis optica spectrum disorders (NMSOD), chronic inflammatory demyelinating polyneuropathy, acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome), and autoimmune encephalitis. METHODS: In this prospective randomized controlled monocentric study, we assessed safety and efficacy of therapy with IA or TPE in patients with neurological autoimmune diseases. Treatment response was assessed using various neurological scores as well by measuring immunoglobulin and cytokine concentrations. Clinical outcome was evaluated by application of specific scores for the underlying diseases. RESULTS: A total of 32 patients were analyzed. Among these, 19 patients were treated with TPE and 13 patients with IA. IA and TPE therapy showed a comparable significant treatment response. In patients with MS and NMOSD, mean EDSS before and after treatment showed a significant reduction after treatment with IA. We observed a significant reduction of the pro-inflammatory cytokines IL-12, IL-17, IL-6, INF-gamma, and tumor necrosis factor alpha during IA treatment, whereas this reduction was not seen in patients treated with TPE. CONCLUSIONS: In summary, both IA and TPE were effective and safe procedures for treating neurological autoimmune diseases. However, there was a trend towards longer therapy response in patients treated with IA compared to TPE, possibly related to a reduction in plasma levels of pro-inflammatory cytokines	OUTCOMES

			seen only in the IA-treated group. Copyright ? 2021 The Authors. Journal of Clinical Apheresis published by Wiley Periodicals LLC.	
Multiple Sclerosis Journal. Conference: Annual Americas Committee for Treatment and Research in Multiple Sclerosis Forum, ACTRIMS 2021. Virtual. 27(1 SUPPL) (pp 81), 2021. Date of Publication: 2021.	Greenberg B. She D. Ratchford J.N. Katz E. Cree B.A.	Immunoglobulin Kinetics and Infection Risk after Long-Term Inebilizumab Treatment for NMOSD	Background: Long-term use of B-cell depleting monoclonal antibodies is associated with reduced immunoglobulin levels that can predispose to infection. The N-MOmentum trial of the anti-CD19 B cell depleting monoclonal antibody inebilizumab enrolled and dosed 230 participants with neuromyelitis optica spectrum disorder (NMOSD). The association between long-term immunoglobulin levels and infection rates was assessed in both the randomized controlled phase (RCP) and open-label extension (OLE) of N-MOmentum. Objective(s): To evaluate changes in immunoglobulin levels and infection rates in inebilizumab treated patients. Method(s): Immunoglobulin levels were measured systematically by a central clinical laboratory. Adverse events, including infections, were collected and recorded. Opportunistic infections were predefined based on medical review. Result(s): Immunoglobulin levels were analyzed for 174 of 230 enrolled participants who were given inebilizumab through 4.75 years after baseline. Ig levels decreased with inebilizumab; the mean decrease in total Ig at 4.75 years was-35%. The mean percent change from baseline through 4.75 years was-62% for IgM,-50% for IgA and-30% for IgG. During the RCP the rate of infection was 140.2 (97.1, 195.9) per 100 person years for participants on placebo and 138.1 (113.9, 165.9) for those on inebilizumab. The rate of infection was lower in the OLE than the RCP: year 2: 69.9, year 3: 61.5, and year 4: 62.3 infections per 100 patient years (614.6 person years of follow-up). The most common infections seen were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis and influenza. The proportion of patients with an infection was similar for patients with IgG levels below and above the lower limit of normal (78.9% vs. 72.9%). An IgG level below 300 mg/dL was observed at least once in 8 subjects, but the proportion of patients with infection did not differ between those with IgG<300 mg/dL and those with IgG700 mg/dL (75.0% vs. 72.9%). Conclusion(s): As expected, immunoglobulin levels decline with continued inebilizumab use. However, the rate of infections did not increase with continued inebilizumab use and infection rates were similar between study subjects with normal and low IgG levels in this cohort.	OUTCOMES

European Journal of Neurology. Conference: 7th Congress of the European Academy of Neurology. Virtual. 28(SUPPL 1) (pp 177), 2021. Date of Publication: June 2021.	Greenberg B. Cree B. She D. Katz E.	Immunoglobulin kinetics and infection risk after long-term inebilizumab treatment for NMOSD	Background and aims: Long-term use of B-cell depleting monoclonal antibodies is associated with reduced immunoglobulin (Ig) levels, increasing infection risk. The association between Ig levels and infection was assessed in the 28-week randomized controlled phase (RCP) and optional open-label period (OLP; minimum two years) of the N-MOmentum trial of inebilizumab for neuromyelitis optica spectrum disorder. Method(s): Ig levels were centrally recorded. Adverse events, including infections, were monitored. Opportunistic infections were predefined based on medical review. Result(s): Ig levels were analyzed for 174/230 participants receiving inebilizumab for 4.75 years. There was a 35% mean decrease in total Ig with inebilizumab. Mean percent change from baseline was -62% for IgM, -50% for IgA and -30% for IgG. During the RCP, the rate of infection per 100 person-years was 140.2 (placebo) and 138.1 (inebilizumab). Infection rates per 100 person-years were lower in the OLP than the RCP: year 2: 69.9, year 3: 61.5, and year 4: 62.3 (follow-up: 614.6 person-years). The most common infections were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis and influenza. The proportion of participants with an infection was similar for those with IgG levels below and above lower limit of normal (78.9% vs. 72.9%). Eight participants had IgG level <300 mg/dL at least once. The proportion of participants with infection did not differ between those with IgG<300 mg/dL and IgG 700 mg/dL (75.0% vs. 72.9%). Conclusion(s): Despite declining Ig levels, infection rate did not increase with long-term inebilizumab treatment or differ between participants with normal and low IgG.	OUTCOMES
European Journal of Neurology. Conference: 6th Congress of the European Academy of Neurology. Paris France. 27(Supplement 1) (pp 381-382), 2020. Date of Publication: May 2020.	Mantegazza R.E. Levine T.D. Oreja-Guevara C. Carrillo-Infante C.	No change in risk of infection among NMOSD and refractory gMG patients treated with eculizumab: Findings from two phase 3 studies and their extensions	Background and aims: PREVENT (NCT01892345) and REGAIN (NCT01997229) were phase 3, randomized, double-blind studies comparing efficacy and safety of eculizumab and placebo in patients with aquaporin-4 antibody-positive (AQP4+) neuromyelitis optica spectrum disorder (NMOSD) and refractory acetylcholine-receptor antibody-positive (AChR+) generalized myasthenia gravis (gMG), respectively. We report infection rates in patients treated with eculizumab with or without concomitant immunosuppressant therapy (IST) in PREVENT, REGAIN and respective open-label extensions (NCT02003144 [interim data] and NCT02301624). Method(s): Patients were vaccinated against Neisseria meningitidis and randomized to eculizumab (maintenance dose, 1200mg/2 weeks) or placebo, with stable-dose concomitant ISTs permitted. Pooled infection rates	OUTCOMES

	Shang S. Kaprielian R. Pittock S.J. Howard J.F.		were analysed post hoc for subgroups determined by number of baseline ISTs (0, 1, 2 or >=3). Result(s): The numbers of patients exposed to eculizumab/ placebo were 137/47 (NMOSD; 276.6/51.5 patient-years) and 123/63 (gMG; 304.4/31.1 patient-years). There were no differences in infection or serious infection rates with extent of IST use (Table) nor an increase in infection risk with long-term eculizumab therapy (data will be presented); although, patient numbers were small in some subgroups. Similar infection types were observed in patients receiving eculizumab for each indication (total n=260): most commonly nasopharyngitis (n=76), upper respiratory tract infections (n=67), urinary tract infections (n=44) and influenza (n=39) (Figure). There was one case of meningococcal meningitis (encapsulated) in a patient with gMG receiving eculizumab (2 IST subgroup); this resolved with antibiotic treatment and eculizumab was reinstated. Conclusion(s): In these complement-mediated neurological conditions, overall risk and types of infections were similar in the eculizumab and placebo groups, regardless of concomitant IST. (Figure Presented).	
Neurology. Conference: 73rd Annual Meeting of the American Academy of Neurology, AAN 2021. Virtual. 96(15 SUPPL 1) (no pagination), 2021. Date of Publication: May 2021.	Yan L. Wang B. She D. Mitchel B. Criste R. Cimbora D. Katz E. Rees W.	Pharmacodynamic modeling and exposure response assessment of inebilizumab in subjects with neuromyelitis optica spectrum disorders	Objective: To conduct population modeling of B cell response following inebilizumab treatment in adult subjects with neuromyelitis optica spectrum disorders (NMOSD), and to assess the impact of drug exposure to outcome. Background(s): NMOSD is an autoantibody-mediated, B cell-driven disease. Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1kappa monoclonal antibody that binds to CD19 resulting in effective depletion of B cells. Design/Methods: In a double-blind, placebo-controlled study (NCT02200770), adult NMOSD patients were randomized in a 3:1 ratio to receive intravenous (IV) infusions of either inebilizumab (300 mg) or placebo on Days 1 and 15 of a randomized-controlled period and every 6 months thereafter during the open label period. A hematopoietic transit model was developed to describe the depletion of circulating CD20+ B cell by inebilizumab. Furthermore, the relationships between inebilizumab pharmacokinetic (PK) exposure and the primary efficacy endpoint (Adjudication Committee (AC)-determined NMOSD attack) and key secondary efficacy endpoints were evaluated. Result(s): Treatment with inebilizumab led to rapid, profound, and sustained depletion of circulating B cells in NMOSD patients. The pharmacodynamic effect of inebilizumab was exerted by joint effects of reducing influx from pro-B cells and accelerating CD20+ B cell depletion in the blood. At the 300 mg dose, there was no apparent relationship between efficacy	OUTCOMES

			(reduction in disease attack risk, worsening from baseline in Expanded Disability Status Scale, cumulative total active MRI lesions, and number of NMOSD-related in-patient hospitalizations) with PK exposure. Subjects with low, medium and high PK exposure had a similar hazard ratio of AC-determined NMOSD attack. Conclusion(s): The pharmacodynamic modeling and exposure-response analyses of primary and key secondary endpoints confirmed effective depletion of B cells is achieved with 300 mg IV dose administered on Day 1 and Day 15 and every 6 months thereafter. The PK variability between patients had no apparent effect on the hazard ratio for NMOSD attack.	
Clinical Pharmacology and Therapeutics. Conference: Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, ASCPT 2021. Online. 109(SUPPL 1) (pp S21-S22), 2021. Date of Publication: March 2021.	Yan L. Wang B. She D. Mitchell B. Criste R. Cimbora D. Katz E. Rees W.	Pharmacodynamic modeling and exposure-response assessment of inebilizumab in subjects with neuromyelitis optica spectrum disorders	BACKGROUND: Neuromyelitis optica spectrum disorders (NMOSD) is an autoantibody-mediated, B cell-driven disease. Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1k monoclonal antibody that binds to CD19 resulting in effective depletion of B cells. METHOD(S): In a double-blind, placebo-controlled study (NCT02200770), adult NMOSD patients were randomized in a 3:1 ratio to receive intravenous (IV) infusions of either inebilizumab (300 mg) or placebo on days 1 and 15 of a randomized-controlled period and every 6 months thereafter during the open label period. A hematopoietic transit model was developed to describe the depletion of circulating CD20 + B cell by inebilizumab. Furthermore, the relationships between inebilizumab pharmacokinetic (PK) exposure and the primary and key secondary efficacy endpoints were evaluated. RESULT(S): Treatment with inebilizumab led to rapid, profound, and sustained depletion of circulating B cells in NMOSD patients. The pharmacodynamic effect of inebilizumab was exerted by joint effects of reducing influx from pro-B cells and accelerating CD20 + B cell depletion in the blood. At the 300 mg dose, there was no apparent relationship between efficacy (reduction in disease attack risk, worsening from baseline in Expanded Disability Status Scale, cumulative total active MRI lesions, and number of NMOSD-related in-patient hospitalizations) with PK exposure. Subjects with low, medium and high PK exposure had a similar hazard ratio of NMOSD attack. CONCLUSION(S): The pharmacodynamic modeling and exposure-response analyses of primary and key secondary endpoints confirmed effective depletion of B cells is achieved with 300 mg IV dose administered on day 1 and day 15 and every 6 months thereafter. The PK variability between patients had no apparent effect on the hazard ratio for NMOSD attack.	OUTCOMES

Multiple Sclerosis Journal. Conference: 8th Joint ACTRIMS-ECTRIMS Meeting. Virtual. 26(3 SUPPL) (pp 94-95), 2020. Date of Publication: December 2020.	Yan L. Wang B. She D. Mitchel B. Criste R. Cimbora D. Katz E. Rees W.	Pharmacodynamic modeling and exposure-response assessment of inebilizumab in subjects with neuromyelitis optica spectrum disorders	Background: Neuromyelitis optica spectrum disorders (NMOSD) is an autoantibody-mediated, B cell-driven disease. Compared to CD20, CD19 is expressed on a wider range of the B cell lineage, from pro-B to plasmablasts and some plasma cells. Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1kappa monoclonal antibody that binds to CD19 resulting in effective depletion of B cells. Objective(s): To conduct population modeling of B cell response following inebilizumab treatment in adult subjects with NMOSD, and to assess the impact of drug exposure to outcome. Method(s): In a double-blind, placebo-controlled study (NCT02200770), adult NMOSD patients were randomized in a 3:1 ratio to receive intravenous infusions of either inebilizumab (300 mg) or placebo on Days 1 and 15 of a randomized-controlled period (RCP, 197 days) and every 6 months thereafter during the open label period. A hematopoietic transit model was developed to describe the depletion of circulating CD20+ B cell by inebilizumab. Furthermore, the relationships between inebilizumab pharmacokinetic (PK) exposure and the primary efficacy endpoint (Adjudication Committee (AC)-determined NMOSD attack) and key secondary efficacy endpoints were evaluated. Result(s): Treatment with inebilizumab led to rapid, profound, and sustained depletion of circulating B cells in NMOSD patients. The pharmacodynamic effect of inebilizumab was exerted by joint effects of reducing influx from pro-B cells and accelerating CD20+ B cell depletion in the blood. At the 300 mg dose, there was no apparent relationship between efficacy (reduction in disease attack risk, worsening from baseline in Expanded Disability Status Scale, cumulative total active MRI lesions, and number of NMOSD-related in-patient hospitalizations) with PK exposure. Subjects with low, medium and high PK exposure had a similar hazard ratio of AC-determined NMOSD attack for inebilizumab. Conclusion(s): The pharmacodynamic modeling and exposureresponse analyses of primary and key secondary endpoints confirmed effective depletion of B cells is achieved with 300 mg dose administered as an IV infusion on Day 1 and Day 15 and every 6 months thereafter. The PK variability between patients had no apparent effect on the hazard ratio for NMOSD attack.	OUTCOMES
British Journal of Clinical Pharmacology.	Yan L Wang B	Pharmacodynamic modelling and exposure-response	AIMS: Neuromyelitis optica spectrum disorders (NMOSD) is an autoantibody-mediated, B cell-driven disease. Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody that binds to the B-cell specific	STUDY DESIGN

88(8):3803-3812, 2022 08.	She D Mitchell B Criste R Cimbora D Katz E Rees WA	assessment of inebilizumab in subjects with neuromyelitis optica spectrum disorders	surface antigen CD19, resulting in rapid, profound and sustained depletion of circulating peripheral B cells in NMOSD subjects (pivotal study). The objective of this study was to conduct population modelling of B-cell response following inebilizumab treatment in adult subjects with NMOSD, and to assess the impact of drug exposure to outcome. METHODS: A haematopoietic transit model was developed to describe the joint effects of reducing influx from pro-B cells and accelerating CD20+ B-cell depletion in the blood by inebilizumab. Furthermore, the relationships between inebilizumab pharmacokinetic (PK) exposure and the primary efficacy endpoint and key secondary efficacy endpoints were evaluated. RESULTS: At the 300-mg dose, there was no apparent relationship between efficacy (reduction in disease attack risk, risk of worsening from baseline in Expanded Disability Status Scale, cumulative total active MRI lesions, and the number of NMOSD-related in-patient hospitalizations) and PK exposure. Subjects with low, medium and high PK exposure had a similar hazard ratio of NMOSD attack vs. placebo group. CONCLUSION: The pharmacodynamic modelling confirmed effective depletion of B cells is achieved with a 300 mg intravenous dose of inebilizumab administered on Day 1 and Day 15 and every 6 months thereafter. The PK variability between patients had no apparent effect on clinical efficacy. Copyright ? 2022 Horizon Therapeutics. British Journal of Clinical Pharmacology published by John Wiley & Sons Ltd on British Pharmacological Society.	
Journal of Clinical Apheresis. 16(1) (pp 39-42), 2001. Date of Publication: 2001.	Weinshenker B.G.	Plasma exchange for severe attacks of inflammatory demyelinating diseases of the central nervous system	Plasma exchange has not been widely accepted as a treatment for multiple sclerosis. However, several uncontrolled studies have suggested that patients with severe attacks of MS and other inflammatory demyelinating disease may improve rapidly after plasma exchange treatment. We recently completed a randomized, sham-controlled, crossover clinical trial of plasma exchange in 22 patients with idiopathic inflammatory demyelinating diseases of the central nervous system. Twelve had MS and ten had other inflammatory demyelinating disease syndromes. Forty-two percent of patients experienced moderate or greater recovery over 2 weeks of active treatment administered every other day while only	STUDY DESIGN

			6% of patients experienced similar improvement while receiving sham treatment. Three patients who failed the sham treatment subsequently improved rapidly after crossover to active treatment; no patient who failed active treatment improved after crossover to sham. This study illustrates the importance of designing randomized clinical trials based on the treatment regimen and patient population studied in the uncontrolled reports that suggested treatment efficacy. Plasma exchange should be considered for patients with idiopathic inflammatory demyelinating disease syndromes when they have failed corticosteroid therapy. ? 2001 Wiley-Liss, Inc.	
Multiple Sclerosis Journal. Conference: Pan-Asian Committee for Treatment and Research in Multiple Sclerosis Congress, PACTRIMS 2019. Singapore Singapore. 26(9) (pp NP80-NP82), 2020. Date of Publication: August 2020.	Paul F. Weinshenker B.G. Wingerchuk D. Green A. Bennett J.L. Kim H.J. Pittock S. Fujihara K. Cutter G. Marignier R. Aktas O. Hartung H-P.	Presentation-1 P-103 diagnosis, severity and recovery of attacks in the n-momentum study of inebilizumab in neuromyelitis optica spectrum disorder	Background: The N-MOmentum trial compared inebilizumab with placebo (3:1 randomization, without background immunosuppression) in 230 patents with neuromyelitis optica spectrum disorder (NMOSD). Primary endpoint was time to first adjudicated NMOSD attack. Objective(s): Assess on-study attack diagnosis, including adjudication- committee (AC) performance, attack characterization and effect of inebilizumab on attack severity and recovery. Method(s): A total of 18 attack criteria were predefined by NMOSD experts, covering optic neuritis (ON), myelitis andbrain/brainstem. Potential attacks were evaluated accordingly by investigators and an independent AC of three experienced NMOSD clinicians. Attack severity and recovery were graded by domain-specific neurological changes. Result(s): Of the 64 potential attacks in N-MOmentum, criteria were met for 51 as determined by investigators and 43 as determined by the AC; 51/64 (80%). AC decisions were unanimous, indicating high inter-member agreement. Of the 43 AC-adjudicated attacks, 27 were myelitis, 20 ON, 2 brainstems (6 affected multiple domains); 16 attacks met criteria requiring MRI. For placebo attacks (n=22), 45% were major and 55% minor; for inebilizumab attacks (n=21), 29% were major and 71% minor. Among placebo attacks with follow-up data (n=17), 53% showed no recovery and 47% had partial recovery. For inebilizumab attacks (n=13), 46% exhibited no recovery and 54% had partial recovery. Conclusion(s): By implementing consistent attack diagnosis/adjudication, the N-MOmentum study provides reliable information on attack risk, severity and recovery with inebilizumab. This study helps establish provisional attack criteria for clinical/ research application, and highlights the diagnostic challenges in NMOSD, the supportive role of neuroimaging and the importance of independent expert review.	OUTCOMES

	Drappa J. Barron G. Madani S. Ratchford J.N. She D. Cimbora D. Katz E. Cree B.A.C.			
BMC Neurology. 17(1):130, 2017 Jul 05.	Li X Mei S Gong X Zhou H Yang L Zhou A Liu Y Li X Zhao Z Zhang X	Relationship between Azathioprine metabolites and therapeutic efficacy in Chinese patients with neuromyelitis optica spectrum disorders	BACKGROUND: Neuromyelitis optica spectrum disorders (NMOSD) are demyelinating autoimmune diseases in the central nervous system (CNS) that are characterized by a high relapse rate and the presence of anti-aquaporin 4 antibodies (AQP4-IgG) in the serum. Azathioprine (AZA) is a first-line immunomodulatory drug that is widely used for the treatment of patients with NMOSD. However, the efficacy and safety of AZA vary in different individuals. METHOD: Thirty-two patients with NMOSD who regularly took AZA were enrolled in the study at Beijing Tiantan Hospital, Capital Medical University. The efficacy of AZA was evaluated using the expanded disability status scale (EDSS) and the annual relapse rate (ARR). The erythrocyte concentrations of AZA metabolites were detected using an LC-MS/MS method. RESULTS: The erythrocyte concentrations of 6-thioguanine nucleotides (6-TGNs) and 6-methylmercaptopurine nucleotides (6-MMPNs) were 202.03 +/- 63.35 pmol/8*108 RBC and 1618.90 +/- 1607.06 pmol/8*108 RBC, respectively. After the patients had received AZA therapy for more than one year, the EDSS score decreased from 5.21 +/- 0.24 to 2.57 +/- 0.33 ($p < 0.0001$), and the ARR decreased from 1.41 +/- 0.23 to 0.36 +/- 0.09 ($p < 0.0001$). The 6-TGN and 6-	STUDY DESIGN

			MMPN levels were significantly different between the non-relapsed and relapsed groups ($p < 0.0001$, $p = 0.006$, respectively). A higher ARR was significantly correlated with higher erythrocyte concentrations of 6-TGNs ($p < 0.0001$) and 6-MMPNs ($p = 0.004$). CONCLUSION: AZA can reduce the EDSS score and ARR in NMOSD patients. Additionally, the efficacy of AZA is significantly related to the erythrocyte concentrations of 6-TGNs and 6-MMPNs. Within the safe upper limits, a higher concentration of 6-TGNs is associated with better efficacy of AZA. TRIAL REGISTRATION NUMBER: ISRCTN16551495 , retrospectively registered on May 22, 2017.	
Journal of the Neurological Sciences. Conference: World Congress of Neurology (WCN 2021). Rome Italy. 429(Supplement) (no pagination), 2021. Article Number: 118787. Date of Publication: October 2021.	Mantegazza R. Levine T. Oreja-Guevara C. Carrillo-Infante C. Laudon-Meyer E. Shang S. Pittock S. Howard J.	Safety of eculizumab in NMOSD and MG: Analysis of the phase 3 studies prevent and regain, and their extensions	Background and aims: Eculizumab (a terminal complement inhibitor) demonstrated efficacy in reducing relapse risk and eliciting clinical improvements in the phase 3, randomised, double-blind PREVENT (NCT01892345) and REGAIN (NCT01997229) studies and their open-label extensions (NCT02003144 and, respectively) in aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD) and acetylcholine receptor antibody-positive generalised myasthenia gravis (AChR+ gMG), respectively. The aim of this analysis was to compare infection rates for eculizumab vs placebo according to number of concomitant immunosuppressive therapies (ISTs) during these studies. Eculizumab is not reimbursed for neurology indications in Italy as of April 2021. Method(s): Patients were randomised to eculizumab or placebo. Post hoc analysis examined infection rates overall and by number of baseline ISTs. Result(s): Infection rates/100 patient-years for eculizumab vs placebo in NMOSD and gMG, respectively, were: no IST, 176.1 vs 192.2 and 236.8 vs 305.6; 1 IST, 171.5 vs 154.1 and 228.8 vs 253.1; 2 ISTs, 186.7 vs 238.2 and 170.5 vs 192.5; >=3 ISTs (gMG only), 97.5 vs 100.1. Serious infection rates/100 patient-years were: no IST, 2.3 vs 8.0 and none observed; 1 IST, 11.2 vs 7.0 and 16.2 vs 34.5; 2 ISTs, 14.8 vs 47.6 and 13.4 vs 24.1; >=3 ISTs (gMG only), 13.9 vs 0.0. One patient with gMG (2 ISTs) had meningococcal meningitis that resolved with antibiotics and eculizumab was resumed. Conclusion(s): In AQP4+ NMOSD and AChR+ gMG, infection rates were similar in eculizumab and placebo groups, regardless of concomitant IST,	STUDY DESIGN

			and were consistent with eculizumab's established safety profile. This study was funded by Alexion Pharmaceuticals, Inc.Copyright ? 2021	
Multiple Sclerosis Journal. Conference: 8th Joint ACTRIMS-ECTRIMS Meeting. Virtual. 26(3 SUPPL) (pp 477), 2020. Date of Publication: December 2020.	Mantegazza R. Levine T. Oreja-Guevara C. Carrillo-Infante C. Laudon-Meyer E. Shang S. Pittock S. Howard J.	Safety of eculizumab in nmosd and mg-analysis of the phase 3 studies prevent and regain and their extensions	Background: Aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD) and acetylcholine receptor antibody-positive generalized myasthenia gravis (AChR+ gMG) are neurological disorders with complement involvement. Eculizumab (a terminal complement inhibitor) demonstrated efficacy in reducing relapse risk and in eliciting clinical improvements during the phase 3, randomized, double-blind PREVENT and REGAIN studies and their open-label extensions (OLEs) (NCT01892345/NCT02003144 [interim data, July 2019] and NCT01997229/NCT02301624) previously published. Objective(s): To compare infection rates in patients with AQP4+ NMOSD or AChR+ gMG receiving eculizumab or placebo with or without concomitant immunosuppressive therapy (IST) during PREVENT, REGAIN and their OLEs. Method(s): Patients were randomized to eculizumab (maintenance dose, 1200 mg/2 weeks) or placebo. Concomitant ISTs, excluding rituximab, were permitted. Post hoc analysis was performed to examine rates of infections in these studies and for subgroups determined by number of ISTs received at baseline. Result(s): Rates/100 patient-years (PY) and types of infection were similar in eculizumab and placebo groups. In patients with NMOSD, rates/100 PY and % (n/N), respectively, were: no IST: 176.1, 80.0% (28/35) vs 192.2, 61.5% (8/13); 1 IST: 171.5, 81.8% (45/55) vs 154.1, 63.6% (14/22); 2 ISTs: 186.7, 85.1% (40/47) vs 238.2, 83.3% (10/12). For patients with gMG, rates/100 PY and % (n/N), respectively, were: no IST: 236.8, 100.0% (2/2) vs 305.6, 50.0% (1/2); 1 IST: 228.8, 82.9% (34/41) vs 253.1, 50.0% (9/18); 2 ISTs: 170.5, 91.0% (71/78) vs 192.5, 58.5% (24/41); >= 3 ISTs: 97.5, 50.0% (1/2) vs 100.1, 50.0% (1/2). In patients with NMOSD or gMG receiving eculizumab vs placebo, serious infection rates/100 PY and % (n/N), respectively, were: no IST: 2.3, 5.7% (2/35) vs 8.0, 7.7% (1/13) and none observed (0/2 vs 0/2); 1 IST: 11.2, 16.4% (9/55) vs 7.0, 9.1% (2/22) and 16.2, 24.4% (10/41) vs 34.5, 5.6% (1/18); 2 ISTs, 14.8, 29.8% (14/47) vs 47.6, 25.0% (3/12) and 13.4, 21.8% (17/78) vs 24.1, 12.2% (5/41); >= 3 ISTs (gMG only), 13.9, 50.0% (1/2) vs 0.0, 0.0% (0/2). One patient with gMG (2 ISTs) had meningococcal meningitis that	OUTCOMES

			resolved with antibiotics and eculizumab was resumed. Conclusion(s): In AQP4+ NMOSD and AChR+ gMG, infection rates/100 PY were similar in eculizumab and placebo groups, regardless of concomitant IST. Infection rates/100 PY were consistent with the established safety profile of eculizumab.	
Neurology. Conference: 73rd Annual Meeting of the American Academy of Neurology, AAN 2021. Virtual. 96(15 SUPPL 1) (no pagination), 2021. Date of Publication: May 2021.	Kielhorn A. Thomas S. Sabatella G. Johnston K.	The potential impact of long-term relapse reduction: A disease model of eculizumab in neuromyelitis optica spectrum disorder	Objective: A disease model was developed to understand the long-term benefits of eculizumab in patients with neuromyelitis optica spectrum disorder (NMOSD). Background(s): NMOSD is an autoimmune disease of the central nervous system characterized by unpredictable relapses and the accumulation of neurological disability, leading to reduced healthrelated quality of life (HRQoL). PREVENT, a randomized, double-blind, placebo-controlled, time-to-event trial, found eculizumab to be effective in reducing the risk of a first adjudicated relapse in patients with aquaporin-4 immunoglobulin G-positive NMOSD. Design/Methods: A Markov cohort model was developed using PREVENT data to estimate time to relapse over a 20-year time horizon, under the assumptions that risk of relapse varies by treatment but is constant over time (provided no change in treatment) and time-to-first-relapse curves are relevant for subsequent relapses. PREVENT data were also used to describe HRQoL based on the European Quality of Life 5-Dimension questionnaire (EQ-5D), allowing life years to be converted to quality-adjusted life years (QALYs). Each relapse was associated with both a short-term, temporary and a cumulative, permanent decline in HRQoL. The model assumed that mortality was 7% per year following the first relapse, incidence of long-term disability was 17.5% per relapse (accounting for a cumulative increase with each relapse), and disability related HRQoL data for multiple sclerosis could be used as a proxy for NMOSD. Result(s): Using this model, the proportion of patients who remained relapse free at 20 years was greater for eculizumab (66.2%) than placebo (0.0%). Patients receiving eculizumab were also estimated to experience 3.9 fewer relapses, 7.6 additional life years, and 7.7 additional QALYs compared with placebo; benefits associated with eculizumab were consistent across multiple sensitivity and scenario analyses. Conclusion(s): The benefits associated with eculizumab in the PREVENT trial were extrapolated over a 20-year time horizon and demonstrated substantial, long-term improvements in clinical outcomes and HRQoL among patients with NMOSD.	OUTCOMES

Annals of Clinical & Translational Neurology. 8(10):2025-2037, 2021 10.	Giovannelli J Ciron J Cohen M Kim HJ Kim SH Stellmann JP Kleiter I McCreary M Greenberg BM Deschamps R Audoin B Maillart E Papeix C Collongues N Bourre B Laplaud D Ayrignac X	A meta-analysis comparing first-line immunosuppressants in neuromyelitis optica	OBJECTIVE: As phase III trials have shown interest in innovative but expensive drugs in the treatment of neuromyelitis optica spectrum disorder (NMOSD), data are needed to clarify strategies in the treatment of neuromyelitis optica (NMO). This meta-analysis compares the efficacy of first-line strategies using rituximab (RTX), mycophenolate mofetil (MMF), or azathioprine (AZA), which are still widely used. METHODS: Studies identified by the systematic review of Huang et al. (2019) were selected if they considered at least two first-line immunosuppressants among RTX, MMF, and AZA. We updated this review. The Medline, Cochrane Central Register of Controlled Trials, Embase, and ClinicalTrials databases were queried between November 2018 and April 2020. To be included, the hazard ratio (HR) [95% CI] for the time to first relapse after first-line immunosuppression had to be available, calculable, or provided by the authors. RESULTS: We gathered data from 919 NMO patients (232 RTX-, 294 MMF-, and 393 AZA-treated patients). The risk of first relapse after first-line immunosuppression was 1.55 [1.04, 2.31] (p = 0.03) for MMF compared with RTX, 1.42 [0.87, 2.30] (p = 0.16) for AZA compared with RTX, and 0.94 [0.58, 1.54] (p = 0.08) for MMF compared with AZA. INTERPRETATION: The findings suggest that RTX is more efficient than MMF as a first-line therapy. Even if the results of our meta-analysis cannot conclude that RTX has a better efficacy in delaying the first relapse than AZA, the observed effect difference between both treatments combined with the results of previous studies using as outcome the annualized relapse rate may be in favor of RTX. Copyright ? 2021 The Authors. Annals of Clinical and Translational Neurology published by Wiley Periodicals LLC on behalf of American Neurological Association.	STUDY DESIGN

	Durand-Dubief F Ruet A Vukusic S Marignier R Dauchet L Zephir H			
Medicine. 101(36):e30347, 2022 Sep 09.	Dong GY Meng YH Xiao XJ	A meta-analysis on efficacy and safety of rituximab for neuromyelitis optica spectrum disorders	BACKGROUND: To assess the efficacy and safety of rituximab (RTX) in the treatment of neuromyelitis optica spectrum diseases (NMOSDs), and give a guideline on clinical medication. METHODS: The databases of Pubmed, Embase, Cochrane Library, CNKI, and Wan fang were systematically searched by computer, and the search period was from the establishment of the databases until January 2022. To collect the trials of RTX in the treatment of NMOSDs, two researchers completed literature screening, quality assessment, and data extraction independently. Statistical analysis was performed using Review Manager 5.3 and Stata 15.1 software. RESULTS: There were 37 studies in the meta-analysis, including 5 randomized controlled trials (RCTs) and 32 observational studies. Meta-analysis results revealed that NMOSDs patients treated with RTX significantly reduced the annualized relapse rate (ARR) (weighted mean difference [WMD] = 1.45, 95% confidence interval [CI]: 1.24-1.66, P < .01) and the Expanded disability status scale (EDSS) scores (WMD = 1.34, 95%CI: 1.25-1.44, P < .01). RTX is more effective than azathioprine (AZA) in the treatment of NMOSDs (ARR: WMD = -0.54, 95% CI: -0.75 to -0.33; EDSS: WMD = -0.65, 95% CI: -0.83 to -0.48; P < .0001). There was no difference in ARR and EDSS scores between anti-aquapor in-4-antibody seropositive NMOSD and seronegative NMOSD patients treated with RTX (ARR: WMD = -0.01, 95% CI: -0.25 to 0.24, P = .96 > 0.05; EDSS: WMD	STUDY DESIGN

			= 0, 95% CI: -0.30 to 0.31, P = .99 > 0.05). In this study, 681 patients were recorded safety data of RTX therapy, 23% (156 patients) had adverse events, and 0.7% (5 patients) of NMOSDs discontinued due to severe adverse reactions. CONCLUSIONS: NMOSDs patients treated with RTX can significantly reduce the relapse frequency and EDSS scores, and also improve neurological dysfunction, besides the efficacy is better than azathioprine. RTX has a high incidence of adverse reactions, which are mild and with certain self limited, it should be cautious in clinical medication. Copyright ? 2022 the Author(s). Published by Wolters Kluwer Health, Inc.	
Multiple Sclerosis and Related Disorders. 45 (no pagination), 2020. Article Number: 102421. Date of Publication: October 2020.	Xie Q. Zheng T. Sun M. Sun J. Wang M.	A meta-analysis to determine the efficacy and safety of tocilizumab in neuromyelitis optica spectrum disorders	Background: Neuromyelitis optica spectrum disorder (NMOSD) is a central nervous system immune disease with a high recurrence rate and high disability rate. Frequent relapses often cause the accumulation of neurological dysfunction, leading to permanent blindness, paralysis or even death. Tocilizumab (TCZ) is a human monoclonal antibody (mAb) directed against the IL-6 receptor and was the first anti-IL6-R mAb tested for the treatment of NMOSD. Our meta-analysis aimed to evaluate the efficacy and safety of tocilizumab in NMOSD patients. Method(s): Relevant studies published prior to May 2020 were retrieved from the PubMed, Cochrane Library and clinicaltrials.gov databases using the following keywords: 'neuromyelitis optic spectrum disorders' or 'NMOSD' and 'tocilizumab' or 'TCZ'. Two authors independently selected the articles and extracted the data. Differences in the annualized relapse rate (ARR) ratio, relapse-free status and EDSS score before and after TCZ therapy were used as the main efficacy measures, and recorded adverse effects were also extracted. The meta-analysis was performed using Review Manager version 5.3 software. Result(s): Five clinical trials comprising a total of 89 patients were selected. Meta-analysis showed that significantly fewer ARR ratio was encountered in after tocilizumab therapy group (MD=-2.25; 95% CI=-2.62 to -1.87; P<0.001). A significant correlation was observed between the proportion of patients with relapse-free NMOSD and tocilizumab therapy (OR=67.78; 95% CI=19.23 to 238.97; P<0.001). Adverse effects were recorded in 75 of 89 (84%) patients treated with tocilizumab, but most adverse effects were mild. Conclusion(s): The present meta-analysis suggested that tocilizumab is a relatively effective and safe treatment for NMOSD.Copyright ? 2020 Elsevier B.V.	STUDY DESIGN

RMD Open. 8(2), 2022 09.	Kastrati K Aletaha D Burmester GR Chwala E Dejaco C Dougados M McInnes IB Ravelli A Sattar N Stamm TA Takeuchi T Trauner M van der Heijde D Voshaar MJH Winthrop K Smolen JS	A systematic literature review informing the consensus statement on efficacy and safety of pharmacological treatment with interleukin-6 pathway inhibition with biological DMARDs in immune-mediated inflammatory diseases	OBJECTIVES: Informing an international task force updating the consensus statement on efficacy and safety of biological disease-modifying antirheumatic drugs (bDMARDs) selectively targeting interleukin-6 (IL-6) pathway in the context of immune-mediated inflammatory diseases. METHODS: A systematic literature research of all publications on IL-6 axis inhibition with bDMARDs published between January 2012 and December 2020 was performed using MEDLINE, EMBASE and Cochrane CENTRAL databases. Efficacy and safety outcomes were assessed in clinical trials including their long-term extensions and observational studies. Meeting abstracts from ACR, EULAR conferences and results on clinicaltrials.gov were taken into consideration. RESULTS: 187 articles fulfilled the inclusion criteria. Evidence for positive effect of IL-6 inhibition was available in various inflammatory diseases such as rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, Takayasu arteritis, adult-onset Still's disease, cytokine release syndrome due to chimeric antigen receptor T cell therapy and systemic sclerosis-associated interstitial lung disease. Newcomers like satralizumab and anti-IL-6 ligand antibody siltuximab have expanded therapeutic approaches for Castleman's disease and neuromyelitis optica, respectively. IL-6 inhibition did not provide therapeutic benefits in psoriatic arthritis, ankylosing spondylitis and certain connective tissue diseases. In COVID-19, tocilizumab (TCZ) has proven to be therapeutic in advanced disease. Safety outcomes did not differ from other bDMARDs, except higher risks of diverticulitis and lower gastrointestinal perforations. Inconsistent results were observed in several studies investigating the risk for infections when comparing TCZ to TNF-inhibitors. CONCLUSION: IL-6 inhibition is effective for treatment of several inflammatory diseases with a safety profile that is widely comparable to other bDMARDs.	STUDY DESIGN

	Kerschbaumer A			
Therapeutic Advances in Neurological Disorders. 14 (no pagination), 2021. Date of Publication: December 2021.	Wang H. Zhou J. Li Y. Wei L. Xu X. Zhang J. Yang K. Wei S. Zhang W.	Adverse events of rituximab in neuromyelitis optica spectrum disorder: a systematic review and meta-analysis	Background: The adverse events (AEs) of rituximab (RTX) for neuromyelitis optica spectrum disorder (NMOSD) are incompletely understood. Aim(s): To collate information on the reported the AEs of RTX in NMOSD and assess the quality of evidence. Method(s): PubMed, EMBASE, Web of Science, Cochrane Library, Wanfang Data, CBM, CNKI, VIP, clinicaltrials.gov, and so on were searched for studies with control groups as well as for case series that had assessed the RTX-associated AEs. The incidence of AEs and the comparison of AE risks among different therapies were pooled. The GRADE was developed for evidence quality. Result(s): A total of 3566 records were identified. Finally, 36 studies (4 RCTs, 6 crochet studies, 2 NRCTs, and 24 case series), including 1542 patients (1299 females and 139 males), were included for final analyses. Rates of patients with any AEs, any serious AEs (SAEs), infusion-related AEs, any infection, respiratory infection, urinary infection, and death were 28.57%, 5.66%, 27.01%, 17.36%, 4.76%, 4.76%, and 0.17%, respectively. The results from subgroup analysis showed that AE rates were most likely not associated with covariates such as duration of illness and study designs. Very low-quality evidence suggested that the risk ratios (RR) of any AEs (0.84, 95% CI = 00.42-1.69, p = 0.62) and any infections (1.24 95% CI = 0.18-8.61) of RTX were similar to that of azathioprine, and the RR of any AEs of RXT was akin to that of mycophenolate mofetil (0.66, 95% CI = 0.32-1.35 p = 0.26). Evidence of low to high quality showed the lower RR of RTX in other AEs, but not in infusion-related AEs. Strategies to handle AEs focused on symptomatic treatments. Conclusion(s): RTX is mostly safer than other immunosuppressants in NMOSD: the incidence of RTX-associated AEs was not high, and when present, the AEs were usually mild or moderate and could be well controlled. Given its efficacy and safety, RTX could be recommended as a first-line treatment for NMOSD.Copyright ? The Author(s), 2021.	STUDY DESIGN

Current Neuropharmacology. 19(2):220-232, 2021.	Lotan I McGowan R Levy M	Anti-IL-6 Therapies for Neuromyelitis Optica Spectrum Disorders: A Systematic Review of Safety and Efficacy	BACKGROUND: Neuromyelitis Optica Spectrum Disorder (NMOSD) is a chronic autoimmune disease of the central nervous system that causes recurrent attacks of optic neuritis, myelitis, and brainstem symptoms, resulting in severe neurological disability. Preventive treatment with immunosuppressive agents reduces relapse rate and improves long-term prognosis. In recent years, the potential therapeutical effect of new agents has been investigated. Two of these, the anti-interleukin 6 (IL-6) agents tocilizumab and satralizumab, have been studied in active NMOSD. OBJECTIVE: To systematically review the current data regarding the efficacy and safety of anti-IL-6 agents in NMOSD. RESULTS: Fourteen case reports and 5 case series of intravenous tocilizumab have shown beneficial clinical and paraclinical effects compared to commonly used therapies, and another case series of subcutaneous tocilizumab has shown it is as effective as the IV formulation. A phase 2 comparative trial has shown tocilizumab IV to be more effective than azathioprine for relapse prevention. A phase 3 trial of subcutaneous satralizumab versus placebo, has shown a lower risk of relapse in the sartralizumab-treated group, both as add-on therapy to stable immunosuppressant and as monotherapy. Tocilizumab also reduced pain severity in two trials and fatigue scores in one trial, but satralizumab did not significantly improve pain and fatigue. Adverse events with both agents were relatively mild and comparable to placebo and azathioprine. CONCLUSION: The anti-Il-6 agents tocilizumab and satralizumab show promising results in active NMOSD. Further randomized, larger-scale trials are needed to better define the role of these agents in the growing arsenal of NMOSD treatments. Copyright? Bentham Science Publishers; For any queries, please email at epub@benthamscience.net.	STUDY DESIGN
Frontiers in neurology [electronic resource].. 11:604445, 2020.	Xue T Yu J	Different Targets of Monoclonal Antibodies in Neuromyelitis Optica Spectrum Disorders: A	Background: Neuromyelitis optica spectrum disorder (NMOSD), an autoimmune inflammatory disorder of the central nervous system, often leads to vision loss or paralysis. This meta-analysis focused on the assessment of the monoclonal antibody therapy in NMOSD and compared different targets of monoclonal	STUDY DESIGN

	Chen S Wang Z Yang Y Chen Z Wang Z	Meta-Analysis Evidenced From Randomized Controlled Trials	antibodies with each other in terms of efficacy and safety outcomes. Method: We searched through the databases of MEDLINE, EMBASE, Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov for randomized controlled trials (RCTs) evaluating monoclonal antibody therapy in NMOSD up to April 2020. Results: We identified seven randomized controlled trials (RCTs), including 775 patients (monoclonal antibody group, n = 485 and placebo group, n = 290). Monoclonal antibody therapy decreased relapse risk (RR 0.33, 95% CI 0.21-0.52, P < 0.00001), annualized relapse rate (ARR) (mean -0.28, 95% CI -0.35-0.20, P < 0.00001), expanded disability status scale score (EDSS) (mean -0.19, 95% CI -0.32-0.07, P = 0.002) and serious adverse events (RR 0.78, 95% CI 0.61-1.00, P = 0.05). However, we did not observe any significant difference in terms of adverse events or mortality. Further, the subgroup analysis demonstrated that the anti-complement protein C5 monoclonal antibody (eculizumab) might have a lower relapse risk (RR 0.07, 95% CI 0.02-0.23, P < 0.0001) in the AQP4 seropositive patients, and anti-interleukin-6 receptor monoclonal antibodies (satralizumab and tocilizumab) showed decreased EDSS score (mean -0.17, 95% CI -0.31-0.02, P = 0.02) more effectively than other monoclonal antibodies. Conclusions: Monoclonal antibodies were effective and safe in NMOSD. Different targets of monoclonal antibodies might have their own advantages. Copyright ? 2020 Xue, Yu, Chen, Wang, Yang, Chen and Wang.	
Annals of Clinical & Translational Neurology. 7(11):2094-2102, 2020 11.	Kosiyakul P Songwisit S Ungprasert P Siritho S Prayoonwiwat N Jitprapaikulsan J	Effect of plasma exchange in neuromyelitis optica spectrum disorder: A systematic review and meta-analysis	OBJECTIVE: To conduct systematic review and meta-analysis for the efficacy of therapeutic plasma exchange (TPE) for neuromyelitis optica spectrum disorder (NMOSD) with an acute attack. METHODS: Systematic review was performed using EMBASE and OVID/Medline database. The eligible studies must be the studies of NMOSD patients treated with TPE during the acute phase. They must report treatment outcomes using either Expanded Disability Status Scale (EDSS) or visual acuity (VA) before and after the therapy. Pooled mean difference (MD) was then calculated by combining MDs of each study using the random-effects model. RESULTS: Fifteen studies were identified; eleven with 241 NMOSD patients reported EDSS outcome and four studies with 103 NMOSD reported visual outcomes. The meta-analysis demonstrated a significantly decreased in EDSS	STUDY DESIGN

			after TPE treatment for NMOSD with an acute attack with the pooled MD of 0.83 (95% CI, 0.26-1.40; I2 69%) comparing pretreatment to immediate posttreatment and 2.13 (95% CI, 1.55-2.70; I2 31%) comparing pretreatment to posttreatment at 6 months to 1-year follow-up. Unfortunately, only one of the four studies evaluating visual outcomes reported standard deviation in association with mean LogMAR; therefore, the meta-analysis cannot be conducted. Nonetheless, all studies consistently demonstrated the benefit of TPE with improved VA and/or LogMAR after treatment. INTERPRETATION: This systematic review and meta-analysis showed the benefit of TPE during the NMOSD attack with a significantly improved disability status immediately after treatment and during follow-up. Copyright ? 2020 The Authors. Annals of Clinical and Translational Neurology published by Wiley Periodicals LLC on behalf of American Neurological Association.	
BMC Neurology. 19(1):36, 2019 Mar 06.	Gao F Chai B Gu C Wu R Dong T Yao Y Zhang Y	Effectiveness of rituximab in neuromyelitis optica: a meta-analysis	BACKGROUND: Neuromyelitis optica (NMO) is a severe inflammatory autoimmune disorder of the central nervous system and often results in paralysis or blindness. Rituximab (RTX) is a mouse-human chimeric monoclonal antibody specific for the CD20 antigen on B lymphocytes and used to treat many autoimmune diseases. Disability and relapses were measured using the Expanded Disability Status Scale (EDSS) and annualized relapse rate (ARR) ratio to evaluate the effectiveness of RTX. This review performed a meta-analysis of the efficacy of RTX in NMO. METHODS: We searched through the databases of PubMed, Embase, and Cochrane Library. We compiled 26 studies, in which 18 used ARR ratio, 22 used EDSS score, and 14 used both variables. Differences in the ARR ratio and EDSS score before and after RTX therapy were used as the main efficacy measures. Publication bias was evaluated after the consistency test, and a sensitivity analysis was performed with mean difference (MD) of the efficacy of RTX. RESULTS: A meta-analysis of 26 studies with 577 participants was conducted. Antibodies against aquaporin-4 autoantibody were recorded in 435 of 577 (75.39%) patients with NMO. RTX therapy resulted in a mean (WMD) - 1.56 (95% CI, - 1.82 to - 1.29) reduction in the mean ARR ratio and a mean (WMD) - 1.16	STUDY DESIGN

			(95% CI, - 1.36 to - 0.96) reduction in the mean EDSS score. A total of 330 of 528 patients (62.9%) reached the relapse-free state. A total of 95 of 577 (16.46%) patients had adverse reactions. CONCLUSIONS: RTX has acceptable tolerance, reduces the relapse frequency, and improves disability in most patients with NMO. Future studies should focus on reducing the health-care costs, improving the functional outcomes, and reducing the adverse effects associated with RTX treatment.	
Multiple Sclerosis and Related Disorders. 43:102166, 2020 Aug.	Xue T Yang Y Lu Q Gao B Chen Z Wang Z	Efficacy and Safety of Monoclonal Antibody Therapy in Neuromyelitis Optica Spectrum Disorders: Evidence from Randomized Controlled Trials	BACKGROUND: Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune inflammatory disorders in central nervous system (CNS) characterized by symptoms of optic nerve, spinal cord, brainstem and cerebrum injuries. Recent studies have shown that monoclonal antibodies (Rituximab, Eculizumab, Inebilizumab, Satralizumab, etc.) were effective for the treatment of NMOSD. We performed a meta-analysis to evaluate the efficacy and safety of these monoclonal antibodies in NMOSD. METHODS: The MEDLINE, EMBASE, Central Register of Controlled Trials (CENTRAL) and clinicaltrials.gov database were searched for randomized controlled trials (RCTs) which had assessed the therapy of monoclonal antibody in NMOSD patients. RESULTS: We pooled 524 (monoclonal antibody group, n = 344 and placebo group, n = 180) from 4 RCTs and 444 patients (84.7%) were AQP4-IgG seropositive. Monoclonal antibody therapy reduced annualized relapse rate (mean -0.27, 95% CI, -0.36 to -0.18, P <0.0001), on-trial relapse risk (RR 0.25, 95% CI 0.12 to 0.52, P = 0.0003), EDSS (Expanded disability status scale) score (mean -0.51, 95% CI, -0.92 to -0.11, P = 0.01) and serious adverse events (RR 0.59, 95% CI 0.37 to 0.96, P = 0.03) but didn't show any significant differences in total adverse events or mortality. In the subgroup analysis, we found that comparing with other monoclonal antibodies, Eculizumab might be more effective in decreasing on-trial relapse risk (Chi2 =9.84, P =0.002) for AQP-4 positive patients. CONCLUSIONS: Monoclonal antibody therapy was effective and safe in NMOSD	STUDY DESIGN

			treatment. More RCTs were expected to assess monoclonal antibodies in NMOSD. Copyright ? 2020 Elsevier B.V. All rights reserved.	
Frontiers in neurology [electronic resource].. 14:1166490, 2023.	Aungsumart S Youngkong S Dejthevaporn C Chaikledkaew U Thadanipon K Tansawet A Khieukhajee J Attia J McKay GJ Thakkinstian A	Efficacy and safety of monoclonal antibody therapy in patients with neuromyelitis optica spectrum disorder: A systematic review and network meta-analysis	Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a devastating inflammatory CNS demyelinating disease. Two groups of monoclonal antibodies (mAbs) are used to prevent disease relapse, i.e., Food and Drug Administration (FDA)-approved mAbs (e.g., eculizumab satralizumab, inebilizumab), and off-label mAb drugs (e.g., rituximab and tocilizumab). The FDA-approved mAbs have high efficacy but more expensive compared to the off-labels, and thus are less accessible. This systematic review and network meta-analysis (NMA) was to assess the efficacy and safety of both classes of mAbs compared to the current standard treatments. Methods: Systematically searches were conducted in MEDLINE and SCOPUS from inception until July 2021. Randomized-controlled trials (RCTs) were eligible if they compared any pair of treatments (mAbs, immunosuppressive drugs, or placebo) in adult patients with NMOSD. Studies with AQP4-IgG positive or negative were used in the analysis. Probability of relapse and time to event were extracted from the Kaplan-Meier curves using Digitizer. These data were then converted into individual patient time-to-event data. A one-stage mixed-effect survival model was applied to estimate the median time to relapse and relative treatment effects using hazard ratios (HR). Two-stage NMA was used to determine post-treatment annualized relapse rate (ARR), expanded disability status score (EDSS) change, and serious adverse events (SAE). Risk of bias was assessed using the revised cochrane risk of bias tool. Results: A total of 7 RCTs with 776 patients were eligible in the NMA. Five of the seven studies were rated low risk of bias. Both FDA-approved and off-label mAbs showed significantly lower risk of relapse than standard treatments, with HR (95% CI) of 0.13 (0.07, 0.24) and 0.16 (0.07, 0.37) respectively. In addition, the FDA-approved mAbs had 20% lower risk of relapse than the off-label mAbs, but this did not reach statistical significance. The ARRs were also lower in FDA-approved and off-label mAbs than the standard treatments with the mean-difference of-0.27 (-	STUDY DESIGN

			0.37,-0.16) and-0.31(-0.46,-0.16), respectively. Conclusion: The off-label mAbs may be used as the first-line treatment for improving clinical outcomes including disease relapse, ARR, and SAEs for NMOSD in countries where resources and accessibility of the FDA-approved mAbs are limited. Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=283424, identifier: CRD42021283424. Copyright ? 2023 Aungsumart, Youngkong, Dejthevaporn, Chaikledkaew, Thadanipon, Tansawet, Khieukhajee, Attia, McKay and Thakkinstian.	
Multiple Sclerosis and Related Disorders. 33:22-32, 2019 Aug.	Espiritu AI Pasco PMD	Efficacy and tolerability of azathioprine for neuromyelitis optica spectrum disorder: A systematic review and meta-analysis	BACKGROUND: Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory and autoimmune disorder of the central nervous system that typically presents with optic neuritis and myelitis. Azathioprine (AZA) is one of the available immunotherapies with purported beneficial effects for patients with NMOSD. At present, there are no systematic reviews that extensively pooled the effects of AZA compared to other interventions for this condition. The objective of this study, therefore, is to determine the efficacy and safety of AZA in patients with NMOSD using systematic review of relevant studies. METHODS: Major health electronic databases, which included CENTRAL, MEDLINE, EMBASE, Scopus, LILACS, ClinicalTrials.gov, and HERDIN, were searched from May 2017 to November 2018 for relevant studies involving adult and pediatric patients with NMOSD. Randomized controlled trials, and either prospective or retrospective cohort designs that assessed the reduction or prevention of relapse or disability and the occurrence of adverse events related to AZA use compared to placebo or to other active drugs were considered. Assessment of risk of bias was performed using the Cochrane Collaboration tool and Newcastle-Ottawa Scale. RESULTS: From a total of 273 records, 9 relevant studies (1 randomized controlled trial (RCT), 3 prospective cohort studies, 5 retrospective studies) which involved a total of 977 patients, were included. One RCT and several	STUDY DESIGN

			observational studies revealed that AZA regimen may be inferior to rituximab in terms of annualized relapse rate, reduction of disability as measured by the expanded disability status scale (EDSS), risk for relapse and relapse-free rate. Efficacy data were very limited in the comparison of AZA to mycophenolate mofetil (MMF), to cyclophosphamide, and to interferon-beta for patients with NMOSD. Occurrence of any adverse event, elevated liver enzymes/hepatoxicity, leukopenia and hair loss associated with AZA use were significantly greater compared to MMF, which may lead to medication noncompliance. CONCLUSION: AZA improves relapses and disability in patients with NMOSD but this regimen is associated with relatively frequent adverse events based on limited published evidences. More well-conducted clinical trials are necessary to establish with certainty the beneficial and harmful effects of AZA in patients with NMOSD. Copyright ? 2019 Elsevier B.V. All rights reserved.	
Frontiers in neurology [electronic resource].. 11:544434, 2020.	D'Souza R Wuebbolt D Andrejevic K Ashraf R Nguyen V Zaffar N Rotstein D Wyne A	Pregnancy and Neuromyelitis Optica Spectrum Disorder - Reciprocal Effects and Practical Recommendations: A Systematic Review	Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disorder of the central nervous system characterized by severe, antibody-mediated astrocyte loss with secondary demyelination and axonal damage, predominantly targeting optic nerves and the spinal cord. Recent publications have alluded to increased disease activity during pregnancy, and adverse maternal and fetal outcomes in patients with NMOSD. Our objective was to systematically review published literature to help counsel and manage women with NMOSD contemplating pregnancy. Methods: We searched five databases including MEDLINE and EMBASE, for English-language publications describing pregnancies in women with NMOSD. Article selection, data extraction, and risk-of-bias assessment using Joanna Briggs' critical appraisal tool for case reports and case series, were performed in duplicate. Pooled incidences were calculated where possible, and a narrative summary was provided. Results: Of 2,118 identified titles, 22 case reports and seven case series, representing 595 pregnancies in 389 women, were included. The mean maternal age was 28.12 +/- 5.19 years. At least 20% of cases were first diagnosed during pregnancy. There were no maternal deaths. Pooled estimates for clinical outcomes could not be obtained due to inadequate reporting. NMOSD-related disability and relapses increased considerably during pregnancy and especially in the immediate postpartum period. Although a high proportion of early pregnancy losses were	STUDY DESIGN

			reported, an association with disease activity or therapeutic interventions could not be established. Apart from one publication which reported an increased risk of preeclampsia, there was no increase in adverse obstetric outcomes including preterm birth, fetal growth restriction or congenital malformations. Initial attacks and relapses were successfully managed with oral or intravenous corticosteroids and immunosuppressants, and refractory cases with immunoglobulin, plasma exchange and immunoadsorption. Conclusion: Increased NMOSD-related disability and relapses during pregnancy the postpartum period may respond to aggressive management with corticosteroids and immunosuppressants such as azathioprine, which are safely administered during pregnancy and lactation. Emerging safety data on monoclonal antibodies during pregnancy, make these attractive options, while intravenous immunoglobulin, plasma exchange and immunoadsorption can be safely used to treat severe relapses. The complex interplay between NMOSD and pregnancy outcomes would be best understood through prospective analysis of data collected through an international registry. Disclosure: Dalia Rotstein has served as a consultant or speaker for Alexion and Roche. She has received research support from Roche Canada. Rohan D'Souza has served as a consultant and speaker for Ferring Canada Inc and Ferring Global Inc, on topics unrelated to this manuscript. The other authors have no relevant relationships to disclose. Copyright ? 2020 D'Souza, Wuebbolt, Andrejevic, Ashraf, Nguyen, Zaffar, Rotstein and Wyne.	
Frontiers in Immunology. 12:788830, 2021.	Kaegi C Wuest B Crowley C Boyman O	Systematic Review of Safety and Efficacy of Second- and Third-Generation CD20-Targeting Biologics in Treating Immune-Mediated Disorders	Background: B cells can contribute to immune-mediated disorders. Targeting CD20 has proved to be efficacious in several B cell-mediated immunopathologies, as illustrated by the use of rituximab, the first anti-CD20 monoclonal antibody (mAb). Following rituximab, second- and third-generation anti-CD20 mAbs have been developed and tried in immune-mediated diseases, including obinutuzumab, ocrelizumab, ofatumumab, ublituximab, and veltuzumab. However, their safety and efficacy has not been systematically reviewed. Objective: To evaluate safety and efficacy of obinutuzumab, ocrelizumab, ofatumumab, ublituximab, and veltuzumab for the treatment of immune-mediated disorders compared to placebo, conventional treatment or other biologics. Methods: The PRISMA checklist guided the reporting of the data. We searched	STUDY DESIGN

			the PubMed database between 4 October 2016 and 22 July 2021 concentrating on immune-mediated disorders. Results: The literature search identified 2220 articles. After screening titles and abstracts against the inclusion and exclusion criteria and assessing full texts, 27 articles were finally included in a narrative synthesis. Conclusions: Obinutuzumab has shown promising results in a case series of patients with phospholipase A2 receptor-associated membranous nephropathy and mixed results in systemic lupus erythematosus. Ocrelizumab has been approved for the use in patients with relapsing-remitting multiple sclerosis and primary progressive multiple sclerosis. Ocrelizumab was also tested in patients with rheumatoid arthritis, demonstrating promising results, and in systemic lupus erythematosus, revealing mixed results; however, in these conditions, its use was associated with increased risk of serious infections. Ofatumumab received approval for treating patients with relapsing-remitting multiple sclerosis. Moreover, ofatumumab showed promising results in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis, and systemic lupus erythematosus, as well as mixed results in phospholipase A2 receptor-associated membranous nephropathy. Ublituximab was assessed in relapsing-remitting multiple sclerosis and neuromyelitis optica spectrum disorder, with promising results, however, the included number of patients was too small to conclude. Veltuzumab was tested in patients with immune thrombocytopenia resulting in improved platelet counts. Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier CRD4201913421. Copyright ? 2022 Kaegi, Wuest, Crowley and Boyman.	
Multiple Sclerosis and Related Disorders. 48:102709, 2021 Feb.	Huang X Wu J Xiao Y Zhang Y	Timing of plasma exchange for neuromyelitis optica spectrum disorders: A meta-analysis	BACKGROUND: Neuromyelitis optica spectrum disorders (NMOSDs) are autoimmune astrocytopathies with predominant involvement of the optic nerves and spinal cord. The current management is high-dose intravenous methylprednisolone, followed by apheresis therapy if it fails. We aimed to investigate plasma exchange (PE) benefits in corticosteroid-refractory NMOSDs. METHODS: From Embase, PubMed, Cochrane, Web of Science, and Clinical	STUDY DESIGN

			Trials, we identified PE-based studies published between Jan 2007 and Dec 2019. We pooled the information of these studies in a binomial meta-analysis. We investigated the factors affecting the efficacy of PE and its adverse events. The effectiveness of PE was assessed using the Expanded Disability Status Scale (EDSS). The timing of PE initiation was assessed using Spearman correlation analysis. RESULTS: We included 561 records and identified 8 observational studies, including 228 NMOSD patients. The mean time to the initiation of PE was 11 days, and the average volume of each exchange was 1.5-2 L. PE treatment reduced the mean EDSS score by -1.04 (95% CI, -1.44 to -0.64). The initiation time of PE significantly affected the outcome (EDSS reduction) (P = 0.01; 95% CI, -1.30 to 0.28). In the <= 7-day and 8-23-day groups, the mean EDSS decreased by 0.64 (95% CI, -0.93 to -0.34) and 1.41 (95% CI, -1.79 to -1.02), respectively. In addition, PE showed the same efficacy for alleviating the symptoms of NMOSDs, regardless of the day between 8 to 23 days on which it was performed (P = 0.29). Thirty-five (20.8%) of the 168 patients had adverse events. CONCLUSION: PE can ameliorate severe NMOSDs. PE effectiveness was associated with the duration between disease and the initiation of PE, and the optimal timing for PE initiation is 8 to 23 days after the onset of the disease. Copyright ? 2020. Published by Elsevier B.V.	
International Immunopharmacology. 110 (no pagination), 2022. Article Number: 109004. Date of Publication: September 2022.	Luo J. Yu J. Sui Z. Zhong Y. Zheng Q. Li L.	Comparison on the effect of seven drugs to prevent relapses of neuromyelitis optica spectrum disorders: A modeling analysis of literature aggregate data	Background: Neuromyelitis optica spectrum disorders (NMOSD) is an immune-mediated demyelinating disease of the central nervous system. This study aimed to perform a comprehensive comparison of the effect of seven drugs to prevent relapses of NMOSD. Method(s): A literature search was conducted using public databases. Clinical studies on the seven drugs (eculizumab, inebilizumab, satralizumab, rituximab, tocilizumab, azathioprine, and mycophenolate mofetil) to prevent relapses of NMOSD were identified. A time-course model was established using the time to first relapse as the primary endpoint, in order to evaluate the long-term effect of each drug in preventing relapse. Result(s): Twenty-four trials, including 2207 patients, were included in the model analysis. The results showed that monoclonal antibody therapy could significantly prolong the time to first relapse. Among all seven drugs, eculizumab can most significantly prevent patient	STUDY DESIGN

			from relapse. The estimated proportion of relapse-free patients treated with eculizumab was 98.9% at 24 months. Conclusion(s): Based on the construction of a time-course pharmacodynamic model, this study made a comprehensive quantitative comparison of seven drugs for the treatment of NMOSD for the first time. These results can not only serve as a quantitative supplement for the rational use of drugs in clinical practice but also provide a pharmacodynamic reference for clinical trial design and decision making in the future.Copyright ? 2022 Elsevier B.V.	
Clinical Neurology. Conference: 62nd Annual Meeting of the Japanese Society of Neurology. Kyoto Japan. 61(Supplement 1) (pp S250), 2021. Date of Publication: 2021.	Araki M. Palace J. Kleiter I. Traboulsee A. Yamamura T. Patti F. Stokmaier D. Klingelschmitt G. Kuenzel T. Von Budingen H.-C. Bennett J.L.	Effect of satralizumab on relapse severity in neuromyelitis optica spectrum disorder (NMOSD)	Objective To assess the impact of satralizumab on relapse severity in patients with NMOSD. Methods Data from the pooled intention-to-treat population across the double-blind periods of both SAkura studies (SAkuraSky, NCT02028884 and SAkuraStar, NCT02073279) were used in this analysis. Severity of protocol-defined relapses (PDRs) was assessed by comparing patients' Expanded Disability Status Scale (EDSS) score at PDR vs their score prior to relapse. A similar analysis on optic neuritis PDRs used visual Functional Systems Score (FSS) instead. A PDR was categorised as severe if there was a 2-point change in EDSS or visual FSS (optic neuritis analysis). Results Of 178 patients included in the analyses, 26% (27/104 patients) vs 46% (34/74 patients) experienced a PDR with satralizumab vs placebo, respectively. The proportion of severe PDRs was lower with satralizumab vs placebo: 19% (5/27 events) vs 35% (12/34 events), respectively. A similar trend was observed for severe optic neuritis PDRs: 25% (2/8 events) vs 39% (5/13 events), respectively. Overall, there was a 79% reduction in severe PDR risk with satralizumab vs placebo (hazard ratio [95% CI]; 0.21 [0.07-0.61]; p=0.002). The proportion of patients prescribed acute therapy with satralizumab vs placebo was 38% vs 58%, respectively (odds ratio [95% CI] 0.46 [0.25-0.86], p=0.015). Conclusions Patients treated with satralizumab had a lower risk of severe relapse and were less likely to require rescue therapy for a relapse vs placebo. The number of patients with severe PDRs was low, so results should be interpreted with caution.	STUDY DESIGN

Current neuropharmacology. (no pagination), 2022. Date of Publication: 22 Sep 2022.	Luo Y. Deng Y. Ran H. Yu L. Ma C. Zhao L. Li Y.	Effectiveness and Safety of Immunosuppressive Drug Therapy for Neuromyelitis Optica Spectrum Disorders: An Overview of Meta-analyses and Systematic Reviews	OBJECTIVE: This study aims to provide an overview of meta-analyses and systematic reviews on the effectiveness and safety of immunosuppressive drug therapy for neuromyelitis optica spectrum disorders (NMOSD) by evaluating the methodological quality and reporting quality of reviews. METHOD(S): The Chinese National Knowledge Infrastructure (CNKI), WanFang Data, China Science and Technology Journal Database, Web of Science, the Cochrane Library, PubMed, and Embase databases were searched to collect systematic reviews or meta-analyses on the effectiveness and safety of immunosuppressive therapy for NMOSD from inception to December 2, 2021. Two researchers independently screened reviews and extracted data. Any differences in the procession of review assessment between the two researchers were re-evaluated, and the disagreement was resolved by discussion with other researchers. The following data were extracted: author, year of publication, the country where the study was conducted, study type, the number of included studies, sample size, risk bias tools, medication of immunosuppressive therapy, and main outcomes. Then, the AMSTAR-2, which is a critical appraisal tool for systematic reviews (2nd edition), and Grades of Recommendation, Assessment, Development and Evaluation (GRADE) were used to evaluate the methodological quality and reporting quality of evidence. A comprehensive analysis was conducted on the outcomes for all included reviews. RESULT(S): A total of 15 reviews were included. Of the included reviews, 3 were systematic reviews, 7 were meta-analyses, and 5 were systematic reviews and meta- analyses. According to the AMSTAR-2 criteria, 6 studies had high quality, 1 study had moderate quality, 4 studies had low quality, and 4 studies had critically low quality. Based on the GRADE, neither evidence quality for effectiveness nor safety was high. CONCLUSION(S): Immunosuppressive drug therapy is effective for patients with NMOSD, but its safety is controversial. Due to the poor quality of evidence, reliability needs to be considered. Thus, large sample, multi-center, double-blind, randomized controlled studies are still needed in the future.Copyright? Bentham Science Publishers; For any queries, please email at epub@benthamscience.net.	STUDY DESIGN
Multiple Sclerosis and Related Disorders. 50:102869, 2021 May.	Velasco M Zarco LA	Effectiveness of treatments in Neuromyelitis optica to	BACKGROUND: Neuromyelitis Optica spectrum disorder (NMOSD) is an inflammatory disease, which manifests mostly as recurrent episodes of optic neuritis or myelitis that cause important disability. Early diagnosis and prompt	STUDY DESIGN

Agudelo-Arrieta M Torres-Camacho I Garcia-Cifuentes E Munoz O	modify the course of disease in adult patients Systematic review of literature	initiation of immunosuppressive therapy are crucial in reducing relapses, disability, and mortality. Even though, there are few prospective randomized controlled trials, several drugs have proved to be both effective and safe. Azathioprine and Rituximab represent the standard of care and are used as first-line treatment agents worldwide. However, recent studies have unveiled new therapies, such as monoclonal antibodies. To make treatment recommendations and management guidelines, it is imperative to define an appropriate standard of care. METHODS: A systematic literature review was performed in MEDLINE, EMBASE, and LILACS databases using the following terms: "(NMO OR Devic OR Neuromyelitis Optica) AND (Azathioprine OR Prednisone OR Rituximab OR Tocilizumab OR Bortezomib OR Inebilizumab OR Eculizumab OR Satralizumab)" including both, randomized clinical trials and observational studies published between January 2006 and January 2021. The inclusion criteria comprised patients aged 18 or older, NMOSD diagnosis following the Wingerchuck criteria, two or more therapies been compared, and the evaluation of both efficacy and safety outcomes. All studies comparing treatment only with placebo were excluded. Quality was assessed according with the design of the study, and results were synthesized through comparative tables for each outcome evaluated, differentiating the results of randomized and non-randomized studies. RESULTS: Thirteen studies with 1447 patients were included. Twelve studies evaluated the expanded disability status scale (EDSS) before and after treatment; in five of seven evaluating rituximab, it outperformed its comparators in improving the disability degree. Eleven studies assessed the annual relapse rate (ARR). Again, in six of seven evaluating rituximab, it was superior to other therapies. Time to relapse (TTR) was reported in five studies. The three studies that included Rituximab revealed a longer time to relapse in this arm of treatment. Finding were consistent in randomized and non-randomized studies. The new molecules Satralizumab, Eculizumab and Tocilizumab were evaluated in one study each, proving to be highly effective and safe. The safety profile analysis showed a higher number of adverse events for Azathioprine. DISCUSSION: This systematic review demonstrates a superiority tendency of Rituximab upon the other treatments strengthening the available evidence about

			NMOSD management. Superiority in EDSS outcomes, annual relapse rate, time to first relapse and relapses during treatment time was evidenced in the Rituximab group compared to other medications, with lower rates of adverse events. New molecules Tocilizumab, Eculizumab and Satralizumab also showed superiority in the evaluated results, especially in the relapses during treatment time outcome, although with subtle differences in EDSS and ARR outcomes. CONCLUSION: Our results suggest that monoclonal antibodies are highly effective and safe for the treatment of NMOSD; Rituximab showed better performance on multiple outcomes and has more evidence available. New molecules: Eculizumab, Tocilizumab, Satralizumab are good options for treatment. Drugs like Azathioprine and Mycophenolate are effective, but with a worse risk-benefit ratio, therefore, they are useful alternatives in places that do not have access to monoclonal antibodies. Copyright ? 2021. Published by Elsevier B.V.	
Multiple Sclerosis and Related Disorders. 46 (no pagination), 2020. Article Number: 102484. Date of Publication: November 2020.	Luo D. Wei R. Tian X. Chen C. Ma L. Li M. Dong X. Zhang E. Zhou Y. Cui Y.	Efficacy and safety of azathioprine for neuromyelitis optica spectrum disorders: A meta-analysis of real-world studies	Objective: This study aimed to perform a meta-analysis of the efficacy and safety of azathioprine (AZA) for neuromyelitis optica spectrum disorders (NMOSD), considering the potential predictive factors related to patient response to AZA in this disease. Method(s): We performed a systematic online query in PubMed, EMBASE, The Cochrane Library, ClinicalTrials.gov, China National Knowledge Infrastructure, WANFANG DATA, and CQVIP DATA. The available studies on the use of AZA in NMOSD patients were included. Result(s): We analyzed a total of 21 studies including 1016 patients. Results demonstrated that AZA significantly decreased annual relapse rate (ARR) by 1.164 (95% confidence intervals (CI), -1.396 to -0.932; $p < 0.001$). Subgroup analysis showed that AZA significantly decreased ARR in both low-dose group (effect size (ES): -1.545) and moderate-dose group (ES: -2.026). AZA therapy also resulted in a significant reduction of 1.117 (95% CI: -1.668 to -0.566; $p < 0.001$) in expanded disability status scale (EDSS) score. AZA did not affect EDSS score in the low-dose subgroup (ES: -0.535; $p = 0.209$) or the moderate-dose subgroup (ES: -0.709; $p = 0.064$). During AZA therapy, 47% of patients did not experience any relapses (95% CI, 39% to 54%). In addition, 13% of patients developed leukopenia, 11% had elevated liver enzyme levels, 8% experienced nausea or vomiting, 5% developed pancytopenia and 6% died during follow-up. Conclusion(s): AZA is effective in reducing relapse and improving patients' neurological function. However, liver function monitoring	STUDY DESIGN

			and routine blood monitoring remain necessary. Within the safe upper limit, a higher dose of AZA may be associated with a better efficacy for NMOSD.Copyright ? 2020	
Advances in Ophthalmology Practice and Research. 2(3) (no pagination), 2022. Article Number: 100064. Date of Publication: 01 Nov 2022.	Xu X. Xie L. Wei L. Li M. Wang H. Zhou H. Sun M. Yang M. Xu Q. Yang K. Wei S.	Efficacy and safety of monoclonal antibodies in neuromyelitis optica spectrum disorders: A survival meta-analysis of randomized controlled trials	Background: Monoclonal antibodies such as rituximab (RTX), eculizumab, inebilizumab, satralizumab, and tocilizumab have been found to be effective therapies for neuromyelitis optica spectrum disease (NMOSD) in several clinical randomized controlled trials. Objective(s): The purpose of this meta-analysis of randomized controlled trials was to assess the efficacy and safety of monoclonal antibodies in the treatment of NMOSD. Method(s): We searched the following databases for relevant English language literature from the establishment of the database to June 2021: PubMed, Embase, Cohorane Library, the Central Register of Controlled Trials (CENTRAL), and Web of Science. Randomized controlled trials of monoclonal antibodies were the targets of the review. Result(s): We included seven trials containing 775 patients (485 in the monoclonal antibody group and 290 in the control group). Patients in the monoclonal group (HR 0.24, 95% CI: 0.14 to 0.40, P < 0.00001), as well as patients with seropositive AQP4-IgG (HR 0.18, 95% CI: 0.11 to 0.29, P < 0.00001), both had a higher free recurrence rate than that in the control group. In the first year (HR 0.25, 95% CI: 0.09 to 0.71, P = 0.009) and the second year (HR 0.32, 95% CI: 0.13 to 0.81, P = 0.02), no relapses were documented. The average changes of the expanded disability status scale (EDSS) score decreased by 0.29 (95% CI: -0.09 to 0.51, P = 0.005). Upper respiratory tract infection (OR 1.52, 95% CI: 0.76 to 3.04, P = 0.24), urinary tract infection(OR 0.79, 95% CI: 0.51 to 1.21, P = 0.27), and headache (OR 1.30, 95% CI: 0.78 to 2.17, P = 0.31) were three most frequent adverse reactions. Conclusion(s): Monoclonal antibodies are particularly effective treatments in avoiding recurrence for NMOSD patients, according to this meta-analysis. The associated adverse responses are not significantly different from those seen with traditional immunosuppressants.Copyright ? 2022 The Authors	STUDY DESIGN
European Journal of Ophthalmology. 32(4) (pp 1857-1871), 2022.	Zhang J. Fan A.	Efficacy and safety of plasma exchange or immunoadsorption for the treatment of option	Background: There are no systematic reviews yet that evaluated the effects of PE/IA in patients with optic neuritis (ON) in demyelinating diseases. A meta-analysis of available study is needed to further explore the value of plasma exchange (PE) or immunoadsorption (IA) in treating ON in demyelinating	STUDY DESIGN

Date of Publication: July 2022.	Wei L. Wei S. Xie L. Li M. Zhang W. Liu Q. Yang K.	neuritis in demyelinating diseases: A systematic review and meta-analysis	diseases. Method(s): All relevant articles published on PubMed, Web of Science, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), VIP Database, Wanfang, Sinomed and ophthalmology professional websites were searched. Study characteristics, demographic characteristics, clinical features and outcome measures were extracted. Response rate, adverse events (AE) rate, serious adverse event (SAE) rate, the log of the minimum angle of resolution (logMAR), visual outcome scale (VOS) and expanded disability status scales (EDSS) were evaluated using a random-effects model. Result(s): 35 studies were included between 1985 and 2020, containing 1191 patients. The response rates of PE and IA in acute attack of ON were 68% and 82% respectively. LogMAR (-0.60 to - 1.42) and VOS (-1.10 to -1.82) had been significantly improved from within 1 month to more than 1 month after PE treatment. Besides, we found that logMAR improved 1.78, 0.95 and 0.38, respectively,when the time from symptom onset to the first PE/IA was less than 21 days, 21-28 days, and more than 28 days. The pooled mean difference of EDSS was -1.14.Adverse effects rate in patients with PE or IA were 0.20 and 0.06, respectively. Conclusion(s): The meta-analysis provided evidence that PE/IA treatment was an effective and safe intervention, and it is recommended that early initiation of PE/IA treatment is critical.Copyright ? The Author(s) 2021.	
Journal of Research in Medical Sciences. 22(1) (no pagination), 2017. Article Number: 18. Date of Publication: 2017.	Etemadifar M. Salari M. Mirmosayyeb O. Serati M. Nikkhah R. Askari M. Fayyazi E.	Efficacy and safety of rituximab in neuromyelitis optica: Review of evidence	Neuromyelitis optica (NMO) is an autoimmune inflammatory disease of the central nervous system with preferential involvement in the optic nerve and spinal cord with a widespread spectrum of clinical features; multiple therapeutic agents have been used with different results. Recent evidence points to B-cell-mediated humoral immunity in the pathogenesis of NMO. Rituximab targets the CD20 antigen on B-cells. Treatment leads to profound B-cell depletion, principally over an antibody-dependent cell cytotoxicity mechanism. The aim of our study was to review clinical trials to elucidate the impact of rituximab on the relapse rate, Expanded Disability Status Scale (EDSS), and progression of disability in NMO. We performed a comprehensive review of all studies that evaluated clinical and paraclinical effects of rituximab on NMO. MEDLINE-PubMed, Web of Sciences, EMBASE, and Cochrane databases up to June 2016 included in our searches. In addition, reference lists from articles identified by search as well as a key review article to identify additional articles included in the study. Rituximab targets the CD20 antigen on B-cells and decreases attack frequency and severity in patients	STUDY DESIGN

			with NMO; however, it does not remove attacks, even when modifying treatment to achieve B-cell depletion. Most of the investigations revealed that EDSS significantly in all patients with rituximab treatment will be decreased after treatment with rituximab. No new or enlarged lesions or pathological gadolinium enhancement was observed in serial brain and spinal cord magnetic resonance imaging, except for those observed concomitantly with clinical relapses and the median length of spinal cord lesions was significantly reduced after therapy. Rituximab targets the CD20 antigen and decreases attack frequency and severity in patients with NMO.Copyright ? 2017 Journal of Research in Medical Sciences.	
JAMA Neurology. 73(11) (pp 1342-1348), 2016. Date of Publication: 01 Nov 2016.	Damato V. Evoli A. Iorio R.	Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: A systematic review and meta-analysis	IMPORTANCE Neuromyelitis optica spectrum disorders (NMOSDs) are autoimmune astrocytopathies characterized by predominant involvement of the optic nerves and spinal cord. In most patients, an IgG autoantibody binding to astrocytic aquaporin 4, the principal water channel of the central nervous system, is detected. Rituximab, a chimeric monoclonal antibody specific for the CD20 B-lymphocyte surface antigen, has been increasingly adopted as a first-line off-label treatment for patients with NMOSDs. OBJECTIVE To perform a systematic review and ameta-analysis of the efficacy and safety of rituximab use in NMOSDs, considering the potential predictive factors related to patient response to rituximab in this disease. EVIDENCE REVIEW English-language studies published between January 1, 2000, and July 31, 2015, were searched in the MEDLINE, Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov databases. Patient characteristics, outcome measures, treatment regimens, and recorded adverse effects were extracted. FINDINGS Forty-six studies were included in the systematic review. Twenty-five studies that included 2 or more patients with NMOSDs treated with rituximab were included in the meta-analysis. Differences in the annualized relapse rate ratio and Expanded Disability Status Scale score before and after rituximab therapy were the main efficacy measures. Safety outcomes included the proportion of deaths, withdrawals because of toxic effects, and adverse effects. RESULTS Among 46 studies involving 438 patients (381 female and 56 male [sex was not specified in 1 patient]; mean age at the outset of treatment, 32 years [age range, 2-77 years]), rituximab therapy resulted in a mean (SE) 0.79 (0.15) (95%CI, -1.08 to -0.49) reduction in the mean annualized relapse rate ratio and a mean (SE) 0.64 (0.27) (95%CI, -1.18 to -0.10) reduction in the mean Expanded Disability Status Scale score. A significant correlation was	STUDY DESIGN

			observed between disease duration and the Expanded Disability Status Scale score. Adverse effects were recorded in 114 of 438 (26%) patients treated with rituximab. Specifically, 45 patients (10.3%) experienced infusion-related adverse effects, 40 patients (9.1%) had an infection, 20 patients (4.6%) developed persistent leukopenia, 2 patients (0.5%) were diagnosed as having posterior reversible encephalopathy, and 7 patients (1.6%) died. CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis provides evidence that rituximab therapy reduces the frequency of NMOSD relapses and neurological disability in patients with NMOSDs. However, the safety profile suggests caution in prescribing rituximab as a first-line therapy.Copyright 2016 American Medical Association. All rights reserved.	
Multiple Sclerosis Journal. Conference: Pan-Asian Committee for Treatment and Research in Multiple Sclerosis Congress, PACTRIMS 2019. Singapore Singapore. 26(9) (pp NP100-NP101), 2020. Date of Publication: August 2020.	Yamamura T. de Seze J. Weinshenker B.G. Terada Y. Kawata Y. Gianella-Borradori A. von Budingen C. Klingelschmitt G. Traboulsee A.	Efficacy and safety of satralizumab for relapse prevention in neuromyelitis optica spectrum disorder: A pooled analysis from two Phase 3 clinical trials	Background: Satralizumab is a humanised monoclonal antibody targeting the interleukin-6 receptor. Satralizumab significantly reduced the risk of protocol-defined relapse (PDR) in patients with NMOSD in two Phase 3 studies: SAkuraSky (NCT02028884) and SAkuraStar (NCT02073279). Hazard ratios (HR) for the risk reduction were 0.38 (95% CI, 0.16-0.88) in SAkuraSky and 0.45 (95% CI, 0.23-0.89) in SAkuraStar. Objective(s): To evaluate the efficacy and safety of satralizumab in a pooled population of NMOSD patientsMethods: Patients were randomised to satralizumab (120mg s.c.) or placebo, administered as monotherapy (SAkuraStar) or add-on to baseline treatment (SAkuraSky) at Weeks 0, 2, 4, and every 4 weeks thereafter. The primary endpoint was time to first PDR. Between-group HRs were calculated based on Cox proportional hazards models, stratified by study. The validity of the data pooling was assessed. Result(s): The pooled analysis included 178 patients (satralizumab, n=104; placebo, n=74). Overall, a 58% reduction in PDR risk with satralizumab vs placebo (HR, 0.42; 95% CI, 0.25-0.71) was observed. HRs were 0.25 (95% CI, 0.12-0.50; 75% risk reduction) in AQP4-IgG seropositive patients, and 0.97 (95% CI, 0.41-2.23) in seronegative patients. Incidence of adverse events was similar between treatment arms, with no deaths or anaphylactic reactions. The validity of data pooling was confirmed, as no interaction between study and treatment effect was observed. Conclusion(s): This pooled analysis demonstrated the consistent efficacy of satralizumab, both in addition to baseline treatment and as monotherapy, in reducing relapse risk in patients with NMOSD. Satralizumab had a favourable safety profile.	STUDY DESIGN

Multiple Sclerosis and Related Disorders. Conference: The Fifth MENACTRIMS Congress. Intercontinental Hotel, Dubai Festival City, Dubai United Arab Emirates. 37 (no pagination), 2020. Article Number: 101592. Date of Publication: January 2020.	De Seze J. Weinshenker B.G. Terada Y. Kawata Y. Gianella-Borradori A. Von Budingen C. Klingelschmitt G. Traboulsee A. Yamamura T.	Efficacy and Safety of Satralizumab for Relapse Prevention in Neuromyelitis Optica Spectrum Disorder: A Pooled Analysis from Two Phase 3 Clinical Trials	Satralizumab is a humanised recycling monoclonal antibody that binds to the interleukin-6 (IL-6) receptor; IL-6 has been implicated in the pathophysiology of neuromyelitis optica spectrum disorder (NMOSD). Satralizumab significantly reduced the risk of NMOSD relapse in two Phase 3 studies: SAkuraSky (SA-307JG; NCT02028884) and SAkuraStar (SA-309JG; NCT02073279). Hazard ratios (HR) for the risk reduction were 0.38 (95% confidence interval [CI] 0.16-0.88) in SA-307JG and 0.45 (95% CI 0.23-0.89) in SA-309JG (both p=0.018). Satralizumab was particularly effective in AQP4-IgG-seropositive patients (HR 0.21 [95% CI 0.06-0.75] in SA-307JG and HR 0.26 [95% CI 0.11-0.63] in SA-309JG). Patients were randomized 1:1 (SA-307JG) or 2:1 (SA-309JG) to satralizumab (120 mg) or placebo, with treatment at Weeks 0, 2, 4, and Q4W thereafter. Satralizumab or placebo were administered as monotherapy (SA-309JG) or add-on to baseline immunosuppressants (SA-307JG). The primary endpoint of both studies and the pooled analysis was time to first protocol-defined relapse (PDR). Efficacy analyses were performed on the pooled intention-to-treat population. Between-group HRs for time to PDR were calculated based on Cox proportional hazards models, stratified by study. To assess the validity of pooling data across the two studies, individual study treatment effects within the pooled analysis and study by treatment interaction effect were calculated. The pooled analysis included 104 patients who received satralizumab and 74 who received placebo. HR for time to first PDR was 0.42 (95% CI 0.25-0.71; 58% risk reduction vs placebo). For AQP4-IgG seropositive patients, the HR was 0.25 (95% CI 0.12-0.50; 75% risk reduction); in the seronegative group, the HR was 0.97 (95% CI 0.41-2.23). The validity of pooling the data was confirmed, as no interaction between study and treatment effect was observed. Incidence of adverse events was similar in satralizumab and placebo groups; there were no deaths or anaphylactic reactions. This pooled analysis of data from two Phase 3 studies demonstrated the efficacy of satralizumab in reducing relapse risk in patients with NMOSD. Satralizumab had a favourable safety profile as monotherapy or alongside immunosuppressants.Copyright ? 2019	STUDY DESIGN
Journal of Neuroimmunology.	Enriquez CAG Espiritu AI	Efficacy and tolerability of mitoxantrone for neuromyelitis optica	The review assessed the efficacy and tolerability of mitoxantrone in patients with neuromyelitis optica spectrum disorder (NMOSD). Eight articles were reviewed with a total of 117 patients. Annualized relapse rate and progression of disability	STUDY DESIGN

332:126-134, 2019 07 15.	Pasco PMD	spectrum disorder: A systematic review	dramatically decreased post-treatment in most studies. Mitoxantrone was generally tolerated. Only one patient developed acute myeloid leukemia, which lead to septicemia and death. No serious cardiotoxicity was reported. Mitoxantrone may be effective in reducing the frequency of relapse and slowing down the progression of disability in patients with NMOSD. The risk of cardiotoxicity and leukemia detains it as a second-line agent for NMOSD. Copyright ? 2019 Elsevier B.V. All rights reserved.	
Multiple Sclerosis Journal. Conference: 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2022. Amsterdam Netherlands. 28(3 Supplement) (pp 134), 2022. Date of Publication: October 2022.	Paul F. Rampal N. Cimbora D. Pedersen M. Aktas O.	Efficacy comparison of time to first adjudicated attack with inebilizumab vs satralizumab in NMOSD: a matching-adjusted indirect comparison of monotherapy registrational trials	Introduction: With the recent availability of three novel, safe and effective biologic therapies for neuromyelitis optica spectrum disorder (NMOSD), physicians and patients are faced with the challenge of selecting an appropriate treatment. Inebilizumab (CD19-targeted B cell depletion therapy) and satralizumab (IL-6 pathway blocker) are both indicated for NMOSD patients who are seropositive for aquaporin-4 antibody (AQP4+). Aim(s): Matching-Adjusted Indirect Comparison (MAIC) analysis was performed to provide a robust and rigorous trial comparison supporting an informed evidence-based therapy decision. Method(s): This analysis compares the efficacy of inebilizumab and satralizumab. To ensure an unbiased and appropriate crossstudy comparison, data from the N-MOmentum (NCT02200770, N=161) and SAkuraStar (NCT02073279, N=41) studies were compared as both were registrational monotherapy studies for inebilizumab and satralizumab respectively. Both were placebocontrolled, employing similar assessments and endpoints including the primary endpoint of time to first adjudicated attack. A detailed MAIC analysis of the AQP4+ population was performed based on prognostic significance as well as differences between the two studies. Seven variables were assessed: sex, age, race, ethnicity, region, baseline EDSS, and prior attacks. Sex, race, and region emerged as the variables significantly different between the two study populations and were the key factors evaluated. Result(s): The primary efficacy endpoint of time to first adjudicated attack was met for both the inebilizumab and satralizumab studies with unadjusted hazard ratios (HRs) of 0.227 for inebilizumab and 0.260 for satralizumab (each vs. placebo; statistically significant). Following the MAIC analysis, which adjusts the N-MOmentum trial population to match most closely that of SAkuraStar, the HR for inebilizumab improved from 0.227 to 0.174. The relative risk ratio for inebilizumab vs. satralizumab was 0.67, representing a 33% increase in efficacy for inebilizumab compared to satralizumab for the primary endpoint. Thus, for every	STUDY DESIGN

			100 attacks that occur in satralizumab-treated patients, only 67 would be anticipated in inebilizumab-treated patients. Multiple sensitivity analyses reinforced the validity of this result. Conclusion(s): While cross-study comparisons have limitations, these results suggest a meaningful efficacy advantage of inebilizumab over satralizumab for the prevention of NMOSD attacks.	
Clinical and Experimental Neuroimmunology. 13(4) (pp 194-207), 2022. Date of Publication: November 2022.	Luitel P. Ghimire A. Upadhyay D. Ojha R.	Efficacy of monoclonal antibodies in neuromyelitis optica: An updated systematic review with meta-analysis	Objective: This is a critical review of studies aiming to assess the safety and efficacy of monoclonal antibodies as compared with the classical regimen in patients with neuromyelitis optica spectrum disorder. Method(s): Various electronic databases were searched for original articles reporting results from the use of monoclonal antibodies in neuromyelitis optica spectrum disorder. The Expanded Disability Status Scale and annualized relapse rate score before and after treatment were the primary effect measures. The pooled standardized mean difference with 95% CI was calculated using the random effects model. The heterogeneity of the included studies was calculated using Cochran's Q test and I2 statistics. Result(s): Of 36 included studies, meta-analysis was carried out from 27 studies. The pooled analysis of 1010 patients showed a mean reduction in the mean annualized relapse rate ratio after tocilizumab therapy -2.45 (95% CI -3.13 to -1.77) to be higher compared with rituximab -1.49 (95% CI -1.81 to -1.17). Likewise, the mean reduction in the Expanded Disability Status Scale after tocilizumab was higher -1.10 (95% CI -1.75 to -0.44) compared with rituximab -0.80 (95% CI -1.11 to -0.48). Conclusion(s): Tocilizumab has a greater effect than rituximab in terms of the reduction of the annualized relapse rate and Expanded Disability Status Scale in neuromyelitis optica spectrum disorder patients. The greater efficacy of tocilizumab could result from its multiple dynamic pharmacodynamics (i.e. its effect on interleukin-6-dependent inflammatory processes, involving CD20-negative plasmablasts, pathogenic T cells and regulatory T cells) and to some degree due to heterogeneity in our study. Satralizumab (monotherapy or add-on), eculizumab and inebilizumab (monotherapy) are effective in aquaporin-4-positive cases with good safety profiles. Ublituximab, bortezomib, bevacizumab and C1-esterase inhibitors are both effective and safe add-on drugs.Copyright ? 2022 Japanese Society for Neuroimmunology.	STUDY DESIGN

Clinical Neurology. Conference: 61st Annual Meeting of the Japanese Society of Neurology. Okayama Japan. 60(Supplement 1) (pp S470), 2020. Date of Publication: 2020.	Songwisit S. Kosiyakul P. Jitprapaikulsan J. Siritho S. Prayoonwiwat N. Ungprasert P.	Efficacy of Mycophenolate Mofetil in NMOSD: A Systematic Review	Objective Mycophenolate mofetil (MMF) is a commonly prescribed medication for relapse prevention in patients with neuromyelitis optica spectrum disorders (NMOSD). However, data on its efficacy are still relatively limited. This study aims to review data on the effects of MMF on disease severity and disability among patients with NMOSD using systematic review technique. Methods Published peer-reviewed studies were independently searched from EMBASE and OVID/Medline database by two investigators. Inclusion criteria were cohort studies of NMOSD patients treated with MMF that reported treatment outcomes, using either Annualized Relapse Rate (ARR) or Expanded Disability Status Scale (EDDS), before and after treatment. Case reports, case series with less than 3 patients, and reviews were excluded. Results We identified 563 potentially relevant articles from the two databases. After two rounds of review, 15 eligible studies with 839 patients were identified. At least 712 patients (85%) were aquaporin-4 immunoglobulin seropositive. Median follow-up time of all studies was greater than 12 months. All 15 studies showed ARR reduction comparing preand post-treatment, in which statistical significance was reached in 13 studies. Of 12 studies analyzing EDSS, 9 showed significant improvement of EDSS, 1 revealed non-significant improvement of EDSS, 1 reported no EDSS change, and 1 showed non-significant increase in EDSS (by one point). Conclusions This systematic review suggests that MMF could be used as a preventive therapy for NMOSD that is associated with improvement of ARR and EDSS.	STUDY DESIGN
Clinical Neurology. Conference: 61st Annual Meeting of the Japanese Society of Neurology. Okayama Japan. 60(Supplement 1) (pp S470), 2020. Date of Publication: 2020.	Kosiyakul P. Songwisit S. Ungprasert P. Siritho S. Prayoonwiwat N.	Efficacy of Plasma exchange in NMOSD: A Systematic Review and Meta-analysis	Objective Plasma exchange (PLEX) is a commonly utilized rescue therapy for severe neuromyelitis optica spectrum disorders (NMOSD) attacks, although data on its efficacy remain relatively unclear. The current systematic review and meta-analysis was conducted to further investigate the efficacy of PLEX for NMOSD attacks. Methods Systematic review was performed using EMBASE and OVID/Medline database. Inclusion criteria were (1) cohort studies of NMOSD patients treated with PLEX in acute phase that (2) reported treatment outcomes using Expanded Disability Status Scale (EDSS) before and after the therapy. Case reports, case series less than 3 patients, and reviews were excluded. Results A total 1,395 unique articles were identified from the two databases. After two rounds of review conducted independently by two investigators, 14 studies (n = 291 and greater than 191 (65.6%) patients were aquaporin-4 immunoglobulin	STUDY DESIGN

	Jitprapaikulsan J.		seropositive) met the inclusion criteria and were included into the meta-analysis. Immediately after treatment, PLEX therapy resulted in a significantly decreased EDSS with the pooled mean difference (MD) of 0.91 (95% CI, 0.3 to 1.52, I2 =72%) comparing pre-treatment to post-treatment. At follow-up (6 months to 1 year), patients who received PLEX therapy continued to have a lower post-treatment EDSS with the pooled MD of 2.21 (95% CI, 1.57 to 2.86, I2 =40%) Conclusions This metaanalysis suggests that PLEX therapy is effective in NMOSD attack that is associated with improvement of disability status immediately after treatment and during follow-up period.	
European Journal of Neurology. 17(8) (pp 1019-1032), 2010. Date of Publication: August 2010.	Sellner J. Boggild M. Clanet M. Hintzen R.Q. Illes Z. Montalban X. Du Pasquier R.A. Polman C.H. Sorensen P.S. Hemmer B.	EFNS guidelines on diagnosis and management of neuromyelitis optica	Background and purpose: Neuromyelitis optica (NMO) or Devic's disease is a rare inflammatory and demyelinating autoimmune disorder of the central nervous system (CNS) characterized by recurrent attacks of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM), which is distinct from multiple sclerosis (MS). The guidelines are designed to provide guidance for best clinical practice based on the current state of clinical and scientific knowledge. Search strategy: Evidence for this guideline was collected by searches for original articles, case reports and meta-analyses in the MEDLINE and Cochrane databases. In addition, clinical practice guidelines of professional neurological and rheumatological organizations were studied. Result(s): Different diagnostic criteria for NMO diagnosis [Wingerchuk et al. Revised NMO criteria, 2006 and Miller et al. National Multiple Sclerosis Society (NMSS) task force criteria, 2008] and features potentially indicative of NMO facilitate the diagnosis. In addition, guidance for the work-up and diagnosis of spatially limited NMO spectrum disorders is provided by the task force. Due to lack of studies fulfilling requirement for the highest levels of evidence, the task force suggests concepts for treatment of acute exacerbations and attack prevention based on expert opinion. Conclusion(s): Studies on diagnosis and management of NMO fulfilling requirements for the highest levels of evidence (class I-III rating) are limited, and diagnostic and therapeutic concepts based on expert opinion and consensus of the task force members were assembled for this guideline. ? 2010 EFNS.	STUDY DESIGN
Open Access Macedonian Journal of Medical Sciences. 8(B)	Archilovna G.M.	Modern methods of devic's disease treatment	BACKGROUND: Neuromyelitis optica (NMO) (also known as opticomyelitis, Devic's syndrome/disease) is an idiopathic inflammatory disorder of the central nervous system characterized by predominant involvement of the optic nerves,	STUDY DESIGN

(pp 1083-1087), 2020. Date of Publication: 02 Jan 2020.	Danilovna K.E. Baikonyrovna B.M. Muratovich S.A. Kabidenovna O.S. Kurmashovich B.N. Andreevich B.R. Ardakovna A.A. Argynovna A.Z. Nagimovna A.Z. Baltalykyzy A.A.		spinal cord, and extensive transverse myelitis. To date, there are no convincing clinical trials that would fully evaluate the efficacy and safety of drugs for the treatment and prevention of NMO exacerbation. Taking into account the malignant course that quickly leads to disability of young, economically active population, the issues of searching for effective methods of NMO treatment remain highly urgent. AIM: The purpose of the study was to examine available modern methods of treatment and prevention of NMO exacerbation, which have potential and require further detailed clinical trials to ensure possible application of these treatment options in clinical practice. MATERIALS AND METHODS: We have reviewed previously applied and modern methods of treatment. We have analyzed systematic reviews, clinical, randomized, and retrospective studies of scientific medical databases: PubMed, Cochrane, The Lancet, UpToDate, and reviews of world medical journals in Russian and English. CONCLUSION(S): The authors concluded that there is a sufficient number of drugs and combinations of methods of Devic's disease treatment. We were interested in combinations of rituximab (RIT) and autologous stem cell transplantation, RIT and fetal hepatocyte transplantation, and RIT and strengthening the effect by plasmapheresis sessions. However, successful implementation of these methods in clinical practice requires conducting controlled clinical trials with a larger number of patients and longer follow-up periods.Copyright ? 2020 Grigolashvili Marina Archilovna, Kim Ekaterina Danilovna, Beisembayeva Mira Baikonyrovna, Smagulov Amirzhan Muratovich, Omarova Sholpan Kabidenovna, Biduysenov Nurdaulet Kurmashovich, Belyaev Ruslan Andreevich, Abildina Akmaral Ardakovna, Abueva Zhanna Argynovna, Aimurzina Zhanargul Nagimovna, Amanzhol Aigerim Baltalykyzy.	
Frontiers in Pharmacology. 12:652759, 2021.	Kong F Wang J Zheng H	Monoclonal Antibody Therapy in Neuromyelitis Optica Spectrum Disorders: a Meta-analysis of	Background: To update the efficacy and safety data of monoclonal antibodies for the treatment of neuromyelitis optica spectrum disorders (NMOSD) and explore the differences in the effect of treatment between patients seropositive and seronegative for AQP4-IgG. METHODS: PubMed, Embase, and the Cochrane Library published up to July	STUDY DESIGN

	Cai H Hua J Li L	Randomized Control Trials	2020 were searched for randomized controlled trials (RCTs) of monoclonal antibodies treatment (mAb) in patients with NMOSD. The primary outcome was the hazard ratio (HR) for relapse. The secondary outcomes included Expanded Disability Status Scale (EDSS) changes from baseline, adverse events (AEs), and serious adverse events (SAEs). A random-effects model was applied for the effect of heterogeneity among trials. RESULTS: We included 603 patients (monoclonal antibody group, n=382, and control group, n=221) from seven RCTs. There were fewer relapses in the mAb group (HR=0.32, 95% CI: 0.23-0.46, p<0.001), as well as in the AQP4-IgG-seropositive patients (HR=0.18, 95% CI: 0.10-0.32, p<0.001), but not in AQP4-IgG-seronegative NMOSD. Similar results were observed when considering satralizumab only. The mAb had no impact on the changes in EDSS scores from baseline (WMD=-0.21, 95% CI: -0.50-0.09, p=0.176). The mAb did not lead to a higher frequency of AEs (OR=1.18, 95% CI: 0.70-1.98, p=0.529) or SAEs (OR=0.99, 95% CI: 0.63-1.56, p=0.975) compared with the control group. CONCLUSIONS: Compared to the control arm, monoclonal antibody therapy showed a significantly better outcome in restraining the HR for relapse among patients with NMOSD but insignificant effects in NMOSD patients with seronegative APQ4-IgG. The safety profile in each arm had no significant difference. Copyright ? 2021 Kong, Wang, Zheng, Cai, Hua and Li.	
Neurology & Therapy. 11(1):123-135, 2022 Mar.	Wingerchuk DM Zhang I Kielhorn A Royston M Levy M Fujihara K	Network Meta-analysis of Food and Drug Administration-approved Treatment Options for Adults with Aquaporin-4 Immunoglobulin G-positive Neuromyelitis Optica Spectrum Disorder	INTRODUCTION: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease defined by attacks on the central nervous system that cause irreversible damage. Recent approval of NMOSD therapies warrants investigations of comparative efficacy to inform treatment decisions. METHODS: A network meta-analysis (NMA) of all U.S. Food and Drug Administration-approved therapies (eculizumab, inebilizumab, and satralizumab) for adults with aquaporin-4 immunoglobulin G-positive (AQP4+) NMOSD was conducted via a systematic literature review (SLR) using data from randomized controlled trials (RCTs). Database searches of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were executed for the SLR. A fixed-effects proportional hazards Bayesian NMA was used to estimate relative	STUDY DESIGN

	Nakashima I Tanvir I Paul F Pittock SJ		treatment effects based on data extracted from RCTs identified during the SLR (search end date: 11 September 2020). Four unique RCTs (N-MOmentum, PREVENT, SAkuraSky, and SAkuraStar) were identified, and data from 29 publications were extracted for analysis. Network scenarios describing the most comparable patient population groups (such as by treatment settings) were evaluated in our analyses. Relative treatment effects were evaluated based on time-to-first relapse and were expressed as hazard ratios (HRs) with 95% credible intervals (CrIs). RESULTS: In patients treated with a monoclonal antibody only, eculizumab was associated with a lower risk of relapse compared with satralizumab (HR 0.10, 95% CrI 0.01, 0.65) and inebilizumab (HR 0.11, 95% CrI 0.02, 0.68). In patients treated with monoclonal antibody with or without background immunosuppressive therapy (IST), patients treated with eculizumab +/- IST were also less likely to relapse than patients treated with satralizumab +/- IST (HR 0.24, 95% CrI 0.06, 0.98). CONCLUSION: The NMA results suggest that complement component 5 (C5) inhibition prevents NMOSD relapses more effectively than broader mechanisms of action. Copyright ? 2021. The Author(s).	
Archivos Venezolanos de Farmacologia y Terapeutica. 41(5) (pp 353-361), 2022. Date of Publication: 2022.	Miguel T.-C.L. Alejandra M.-G.K. Javier A.-C.M. Anaiz C.-C.M.	Neuromyelitis optica spectrum disorder diagnostic-therapeutic update Systematic review	Neuromyelitis Optica spectrum disorder (NMOSD) is a rare pathology characterized by recurrent inflammatory crises of the central nervous system focused on the level of the spi-nal cord and the optic chiasm. This disease can alter other regions of the CNS and its pathophysiology is immunologic and heterogeneous, which makes us think of a spectrum of the disease. It is believed that NMOSD is caused by the presence of two classes of antibodies called: Anti-aquaporin 4 NMO IgG and Anti-MOG-IgG, the disease can present with one of the antibodies or with both, in this last case the sever-ity of the disease increases exponentially. The pathophysiology of this condition is not completely clear since it is known that the mentioned antibodies trigger inflammatory processes and demyelination of astrocytic cells, but it is not known by what mechanisms they do it. However, MRI studies can adequately delimit the lesions in the areas mentioned earlier and immunohistochemically localize the antibodies. The ini-tial clinical picture is characterized by simultaneous involve-ment of both the optic chiasm and the medulla in the early stage of the disease, although in most cases	STUDY DESIGN

			there is a vari-able period of months and years to evidence lesions in the involved structures. The manifestations are severe and are characterized by a progressive decrease in a vision leading to blindness and total flaccid paraplegia. The prognosis of this disease is not encouraging, since in 18% of cases suf-ferers lose sight in both eyes; irreversible motor disability oc-curs in 34% of patients, and in 23% of cases the use of a wheelchair is permanent. This disease has a mortality rate of 9%. We conducted a systematic review of the therapeutic and diagnostic advances in the pathology of neuromyelitis optica using complete, updated articles written in the last 5 years, which will be obtained from digital databases such as PubMed, Scopus, Chrocane Library, UpToDate, and Scielo.	
Journal of Clinical Medicine. 9(5), 2020 May 25.	Lipphardt M Wallbach M Koziolek MJ	Plasma Exchange or Immunoadsorption in Demyelinating Diseases: A Meta-Analysis	Multiple sclerosis (MS) is an inflammatory disease mainly affecting the central nervous system. In MS, abnormal immune mechanisms induce acute inflammation, demyelination, axonal loss, and the formation of central nervous system plaques. The long-term treatment involves options to modify the disease progression, whereas the treatment for the acute relapse has its focus in the administration of high-dose intravenous methylprednisolone (up to 1000 mg daily) over a period of three to five days as a first step. If symptoms of the acute relapse persist, it is defined as glucocorticosteroid-unresponsive, and immunomodulation by apheresis is recommended. However, several national and international guidelines have no uniform recommendations on using plasma exchange (PE) nor immunoadsorption (IA) in this case. A systematic review and meta-analysis was conducted, including observational studies or randomized controlled trials that investigated the effect of PE or IA on different courses of MS and neuromyelitis optica (NMO). One thousand, three hundred and eighty-three patients were included in the evaluation. Therapy response in relapsing-remitting MS and clinically isolated syndrome was 76.6% (95%CI 63.7-89.8%) in PE- and 80.6% (95%CI 69.3-91.8%) in IA-treated patients. Based on the recent literature, PE and IA may be considered as equal treatment possibilities in patients suffering from acute, glucocorticosteroid-unresponsive MS relapses.	STUDY DESIGN

Clinical Neurology. Conference: 61st Annual Meeting of the Japanese Society of Neurology. Okayama Japan. 60(Supplement 1) (pp S352), 2020. Date of Publication: 2020.	De Seze J. Weinshenker B.G. Terada Y. Kawata Y. Gianella-borradori A. Von Budingen H.-C. Klingelschmitt G. Traboulsee A. Yamamura T.	Pooled analysis from the SAkura trials with satralizumab in neuromyelitis optica spectrum disorder	Objective To evaluate satralizumab for neuromyelitis optica spectrum disorder (NMOSD) using pooled data from the SAkuraSky (NCT02028884) and SAkuraStar (NCT02073279) Phase 3 studies, which combined provide a large data set for analysis. Methods Patients were randomized 1:1 (SAkuraSky) or 2:1 (SAkuraStar) to satralizumab (120 mg) or placebo, administered at Weeks 0, 2, 4, and Q4W thereafter. Study drugs were given as monotherapy (SAkuraStar) or add-on to baseline immunosuppressants (SAkuraSky). The primary endpoint of both studies and the pooled analysis was time to first protocol-defined relapse (PDR). Efficacy analyses were performed on the pooled intention-to-treat population. Between-group HRs for time to PDR were calculated based on Cox proportional hazards models, stratified by study. Results Satralizumab significantly reduced risk of PDR in both trials. The pooled analysis included 104 patients on satralizumab and 74 on placebo. HR for time to first PDR was 0.42 (95% CI 0.25-0.71; 58% risk reduction vs placebo). For AQP4-IgG seropositive patients, the HR was 0.25 (95% CI 0.12-0.50; 75% risk reduction); in the seronegative group, the HR was 0.97 (95% CI 0.41-2.23). No interaction was observed between the individual studies and treatment effect, confirming the validity of pooling the data. Incidence of adverse events was similar across groups; no deaths or anaphylactic reactions were reported. Conclusions This pooled analysis from the SAkura studies demonstrates the efficacy and favourable safety profile of satralizumab in reducing relapse risk in patients with NMOSD.	STUDY DESIGN
Clinical Neurology. Conference: 61st Annual Meeting of the Japanese Society of Neurology. Okayama Japan. 60(Supplement 1) (pp S349), 2020. Date of Publication: 2020.	Fujihara K. Greenberg B. De Seze J. Fox E. Saiz A. Yamamura T.	Pooled safety analysis from Phase 3 trials of satralizumab in neuromyelitis optica spectrum disorder	Objective To evaluate the safety of satralizumab in neuromyelitis optica spectrum disorder (NMOSD) using pooled data from the SAkura studies. Methods SAkuraSky (NCT02028884) and SAkuraStar (NCT02073279) were randomized, double-blind, placebo-controlled studies of satralizumab in patients with NMOSD. Safety was evaluated in the pooled safety analysis population throughout the doubleblind period using adverse event(AE) rates per 100 patient-years(PY). Results The pooled population included 178 patients (satralizumab, n=104; placebo, n=74). The mean (standard deviation) duration of the double-blind period for safety analysis was longer with satralizumab vs placebo (97.2 [61.2] vs 70.6 [55.8] weeks). Rates of AEs and serious AEs were comparable between satralizumab and placebo groups (AEs: 478.49 vs 506.51 events/100PY, respectively; serious AEs: 14.97 vs 17.98 events/100PY, respectively). Infection	STUDY DESIGN

	Marcillat C. Kou X. Weber K. Weinshenker B.G.		rates were lower with satralizumab vs placebo(113.04 vs 154.85 events/100PY), with no increased risk of opportunistic infections. The most common AEs in both groups were urinary tract infection and upper respiratory tract infection. The injection-related reaction (IRR) rate was higher with satralizumab vs placebo (18.58 vs 8.99 events/100PY); IRRs were mostly mild-to-moderate and did not lead to treatment discontinuation. Four patients (3.8%) in the satralizumab group and six (8.1%) in the placebo group withdrew from the study due to an AE. No deaths or anaphylactic reactions were reported. Conclusions Satralizumab shows a favourable safety profile in patients with NMOSD.	
Value in Health. Conference: ISPOR Europe 2021. Virtual, Online. 25(1 Supplement) (pp S19), 2022. Date of Publication: January 2022.	Wingerchuk D. Pittock S.J. Levy M. Fujihara K. Nakashima I. Paul F. Kielhorn A. Royston M. Tanvir I. Zhang I.	POSA8 Indirect Comparison Analysis of United States Food and Drug Administration-Approved Treatment Options for Adults with Aquaporin-4 Immunoglobulin G-Positive Neuromyelitis Optica Spectrum Disorder	Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease that attacks the central nervous system and can cause irreversible damage. In light of several approved treatment options, a comparison of relative treatment effects would facilitate the treatment selection process. Objective(s): The objective of this study was to perform an indirect treatment comparison (ITC) on the efficacy of all United States Food and Drug Administration-approved treatments (eculizumab, inebilizumab, and satralizumab) in adults with aquaporin-4 immunoglobulin G-positive (AQP4+) NMOSD using published data from randomized controlled trials (RCTs). Method(s): A Bayesian network meta-analysis (NMA) was performed to estimate the relative treatment effects between eculizumab, inebilizumab, and satralizumab based on data extracted from RCTs. Analyses were performed for clinically relevant subpopulations based on 3 treatment networks (monotherapy, combination therapy, and mono-combination therapy). For time-to-first relapse, the NMA was performed using a regression model with a contrast-based normal likelihood for the log hazard ratio (HR) and corresponding standard error for each trial (or comparison) in the network. Relative treatment effects were expressed as HRs, which is standard for an ITC. Result(s): Time-to-first relapse was the only outcome measure shared across all RCTs. In the monotherapy network, patients on eculizumab were 90% less likely to experience a first relapse compared with satralizumab (HR: 0.10, 95% credible interval [CrI]: 0.01, 0.65) and 89% less likely to relapse than with inebilizumab (HR: 0.11, 95% CrI: 0.02, 0.68). In addition, patients treated with eculizumab +/- immunosuppressant therapy (IST) were 76% less likely to experience a first relapse when compared with satralizumab +/- IST (HR: 0.24, 95% CrI: 0.06, 0.98). Conclusion(s): Using available RCT data, NMA results showed that eculizumab	STUDY DESIGN

			monotherapy and eculizumab +/- IST demonstrated greater efficacy in prolonging time-to-first relapse when compared with either satralizumab or inebilizumab for treating adults with AQP4+ NMOSD.Copyright ? 2021	
Value in Health. Conference: ISPOR 2020. Orlando United States. 23(Supplement 1) (pp S329), 2020. Date of Publication: May 2020.	Kochar P. Randhawa S. Singh R. Goyal R. Lakkakula U.S. Bathla A.	PRO5 COMPARATIVE EFFICACY AND SAFETY OF PREVENTIVE THERAPIES FOR NEUROMYELITIS OPTICA: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS	Objectives: Neuromyelitis Optica (NMO, also known as Devic's disease) is a rare, debilitating autoimmune disorder of the central nervous system, dominated by inflammation of the optic nerve (optic neuritis) and spinal cord (myelitis). Several immunosuppressants and monoclonal antibodies such as corticosteroids, azathioprine, and rituximab have been prescribed widely as preventive treatment for NMO. However, there is a dearth of evidence on the optimal use of these therapies. The objective of this study, therefore, is to compare and rank the efficacy and safety of all preventive therapies for NMO by conducting systematic literature review (SLR) and network meta-analysis (NMA) of relevant studies. Method(s): Qualified studies were identified in a search of MEDLINE, Embase, CENTRAL, and databases, from 2019 to the inception of databases. Studies assessing freedom from relapse, reduction of disability and the occurrence of adverse events were considered. Outcomes were analyzed using a Bayesian NMA adopting a fixed-effect model. Mean differences in change from baseline and mean odds ratios (OR) with 95% credible intervals (CrIs) were calculated. Result(s): The SLR identified 18 relevant studies that were subject to feasibility assessment, of which 10 studies (two RCTs, six retrospective and two prospective observational studies) were included in the NMA. Tocilizumab (OR: 4.48; 95%CrI: 1.73, 13.34) and tacrolimus (OR: 2.85; 95% CrI: 0.93, 9.54) demonstrated greater relapse-free rate in comparison to azathioprine in NMO patients. For disability, measured by change in expanded disability status scale score, rituximab was hierarchically superior with significant mean difference versus azathioprine (0.63; 95% CrI: 0.31, 0.96). As compared to azathioprine, rituximab had a favorable safety profile, followed by tocilizumab and tacrolimus. Conclusion(s): Tocilizumab and tacrolimus may be considered as optimal treatments to prevent relapse in NMO. Rituximab improves disability in patients and is associated with relatively lesser adverse events compared to other preventive therapies.Copyright ? 2020	STUDY DESIGN

Neurology neuroimmunology & neuroinflammation. 5(3):e453, 2018 May.	Das G Damotte V Gelfand JM Bevan C Cree BAC Do L Green AJ Hauser SL Bove R	Rituximab before and during pregnancy: A systematic review, and a case series in MS and NMOSD	OBJECTIVE: To evaluate the safety of rituximab treatment before and during pregnancy in women with MS and neuromyelitis optica spectrum disorders (NMOSDs) who may be at risk of relapses by performing a systematic literature review combined with a retrospective single-center case series. METHODS: Studies were systematically identified in the PubMed, Google Scholar, and EMBASE using the key terms "pregnancy" and "rituximab"; 22 articles were included for review (>17,000 screened). Then, patients with MS and NMOSD from 1 center (University of California, San Francisco) exposed to rituximab before conception were identified through medical record review. RESULTS: Systematic review: We identified 102 pregnancies with rituximab use within 6 months of conception: 78 resulted in live births and 12 in spontaneous abortions. Of 54 live births with reported gestational age, 31 occurred at term (37 weeks+) and 2 before 32 weeks. When checked, B-cell counts were low in 39% of newborns and normalized within 6 months. Case series: we identified 11 pregnancies (1 ongoing) in 10 women (7 MS and 3 NMOSD) treated with rituximab within 6 months of conception. All completed pregnancies resulted in term live births of healthy newborns (1 lost to follow-up at term). No maternal relapses occurred before/during pregnancy; 1 occurred postpartum (NMOSD). CONCLUSION: No major safety signal was observed with rituximab use within 6 months of conception. Beyond the need for monitoring neonatal B cells, these observations support prospectively monitoring a larger patient cohort to determine whether rituximab may safely protect women with MS and NMOSD who are planning a pregnancy against relapses.	STUDY DESIGN
European Journal of Neurology. Conference: 6th Congress of the European Academy of Neurology. Paris France. 27(Supplement	Greenberg B.G. De Seze J. Fox E.	Safety of satralizumab based on pooled data from phase 3 studies in patients with neuromyelitis optica spectrum disorder (NMOSD)	Background and aims: Satralizumab reduced NMOSD relapse risk in 2 phase 3 studies: SAkuraSky (satralizumab in combination with baseline immunosuppressants; NCT02028884), and SAkuraStar (satralizumab monotherapy; NCT02073279). We evaluated the safety of satralizumab vs placebo across both SAkura studies. Method(s): SAkuraStar and SAkuraSky are randomized studies, consisting of a double-blind (DB) period (satralizumab 120mg Q4W vs placebo) followed by an open-label extension period (satralizumab only).	STUDY DESIGN

1) (pp 345-346), 2020. Date of Publication: May 2020.	Saiz A. Yamamura T. Marcillat C. Kou X. Weber K. Weinshenker B.G.		The combined DB/extension period was defined as the overall satralizumab treatment (OST) period (cut-off 7 June 2019). Safety was evaluated in the DB and OST periods using adverse event (AE) rates per 100 patient-years. Result(s): The pooled DB population included 178 patients (satralizumab, n=104; placebo, n=74). 166 patients received satralizumab in the OST period. Mean/median satralizumab exposures in the OST period were 133.3 and 128.6 weeks, respectively. Rates of AEs and serious AEs were comparable between treatment groups in the DB period (Table). Infection rates were lower with satralizumab vs placebo, with no increased risk of opportunistic infections (Table). AE, serious AE, and infection rates were comparable between the DB and OST periods (Table). 4 patients (3.8%) on satralizumab and 6 (8.1%) on placebo withdrew from the DB period due to an AE. The injection-related reaction (IRR) rate was higher with satralizumab vs placebo (Table); IRRs were mostly mild-to-moderate and did not lead to treatment discontinuation. No deaths or anaphylactic reactions were reported. Conclusion(s): In patients with NMOSD, satralizumab was well tolerated and showed a favourable safety profile. The long-term OST data were consistent with the DB periods. (Table Presented).	
Frontiers in Immunology. 10:1990, 2019.	Kaegi C Wuest B Schreiner J Steiner UC Vultaggio A Matucci A Crowley C Boyman O	Systematic Review of Safety and Efficacy of Rituximab in Treating Immune-Mediated Disorders	Background: During the past years biologic agents (also termed biologicals or biologics) have become a crucial treatment option in immunological diseases. Numerous articles have been published on biologicals, which complicates the decision making process on the use of the most appropriate biologic for a given immune-mediated disease. This systematic review is the first of a series of articles assessing the safety and efficacy of B cell-targeting biologics for the treatment of immune-mediated diseases. Objective: To evaluate rituximab's safety and efficacy for the treatment of immune-mediated disorders compared to placebo, conventional treatment, or other biologics. Methods: The PRISMA checklist guided the reporting of the data. We searched the PubMed database between 4 October 2016 and 26 July 2018 concentrating on immune-mediated disorders. Results: The literature search identified 19,665 articles. After screening titles and abstracts against the inclusion and exclusion criteria and assessing full texts, 105 articles were finally included in a narrative synthesis. Conclusions: Rituximab is both safe and effective for the treatment of acquired angioedema with C1-inhibitor deficiency, ANCA-associated vasculitis, autoimmune hemolytic anemia, Behcet's disease, bullous pemphigoid, Castleman's disease, cryoglobulinemia,	STUDY DESIGN

			Goodpasture's disease, IgG4-related disease, immune thrombocytopenia, juvenile idiopathic arthritis, relapsing-remitting multiple sclerosis, myasthenia gravis, nephrotic syndrome, neuromyelitis optica, pemphigus, rheumatoid arthritis, spondyloarthropathy, and systemic sclerosis. Conversely, rituximab failed to show an effect for antiphospholipid syndrome, autoimmune hepatitis, IgA nephropathy, inflammatory myositis, primary-progressive multiple sclerosis, systemic lupus erythematosus, and ulcerative colitis. Finally, mixed results were reported for membranous nephropathy, primary Sjogren's syndrome and Graves' disease, therefore warranting better quality trials with larger patient numbers.	
Human Vaccines and Immunotherapeutics. 11(12) (pp 2749-2763), 2015. Date of Publication: 01 Jan 2015.	Vitaliti G. Tabatabaie O. Matin N. Ledda C. Pavone P. Lubrano R. Serra A. Di Mauro P. Cocuzza S. Falsaperla R.	The usefulness of immunotherapy in pediatric neurodegenerative disorders: A systematic review of literature data	Immunotherapeutic strategies to treat neurodegenerative disorders have inspired the scientific community. The aim of our review is to address the translational aspects of neuroimmunology to describe the efficacy of immunotherapy in the treatment of pediatric neurodegenerative disorders. In the studies we analyzed IVIG were found to be efficient in the treatment of post-streptococcal neurodegenerative disorders, even if in PANDAS, plasma-exchange (PE) showed a higher efficiency. IVIG were also successfully used in ADEM and Guillan-Barre syndrome. In Sydenham Chorea the use of methylprednisolone was found in most cases as efficient as IVIG, while in Tourette's Syndrome, Colecoxib was successfully used in one patient. Pediatric Multiple Sclerosis seems to respond better to immunosuppressant agents (Mitoxantrone, Cyclophosphamide, Natalizumab), as well as Neuromyelitis optica (Rituximab, Mycofenolate). The importance of this review relies in the attempt to draw standardized guidelines for immunotherapy in pediatric neurodegeneratve disordersCopyright ?2015 Taylor & Francis Group, LLC.	STUDY DESIGN
Innovations in Clinical Neuroscience. 19(4-6):51-64, 2022 Apr-Jun.	Magdalena C Clarissa A Sutandi N	Comparative Analysis of Treatment Outcomes in Patients with Neuromyelitis Optica Spectrum Disorder	Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a neurological condition consisting of relapse-related disability. Treatment options are limited. This systematic review and meta-analysis aimed to evaluate the effectiveness and tolerability of rituximab (RTX) in comparison to azathioprine (AZT) and mycophenolate mofetil (MMF) for the treatment of NMOSD.	STUDY DESIGN

		Treated with Rituximab, Azathioprine, and Mycophenolate Mofetil: A Systematic Review and Meta-analysis [Review]	Methods: A systematic search was conducted among electronic databases, including PubMed, Scopus, EBSCO, and Cochrane, for relevant studies. We included randomized, controlled trials and prospective and retrospective studies evaluating the efficacy and safety of RTX compared to AZT and/or MMF in adult and pediatric patients with NMOSD. The Newcastle-Ottawa Scale (NOS) and Cochrane Collaboration tool were used to determine the risk of bias. Results: Eleven studies involving 1,086 patients were included in our study. Treatment with RTX generally yielded favorable annualized relapse rate (ARR) and Expanded Disability Status Scale (EDSS) results in comparison to AZT and MMF, despite its variable statistical significance. RTX treatment reduced the relapse rate and hazard risk for relapse (HRR). Patients in the RTX group experienced significantly fewer adverse events, among which the most common were allergies, infections, and leukopenia. Conclusion: In this study, RTX appeared to be superior to AZT and MMF in improving disability and reducing relapse in patients with NMOSD. RTX is also associated with fewer adverse events based on pooled analysis. Future randomized clinical trials are needed to establish the efficacy and safety of RTX in patients with NMOSD. Copyright ? 2022. Matrix Medical Communications. All rights reserved.	
Multiple Sclerosis and Related Disorders. 68:104127, 2022 Dec.	Wei K Nie Q Zhu Y Lu H Xue Q Chen G	Different doses of Rituximab for the therapy of Neuromyelitis optica spectrum disorder: A systematic review and meta-analysis [Review]	BACKGROUND: Neuromyelitis optica spectrum disease(NMOSD) is an autoimmune neurological disease that primarily affects the spinal cord, optic nerve, and periventricular organs. Rituximab plays an important role in the prevention of relapse in NMOSD. In this study, we evaluated the efficacy and safety of different doses of the anti-monoclonal antibody rituximab in NMOSD. OBJECTS: Our study aimed to implement a meta-analysis to systematically assess the efficacy and safety of different doses of rituximab in the treatment of NMOSD. METHODS: We searched Pubmed, Embase, the Cochrane Library, and Clinicaltrials.gov for relevant studies evaluating rituximab for NMOSD up to March	STUDY DESIGN

			2022. Data were assessed using Review Manager 5.3 and Stata 14 softwares. Means and standard deviations(SD) were analyzed using random effects models with continuous outcomes. Risk radio was analyzed using random effects models with dichotomous outcomes. RESULTS: We collected 576 patients from 17 studies. The endpoint of efficacy was the change in annual recurrence rate(ARR), expanded disability status scale (EDSS), and the number of patients free of relapse between pre-treatment and post-treatment of rituximab. We found that rituximab reduced ARR and EDSS, with a significant reduction in ARR(MD= -1.79, 95% CI: -3.18 ~ -0.39, P= 0.01) and EDSS(MD= -1.35, 95% CI: -1.5 ~ -1.19, P < 0.00001) at 100 mg intravenous infusion per week for 3 consecutive weeks, meanwhile making the number of patients free of relapse increased (RR= 24.61 [5.11, 118.55], P<0.0001) and being relatively safe and without serious adverse events(SAEs). In terms of safety, we compared and summarised the adverse events(AEs) and SAEs from 17 studies. CONCLUSION: In this study, we found rituximab to be relatively safe and efficacious in the treatment of NMOSD, particularly at a dose of 100mg intravenous infusion per week for 3 consecutive weeks. Copyright ? 2022 Elsevier B.V. All rights reserved.	
Multiple Sclerosis and Related Disorders. 35:246-252, 2019 Oct.	Huang W Wang L Zhang B Zhou L Zhang T Quan C	Effectiveness and tolerability of immunosuppressants and monoclonal antibodies in preventive treatment of neuromyelitis optica spectrum disorders: A systematic review and network meta-analysis [Review]	BACKGROUND: Several immunosuppressants or monoclonal antibodies have been used as preventive treatment for neuromyelitis optica spectrum disorders (NMOSD); however, the optimal therapies have not been clarified. In this study, we aimed to compare and rank the effectiveness and tolerability of all preventive therapies for NMOSD. METHODS: Qualified studies were identified in a search of MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases. We combined direct and indirect evidence via meta-analyses. The annualized relapse rate (ARR) was defined as the primary outcome. Secondary outcomes included the Expanded Disability Status Scale (EDSS) score and hazard ratios (HR) for the counts of adverse events (AEs). RESULTS: We identified one randomized controlled trial (RCT) and five	STUDY DESIGN

			observational studies including a total 631 patients with NMOSD. Among these, the follow-up time ranged from 12 to 40 months. For the primary outcome, rituximab (RTX) was hierarchically superior, with the significant standardized mean difference versus azathioprine (-0.86; 95% confidence interval: -1.60, -0.11). Mycophenolate mofetil (MMF) was ranked the most tolerable therapy, whereas cyclophosphamide was the least tolerable. CONCLUSION: RTX and MMF may be recommended as optimal treatments to prevent relapse in NMOSD. Low-dose cyclosporine A could be a promising alternative therapy. Copyright ? 2019 Elsevier B.V. All rights reserved.	
Journal of Neurology, Neurosurgery & Psychiatry. 94(1):62-69, 2023 01.	Spagni G Sun B Monte G Sechi E Iorio R Evoli A Damato V	Efficacy and safety of rituximab in myelin oligodendrocyte glycoprotein antibody-associated disorders compared with neuromyelitis optica spectrum disorder: a systematic review and meta-analysis	BACKGROUND: Rituximab (RTX) efficacy in patients with myelin oligodendrocyte glycoprotein (MOG) antibody-associated disorders (MOGADs) is still poorly understood, though it appears to be lower than in aquaporin-4-IgG-positive neuromyelitis optica spectrum disorders (AQP4-IgG+NMOSDs). The aim of this systematic review and meta-analysis is to assess the efficacy and safety profile of RTX in patients with MOGAD and to compare RTX efficacy between MOGAD and AQP4-IgG+NMOSD. METHODS: We searched original English-language articles published between 2012 and 2021 in MEDLINE, Cochrane, Central Register of Controlled Trials and clinicaltrials.gov, reporting data on RTX efficacy in patients with MOGAD. The main outcome measures were annualised relapse rate (ARR) and Expanded Disability Status Scale (EDSS) score mean differences (MDs) after RTX. The meta-analysis was performed with a random effects model. Covariates associated with the outcome measures were analysed with a linear meta-regression. RESULTS: The systematic review included 315 patients (138 women, mean onset age 26.8 years) from 32 studies. Nineteen studies (282 patients) were included in the meta-analysis. After RTX, a significant decrease of ARR was found (MD: -0.92, 95% CI -1.24 to -0.60, p<0.001), markedly different from the AQP4-IgG+NMOSD (MD: -1.73 vs MOGAD -0.92, subgroup difference testing: Q=9.09, p=0.002). However, when controlling for the mean ARR pre-RTX, this difference was not significant. After RTX, the EDSS score decreased significantly (MD: -0.84, 95% CI -1.41 to -0.26, p=0.004). The frequency of RTX-related adverse events	STUDY DESIGN

			was 18.8% (36/192) and overall RTX-related mortality 0.5% (1/192). CONCLUSIONS: RTX showed effective in MOGAD, although to a lesser extent than in AQP4-IgG+NMOSD, while the safety profile warrants some caution in its prescription. Randomised-controlled trials are needed to confirm these findings and provide robust evidence to improve treatment strategies in patients with MOGAD. PROSPERO REGISTRATION NUMBER: CRD42020175439. Copyright ? Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.	
Multiple Sclerosis and Related Disorders. 50:102843, 2021 May.	Wang Y Chang H Zhang X Yin L	Efficacy of rituximab in the treatment of neuromyelitis optica spectrum disorders: An update systematic review and meta - analysis [Review]	BACKGROUND: Neuromyelitis optica spectrum disorders (NMOSD) is an autoimmune astrocyte disease that mainly affects the optic nerve and spinal cord resulting in blindness or paralysis. Rituximab (RTX) is a chimeric monoclonal antibody directed against the surface antigen of CD20 on B lymphocytes and is an emerging treatment option in NMOSD. The present review aimed to conduct an update systematic review and meta-analysis for the efficacy of RTX in the treatment of NMOSD and analyze main factors affecting the efficacy of RTX. METHODS: The following Medical Subject Heading (MeSH) and related entry terms are used to search English literature in PubMed, MEDLINE and CENTRAL databases, respectively. MeSH include: Neuromyelitis optic and Rituximab; entry terms include: NMO Spectrum Disorder, NMO Spectrum Disorders, Neuromyelitis Optica (NMO) Spectrum Disorder, Neuromyelitis Optica Spectrum Disorders, Devic Neuromyelitis Optica, Neuromyelitis Optica, Devic, Devic's Disease, Devic Syndrome, Devic's Neuromyelitis Optica, Neuromyelitis Optica (NMO) Spectrum Disorders, CD20 Antibody, Rituximab CD20 Antibody, Mabthera, IDEC-C2B8 Antibody, GP2013, Rituxan; (note: literature retrieval operators "AND" "OR" "NOT" are used to link MeSH with Entry Terms.) 54 studies were included in this systematic review and 29 studies were included in meta-analysis. The main efficacy indicators were the difference of the expanded disability status scale (EDSS) and annualized relapse rate (ARR) between before and after rituximab treatments.	STUDY DESIGN

			RESULTS: In 29 studies involving 732 patients (643 women, 84 men, 5 with unknown gender), the EDSS and ARR were reduced by an average of -0.57 (95%CI, -0.69 to -0.44), -1.57 (95%CI, -1.78 to -1.35), respectively. CONCLUSION: Our systematic review and update meta-analysis provide new evidences that RTX can effectively improve disability and reduce ARR ratio.	
Journal of Neurology. 268(12):4549-4562, 2021 Dec.	Siritho S Nopsopon T Pongpirul K	Therapeutic plasma exchange vs conventional treatment with intravenous high dose steroid for neuromyelitis optica spectrum disorders (NMOSD): a systematic review and meta-analysis [Review]	BACKGROUND: Therapeutic plasma exchanges (TPE) has been recommended for neuromyelitis optica spectrum disorders (NMOSD) as a rescue therapy after nonresponding from the high-dose steroid and as an early therapy in severe attacks. We performed a systematic review to evaluate whether therapeutic plasma exchange (TPE) is better than conventional intravenous methylprednisolone (IVMP) in neuromyelitis optica spectrum disorders (NMOSD) patients. METHODS: Systematic search was conducted in five databases: PubMed, Embase, Scopus, Web of Science, and CENTRAL for randomized controlled trials and observational studies of TPE compared to intravenous steroid in NMOSD patients with neurological or visual outcomes in English without publication date restriction. Quality assessment was performed using ROB2 and ROBINS-I. The meta-analysis was done using a random-effects model. Pooled risk ratio (RR) or mean difference with a 95% CIs of efficacy outcomes included the Expanded Disability Status Scale (EDSS), visual acuity, and LogMAR were measured. RESULTS: Of 3439 potential studies, seven were included in the systematic review (1211 attacks; 433 patients) and three studies were included in the meta-analysis. Compared to high dose steroid alone, the add-on TPE increases a chance for the returning of EDSS to baseline at discharge (RR 3.02, 95% CI 1.34-6.81) and last follow-up (RR 1.68, 95% CI 1.01-2.79) as well as improves visual acuity at last follow-up. CONCLUSION: TPE as an add-on therapy to high-dose steroid injection during an acute attack in NMOSD patients is associated with returning to baseline EDSS at	STUDY DESIGN

			discharge and last follow-up, and a trend to have a lower disability at 6-12 months. Copyright ? 2020. Springer-Verlag GmbH Germany, part of Springer Nature.	
Multiple Sclerosis and Related Disorders. 55:103181, 2021 Oct.	Wang Y Ma J Chang H Zhang X Yin L	Efficacy of mycophenolate mofetil in the treatment of neuromyelitis optica spectrum disorders: An update systematic review and meta - analysis [Review]	BACKGROUND: Neuromyelitis optica spectrum disorders (NMOSD) is an autoimmune astrocyte disease that mainly affects the optic nerve and spinal cord resulting in blindness or paralysis. Mycophenolate mofetil (MMF) is one of the available immunotherapies with purported beneficial effects for patients with NMOSD. The present review aimed to conduct an update systematic review and meta-analysis for the efficacy of mycophenolate mofetil in the treatment of NMOSD and analyze main factors affecting the efficacy of mycophenolate mofetil. METHODS: The following Medical Subject Heading (MeSH) and related entry terms are used to search English literature in PubMed, MEDLINE and CENTRAL databases, respectively. MeSH include: Neuromyelitis optic and Mycophenolic Acid; entry terms include: NMO Spectrum Disorder, NMO Spectrum Disorders, Neuromyelitis Optica (NMO) Spectrum Disorder, Neuromyelitis Optica Spectrum Disorders, Devic Neuromyelitis Optica, Neuromyelitis Optica, Devic, Devic's Disease, Devic Syndrome, Devic's Neuromyelitis Optica, Neuromyelitis Optica (NMO) Spectrum Disorders, Mycophenolate Mofetil, Mofetil, Mycophenolate, Mycophenolic Acid Morpholinoethyl Ester, Cellcept, Mycophenolate Sodium, Myfortic, Mycophenolate Mofetil Hydrochloride, Mofetil Hydrochloride, Mycophenolate, RS 61,443, RS-61,443, RS61443; (note: literature retrieval operators "AND" "OR" "NOT" are used to link MeSH with Entry Terms.) 30 studies were included in this systematic review and 14 studies were included in meta-analysis. The main efficacy indicators were the difference of the annualized relapse rate (ARR) between before and after mycophenolate mofetil treatments. RESULTS: In 14 studies involving 930 patients (815 women, 115 men), the ARR were reduced by an average of -1.17 (95%CI, -1.28 to -1.07). CONCLUSION: Our systematic review and update meta-analysis provide new evidences that mycophenolate mofetil can substantially reduce ARR ratio. Copyright ? 2021 Elsevier B.V. All rights reserved.	STUDY DESIGN

H.1.4 Unpublished data

Not applicable, as no unpublished data was included in the SLR.

Appendix I. Literature searches for health-related quality of life

Health-related quality-of-life search

The objective of this SLR was to identify studies on the humanistic burden associated with patients with NMOSD. This appendixreports the details of the humanistic SLR. It was conducted to to identify studies on the humanistic burden associated with patients with NMOSD.

The SLR was designed to meet the standards of most HTA bodies. It was performed in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Intervention (124), guidance from the Centre for Reviews and Dissemination (CRD) for undertaking reviews in healthcare (125), and guidance from the National Institute for Health and Care Excellence (NICE) (126). The SLR results have been presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (126).

The database searches were conducted on May 23, 2023, in the Embase, MEDLINE, and Cochrane databases via the Ovid platform, which provides standardized access to a wide range of clinical literature databases and is a generally accepted tool for conducting SLRs. The CRD York database was also searched. A full list of database sources is provided in Table 83.

The above data sources were selected in accordance with the list of databases suggested by the HTA organizations of interest, such as NICE, the Canadian Agency for Drugs and Technologies in Health (CADTH), Pharmaceutical Benefits Advisory Committee, and the Scottish Medicines Consortium, as well as the Institute for Clinical and Economic Review (a non-profit organization).

Table 83 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to 23.05.2023	23.05.2023
Medline	Ovid	1946 to 23.05.2023	23.05.2023
CENTRAL	Ovid	1991 23.05.2023	23.05.2023
CDSR	Ovid	2005 23.05.2023	23.05.2023
DARE	CRD York	1991 to 2015	23.05.2023

Database	Platform	Relevant period for the search	Date of search completion
NHS EED search strategy	CRD York	1995 to 2015	23.05.2023
Econlit search strategy	Ovid	Until 23.05.2023	23.05.2023

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; NHS EED, National Health Service Economic Evaluation Database

The bibliographies of systematic reviews and meta-analyses identified through database searches were used to identify studies that met the population, intervention, comparators, outcomes, and study design (PICOS) criteria for the SLR. Furthermore, bibliographies from selected studies were also reviewed to identify relevant studies. This process ensured that papers and articles not picked up in the initial search were included in the review.

The trial registration website, Cost-Effectiveness Analysis Registry, was searched in parallel with the Ovid search. Information from ClinicalTrials.gov was used as a quality assurance tool to ensure all relevant studies were identified in the SLR, as well as to supplement information on study and treatment characteristics where needed (e.g., for the purposes of the network meta-analysis/indirect treatment comparison feasibility study). Baseline characteristics and results were extracted from clinical trial registries. Search terms used on the website included: "Neuromyelitis Optica," "Neuromyelitis Optica Spectrum Disorder," and "NMOSD."

Additional resources reviewed are listed Table 84.

Table 84 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
National Institute for Health and Care Excellence	www.nice.org.uk	Manual search of HTA submission with search terms "Neuromyelitis Optica" "NMOSD"	05.06.2023
Haute Autorité de Santé	www.has-sante.fr	Manual search of HTA submission with search terms "Neuromyelitis Optica" "NMOSD"	05.06.2023
Germany's Federal Joint Committee (Gemeinsamer	www.g-ba.de	Manual search of HTA submission with search terms "Neuromyelitis Optica" "NMOSD"	05.06.2023

Source name	Location/source	Search strategy	Date of search
Bundesausschus)			
Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)	www.iqwig.de	Manual search of HTA submission with search terms "Neuromyelitis Optica" "NMOSD"	05.06.2023
Canadian Agency for Drugs and Technologies in Health	www.cadth.ca	Manual search of HTA submission with search terms "Neuromyelitis Optica" "NMOSD"	05.06.2023
Institut national d'excellence en santé et services sociaux	www.inesss.qc.ca	Manual search of HTA submission with search terms "Neuromyelitis Optica" "NMOSD"	05.06.2023
Institute for Clinical and Economic Review	www.icer.org	Manual search of HTA submission with search terms "Neuromyelitis Optica" "NMOSD"	05.06.2023
Cost-Effectiveness Analysis Registry	https://cear.tuftsmedicalcenter.org/	: "Neuromyelitis Optica," "Neuromyelitis Optica Spectrum Disorder," and "NMOSD."	05.06.2023-28.08.2023
ClinicalTrials.gov	www.clinicaltrials.gov	"Neuromyelitis Optica," "Neuromyelitis Optica Spectrum Disorder" and "NMOSD"	05.06.2023-28.08.2023
Bibliography list of relevant SLRs/meta-analyses identified by the database searches		Manual search	Conducted as part of the main SLR database screening

Abbreviations: HTA, health technology assessment; SLR, systematic literature review

All conference abstracts indexed via Ovid were searched per the population, intervention, comparators, outcomes, and study design (PICOS) criteria. In addition, proceedings from the last three editions of selected conferences and congresses were manually reviewed to retrieve the latest abstracts and results not yet published in journals as full-text articles, or to supplement the results of previously published studies. The conference proceedings reviewed are listed in Table 85.

Table 85 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ACTRIMS 2021-2023	https://www.abstractsonline.com/pp8/#!/10822	Manual search	"Neuromyelitis Optica" "NMOSD"	23.05.2023 – 1.06.2023
CNSC 2021-2023	https://cmsc.confex.com/cmsc/2022/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1&searchterm=neuromyelitis	Manual search	"Neuromyelitis Optica" "NMOSD"	23.05.2023 – 1.06.2023
CONy 2021-2023	https://cony.comtecmed.com/e-posters/	Manual search	"Neuromyelitis Optica" "NMOSD"	23.05.2023 – 1.06.2023
ECTRIMS 2021-2023	https://journals.sagepub.com/doi/full/10.1177/1352458520974937	Manual search	"Neuromyelitis Optica" "NMOSD"	23.05.2023 – 1.06.2023
JNLF 2021-2023	https://mediatheque.jnlf.fr	Manual search	"Neuromyelitis Optica" "NMOSD"	23.05.2023 – 1.06.2023
NANoS 2021-2023	https://collections.lib.utah.edu/search?sort=az_title+asc&year_start=2020&year_end=2022&facet_setname_s=ehsl_novel_nam	Manual search	"Neuromyelitis Optica" "NMOSD"	23.05.2023 – 1.06.2023

Abbreviations: ACTRIMS, Congress of the American Committee for Treatment and Research in Multiple Sclerosis; CMSC, Consortium of Multiple Sclerosis Centers; CONy, World Congress on Controversies in Neurology; ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis; JNLF, Journees de Neurologie de Langue Francaise; NANOS, North American Neuro-Ophthalmology Society

The eligibility of studies was defined in terms of the PICOS criteria are presented in Table 86.

In some instances, studies included a broader patient population than the target population of this SLR. Based on guidance from the Institute for Quality and Efficiency in Health Care (120), studies were included if at least 80% of the study population met the PICOS criteria outlined below or if relevant subgroup data were available.

Neither geographic nor time limit restrictions were applied. Upon discussion regarding the project scope, publications were further selected for data extraction based on the following additional criteria:

- HTA compliant: Reporting utilities or scores from HRQoL scales that can be converted to utilities (e.g., EQ-5D, 36-Item Short Form health survey [SF-36], MSIS-29)
- Only reporting HRQoL outcomes that cannot be converted to utilities (e.g., MSQoL-54, VisQoL, etc.) with highly relevant PRO measures, including measures for sleep, pain, fatigue, bowel/bladder function, sexual health, and mental health

Table 86 PICOS inclusion/exclusion criteria for humanistic SLR

Inclusion criteria	Exclusion criteria
Population	
Patients with NMOSD	• Disease other than NMOSD • Non-human • Healthy volunteers
Interventions	
No restrictions	None
Comparators	
No restrictions	None
Outcomes	
• HRQoL outcomes measured by general instruments (i.e., SF-36) • Disease-specific HRQoL scales (e.g., MSIS-29, VisQOL) • Disease-related PROs • Studies reporting pain and disability outcomes related to NMOSD • Health state utilities (e.g., EQ-5D, SF-36, HUI-3) • Work productivity (e.g., WPAI) • Disutility for health states	• Only reporting HRQoL outcomes that are not convertible to utilities without informative PRO measures • Only reporting PRO measures
Study design	
• Clinical trials assessing HRQoL/PROs • Retrospective, prospective, and cross-sectional studies assessing HRQoL/PROs • Studies reporting utility data • Utility validation or elicitation studies	• Non-human, pre-clinical studies • Reviews, editorials, notes, comments, letters • Case reports/case series

- Mapping studies
- Economic studies reporting utilities.
- Systematic reviews and meta-analyses (for cross-checking only)

Additional limits	
Language	
English	Full-text articles not published in English

Abbreviations: HRQoL, health-related quality of life; HUI-3, Health Utility Index; MSIS-29, 29-item Multiple Sclerosis Impact Scale; NMOSD, neuromyelitis optica spectrum disorder; PRO, patient-reported outcome; SF-36, 36-Item Short Form health survey; SLR, systematic literature review; VisQoL, Vision and Quality of Life Index; WPAI, Work Productivity and Activity Impairment

The publications identified through the SLR were evaluated in a two-step process to assess whether they should be included for data extraction. The inclusion/exclusion criteria used to evaluate the publications were developed using the PICOS format. This procedure complies with stringent HTA guidelines surrounding methodology of systematic reviews.

All records were screened at the title/abstract level by two independent reviewers with disagreements resolved by a third, independent researcher. All papers included by the reviewers at the end of this stage were retained for Step 2. Papers excluded at this level were disregarded and the rejection reason was recorded for use in the PRISMA flow diagram.

The publications included after abstract review (from Step 1) were obtained for a full review of the text. Two independent reviewers screened all citations and full-text articles and any discrepancies in their decisions were resolved by a third, independent reviewer. All papers included after the full-text review were retained for data extraction. A record was kept of papers excluded at this stage along with a clear justification for their exclusion; this was reported in table format in the Excel® report as per the NICE guidance (121). The details for the inclusion/exclusion criteria were consulted throughout this step to assist with data collection. This ensured that all decisions regarding the inclusion and exclusion of studies were consistent throughout the review process. Specific exclusion reasons as per the PICOS criteria were recorded at the full-text screening stage. The study selection process was reported in a PRISMA flow diagram.

Once the list of studies for inclusion was finalized, data extraction was carried out using a pre-defined Microsoft Excel®-based template, ensuring that data were extracted uniformly and that the extracted data were comparable across studies. Data were extracted by two independent reviewers and independently checked by a third, senior reviewer in accordance with CRD guidance(122). In the event of a discrepancy, a consensus-based discussion or a third reviewer was consulted to make the final decision.

I.1.1 Search strategies

The search strategies include a combination of free-text and controlled vocabulary terms specific to each database (e.g., Emtree terms for Embase or Medical Subject Headings in MEDLINE).

Available (validated) search filters are available from key HTA bodies for study design and outcomes (the search terms have been adapted from NICE TSD9, available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list), not for population terms. Internal search terms were used to identify relevant literature. These have been cross-checked with key publications to ensure search identifies most relevant studies. For language restrictions, standard limits from Ovid were applied.

Table 87 Search strategy for Embase

No.	Query	Results
#1	exp myelooptic neuropathy/	12307
#2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	11376
#3	or/1-2	13593
#4	exp "Quality of Life"/ or exp questionnaire/ or exp "quality of life assessment"/	1476673
#5	(quality adj2 well?being).tw.	793
#6	quality adjusted life year/	35224
#7	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).tw.	32807
#8	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).tw.	33797
#9	patient-reported outcome/	52986
#10	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).tw.	62364
#11	PRO.tw.	380979
#12	exp Health Status/ or exp health survey/	557255
#13	(euroqol* or euro qol* or euro-qol* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eqoL-5d* or eqoL5D* or eqoL 5d*).tw.	30428
#14	(utilit* or disutilit*).tw.	375889
#15	(hye* or health* year* equivalent* or hui*).tw.	9165

No.	Query	Results
#16	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	7012
#17	willingness to pay.tw.	12844
#18	(SG or TTO or WTP or DCE).tw.	38193
#19	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).tw.	884938
#20	(VAS or visual analog* scale* or visual-analog* scale*).tw.	148823
#21	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).tw.	96361
#22	quality of life.ti,ab,kf.	601625
#23	(Functional Assessment of Chronic Illness Therapy or Functional Assessment of Chronic Illness Therapy-Fatigue or FACIT* or FACIT-fatigue).ti,ab,kf.	3991
#24	(Functional Assessment of Multiple Sclerosis or FAMS or Pediatric Quality of life Inventory or PedsQL* or Multiple Sclerosis Impact scale or MSIS-29 or MSIS29 or "MSIS 29" or Brief pain inventory or BPI* or Beck Depression Inventory* or BDI-II or VisQOL or "Vision and Quality of Life Index" or HADS or "Hospital Anxiety and Depression Scale" or anxiety or depress* or activities of daily living or ADL* or McGill Pain questionnaire or MPQ* or MPQ-SF* or MPQ SF* or PainDetect Questionnaire or PDQ* or Numeric Rating Scale or NRS*).ti,ab.	1013701
#25	or/4-24	4280914
#26	3 and 25	1339
#27	case report/	2904053
#28	(animal* not human*).sh,hw.	4844367
#29	(book or chapter or conference review or editorial or erratum or letter or note or short survey or tombstone).pt.	3749414
#30	or/27-29	11067395
#31	26 not 30	1167
#32	limit 31 to english language	1135

Table 88 Search strategy for Ovid MEDLINE(R)

No.	Query	Results
#1	exp neuromyelitis optica/	4248
#2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	6263
#3	or/1-2	6263
#4	exp "Quality of Life"/ or exp "Surveys and Questionnaires"/	1378976
#5	(quality adj2 well?being).tw.	486
#6	Quality-Adjusted Life Years/	15620
#7	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).tw.	21983
#8	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).tw.	19356
#9	Patient Reported Outcome Measures/	13366
#10	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).tw.	36903
#11	PRO.tw.	245576
#12	exp Health Status/ or exp Health Surveys/	999949
#13	(euroqol* or euro qol* or euro-qol* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eqoL-5d* or eqoL5D* or eqoL 5d*).tw.	16424
#14	(utilit* or disutilit*).tw.	264192
#15	(hye* or health* year* equivalent* or hui*).tw.	7212
#16	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	4810
#17	willingness to pay.tw.	8297
#18	(SG or TTO or WTP or DCE).tw.	24732

No.	Query	Results
#19	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).tw.	672908
#20	(VAS or visual analog* scale* or visual-analog* scale*).tw.	96643
#21	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).tw.	62915
#22	quality of life.ti,ab,kf.	374596
#23	(Functional Assessment of Chronic Illness Therapy or Functional Assessment of Chronic Illness Therapy-Fatigue or FACIT* or FACIT-fatigue).ti,ab,kf.	1565
#24	(Functional Assessment of Multiple Sclerosis or FAMS or Pediatric Quality of life Inventory or PedsQL* or Multiple Sclerosis Impact scale or MSIS-29 or MSIS29 or "MSIS 29" or Brief pain inventory or BPI* or Beck Depression Inventory* or BDI-II or VisQOL or "Vision and Quality of Life Index" or HADS or "Hospital Anxiety and Depression Scale" or anxiety or depress* or activities of daily living or ADL* or McGill Pain questionnaire or MPQ* or MPQ-SF* or MPQ SF* or PainDetect Questionnaire or PDQ* or Numeric Rating Scale or NRS*).ti,ab.	739374
#25	or/4-24	3305137
#26	3 and 25	650
#27	case reports/	2336806
#28	(animal* not human*).sh,hw.	5079797
#29	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	5038793
#30	or/27-29	9980459
#31	26 not 30	577
#32	limit 31 to english language	561

Table 89 Search strategy for EBM Reviews search strategy Cochrane Central Register of Controlled Trials (via Ovid)

No.	Query	Results
#1	exp neuromyelitis optica/	75
#2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	456
#3	or/1-2	456
#4	exp "Quality of Life"/ or exp "Surveys and Questionnaires"/	101724
#5	(quality adj2 well?being).tw.	186
#6	Quality-Adjusted Life Years/	1932
#7	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).tw.	5544
#8	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).tw.	5082
#9	Patient Reported Outcome Measures/	1340
#10	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).tw.	14133
#11	PRO.tw.	15433
#12	exp Health Status/ or exp Health Surveys/	82674
#13	(euroqol* or euro qol* or euro-qol* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eqoL-5d* or eqoL5D* or eqoL 5d*).tw.	12660
#14	(utilit* or disutilit*).tw.	18315
#15	(hye* or health* year* equivalent* or hui*).tw.	592
#16	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	525
#17	willingness to pay.tw.	1855
#18	(SG or TTO or WTP or DCE).tw.	2679
#19	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).tw.	160169

No.	Query	Results
#20	(VAS or visual analog* scale* or visual-analog* scale*).tw.	72172
#21	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).tw.	25936
#22	quality of life.ti,ab,kf.	128907
#23	(Functional Assessment of Chronic Illness Therapy or Functional Assessment of Chronic Illness Therapy-Fatigue or FACIT* or FACIT-fatigue).ti,ab,kf.	1632
#24	(Functional Assessment of Multiple Sclerosis or FAMS or Pediatric Quality of life Inventory or PedsQL* or Multiple Sclerosis Impact scale or MSIS-29 or MSIS29 or "MSIS 29" or Brief pain inventory or BPI* or Beck Depression Inventory* or BDI-II or VisQOL or "Vision and Quality of Life Index" or HADS or "Hospital Anxiety and Depression Scale" or anxiety or depress* or activities of daily living or ADL* or McGill Pain questionnaire or MPQ* or MPQ-SF* or MPQ SF* or PainDetect Questionnaire or PDQ* or Numeric Rating Scale or NRS*).ti,ab.	146765
#25	or/4-24	494670
#26	3 and 25	118
#27	(animal* not human*).sh,hw.	2747
#28	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	21469
#29	27 or 28	24207
#30	26 not 29	117
#31	limit 30 to english language	116

Table 90 Search strategy for EBM Reviews search strategy Cochrane Database of Systematic Reviews

No.	Query	Results
#1	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).ti,ab,kw.	0

Table 91 Search strategy for EBM Reviews - Database of Abstracts of Reviews of Effects

No.	Query	Results
#1	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	0

Table 92 Search strategy for NHS EED search strategy (via CRD York)

No.	Query	Results
#1	Any field: ("neuromyelitis optica" or devic or devic's or myeloopticoneuropathy or "myeloptico neuropathy" or myelopticoneuropathy or "neuromyelitis optica spectrum disorder*" or NMOSD)	0

Table 93 Search strategy for Econlit search strategy (via Ovid)

No.	Query	Results
#1	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	0

The search of specified databases from inception to May 23, 2023, identified 1,812 records for screening. Following the title and abstract screening of citations, 1,551 records were excluded. Of the potentially relevant 261 records, full-text reports were obtained for detailed evaluation. Following detailed evaluation, 81 reports were excluded. Following the grey literature search, two relevant reports from the HTA review, three from the congress review, and one from the bibliographic search met the inclusion criteria. In total, 186 reports from 169 original studies were included in the SLR (see Figure 21). The number of excluded reports along with the reasons for exclusion at each stage of review are presented in the SLR PRISMA flow diagram (Figure 21)

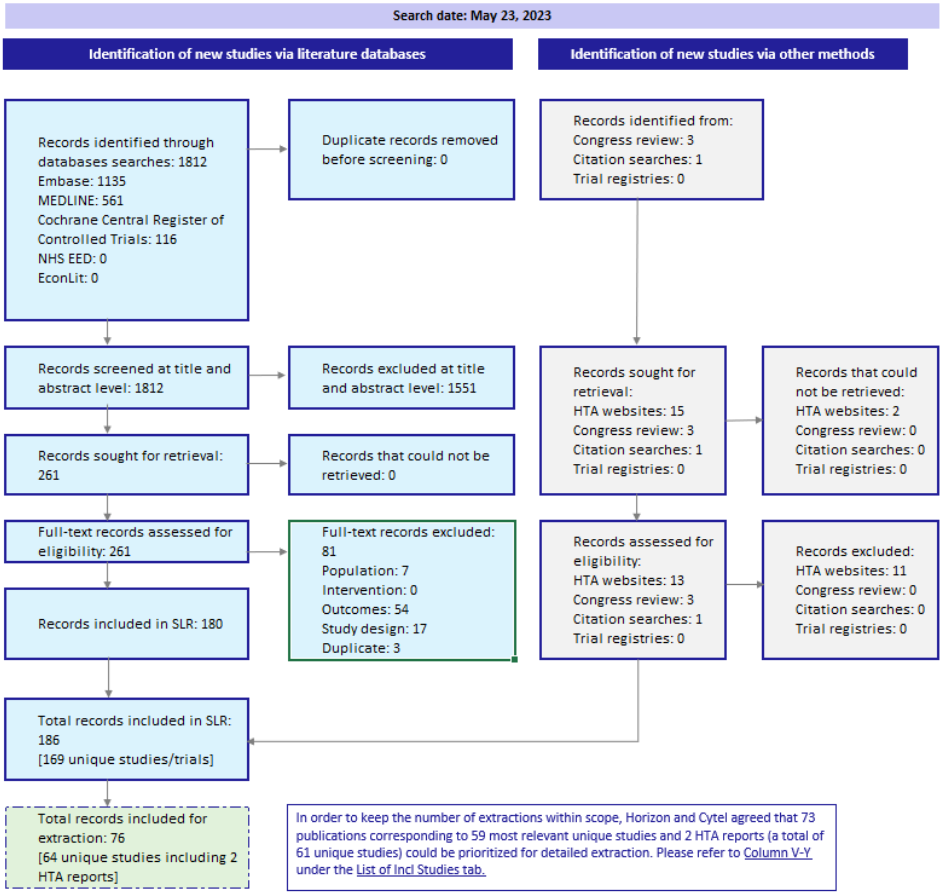


Figure 21 PRISMA flow diagram humanistic SLR

Literature search results included in the model/analysis:

The publication by Hümmert et al. was the only publication deemed relevant for the following reasons. Firstly, the CHANCE^{NMO} study which included 212 patients across 17 centers of which 66% were AQP4+ and is thus a large multi-centre cross-sectional European study conducted in NMOSD and is reflective of the Danish population. Second, this was the only study identified that presented a recent (2022) variant of HRQoL mapping to HSUVs by EDSS state (0-3, 3.5-6.0 and 6.5 to 8.5), based on EQ-5D merged with NEMOS data, *specifically for NMOSD* (as opposed to more widely applied Rowen method used in our base case). The use of the Hümmert HSUV system as a scenario analysis increases the robustness of this analysis specific to this disease.

Table 94 Humanistic studies included in the analysis

Short reference	Geographical locations	Data source/database	Study design	Study N (overall)	Study N (per arm)	Population	Subpopulation	Intervention

Hümmert 2022 (64)	Germany	17 German NEMOS centers	Cross-sectional	212	212	NMOSD	NR	NA

I.1.2 Quality assessment and generalizability of estimates

Quality assessment was performed by one reviewer using the adapted NICE single technology appraisal quality appraisal tool for assessment of risk of bias (using the Efficace checklist (127)). The findings were then independently verified by a second senior reviewer (128). The quality assessment of the studies included in this analysis is presented in Table 95.

A list of excluded full text studies is embedded below.

NMOSD_HRQOL SLR_List of rejected s

SOURCE	AUTHORS	TITLE	ABSTRACT	REASON FOR REJECTION
Neurology. 98(11):e1184-e1196, 2022 03 15.	Hummert MW Schoppe LM Bellmann-Strobl J Siebert N Paul F Duchow A Pellkofer H Kumpfel T Havla J Jarius S Wildemann B Berthele A Bergh FT Pawlitzki M	Costs and Health-Related Quality of Life in Patients With NMO Spectrum Disorders and MOG-Antibody-Associated Disease: CHANCENMO Study	BACKGROUND AND OBJECTIVES: To evaluate costs and health-related quality of life (HRQoL) of neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). METHODS: In this multicenter cross-sectional study, data on consumption of medical and nonmedical resources and work ability were assessed via patient questionnaires. Costs were analyzed in Euros for 2018 from the societal perspective. HRQoL was captured by the EuroQoL Group 5 Dimension 5 Level Scale (EQ-5D-5L) questionnaire. Clinical data were retrieved from the Neuromyelitis Optica Study Group (NEMOS) database. RESULTS: Two hundred twelve patients (80% women, median age 50 [19-83] years, median disease duration 7 [0-43] years, median Expanded Disability Status Scale [EDSS] score 3.5 [0-8.5], 66% aquaporin-4 immunoglobulin G [IgG] positive, 22% MOG IgG positive, 12%	Population

Klotz L Kleiter I Stangel M Gingele S Weber MS Faiss JH Pul R Walter A Zettl UK Senel M Stellmann JP Hausler V Hellwig K Ayzenberg I Aktas O	double seronegative) were analyzed. The mean total annual per capita cost of illness accounted for 59,574 (95% CI 51,225-68,293 or US dollars [USD] 70,297, 95% CI 60,445-80,586), and the mean index value of the EQ-5D-5L was 0.693 (95% CI 0.65-0.73). The most important cost drivers were informal care costs (28% of total costs), indirect costs (23%), and drugs (16%), especially immunotherapeutics. Costs showed a positive correlation with disease severity (rho = 0.56, 95% CI 0.45-0.65); in the EDSS score 6.5 to 8.5 subgroup, the mean annual costs were 129,687 (95% CI 101,946-160,336 or USD 153,031, 95% CI 120,296-189,196). The HRQoL revealed a negative correlation to disease severity (rho = -0.69, 95% CI -0.76 to -0.61); in the EDSS score 6.5 to 8.5 subgroup, the EQ-5D-5L mean index value was 0.195 (95% CI 0.13-0.28). Neither antibody status nor disease duration influenced the total annual costs or HRQoL. DISCUSSION: These German data from the era without approved preventive immunotherapies show enormous effects of the diseases on costs and quality of life. An early and cost-effective therapy

	Ringelstein M Schreiber-Katz O Trebst C		should be provided to prevent long-term disability and to preserve quality of life. Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.	
Multiple Sclerosis and Related Disorders. 45 (no pagination), 2020. Article Number: 102387. Date of Publication: October 2020.	Ramezani N. Yarahmadi P. Alirezaei M. Forouzannia S.M. Kazemi Mozdabadi R.S. Rezaei Aliabadi H. Gheini M.R. Sahraian M.A. Naser Moghadasi A.	Evaluation of emotional intelligence (EI) in neuromyelitis optica spectrum disorder (NMOSD) patients compared to healthy individuals	Background: Neuromyelitis optica spectrum disorder (NMOSD) is known as an autoimmune astrocytopathic disorder involving central nervous system (CNS). The aim of this study was to compare Emotional Intelligence (EI) score between NMOSD patients and healthy individuals, and to find out the possible effect of this disease on EI. Method(s): A total of 45 NMOSD participants and 48 healthy individuals were enrolled in this study. Demographic information (e.g., gender and age) of all participants as well as their level of education, and data on the patients' duration of disease were collected. EI of each participant was assessed using Persian version of Emotional Quotient inventory (EQ-i) questionnaire. Result(s): The mean total EI score was significantly different between the participants and controls (322+/-36.7 vs 338+/-31.5, p value<0.03). Compared to controls, patients had a poor performance in 4 of 15 EI subscales including emotional self-awareness	Outcomes

			(21.29+/-3.6 vs 22.85+/-3, p value<0.03), optimism (22.4+/-4 vs 24.1+/-3.1, p value<0.03), self-regard (22.7+/-4.6 vs 24.5+/-3.4, p value<0.04), and impulse control (16.9+/-6.5 vs 19.5+/-5.5, p value<0.05). No difference was found between anti-aquaporin-4 antibody (AQP4-IgG) positive and AQP4-IgG negative patients regarding EI score or its subscale scores, except for self-actualization (p value<0.05). Conclusion(s): Our study showed that EI could be regarded as a tool for understanding emotions, thoughts, and behavior of NMOSD patients. It was implied that taking therapeutic steps could improve the performance of NMOSD patients with EI impairment in social life.Copyright © 2020 Elsevier B.V.	
Multiple Sclerosis and Related Disorders. 45:102421, 2020 Oct.	Xie Q Zheng T Sun M Sun J Wang M	A meta-analysis to determine the efficacy and safety of tocilizumab in neuromyelitis optica spectrum disorders	BACKGROUND: Neuromyelitis optica spectrum disorder (NMOSD) is a central nervous system immune disease with a high recurrence rate and high disability rate. Frequent relapses often cause the accumulation of neurological dysfunction, leading to permanent blindness, paralysis or even death. Tocilizumab (TCZ) is a human monoclonal antibody (mAb) directed against the IL-6 receptor and was the first anti-IL6-R mAb tested for the treatment of NMOSD. Our meta-analysis	Study Design

aimed to evaluate the efficacy and safety of tocilizumab in NMOSD patients.

METHODS: Relevant studies published prior to May 2020 were retrieved from the PubMed, Cochrane Library and clinicaltrials.gov databases using the following keywords: 'neuromyelitis optic spectrum disorders' or 'NMOSD' and 'tocilizumab' or 'TCZ'. Two authors independently selected the articles and extracted the data. Differences in the annualized relapse rate (ARR) ratio, relapse-free status and EDSS score before and after TCZ therapy were used as the main efficacy measures, and recorded adverse effects were also extracted. The meta-analysis was performed using Review Manager version 5.3 software.

RESULTS: Five clinical trials comprising a total of 89 patients were selected. Meta-analysis showed that significantly fewer ARR ratio was encountered in after tocilizumab therapy group (MD=-2.25; 95% CI=-2.62 to -1.87; P<0.001). A significant correlation was observed between the proportion of patients with relapse-free NMOSD and tocilizumab therapy (OR=67.78; 95% CI=19.23 to

			238.97; P<0.001). Adverse effects were recorded in 75 of 89 (84%) patients treated with tocilizumab, but most adverse effects were mild. CONCLUSIONS: The present meta-analysis suggested that tocilizumab is a relatively effective and safe treatment for NMOSD. Copyright © 2020 Elsevier B.V. All rights reserved.	
Multiple Sclerosis. Conference: 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Lyon France. Conference Publication: (var.pagings). 18(4 SUPPL. 1) (pp 291), 2012. Date of Publication: October 2012.	Mutch K.P. Methley A. Boot J. Jacob A.	A qualitative study investigating the experiences of affected persons and family members living with neuromyelitis optica	Introduction: Neuromyelitis Optica (NMO) is an inflammatory demyelinating disorder of the central nervous symptom characterised by relapses affecting optic nerves and longitudinal extensive transverse myelitis resulting in visual and physical disabilities. The unpredictable nature and diversity of NMO and often increasing level of disability can result in NMO being a difficult condition to live with, for both the person with NMO and their family/caregivers. The majority of research on NMO is medical in nature and no previous studies have been identified investigating the experience of living with NMO from the perspective of the patient or those close to them. Objective(s): * To gain an understanding of the experience of person and family member living with NMO. * To explore their perception of quality of life * To	Outcomes

identify coping strategies of person and family member living with NMO Methods: Patients attending The National NMO Centre in Liverpool, UK were invited to participate in this study. They nominated a family member to be invited to participate. All patients fulfilled the Wingerchuk criteria 2006 of NMO or NMO spectrum disorder. In total 14 patients (8 positive for aquaporin-4 antibodies) and 13 partners or parents participated aged from 24 years to 74 years, NMO diagnosis 2-13 years although initial relapse causing disability ranged from 4 years to 37 years ago. Either a Specialist NMO Nurse or Assistant Psychologist interviewed participants using a semi-structured interview investigating the daily impact of their NMO symptoms (both physical and psychological), their experience of diagnosis, the changing nature of their NMO, their experiences of health care services and any benefits of their NMO diagnosis. Either Results: Data was analysed using thematic analysis to identify major themes from the interviews. Early analysis includes themes such as 'Fear of Relapse,' 'tiredness,' 'planning,' 'lack of control,' 'stability.' These findings have major significance for clinical practice and care of both people with

			NMO and their families. This research highlights the importance of the subjective assessment of the impact of NMO, and clinicians should therefore investigate patient's perceptions of NMO in addition to clinically relevant measures of disability and impact.	
Journal of Managed Care & Specialty Pharmacy. 28(12-a Suppl):S3-S27, 2022 Dec.	Wingerchuk DM Weinshenker BG McCormick D Barron S Simone L Jarzylo L	Aligning payer and provider strategies with the latest evidence to optimize clinical outcomes for patients with neuromyelitis optica spectrum disorder [Review]	BACKGROUND: Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disorder affecting the central nervous system that is associated with significant morbidity and mortality. Early diagnosis and treatment are essential to minimize long-term disability. Recent advances in the understanding of the pathophysiology of NMOSD have led to multiple new therapies, but significant care and knowledge gaps persist. OBJECTIVES: To summarize current knowledge about the burden of disease and diagnosis and treatment of NMOSD in order to support managed care professionals and health care providers in making collaborative, evidence-based decisions to optimize outcomes among patients with NMOSD. In addition, this review also presents findings of a patient survey that provides insight into real-world experiences of those living with NMOSD. SUMMARY: Diagnosis of NMOSD is based on detection of	Study Design

immunoglobulin G antibodies to the water channel protein aquaporin-4 (AQP4-IgG) in the context of compatible clinical and magnetic resonance imaging features. Patients who are AQP4-IgG seronegative and/or who are positive for myelin oligodendrocyte glycoprotein antibodies may also satisfy criteria for NMOSD. The rarity of the condition combined with the significant overlap in clinical features with other autoimmune diseases affecting the central nervous system, most notably multiple sclerosis, can delay accurate diagnosis, which in turn can delay appropriate treatment, leading to the accumulation of long-term disability. Accumulating disability associated with NMOSD has a substantial negative impact on quality of life. The disease typically evolves as relapsing (ie, repeated) acute attacks. Treatment consists of management of acute attacks, prevention of subsequent attacks, and management of acute and chronic symptoms. The armamentarium of therapies to prevent attacks consists of several monoclonal antibodies (mAbs) approved to treat AQP4-IgG-seropositive disease and several off-label therapies used for patients with either seropositive or seronegative disease. There is limited

evidence to guide treatment decision-making, including which therapies to use first line, when to switch, and when to use monotherapy vs combination therapy. In addition, therapies with the greatest demonstrated safety and efficacy in NMOSD are costly and may not be accessible to all patients. Moreover, the results of the patient survey revealed significant clinical and financial burdens to patients with NMOSD including frequent attacks, delays in therapy initiation, need for urgent care and repeat hospitalizations, new and worsening symptoms, accumulating disability, and difficulties affording care. As such, key stakeholders must weigh them against the substantial economic costs of untreated or suboptimal treatment of disease. DISCLOSURES: Dr Wingerchuk has served on the advisory board or panel for Alexion, Biogen, Genentech, Horizon, Mitsubishi Tanabe, Novartis, Roche, UCB, and Viela Bio and has received grants of research support from Alexion. Dr Weinshenker has served as a consultant or on the advisory board or panel for Alexion, Genentech, Horizon, Mitsubishi Tanabe, Roche, UCB, and Viela Bio, served on the speakers bureau or other promotional education for

			Genentech and Roche, and has received royalties from RSR Ltd.	
European Journal of Neurology. Conference: 7th Congress of the European Academy of Neurology. Virtual. 28(SUPPL 1) (pp 96), 2021. Date of Publication: June 2021.	Cacciaguerra L. Mistri D. Valsasina P. Martinelli V. Filippi M. Rocca M.	Altered resting state dynamic functional connectivity of the precuneus contributes to cognition and depression in NMOSD	Background and aims: In neuromyelitis optica spectrum disorders (NMOSD), cognitive impairment (CI) is frequent, but its substrates are unclear. Functional MRI (fMRI) studies disclosed an association between CI and damage of the precuneus (PCUN) in several neurological conditions. Dynamic changes of resting-state (RS) functional connectivity (FC) might contribute to brain functional reorganization. Method(s): In this 3.0 T RS fMRI study, 27 aquaporin-4 (AQP4)-positive NMOSD patients and 30 age- and sexmatched healthy controls (HC) underwent a neuropsychological evaluation including Rao's battery and Beck Depression Inventory II scores. A cognitive impairment index (CII) was derived. Dynamic FC (DFC) of bilateral PCUN was assessed by means of sliding-window seed-voxel correlation analysis and its standard deviation across windows used as a measure of dynamicity (the higher the better). Age- and sex-adjusted between-group dFC comparisons and correlations with cognitive scores were assessed using	Duplicate

			full-factorial models. Result(s): Compared to HC, patients had reduced PCUNdFC with rectus/olfactory bulb, post-central gyrus, superior temporal gyrus, inferior occipital/fusiform gyri and the caudate nucleus. Conversely, increased dFC within the PCUN and between PCUN and middle temporal gyrus, thalamus, insula, putamen, and cerebellar crus-1 was observed. 63% of patients had depressive symptoms, whose burden correlated with intra-PCUN-dFC and with PCUNdFC with insula and cerebellar crus-1. 48t% of patients had CI and global CII correlated with intra-PCUN-dFC and with PCUN-dFC with the insula and the middle temporal gyrus. Conclusion(s): In NMOSD, PCUN-dFC abnormalities contribute to neuropsychological performance. Higher dynamic connections with the temporal lobe and limbic/ cerebellar regions were detrimental for cognition and depression, respectively.	
Multiple Sclerosis. Conference: 6th Pan Asian Committee for Treatment and Research in Multiple Sclerosis, PACTRIMS 2013. Kyoto Japan.	Cheng X.J. Wang F. Zhao Y.W.	Analyses of influential factors to quality of life in patients with neuromyelitis optica	Objective: To explore the influential factors to quality of life in patients with neuromyelitis optica (NMO). Method(s): Retrospective study was carried out to study the inpatients with NMO in Shanghai sixth hospital from March 1995 to May 2012. The neurological function of	Outcomes

Conference Publication: (var.pagings). 19(5) (pp 660), 2013. Date of Publication: April 2013.			36 diagnosed NMO patients were evaluated by Activities of Daily Living (ADL) scale at discharge. The influential factors of related disablement were analyzed with unvaried analysis and multivariate logistic regression analysis. Result(s): There were 36 (10 male and 26 female) patients with NMO in our study. Disease duration, age at onset, time to definite NMO, the location and length of the lesions in the spinal cord could not predict the prognosis. Variables of gender (OR: 1.039, 95% CI: 1.005~1.078), number of attacks (OR: 1.078, 95% CI: 1.014~1.164) and the presence of Aqp-4-Ab (OR: 2.529, 95% CI: 1.050~5.836) were left in the final model of multivariate logistic regression analysis for associations with the severity of disability. Conclusion(s): Female, more episodes and the presence of Aqp- 4-Ab were significantly associated with a more severe disability. Further longitudinal investigations are needed to evaluate the prognosis of patients with NMO in China.	
Neurology. 91(17):e1642-e1651, 2018 10 23.	Shosha E Dubey D Palace J	Area postrema syndrome: Frequency, criteria, and severity in AQP4-IgG-positive NMOSD	OBJECTIVE: To define the frequency, duration, and severity of intractable nausea, vomiting, or hiccups in aquaporin-4-immunoglobulin G (AQP4-IgG)-positive neuromyelitis optica spectrum disorder (NMOSD) and propose	Outcomes

Nakashima I Jacob A Fujihara K Takahashi T Whittam D Leite MI Misu T Yoshiki T Messina S Elsone L Majed M Flanagan E Gadoth A Huebert C Sagen J Greenberg BM	diagnostic criteria and a severity scale for area postrema syndrome (APS). METHODS: An International NMOSD database was interrogated for frequency of APS. Patients with AQP4-IgG-positive NMOSD completed an APS symptom questionnaire. Nausea and vomiting severity was derived from the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score. The diagnostic criteria, severity scale, and immunotherapy response was applied to a prospective validation cohort of patients from multiple centers. RESULTS: Analysis of an international database for AQP4-IgG-seropositive NMOSD (n = 430) revealed a high prevalence of isolated APS attacks (onset 7.1%-10.3%; subsequent 9.4%-14.5%) across continents. For 100 patients with 157 episodes of APS, nausea (n = 127, 81%) lasted for a median of 14 days (range 2-365), vomiting (113, 72%) with a median of 5 episodes/d (2-40) lasted 1-20 minutes, and hiccups (102, 65%) lasted a median of 14 days (2-365). Symptoms consistently and completely resolved following immunotherapy. Data were used to propose APS diagnostic criteria and

	Levy M Banerjee A Weinshenker B Pittock SJ		repurpose PUQE score (hiccups severity grade based on symptom duration). The clinical utility was demonstrated in a prospective validation cohort. CONCLUSION: Isolated APS attacks are frequently encountered both at onset and during the NMOSD course. The diagnostic criteria proposed here will assist clinicians in recognizing APS. Diagnosis of an APS attack earlier than 48 hours is possible if a dorsal medulla lesion is detected. Accurate diagnosis and evaluation of APS attack severity will assist in outcome measurement in NMOSD clinical trials. Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.	
Bone Marrow Transplantation. Conference: 45th Annual Meeting of the European Society for Blood and Marrow Transplantation. Frankfurt Germany. 54 (pp 35-36), 2019. Date of Publication: 2019.	Burt R. Han X. Jitprapaikulsan J. Pittock S.	Autologous non-myeloablative hematopoietic stem cell transplantation in patients with neuromyelitis optica spectrum disorder (NMOSD): An open-label pilot study	Background: Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory central nervous system disorder characterized, despite immunotherapy treatments, by life-long, severe, and disabling attacks of optic neuritis and myelitis. The aim is to determine if autologous nonmyeloablative hematopoietic stem cell transplantation could be an alternative treatment option. Method(s): Following stem cell mobilization with cyclophosphamide (2	Outcomes

g/m2) and filgrastim, patients were treated with cyclophosphamide (200 mg/kg) divided as 50 mg/kg intravenously (IV) on day-5 to day-2, rATG (thymoglobulin) given IV at 0.5 mg/kg on day-5, 1 mg/kg on day-4, and 1.5 mg/kg on days-3,-2, and-1 (total dose 6 mg/kg), and rituximab 500 mg IV on days-6 and +1. Unselected peripheral blood stem cells were infused on day 0. AQP4-IgG antibody status was determined by CLIA validated ELISA or flow cytometry assays. Cell killing activity was measured using a flow cytometry based complement assay. Result(s): Twelve (eleven AQP4-IgG positive) patients were treated with a median follow-up of 54 months. Ten patients are more than five years post-transplant. At five years, 80% of patients were relapse-free off all immunosuppression ($p< 0.001$). At one and five years after HSCT, EDSS improved from a baseline mean of 4.3 to 2.8 ($P<0.001$) and 3.25 ($P<0.001$), respectively. NRS improved after HSCT from a baseline mean of 69.5 to 83.8 at one year ($p<0.001$) and 85.9 at five years ($P<0.001$). The SF-36 quality of life total score improved from mean 34.2 to 55.1 ($P=0.03$) and 62.1 ($P=0.001$). AQP4-IgG serostatus converted to negative in nine

			patients and complement activating and cell killing ability of patient serum was switched off. Two patients remained AQP4-IgG seropositive (with persistent cell killing ability) and relapsed within two years of HSCT (P< 0.01). Conclusion(s): Prolonged drug-free remission with AQP4-IgG seroconversion to negative following nonmyeloablative autologous HSCT warrants further investigation in larger randomized controlled trial.	
Multiple Sclerosis Journal. Conference: 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2018. Berlin Germany. 24(2 Supplement) (pp 1018), 2018. Date of Publication: October 2018.	Amezcua L. Cook L. Yeaman M. Kister I. Levy M.	Black race is an independent risk factor for disability in neuromyelitis optica spectrum disorder	Objective: To evaluate race as a risk factor for disability in Neuromyelitis Optica Spectrum Disorder (NMOSD). Method(s): This is a retrospective study performed in context of the multi-ethnic, multi-center Collaborative International Research in Clinical & Longitudinal Experience Study (CIRCLES) of NMOSD patients. Inclusion criteria for analysis were diagnosis of NMOSD per the 2006 Wingerchuk or 2015 International Panel for Neuromyelitis Optica Diagnosis (IPND) guidelines. Race was self-reported in data elements collected at standardized clinical study visits. Clinical demographic and therapeutic information were extracted from medical records using a standardized intake form. Disability was assessed as ambulatory ability and visual acuity. Comparisons among study cohorts	Outcomes

were statistically analyzed using Fisher's exact test or Chi-square. Result(s): 553 NMOSD patients met inclusion criteria for this study, 54% of whom were white, 26% black, 12% Latino, and 8% Asian. Age at symptom onset was younger for black age (Mean [Range] 36.7 [26.4, 45.7] and Latino 36.7 [26.4, 45.7] as compared to whites (40.9 [31.2, 53.2]; p< 0.001). Black patients were the most likely of the racial groups to be partially or completely dependent on others for mobility (p=0.0013). A higher proportion of black were more likely to be legally blind in one or both eyes (47.3%) compared to whites (23.8%; p< 0.001). No significant differences to access to care and exposure to immunotherapy such as rituximab, plasmapheresis and immunoglobulin were observed among the groups. Conclusion(s): In the CIRCLES cohort, black race is associated with higher disability in NMOSD. This result appears to be independent of access to care and immunotherapy. The reasons for this racial disparity in disability are unknown, but similar results were observed in some, but not all observational studies of NMOSD. Contributing factors may include both genetic and environmental factors and

			factors related to social determinants of health not yet assessed that may impact disease severity. Understanding immunobiological factors that underlie the observed differences in outcomes will lead to better understanding of disease pathogenesis.	
Journal of Neurology, Neurosurgery & Psychiatry. 88(2):165-169, 2017 Feb.	Tackley G Vecchio D Hamid S Jurynczyk M Kong Y Gore R Mutch K Woodhall M Waters P Vincent A Leite MI Tracey I	Chronic neuropathic pain severity is determined by lesion level in aquaporin 4-antibody-positive myelitis	IMPORTANCE: Chronic, intractable neuropathic pain is a common and debilitating consequence of neuromyelitis optica spectrum disorder (NMOSD) myelitis, with no satisfactory treatment; few studies have yet to explore its aetiology. OBJECTIVE: To establish if myelitis-associated chronic pain in NMOSD is related to the craniocaudal location of spinal cord lesions. METHOD: (1) Retrospective cohort of 76 aquaporin 4-antibody (AQP4-Ab)-positive patients from Oxford and Liverpool's national NMOSD clinics, assessing current pain and craniocaudal location of cord lesion contemporary to pain onset. (2) Focused prospective study of 26 AQP4-Ab-positive Oxford patients, a subset of the retrospective cohort, assessing current craniocaudal lesion location and current pain.	Outcomes

Jacob A

Palace J

RESULTS: Patients with isolated thoracic cord myelitis at the time of pain onset were significantly more disabled and suffered more pain. Cervical and thoracic lesions that persisted from pain onset to 'out of relapse' follow-up (current MRI) had highly significant ($p<0.01$) opposing effects on pain scores (std. beta=-0.46 and 0.48, respectively). Lesion length, total lesion burden and number of transverse myelitis relapses did not correlate with pain.

CONCLUSIONS: Persistent, caudally located (ie, thoracic) cord lesions in AQP4-Ab-positive patients associate with high postmyelitis chronic pain scores, irrespective of number of myelitis relapses, lesion length and lesion burden. Although disability correlated with pain in isolation, it became an insignificant predictor of pain when analysed alongside craniocaudal location of lesions.

Clinical and Experimental Neuroimmunology. Conference: 25th Annual Meeting of the Japanese Society for Neuroimmunology, JSNI 2013. Yamaguchi Japan. Conference Publication: (var.pagings). 5(2) (pp 241), 2014. Date of Publication: June 2014.	Araki M. Matsuoka T. Miyamoto K. Kusunoki S. Okamoto T. Murata M. Miyake S. Aranami T. Yamamura T.	Clinical efficacy of anti-IL-6 receptor monoclonal antibody tocilizumab for the treatment of intractable neuromyelitis optica	Background: Neuromyelitis optica (NMO) is an autoimmune disease associated with anti-aquaporin 4 autoantibodies (AQP4-Ab). We previously described that plasmablasts (PB, CD19+ CD27high CD38high CD180 - cells) are anti-AQP4 antibody-producing cells in the peripheral blood of NMO and IL-6 receptor (IL-6R) signaling pathways are involved in the pathogenesis (Chihara et al. 2011). Objective(s): We performed an exploratory open-label study to evaluate the safety and efficacy of tocilizumab (TCZ), humanized anti-IL-6R monoclonal antibody, in patients with NMO who are refractory to standard immunotherapy. Method(s): Seven female and a male patients were given monthly TCZ of 8 mg/kg. We evaluated the annualized relapse rate (ARR), expanded disability status scale (EDSS), Numeric Rating Scale (NRS) as representative pain and fatigue severity scale before and after starting TCZ. Serum levels of AQP4-Ab and IL-6, as well as the numbers of PB in the peripheral blood were analyzed. Result(s): The ARR was reduced from 2.8 +/- 1.0 to 0.4 +/- 0.7 (P < 0.001) after starting TCZ. Notably, the EDSS, neuropathic pain and fatigue refractory to standard therapy gradually improved.	Outcomes

			Serum AQP4-Ab levels was also significantly reduced. Adverse events associated with TCZ included lymphocytopenia, anemia, and infectious diseases. Conclusion(s): TCZ contributed to stable remission in NMO. The improvement of neuropathic pain and fatigue would add significant values on TCZ for treatment of NMO.	
Multiple Sclerosis. Conference: 6th Pan Asian Committee for Treatment and Research in Multiple Sclerosis, PACTRIMS 2013. Kyoto Japan. Conference Publication: (var.pagings). 20(7) (pp 911-912), 2014. Date of Publication: June 2014.	Araki M. Matsuoka T. Aranami T. Nakamura M. Okamoto T. Murata M. Miyake S. Yamamura T.	Clinical efficacy of anti-IL-6 receptor monoclonal antibody tocilizumab in patients with neuromyelitis optica	Neuromyelitis optica (NMO) is an autoimmune disease, associated with elevation of serum anti-aquaporin 4 (AQP4) autoantibodies. We previously described that plasmablasts (PB) are anti-AQP4 antibody-producing cells in the peripheral blood of NMO (Chihara et al. 2011). We also revealed that IL-6 receptor (IL-6R) signaling pathways are involved in the pathogenesis. Therefore, we performed an exploratory open-label study to evaluate the safety and efficacy of tocilizumab (TCZ), humanized anti-IL-6R monoclonal antibody, in patients with NMO who are refractory to currently available drugs in Japan. Prior medications to the patients included mitoxantrone, corticosteroid, azathioprine, and interferon-beta. Here we describe the results of the first four patients (three female and one male) out of nine. These patients were given monthly TCZ of 8 mg	Duplicate

/ kg for 12 months period. We evaluated the number of relapses, expanded disability status scale (EDSS), Numeric Rating Scale (NRS) as representative pain scale and fatigue severity scale before and after starting TCZ. Serum levels of anti-AQP4 antibody and IL-6, as well as proportions and absolute numbers of PB (CD19+CD27highCD38highCD180- cells) in the peripheral blood were analyzed. The annualized relapse rate (ARR) was reduced from 2.0 to 0.5 after starting TCZ. Notably, the neuropathic pain refractory to standard therapy gradually improved in all patients after starting TCZ, resulting in complete resolution of pain in three. Mean NRS as pain scale reduced from 3.5 to 1.3. Relief from serious fatigue hampering daily life activity was also confirmed in all. There was also a trend for improvement in EDSS. Serum IL-6 level was increased in all patients after the TCZ administration, reflecting the reduced consumption of endogenously produced IL-6 by blocking IL-6R with TCZ. In a most active NMO patient, the numbers of abnormally expanded PB was sharply declined after injecting TCZ. The PB numbers in the other patients were not elevated, probably due to prior exposure to

			immunosuppressive treatments. Adverse events included lymphocytopenia, anemia, viral enteritis, upper respiratory infection, and acute pyelonephritis. None of those events were severe. In addition to its ability to maintain stable remission in NMO, effects on neuropathic pain, paresthesia and fatigue would add significant values on TCZ for treatment of NMO.	
Journal of Neurology. 264(8):1549-1558, 2017 Aug.	Meng H Xu J Pan C Cheng J Hu Y Hong Y Shen Y Dai H	Cognitive dysfunction in adult patients with neuromyelitis optica: a systematic review and meta-analysis [Review]	The objective of this study was to investigate cognitive dysfunction in 24-60-year-old neuromyelitis optica (NMO) patients, demographically matched healthy subjects, and MS patients. We conducted a comprehensive literature review of the PubMed, Medline, EMBASE, CNKI, Wan Fang Date, Web of Science, and Cochrane Library databases from inception to May 2016 for case-control studies that reported cognitive test scores in NMO patients, healthy subjects, and MS patients. Outcome measures were cognitive function evaluations, including performance on attention, language, memory, information processing speed, and executive function tests. The meta-analysis included eight studies. NMO patients performed significantly worse on attention ($P < 0.00001$), language ($P = 0.00008$),	Study Design

			memory (P = 0.00004), information processing speed (P < 0.00001), and executive function tests (P = 0.00009) than healthy subjects. There were no significant differences in performance between NMO patients and MS patients on these tests. This meta-analysis indicates that NMO patients aged 24-60 years have significantly worse cognitive performance than demographically matched healthy subjects. However, this was comparable to the performance of demographically matched MS patients. There is a need for further rigorous randomized controlled trials with focus on elucidating the underlying mechanism of cognitive dysfunction in NMO patients.	
Clinical Neurology & Neurosurgery. 189:105621, 2020 02.	Salama S Marouf H Reda MI Mansour AR ELKholy O Levy M	Cognitive functions in Egyptian neuromyelitis optica spectrum disorder	BACKGROUND: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease of the central nervous system, characterized by optic neuritis and longitudinally extensive transverse myelitis. Magnetic resonance imaging abnormalities may be observed in various brain regions of NMOSD patients. Only a few studies have addressed the cognitive functions in NMOSD, but none among Egyptian patients. OBJECTIVE: To investigate cognitive	Outcomes

performance in a cohort of 20 Egyptian patients with NMOSD.

DESIGN: Observational, prospective study.

PATIENTS: We studied 20 Egyptian patients with NMOSD and compared them with 18 healthy Egyptian controls matched for age, sex, and educational level.

MAIN OUTCOME MEASURE: We applied an Arabic translation of MOCA and BICAMS Tests for Multiple Sclerosis.

RESULTS: Cognitive performance was significantly worse in the NMOSD group than in healthy controls for CVLT (P = 0.0099), SDMT (P = 0.0112), BVSMT (P = 0.019) and BICAMS in total (P = 0.0014). Patients with a later disease onset performed worse in MOCA and BVSMT.

CONCLUSIONS: This study confirms the concept of cognitive involvement in NMOSD among Egyptian patients. Information processing speed was the function most commonly impaired.

Multiple Sclerosis. Conference: 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2015. Barcelona Spain. Conference Publication: (var.pagings). 23(11 SUPPL. 1) (pp 49-50), 2015. Date of Publication: September 2015.	Kim S.-H. Kwak K. Hyun J.-W. Jeong I.H. Huh S.-Y. Cho H.-J. Yu E.-S. Kim J.-H. Yang J. Lee S.H. Yun S. Joo J. Lee D.-K. Lee J.-M.	Cognitive impairment differs between neuromyelitis optica spectrum disorder and multiple sclerosis	Objective: To investigate the frequency and pattern of cognitive impairment (CI) in neuromyelitis optica spectrum disorder (NMOSD) patients compared with multiple sclerosis (MS) patients and healthy controls (HCs), and its relationship with conventional MRI disease measures. Method(s): Eighty-two NMOSD patients, 54 MS patients and 45 HCs underwent a neuropsychological assessment. CI was considered if at least three subdomains were inferior to the fifth percentile of HCs. A global cognitive z-score was calculated based on normative data. Brain volumes of gray matter and white matter as well as FLAIR-hyperintense lesion volume on MRI were also assessed. Result(s): CI was observed in 29% of NMOSD and 50% of MS patients (P < 0.001). MS patients performed worse on verbal and visual memory tests, symbol digit modalities test (SDMT) and paced auditory addition test (PASAT) compared with HCs. NMOSD patients revealed impaired performance only in digit span, SDMT and delayed recall of visual memory compared with	Outcomes

	Kim H.J.		HCs. MS patients performed worse than NMOSD patients on verbal and visual episodic memory tests. MS patients also had significantly lower global cognitive z-scores compared with NMOSD and HCs. Low education, delayed interval from disease onset to initiation of treatment, depression and decreased gray matter volume were independent predictors of cognitive decline in NMOSD patients. Conclusion(s): MS patients exhibited more frequent and severe CI, particularly in episodic memory test compared with NMOSD patients. The different prevalence and patterns of CI between NMOSD and MS patients suggest that the two diseases may have different mechanisms of brain injury.	
Multiple Sclerosis and Related Disorders. 18:225-229, 2017 Nov.	Eizaguirre MB Alonso R Vanotti S Garcea O	Cognitive impairment in neuromyelitis optica spectrum disorders: What do we know? [Review]	The aim of this study is to make a descriptive review of the bibliography available on cognitive dysfunction in patients with neuromyelitis optica spectrum disorders (NMOSD). We selected fifteen studies that quantitatively assess the relationship between NMOSD and one or more cognitive variables. Results showed that patients with NMOSD had a decrease in cognitive functions. Cognitive dysfunctions were found in 35-67% of patients with NMOSD, specifically in the attention, memory and	Study Design

			information processing speed. Cognitive dysfunctions were found to relate to injuries in white matter as well as clinical variables and depression. Copyright © 2017 Elsevier B.V. All rights reserved.	
Brain and Behavior. 10(11) (no pagination), 2020. Article Number: e01842. Date of Publication: November 2020.	Czarnecka D. Oset M. Karlinska I. Stasiolek M.	Cognitive impairment in NMOSD-More questions than answers	Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a type of central nervous system antibody-mediated disease which affects mainly optic nerves and spinal cord, but may also present with acute brainstem syndrome, acute diencephalic syndrome, and cerebral syndrome with typical brain lesions. One of the most disabling symptoms, diagnosed in 29%-67% of cases, is cognitive dysfunction, with such processes as memory, processing speed, executive function, attention, and verbal fluency being predominantly affected. However, description of cognition in NMOSD patients is still a relatively new area of research. Method(s): A systematic MEDLINE search was performed to retrieve all studies that investigated cognitive impairment and its clinical correlates in patients with NMOSD. Result(s): We summarize the current knowledge on cognitive impairment profile, neuropsychological tests used to examine NMOSD patients, clinical and demographical variables affecting	Study Design

			cognition, and magnetic resonance imaging correlates. We provide a comparison of cognitive profile of patients with multiple sclerosis and NMOSD. Conclusion(s): Patients with NMOSD are at significant risk of cognitive deficits. However, the knowledge of cognitive symptoms in NMOSD and potential modifying interventions is still scarce. Further accumulation of clinical data may facilitate effective therapeutic interventions.Copyright © 2020 The Authors. Brain and Behavior published by Wiley Periodicals LLC	
Neurology. Conference: 74th Annual Meeting of the American Academy of Neurology, AAN 2022. Virtual. 98(18 SUPPL) (no pagination), 2022. Date of Publication: May 2022.	Lopez-Soley E. Llufriu S. Gomez-Ballesteros R. Maurino J. Perez-Miralles F. Forero L. Sepulveda M. Calles C. Gines M.L.M.	Cognitive performance and health-related quality of life in patients with neuromyelitis optica spectrum disorder	Objective: To describe the cognitive performance of a cohort of neuromyelitis optica spectrum disorder (NMOSD) patients, and assess the influence of demographic and clinical characteristics, and the relation with health-related quality of life (HRQoL) and other symptoms. Background(s): The frequency of cognitive impairment reported in NMOSD is highly variable, and its relationship with demographic and clinical characteristics is poorly understood. Design/Methods: A non-interventional, cross-sectional study was conducted in 13 Spanish centers. Demographic and clinical features were collected along with a cognitive z-score (Rao's Battery), and patient-centered	Outcomes

Gonzalez I. Boyero S. Romero-Pinel L. Sempere A.P. Meca-Lallana V. Querol L. Franca L.C. Saiz A. Meca-Lallana J.E. Solana E.	measures (29-item Multiple Sclerosis Impact Scale, Satisfaction with Life Scale, SymptoMScreen, 8-item Stigma Scale for Chronic Illness, Beck Depression Inventory (BDI-FS), Pain Effects Scale and Fatigue Impact Scale for Daily Use). The associations between cognition, demographic and clinical characteristics, and patient-centered questionnaires were explored with linear correlation analysis adjusted by age and gender. We used Akaike Information Criterion (AIC) to select the features that best fit the model. Result(s): Forty-one patients were studied (median age: 44 years, 85% female, median disease duration: 8.1 years). Fourteen (35%) patients had cognitive impairment (z-scores below -1.5 standard deviation in at least two tests), and the most affected cognitive domain was visual memory, followed by attention and information processing speed. Patients with cognitive impairment and those cognitively preserved were similar regarding age and gender (p>0.05). The final linear regression model included as variables associated with cognition: gender (beta=-0.42, 95% confidence interval [CI]=-0.92,0.09, p=0.122), mood scores (BDI-FS, beta=0.65, 95% CI=0.26,1.05, p= 0.012), fatigue (beta=-

			0.39, 95% CI=-0.72, -0.05, p=0.036), satisfaction with life (beta=0.34, 95% CI=0.08,0.6, p=0.031) and perception of stigma (beta=-0.36, 95%CI=-0.64, -0.07, p=0.031); adjusted R2=0.396, p<0.001. Conclusion(s): These results highlight the association between cognition and emotional status in NMOSD patients. Cognitive and psychological assessments may be crucial to achieve a holistic approach in NMOSD patient care.	
Multiple Sclerosis. Conference: 9th Congress of the Pan-Asian Committee for Treatment and Research in Multiple Sclerosis, PACTRIMS 2016. Bangkok Thailand. 22(3) (pp 411), 2016. Date of Publication: March 2016.	Altunrende B. Yabalak A. Polat E. Kocaslan M. Topcular B. Akman Demir G.	Cognitive profile in neuromyelitis optica spectrum disorder	Background: Cognitive impairment in Neuromyelitis Optica Spectrum Disorder (NMOSD) can be seen however the features and influencing factors of cognitive impairment of Turkish NMOSD patients are unclear. Objective(s): To investigate cognitive function in a cohort of 22 Turkish patients with NMOSD. Method(s): 22 patients with the diagnosis of NMOSD, underwent neuropsychological tests (Brief Repeatable Battery- Neuropsychology (BRB-N), Addenbrooke's Cognitive Examination (ACE-R) and Beck Depression Inventory (BDI)). Cognitive impairment was considered if at least two cognitive domains were inferior to the 5th percentile for normal values for BRB-N test. The specificity and sensitivity of ACE-R test on detecting cognitive	Duplicate

			impairment were assessed through ACE-R test results. Result(s): The mean age of the patients was 42,86+/-10,98 (25-65). 45,5% (n=10) of the patients had cognitive impairment and 50% (n=11) had depression. The mostly affected cognitive profile was found to be memory impairment, attention and processing dysfunction. The group with cognitive impairment had significantly older age, lower educational status, higher EDSS and BDI scores (p<0,05). The diagnostic level of ACE-R test was found to be statistically good since it can detect cognitive impairment with a sensitivity of 88% and specificity of 75% on a cut off level of 82,5. Conclusion(s): In our study, approximately half of the patients had depression or cognitive impairment. It has been concluded that ACE-R test can be used to detect cognitive impairment in NMOSD patients. Since cognitive impairment and depression are frequent in NMOSD patients, for their quality of life, it is important to evaluate these aspects of the disease.	
Multiple Sclerosis. Conference: 8th Congress of the Pan Asian Committee for Treatment and	Nasr Esfahani F. Ebrahimian S. Dehghani L.	Comparing urinary symptoms in ms patients versus devic patients	Background: Multiple Sclerosis and Neuromyelitis Optica (NMO) also known as Devic disease are 2 different neurological autoimmune diseases with almost same signs and symptoms [1, 2].	Outcomes

Research in Multiple Sclerosis, PACTRIMS 2015. Seoul South Korea. 21(6) (pp 814), 2015. Date of Publication: May 2015.	Vesal S. Shaygannejad V.	One of their differences is the place and type of spinal involvement. Length of spinal segment involved in Devic disease is more, in comparison to MS disease [3]. Thus, it seems that urinary reflex become weaker and urinary symptoms are more common in Devic disease. Objective(s): Aim of the present study was to measure urinary complications in Devic patients and MS patients and compare them. Method(s): Twenty patients with definitely diagnosed Devic disease and 56 patients with definitely diagnosed MS disease, with no other systemic and neurologic disorders, were included in this study. All patients were subjected to complete International Prostatic Symptom Score (IPSS) questionnaire. Data were analyzed using Mann Whitney U test by SPSS software Results: According to statistical analyses, severe, moderate and mild urinary complications were found in 25%, 50% and 10% of Devic patients and 16.1%, 32.1% and 39.3% of MS patients, respectively. Although the differences were seen, they were not statistically significant (p=0.125). In details, frequency and urgency had higher rate in Devic patients (p<0.05) but incomplete emptying of the bladder, intermittency, weak stream, straining on urinating and

			nocturia, did not have any difference, statistically. Conclusion(s): Frequency and urgency were more common in Devic patients. But other symptoms did not have any significantly difference.	
Multiple Sclerosis Journal. Conference: 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2019. Stockholm Sweden. 25(Supplement 2) (pp 401-402), 2019. Date of Publication: September 2019.	Hyun J.-W. Jang H. Yu J. Park N.Y. Kim S.-H. Huh S.-Y. Kim W. Park M.S. Oh J. Park K.D. Kim H.J.	Comparison of neuropathic pain in neuromyelitis optica spectrum disorder and multiple sclerosis	Introduction: Pain in NMOSD patients was reported more common and severe than that in MS patients. However, in the previous studies, neuropathic pain and non-neuropathic pain have not been differentiated, and thorough comparative analyses focused on neuropathic pain and its impact on daily life in NMOSD and MS patients have not been conducted. Objective(s): To compare the characteristics of neuropathic pain in neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS). Method(s): From 2016 to 2018, 500 patients with NMOSD and MS from 6 referral hospitals in Korea underwent pain investigation. After the patients with current pain were matched for sex ratio and disease duration as confounding factors, PainDETECT questionnaires were assessed in 99 NMOSD and 58 MS patients to investigate neuropathic pain. The short form of the Brief Pain Inventory from 74 patients with neuropathic pain component was also analysed. Result(s): According to the PainDETECT,	Outcomes

		mechanical allodynia (p=0.014), and thermal hyperalgesia (p=0.011) were more severe in NMOSD patients than in MS patients. In domains of tingling/ prickling sensation (p = 0.024), mechanical allodynia (p=0.027), sudden pain attacks (p=0.018) and thermal hyperalgesia (p=0.002), strong involvement (score >3) were significantly more frequently observed in NMOSD compared to MS patients. Among the patients with neuropathic pain component, total pain-related interference (p=0.045) scores were significantly higher in NMOSD patients than in MS patients. In daily life, normal work (p=0.045), and relationships with other people (p=0.039) were more interfered by pain in NMOSD compared to MS patients. Although pain medication was more frequently prescribed in NMOSD patients, the percentage of pain relief achieved via medication was lower. Conclusion(s): Neuropathic pain and interference in daily life caused by neuropathic pain were more severe in NMOSD patients than in MS patients. Individualized analgesic management should be considered based on a comprehensive understanding of neuropathic pain in these patients.

Annals of Indian Academy of Neurology. Conference: 25th Annual Meeting of the Indian Academy of Neurology, IANCON 2017. Chennai India. 20(SUPPL 2) (pp S73), 2017. Date of Publication: September 2017.	Sreevidya L.K. Pal P.K. Netravathi M. Satishchandra P. Bharath R.D.	Correlates of motor disability and fatigue with quantitative MRI parameters in relapsing remitting multiple sclerosis and neuromyelitis optica	Background: Relapsing Remitting Multiple sclerosis (MS) and Neuromyelitisoptica (NMO) are primary demyelinating disorders with almost similar clinical symptoms but have varied etiology and response to treatment. Objective(s): To study and compare clinical (fatigue depression and disability scores), electrophysiological and imaging characteristics of RRMS and NMO. Patients and Methods / Material(s) and Method(s): 23 RRMS and 14 NMO patients were recruited over a period of 5 years and all parameters were done pre and post steroid therapy. Result(s): Mean age at presentation -RRMS-31.1a 12.2 years; NMO-34.8a 10.9 years. Mean duration of illness- RRMS50.9a 58.1 months; NMO-42.9a 48.6 months. Age at onset of illness -RRMS-26.9a 10.7 years; NMO-31.9 a 9.2 years. Frequencies of episodes were high in NMO (predominantly myelopathy) as opposed to RRMS (Brainstem syndrome). Disability, fatigue scores and Cerebrospinal fluid pleocytosis were significantly high than MS. Somatosensory Evoked Potentials (EPs) showed significant prolongation in RRMS while Visual EPs showed no difference between both entities. Duration of illness	Outcomes

			correlated positively with total T1, T2 lesion load and disability scores with T1 lesion load in RRMS. No correlation was found in any clinical scores and lesion load in NMO. As compared to NMO right uncus, insula and anterior cingulate gyrus were relatively preserved in RRMS with atrophy of left pre cuneus, cuneus, occipital gyrus, cerebellum and bilateral pulvinar as identified by voxel based morphometric analysis. Conclusion(s): Patients of NMO were of later age at onset with more disability and fatigue compared to RRMS. Duration of illness correlated with total MRI lesion load and disability with T1 lesion load in RRMS.	
Multiple Sclerosis. Conference: 6th Pan Asian Committee for Treatment and Research in Multiple Sclerosis, PACTRIMS 2013. Kyoto Japan. Conference Publication: (var.pagings). 19(5) (pp 662), 2013. Date of Publication: April 2013.	Xu W. Wu A. Dai Y. Wang H. Cheng C. Bao J. Qiu W. Lu Z.	Correlation of neuropathic pain and spinal cord magnetic resonance imaging findings in neuromyelitis optica patients	Background: Neuropathic pain is often experienced by multiple sclerosis (MS) patients. However, the occurrence of neuropathic pain in neuromyelitis optica (NMO) patients is less well studied. Objective(s): To assess the clinical characteristics of neuropathic pain in NMO patients, and analyze the relationship between the length of spinal cord lesions and neuropathic pain severity. Method(s): Thirty-five patients with NMO and 15 with MS were analyzed retrospectively. DN4 and ID pain questionnaires were used to assess neuropathic pain. Clinical data and spinal	Outcomes

	Zhong X. Shu Y. Hu X.		cord MRI findings for all NMO patients were analyzed. Result(s): Neuropathic pain was more severe in NMO patients than in MS patients. In all, 82.9% of NMO patients had DN4 scores >=4, compared with only 46.2% of MS patients (p=0.017). Numbness, hypoesthesia to touch, and hypoesthesia to prick were the most common symptoms in NMO patients. Pain most commonly occurred in the lower limbs (85.7%), upper limbs (42.9%) and head (37.1%, including eye pain) in NMO patients. DN4 scores were correlated with spinal cord length in NMO-IgG-seropositive NMO patients (r=0.394, p=0.046). Conclusion(s): Neuropathic pain is more severe and frequent in NMO patients than MS patients. Neuropathic pain scores may be correlated with spinal cord lesion length in NMO-IgG-seropositive NMO patients.	
Multiple Sclerosis. Conference: 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2015. Barcelona Spain. Conference Publication: (var.pagings). 23(11	Nakashima I. Akaishi T. Misu T. Fujihara K.	Depressive state and chronic fatigue in neuromyelitis optica	Background: Depression and chronic fatigue are frequently present in multiple sclerosis (MS); however, the prevalence rates have not been investigated in neuromyelitis optica (NMO). The effectiveness of levocarnitine for fatigue in NMO is also unknown. Material(s) and Method(s): Thirty-nine consecutive NMO and 75 MS patients at Tohoku University Hospital were compared using self-rating	Outcomes

SUPPL. 1) (pp 607-608), 2015. Date of Publication: September 2015.	questionnaires for depressive states (self-reported Quick Inventory of Depressive Symptomatology: QIDS-SR), daily activity (Performance Status: PS), and fatigue (Chalder Fatigue Scale: ChFS), as well as serum carnitine levels. A subgroup of patients with low carnitine levels were reevaluated regarding depression and fatigue after levocarnitine treatment. Result(s): Abnormal QIDS-SR and ChFS scores were identified in 70-80% of both diseases, and the severities of these symptoms were also comparable in MS and NMO. In both diseases, strong correlations were identified between the QIDS-SR and ChFS ($p < 0.0001$), as well as the EDSS and PS ($p < 0.0001$). Both the QIDS-SR and ChFS exhibited weak correlations with gait disturbance in MS and disease duration in NMO. The carnitine level was decreased in approximately 20% of both diseases; however, it was not correlated with the QIDS-SR or ChFS. Levocarnitine did not improve the QIDS-SR or ChFS. Conclusion(s): Depression and fatigue are equally prevalent in MS and NMO and are strongly correlated with one another. The measurement of serum carnitine levels and administration of levocarnitine are suggested to be unfounded.

Neurology. Conference: 67th American Academy of Neurology Annual Meeting, AAN 2015. Washington, DC United States. Conference Publication: (var.pagings). 84(SUPPL. 14) (no pagination), 2015. Date of Publication: 06 Apr 2015.	Akaishi T. Nakashima I. Misu T. Fujihara K. Aoki M.	Depressive state and chronic fatigue in neuromyelitis optica	OBJECTIVE: To study the chronic fatigue, depressive state, and effectiveness of lovecarnitine (L-carnitine) in neuromyelitis optica (NMO). BACKGROUND: In patients with multiple sclerosis (MS), depression and chronic fatigue are frequently seen and often affect their daily life; they are believed to be caused by disseminated demyelination, which disturbs nerve conduction. In contrast, these symptoms have not been assessed in NMO. The effectiveness of L-carnitine for chronic fatigue in NMO is still unknown. DESIGN/METHODS: Thirty-nine consecutive NMO patients and 75 MS patients seen at Tohoku University Hospital between June and September in 2014 were compared by self-rating questionnaires for depressive state (Quick Inventory of Depressive Symptomatology: QIDS-SR), daily activity (Performance Status: PS), and fatigue (Chalder Fatigue Scale: ChFS), together with the simultaneously measured serum carnitine levels. L-carnitine was administered to those with low serum carnitine levels, and their scores were reassessed after one month treatment. RESULT(S): Abnormal scores of QIDS-SR and ChFS were observed in more	Outcomes

			than 70[percnt] of NMO and MS patients. The prevalence and severity of depressive state and fatigue were the same between MS and NMO. In both diseases, strong correlations were observed between QIDS-SR and ChFS ($p<0.0001$), and between EDSS and PS ($p<0.0001$). Though the serum carnitine level was decreased in about 20[percnt] of patients with both diseases, it didn't correlate with the level of depressive state or fatigue. Moreover, the administration of L-carnitine didn't improve those symptoms assessed by the questionnaires. CONCLUSION(S): NMO patients showed the same level of depressive state and fatigue as MS patients. Fatigue in NMO seemed to be strongly associated with depressive state, as in MS. A decreased serum carnitine level was not associated with these symptoms, and medications other than L-carnitine should be sought for the fatigue in these diseases.	
Multiple Sclerosis Journal. Conference: 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS	Royston M. Kielhorn A. Tanvir I. Sabatella G.	Disease outcomes in the absence of a relapse in patients with neuromyelitis optica spectrum disorder	Introduction: Aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD) is characterized by unpredictable relapses that can lead to severe impairment through vision loss, neurological disability, and poor health-related quality of life	Outcomes

2021. Virtual. 27(2 SUPPL) (pp 151), 2021. Date of Publication: October 2021.

(HRQoL). Current therapeutic strategies focus on preventing relapses. However, it is unclear if any disease worsening occurs in the absence of a relapse. Objective(s): To investigate changes in disability and HRQoL outcomes in the absence of an adjudicated relapse in patients with AQP4+ NMOSD. Method(s): Analyses were based on data collected from the phase 3 PREVENT study and its open label extension (OLE). Key outcome measures for these post hoc analyses included: Expanded Disability Status Scale for general disability progression, Hauser Ambulation Index for mobility, Modified Rankin Score for dependence in daily activities, and the European Quality of Life 5-Dimension questionnaire and the 36-Item Short Form Survey for HRQoL. Four different subsets of patient data were used, none of which included relapse events irrespective of the treatment arm: all patients who were enrolled until an adjudicated on-trial relapse or end of the study; patients who did not experience any on-trial relapse; all patients who reached the 1-year mark in PREVENT; and all patients from the OLE (up to 222 weeks). Result(s): For all patient data sets analyzed, no significant worsening was observed in the absence

	of a relapse across all outcomes. These findings were consistent for all assessment timepoints over the 120-week study period for all patients enrolled in PREVENT and for the subset of non-relapsing patients. Similar findings were observed across the 48-week period for the patient population (n = 82) who completed at least 1 year of the study, suggesting these analyses were not influenced by the number of patients completing the study. Also, in the absence of a relapse, no disease worsening was observed on key outcomes at the 19 assessment timepoints in the PREVENT extended study timeframe. Conclusion(s): Studies have shown that patients worsen after NMOSD relapses. Here, we show that in the absence of relapses and regardless of the analytical approach, current disease outcome measures could not detect a clinically meaningful worsening of disability or HRQoL. These findings reinforce the critical importance of a therapeutic approach aimed at preventing relapses in patients with AQP4+ NMOSD to avoid disability worsening.

Value in Health. Conference: ISPOR Europe 2022. Vienna Austria. 25(12 Supplement) (pp S130-S131), 2022. Date of Publication: December 2022.	Aggarwal A. Dasari A. Belekar V. Dovari A. Hyderboini R. Chidirala S. Goyal R. Singh R. Kataria A.K.	EE384 A Targeted Literature Review of Health State Utility Values in Neuromyelitis Optica Spectrum Disorder	Objectives: Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease that effects mainly the optic nerves and spinal cord and if untreated can cause blindness, spinal cord damage and even death. Due to its relapsing and debilitating nature, NMOSD, has a negative impact on patients' quality of life (QoL). Understanding health utility values (HUVs) while living with this severe disease is important for health technology evaluations and was the focus of this review. Method(s): A targeted literature search was performed in Embase and MEDLINE without geographical and time-period restrictions, followed by grey literature searches. Studies investigating the HUVs in NMOSD patients and published in English language were included without restricting to age and study design. Quality assessment was conducted using Cochrane risk of bias tool (for randomized controlled trials (RCTs)) and Newcastle-Ottawa Scale (for observational studies). A single reviewer process was followed across steps. Result(s): Out of 819 records, 8 studies (3 RCTs and 5 observational) were included. Except one study (low-quality), remaining studies were graded as high-quality. All studies derived the HUVs using EQ-5D.	Study Design

			The baseline mean HUVs in NMOSD patients were lower [0.41 (Thailand), 0.54 (the UK), 0.693 (Germany) and 0.738 (the US)] compared to world general population (0.902). Lower HUVs were reported in patients with higher Expanded Disability Status Scale (EDSS: higher score indicates high disability) score, 0.20, 0.31, 0.54 and 0.80 for EDSS score 8-9.5, 7-7.5, 4.5-6.5, and <=4.0, respectively. HUVs also decreased from pre-relapse (0.656) to post-relapse (0.595) state. In addition to EQ-5D, two studies also used VisQol and EQ-VAS scales with mean HUVs as 0.79 (UK) and 0.65 (Thailand), respectively. Conclusion(s): The HUVs were reduced significantly with the increase in EDSS score and relapse. Although, few studies reported HUVs data, but these were of good quality and can further aid in decision-making.Copyright © 2022	
European Journal of Ophthalmology. 32(4) (pp 1857-1871), 2022. Date of Publication: July 2022.	Zhang J. Fan A. Wei L. Wei S. Xie L.	Efficacy and safety of plasma exchange or immunoadsorption for the treatment of option neuritis in demyelinating diseases: A systematic review and meta-analysis	Background: There are no systematic reviews yet that evaluated the effects of PE/IA in patients with optic neuritis (ON) in demyelinating diseases. A meta-analysis of available study is needed to further explore the value of plasma exchange (PE) or immunoadsorption (IA) in treating ON in demyelinating diseases. Method(s): All relevant articles published	Study Design

Li M. Zhang W. Liu Q. Yang K.	on PubMed, Web of Science, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), VIP Database, Wanfang, Sinomed and ophthalmology professional websites were searched. Study characteristics, demographic characteristics, clinical features and outcome measures were extracted. Response rate, adverse events (AE) rate, serious adverse event (SAE) rate, the log of the minimum angle of resolution (logMAR), visual outcome scale (VOS) and expanded disability status scales (EDSS) were evaluated using a random-effects model. Result(s): 35 studies were included between 1985 and 2020, containing 1191 patients. The response rates of PE and IA in acute attack of ON were 68% and 82% respectively. LogMAR (-0.60 to - 1.42) and VOS (-1.10 to -1.82) had been significantly improved from within 1 month to more than 1 month after PE treatment. Besides, we found that logMAR improved 1.78, 0.95 and 0.38, respectively,when the time from symptom onset to the first PE/IA was less than 21 days, 21-28 days, and more than 28 days. The pooled mean difference of EDSS was -1.14.Adverse effects rate in patients with PE or IA were 0.20 and 0.06, respectively.

			Conclusion(s): The meta-analysis provided evidence that PE/IA treatment was an effective and safe intervention, and it is recommended that early initiation of PE/IA treatment is critical.Copyright © The Author(s) 2021.	
Journal of Neurology, Neurosurgery & Psychiatry. 94(1):62-69, 2023 01.	Spagni G Sun B Monte G Sechi E Iorio R Evoli A Damato V	Efficacy and safety of rituximab in myelin oligodendrocyte glycoprotein antibody-associated disorders compared with neuromyelitis optica spectrum disorder: a systematic review and meta-analysis	BACKGROUND: Rituximab (RTX) efficacy in patients with myelin oligodendrocyte glycoprotein (MOG) antibody-associated disorders (MOGADs) is still poorly understood, though it appears to be lower than in aquaporin-4-IgG-positive neuromyelitis optica spectrum disorders (AQP4-IgG+NMOSDs). The aim of this systematic review and meta-analysis is to assess the efficacy and safety profile of RTX in patients with MOGAD and to compare RTX efficacy between MOGAD and AQP4-IgG+NMOSD. METHODS: We searched original English-language articles published between 2012 and 2021 in MEDLINE, Cochrane, Central Register of Controlled Trials and clinicaltrials.gov, reporting data on RTX efficacy in patients with MOGAD. The main outcome measures were annualised relapse rate (ARR) and Expanded Disability Status Scale (EDSS) score mean differences (MDs) after RTX.	Study Design

The meta-analysis was performed with a random effects model. Covariates associated with the outcome measures were analysed with a linear meta-regression.

RESULTS: The systematic review included 315 patients (138 women, mean onset age 26.8 years) from 32 studies. Nineteen studies (282 patients) were included in the meta-analysis. After RTX, a significant decrease of ARR was found (MD: -0.92, 95% CI -1.24 to -0.60, p<0.001), markedly different from the AQP4-IgG+NMOSD (MD: -1.73 vs MOGAD -0.92, subgroup difference testing: Q=9.09, p=0.002). However, when controlling for the mean ARR pre-RTX, this difference was not significant. After RTX, the EDSS score decreased significantly (MD: -0.84, 95% CI -1.41 to -0.26, p=0.004). The frequency of RTX-related adverse events was 18.8% (36/192) and overall RTX-related mortality 0.5% (1/192).

CONCLUSIONS: RTX showed effective in MOGAD, although to a lesser extent than in AQP4-IgG+NMOSD, while the safety profile warrants some caution in its prescription. Randomised-controlled trials

			are needed to confirm these findings and provide robust evidence to improve treatment strategies in patients with MOGAD. PROSPERO REGISTRATION NUMBER: CRD42020175439. Copyright © Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.	
JAMA Neurology. 73(11):1342-1348, 2016 Nov 01.	Damato V Evoli A Iorio R	Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis [Review]	IMPORTANCE: Neuromyelitis optica spectrum disorders (NMOSDs) are autoimmune astrocytopathies characterized by predominant involvement of the optic nerves and spinal cord. In most patients, an IgG autoantibody binding to astrocytic aquaporin 4, the principal water channel of the central nervous system, is detected. Rituximab, a chimeric monoclonal antibody specific for the CD20 B-lymphocyte surface antigen, has been increasingly adopted as a first-line off-label treatment for patients with NMOSDs. OBJECTIVE: To perform a systematic review and a meta-analysis of the efficacy and safety of rituximab use in NMOSDs, considering the potential predictive factors related to patient response to	Study Design

rituximab in this disease.

EVIDENCE REVIEW: English-language studies published between January 1, 2000, and July 31, 2015, were searched in the MEDLINE, Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov databases. Patient characteristics, outcome measures, treatment regimens, and recorded adverse effects were extracted.

FINDINGS: Forty-six studies were included in the systematic review. Twenty-five studies that included 2 or more patients with NMOSDs treated with rituximab were included in the meta-analysis. Differences in the annualized relapse rate ratio and Expanded Disability Status Scale score before and after rituximab therapy were the main efficacy measures. Safety outcomes included the proportion of deaths, withdrawals because of toxic effects, and adverse effects.

RESULTS: Among 46 studies involving 438 patients (381 female and 56 male [sex was not specified in 1 patient]; mean age at the outset of treatment, 32 years [age range, 2-77 years]), rituximab

therapy resulted in a mean (SE) 0.79 (0.15) (95% CI, -1.08 to -0.49) reduction in the mean annualized relapse rate ratio and a mean (SE) 0.64 (0.27) (95% CI, -1.18 to -0.10) reduction in the mean Expanded Disability Status Scale score. A significant correlation was observed between disease duration and the Expanded Disability Status Scale score. Adverse effects were recorded in 114 of 438 (26%) patients treated with rituximab. Specifically, 45 patients (10.3%) experienced infusion-related adverse effects, 40 patients (9.1%) had an infection, 20 patients (4.6%) developed persistent leukopenia, 2 patients (0.5%) were diagnosed as having posterior reversible encephalopathy, and 7 patients (1.6%) died.

CONCLUSIONS AND RELEVANCE: This systematic review and meta-analysis provides evidence that rituximab therapy reduces the frequency of NMOSD relapses and neurological disability in patients with NMOSDs. However, the safety profile suggests caution in prescribing rituximab as a first-line therapy.

Clinical and Experimental Neuroimmunology. 13(4) (pp 194-207), 2022. Date of Publication: November 2022.	Luitel P. Ghimire A. Upadhyay D. Ojha R.	Efficacy of monoclonal antibodies in neuromyelitis optica: An updated systematic review with meta-analysis	Objective: This is a critical review of studies aiming to assess the safety and efficacy of monoclonal antibodies as compared with the classical regimen in patients with neuromyelitis optica spectrum disorder. Method(s): Various electronic databases were searched for original articles reporting results from the use of monoclonal antibodies in neuromyelitis optica spectrum disorder. The Expanded Disability Status Scale and annualized relapse rate score before and after treatment were the primary effect measures. The pooled standardized mean difference with 95% CI was calculated using the random effects model. The heterogeneity of the included studies was calculated using Cochran's Q test and I2 statistics. Result(s): Of 36 included studies, meta-analysis was carried out from 27 studies. The pooled analysis of 1010 patients showed a mean reduction in the mean annualized relapse rate ratio after tocilizumab therapy -2.45 (95% CI -3.13 to -1.77) to be higher compared with rituximab -1.49 (95% CI -1.81 to -1.17). Likewise, the mean reduction in the Expanded Disability Status Scale after tocilizumab was higher -1.10 (95% CI -1.75 to -0.44) compared with rituximab -0.80 (95% CI -1.11 to -	Study Design

			0.48). Conclusion(s): Tocilizumab has a greater effect than rituximab in terms of the reduction of the annualized relapse rate and Expanded Disability Status Scale in neuromyelitis optica spectrum disorder patients. The greater efficacy of tocilizumab could result from its multiple dynamic pharmacodynamics (i.e. its effect on interleukin-6-dependent inflammatory processes, involving CD20-negative plasmablasts, pathogenic T cells and regulatory T cells) and to some degree due to heterogeneity in our study. Satralizumab (monotherapy or add-on), eculizumab and inebilizumab (monotherapy) are effective in aquaporin-4-positive cases with good safety profiles. Ublituximab, bortezomib, bevacizumab and C1-esterase inhibitors are both effective and safe add-on drugs.	
Danish Medical Journal. 60(10) (no pagination), 2013. Article Number: B4730. Date of Publication: October 2013.	Asgari N.	Epidemiological, clinical and immunological aspects of neuromyelitis optica (NMO)		Outcomes

Neurology. Conference: 2022 Summer Conference. Virtual. 93(23 Supplement 2) (pp S34), 2022. Date of Publication: December 2022.	Tisavipat N. Jitpratoom P. Siritho S. Prayoonwiwat N. Apiwattanakul M. Rattanathamsakul N. Jitprapaikulsan J.	Epidemiology and Burden of NMOSD, MS, and MOGAD in Thailand: a Population-Based Study	Objective To determine cumulative incidence and point prevalence of neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) in Thailand using population-based data of Chumphon province. Background CNS inflammatory demyelinating diseases (CNSIDDs) have a great interracial heterogeneity. The epidemiology of CNSIDDs in Thailand, a Mainland Southeast Asian country, is unknown. Design/Methods Searching for CNSIDD patients at a public secondary care hospital in Chumphon from January 2016 to December 2021 was performed using relevant ICD-10-CM codes. All neurology patients were systematically referred to this hospital as it was the only hospital in the province with a neurologist. Diagnoses were individually ascertained by retrospective chart review. Cumulative incidence over 2016-2021, point prevalence on December 31st, 2021, attack rate, mortality rate, and disabilityadjusted life years (DALYs) were calculated. Population data were obtained from the National Statistical Office of Thailand. As of December 31st, 2021, the population census of Chumphon was	Outcomes

			509,479. Results NMOSD was the most prevalent CNSIDD in adult Thai population at 3.33 per 100,000 persons (crude prevalence 2.55). The age-adjusted prevalence of aquaporin-4 antibody-positive NMOSD alone was 3.08 per 100,000 persons. Age-adjusted incidence rate of NMOSD was 1.65 per 100,000 persons/year (crude incidence rate 0.20). Age-adjusted prevalence of MS followed at 0.77 and MOGAD at 0.51 per 100,000 persons (crude prevalence 0.59 and 0.39, respectively). Although most had a fair recovery, disability was worst amongNMOSD with a DALY of 3.47 years per 100,000 persons. Mortality and attack rates were highest in NMOSD as well. No increase in incidence or attack rate were observed during the COVID-19 pandemic. Conclusions CNSIDDs are rare diseases in Thailand. The prevalence is comparable to that of East Asian countries. NMOSD caused the highest DALYs among CNSIDDs.	
Multiple Sclerosis. Conference: 4th Congress of the Pan-Asian Committee for Treatment and Research in Multiple Sclerosis, PACTRIMS	Kanamori Y. Nakashima I. Takai Y. Nishiyama S.	Evaluation of the health-related quality of life in nmo	Background: Neuromyelitis optica (NMO) is an inflammatory disease characterised by severe optic neuritis and transverse myelitis, and is often accompanied by severe motor and sensory disability. The Health-related Quality of Life (HRQoL) in NMO has not been evaluated in detail.	Outcomes

2011. Singapore Singapore. Conference Publication: (var.pagings). 18(4) (pp 539), 2012. Date of Publication: April 2012.	Kuroda H. Takahashi T. Kanaoka-Suzuki C. Misu T. Fujihara K. Itoyama Y.	Objective(s): To evaluate the HRQoL in NMO. Method(s): We evaluated the HRQoL of 22 consecutive patients with NMO at the outpatient clinic of Tohoku University Hospital by Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), Euroqol 5D (EQ-5D) and Functional Assessment of Multiple Sclerosis (FAMS). Thirty seven patients with consecutive Multiple Sclerosis (MS) were also analysed as controls. The definition of NMO was set as patients who met Wingerchuk 2006 criteria or who were anti-aquaporin-4 antibodypositive. The definition of MS was as per McDonald Classification 2005. Result(s): SF-36 scores were lower both in NMO and MS than Japanese- Norm in all domains. In comparison between NMO and MS, the SF-36 scores were lower in NMO than in MS in all domains. After PACTRIMS 2011 Programme & Abstracts 37 Analysis of Covariance (ANCOVA) adjusting age, gender, onset age and DSS scores, the difference was significant only in Bodily Pain (p=0.03). The HRQoL scores in all 5 domains in EQ-5D and in 5 out of 6 domains in FAMS were lower in NMO than in MS. Conclusion(s): Our study suggests that the overall HRQoL in NMO is lower

			compared to that in MS. Pain-related HRQoL, in particular, was also found to be low. We should pay attention to pain as much as physical function. Relieving pain may improve the HRQoL in NMO.	
Multiple Sclerosis. Conference: 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 18th Annual Conference of Rehabilitation in MS, RIMS. Copenhagen Denmark. Conference Publication: (var.pagings). 19(11 SUPPL. 1) (pp 326-327), 2013. Date of Publication: October 2013.	Araki M. Matsuoka T. Aranami T. Nakamura M. Okamoto T. Murata M. Miyake S. Yamamura T.	Exploring anti-IL6 receptor monoclonal antibody tocilizumab in neuromyelitis optica	Neuromyelitis optica (NMO) is an autoimmune disease, associated with elevation of serum anti-aquaporin 4 (AQP4) autoantibodies. We previously described that plasmablasts (PB) are anti-AQP4 antibody-producing cells in the peripheral blood of NMO (Chihara et al. 2011). We also revealed that IL-6 receptor (IL-6R) signaling pathways are involved in the pathogenesis. Therefore, we performed an exploratory open-label study to evaluate the safety and efficacy of tocilizumab (TCZ), humanized anti-IL-6R monoclonal antibody, in patients with NMO who are refractory to currently available drugs in Japan. Prior medications to the patients included mitoxantrone, corticosteroid, azathioprine, and interferon-beta. Here we describe the results of the first four patients (three female and one male) out of nine. These patients were given monthly TCZ of 8 mg / kg for 12 months period. We evaluated the number of relapses, expanded disability status scale (EDSS), Numeric Rating Scale (NRS) as representative	Outcomes

pain scale and fatigue severity scale before and after starting TCZ. Serum levels of anti-AQP4 antibody and IL-6, as well as proportions and absolute numbers of PB (CD19+CD27highCD38highCD180- cells) in the peripheral blood were analyzed. The annualized relapse rate (ARR) was reduced from 2.0 to 0.5 after starting TCZ. Notably, the neuropathic pain refractory to standard therapy gradually improved in all patients after starting TCZ, resulting in complete resolution of pain in three. Mean NRS as pain scale reduced from 3.5 to 1.3. Relief from serious fatigue hampering daily life activity was also confirmed in all. There was also a trend for improvement in EDSS. Serum IL-6 level was increased in all patients after the TCZ administration, reflecting the reduced consumption of endogenously produced IL-6 by blocking IL-6R with TCZ. In a most active NMO patient, the numbers of abnormally expanded PB was sharply declined after injecting TCZ. The PB numbers in the other patients were not elevated, probably due to prior exposure to immunosuppressive treatments. Adverse events included lymphocytopenia, anemia, viral enteritis, upper respiratory infection, and acute pyelonephritis. None

			of those events were severe. In addition to its ability to maintain stable remission in NMO, effects on neuropathic pain, paresthesia and fatigue would add significant values on TCZ for treatment of NMO.	
Multiple Sclerosis. Conference: 19th Annual Rehabilitation in Multiple Sclerosis Conference, RIMS 2014. Brighton United Kingdom. Conference Publication: (var.pagings). 20(7) (pp 984), 2014. Date of Publication: June 2014.	Methley A. Mutch K. Elsone L. Moore P. Jacob A.	Factors that contribute to improved quality of life for people with neuromyelitis optica	Introduction: Neuromyelitis optica (NMO) is characterised by relapses causing optic neuritis and extensive transverse myelitis resulting in visual and physical disability. Aim(s): This qualitative study explored the perception of quality of life in people living with NMO and identified contributing factors for a poor or good quality of life. Method(s): 15 patients (11 women and 4 men, age 24-74 years), who fulfilled the Wingerchuk 2006 criteria for NMO spectrum disorder agreed to participate. 9 tested positive for aquaporin-4 antibodies. NMO diagnosed 2-13 years prior to the study, although initial episode occurred 4-37 years prior to the study. A semi-structured interview asking 'What does quality of life mean to you?' and 'what impact does NMO have on your quality of life?' was used. Result(s): Data was analysed using thematic analysis to identify 4 major themes from the interviews. * Role in life and purpose-included meaningful activity/ routine and meaningful social relationships and social	Outcomes

role e.g. I don't like seeing my husband taking the washing out of the machine, I feel that's my job. * Expectations/perceptions of peers-included matching of goals e.g. I want to do everything in my life that I would have done regardless of my illness. I want to go to work, to get my own place, I would like to meet somebody and have a family. I want to do everything that my sisters are doing. * Independence versus support- to achieve goals and empowerment versus control and choice e.g. The thing I find the hardest is the fact that I will always need somebody there to do things for me, never having a day by myself when I can just get in the car, drive to the shops, normal day things really. * Impact of physical symptoms on normality-included impact of NMO on quality of life and adaptations e.g. I'm aware that I look different if I haven't seen anybody for a while I'll sit with my arms over my stomach to hide the weight gain, I'm so embarrassed. I don't feel confident in my own body anymore, I feel people are looking at me differently and it's just vile. Conclusion(s): Quality of life was improved when the participants felt in control of their situation and able to match their peer achievements such as going to

			work or getting married. Decreased independence was strongly linked to a lower quality of life. Health care professionals should provide a person-centred care with shared decision making to help patients maximise their quality of life.	
Journal of Pediatric Psychology. 43(2):133-142, 2018 03 01.	Self MM Fobian A Cutitta K Wallace A Lotze TE	Health-Related Quality of Life in Pediatric Patients With Demyelinating Diseases: Relevance of Disability, Relapsing Presentation, and Fatigue	Objective: Decreased health-related quality of life (HRQOL) in pediatric patients with multiple sclerosis is established, but little research has examined HRQOL in the broader pediatric demyelinating disease population, and predictors of reduced HRQOL are largely unexplored. We sought to (1) compare generic HRQOL and fatigue of pediatric patients with relapsing (i.e., multiple sclerosis and neuromyelitis optica) versus monophasic demyelinating diseases (i.e., acute disseminated encephalomyelitis, optic neuritis, transverse myelitis, clinically isolated syndrome) and (2) examine the extent to which disability, relapsing disease, and fatigue predict HRQOL. Methods: Child and/or parent-proxy reports of generic and fatigue-related HRQOL were collected for 64 pediatric patients with demyelinating diseases. HRQOL of the sample was compared	Population

with published healthy child norms. Independent samples t-tests compared HRQOL and fatigue for children with monophasic versus relapsing diseases. Regression analyses examined disability, disease presentation, and fatigue as potential predictors of HRQOL.

Results: Compared with healthy child norms, generic HRQOL was significantly lower for the demyelinating disorder group, for both child and parent reports across multiple domains. As hypothesized, the relapsing disease group reported lower overall HRQOL and more fatigue than the monophasic group. Disability and relapsing disease predicted lower HRQOL for both parents and children, whereas fatigue was only predictive per the child perspective.

Conclusions: Children with demyelinating diseases evidence significantly lower HRQOL than healthy peers, supporting need for intervention. Those with relapsing disease appear particularly at risk; targeting disability and fatigue may be fruitful areas for intervention.

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Frontiers in neurology [electronic resource].. 13:860083, 2022.	Yao XY Xie L Cai Y Zhang Y Deng Y Gao MC Wang YS Xu HM Ding J Wu YF Zhao N Wang Z Song YY Wang LP	Human Umbilical Cord Mesenchymal Stem Cells to Treat Neuromyelitis Optica Spectrum Disorder (hUC-MSC-NMOSD): A Study Protocol for a Prospective, Multicenter, Randomized, Placebo-Controlled Clinical Trial	Background: Neuromyelitis Optica spectrum disorder (NMOSD) is severe relapsing and disabling autoimmune disease of the central nervous system. Its optimal first-line treatment to reduce relapse rate and ameliorate neurological disability remains unclear. We will conduct a prospective, multicenter, randomized, placebo-controlled clinical trial to study the safety and effectiveness of human umbilical cord mesenchymal stem cells (hUC-MSCs) in treating NMOSD. Methods: The trial is planned to recruit 430 AQP4-IgG seropositive NMOSD patients. It consists of three consecutive stages. The first stage will be carried out in the leading center only and aims to evaluate the safety of hUC-MSCs. Patients will be treated with three different doses of hUC-MSCs: 1, 2, or 5 x 106 MSC/kg.weight for the low-, medium-, and high-dose group, respectively. The second and third stages will be carried out in six centers. The second stage aims to find the optimal dosage. Patients will	Outcomes

Xie C

Li ZZ

Wan WB

Lin Y

Jin HF

Wang K

Qiu HY

Zhuang L

Zhou Y

Jin YY

Ni LP

Yan JL

Guo Q

Xue JH

Qian BY

be 1:1:1:1 randomized into the low-, medium-, high-dose group and the controlled group. The third stage aims to evaluate the effectiveness. Patients will be 1:1 randomized into the optimal dose and the controlled group. The primary endpoint is the first recurrent time and secondary endpoints are the recurrent times, EDSS scores, MRI lesion numbers, OSIS scores, Hauser walking index, and SF-36 scores. Endpoint events and side effects will be evaluated every 3 months for 2 years.

Discussion: Although hUC-MSC has shown promising treatment effects of NMOSD in preclinical studies, there is still a lack of well-designed clinical trials to evaluate the safety and effectiveness of hUC-MSC among NMOSD patients. As far as we know, this trial will be the first one to systematically demonstrate the clinical safety and efficacy of hUC-MSC in treating NMOSD and might be able to determine the optimal dose of hUC-MSC for NMOSD patients.

Trial registration: The study was registered with the Chinese Clinical Trial Registry (CHICTR.org.cn) on 2 March 2016 (registration No. ChiCTR-INR-

	Guan YT		16008037), and the revised trial protocol (Protocol version 1.2.1) was released on 16 March 2020. Copyright © 2022 Yao, Xie, Cai, Zhang, Deng, Gao, Wang, Xu, Ding, Wu, Zhao, Wang, Song, Wang, Xie, Li, Wan, Lin, Jin, Wang, Qiu, Zhuang, Zhou, Jin, Ni, Yan, Guo, Xue, Qian and Guan.	
Multiple Sclerosis Journal. Conference: 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2021. Virtual. 27(2 SUPPL) (pp 150), 2021. Date of Publication: October 2021.	Berthele A. Levy M. Wingerchuk D. Pittock S. Shang S. Kielhorn A. Royston M. Sabatella G. Palace J.	Impact of a single relapse on disability and health-related quality of life in neuromyelitis optica spectrum disorder	Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is characterised by unpredictable, disabling relapses that primarily affect the optic nerves and spinal cord. Most patients with NMOSD have anti-aquaporin-4 antibodies (AQP4+), which cause complement activation and neuronal cell death. Cumulative damage from NMOSD relapses has been associated with poor health-related quality of life (HRQoL) and long-term disability. Objective(s): To assess the impact of an individual NMOSD relapse on HRQoL and disability outcomes. Method(s): Data were pooled from the placebo-controlled phase 3 PREVENT study and its open-label extension, which evaluated the efficacy and safety of eculizumab in patients with AQP4+ NMOSD. Post hoc analyses examined the effect of a single relapse on disability (modified Ranking Scale [mRS], Expanded Disability Status Scale [EDSS],	Outcomes

Hauser Ambulation Index) and HRQoL (36-item Short-Form Health Survey [SF-36] mental and physical component summary [MCS and PCS, respectively] scores, and European Quality of Life 5-Dimension questionnaire 3-Level [EQ-5D-3L] visual analogue scale (VAS) and index scores). Assuming the impact of one relapse extends to multiple relapses, an extrapolation was done to assess the impact of multiple relapses on these outcomes. Result(s): In 27 patients (placebo: n=20; eculizumab: n=7) who experienced an independently adjudicated relapse, one relapse led to significantly worse mRS, EDSS, SF-36 MCS and PCS, and EQ-5D-3L VAS and index scores during the study. Relapsing patients exhibited clinically meaningful worsening of disability and HRQoL outcomes within the first 90 days post-relapse, which then did not worsen by 120 days post-relapse. In 4 of 7 outcomes, relapsing patients were more likely to exhibit clinically meaningful worsening than non-relapsing patients. Extrapolation of one relapse to multiple relapses predicted that each relapse led to an incremental worsening of disability, with the EQ-5D utility index score decreasing from 0.7 to 0.3 (-43%) and

		EDSS score increasing from 4.2 to 5.7 (+35%) after 5 relapses. Conclusion(s): This study shows that a single relapse can lead to significant and sustained worsening of disability and HRQoL outcomes in patients with AQP4+ NMOSD. Thus, each relapse drives the stepwise accumulation of disability characterizing NMOSD. These results stress the need for relapse prevention, warranting head-to-head trials and indirect treatment comparisons to identify high-efficacy therapies.	
2015. [No additional source data available.]	Intravenous immunoglobulin (IVIg) treatment of transverse myelitis in adults and children	INTERVENTION: Admin of immunoglobulin, Eligible participants will be randomised to treatment or control group. 1. Participants randomised to the control arm of this study will be prescribed intravenous methylprednisolone in line with the local clinical practice (variations of practice will be recorded) 2. Paediatric patients (treatment arm) will receive 30mg/kg or 500 mg/m2 capped to a maximum dose of 1g/day for 5 days 3. Adult patients (treatment arm) will be given 1gram/day for 5 days CONDITION: Topic: Children, Neurological disorders; Subtopic: All Diagnoses, Neurological (all Subtopics); Disease: Nervous system disorders, All Diseases ; Nervous System Diseases	Outcomes

		PRIMARY OUTCOME: Improvement of 2 points or greater on the ASIA Impairment scale (classfiied A-E); Timepoint(s): 6 months SECONDARY OUTCOME: 1. Change in ASIA motor scale (0-100) and ASIA sensory scale (0-112) at 3, 6, and 12 months post randomisation ; 2. Change in Kurtzke expanded disability status scale (EDSS) measured by Neurostatus scoring at 3, 6, and 12 months ; 3. EQ-5D-Y for patients aged 8-12 years (at presentation) at 3,6 and 12 months post randomisation; 4. EQ-5D-5L for patients aged = 13 years (at presentation) at 3, 6 and 12 months post randomisation; 5. Individuals = 13 years at presentation: International SCI Quality of Life Basic Data Set at 3, 6 and 12 months post randomisation; 6. Client Service Receipt Inventory (CSRI) at 3, 6 and 12 months post randomisation INCLUSION CRITERIA: Patients will be eligible for inclusion on the trial if on presentation they: 1. Are aged 1 year or over 2. Have been diagnosed with: 2.1. EITHER acute first onset transverse myelitis (The TM CONSORTIUM WORKING GROUP 2002 criteria for probable TM will be used. Hence, following clinical and radiological exclusion of a compressive myelopathy,

			patient will be diagnosed to have TM if they meet all the following criteria: 2.1.1. Sensory, motor, or autonomic dysfunction attributable to the spinal cord 2.1.2. Bilateral signs and/or symptoms (not necessarily symmetric) 2.1.3. Sensory level (except in young children <5 years where this is difficult to evaluate) 2.1.4. Lack of MRI brain criteria consistent with MS (McDonald 2010 space criteria) 2.1.5. Progression to nadir between 4 h and 21 days) 2.2. OR Have been diagnosed with first presentation of neuromyelitis optica. (Patients with definite modified NMO will meet the following criteria (W	
Multiple Sclerosis and Related Disorders. 74 (no pagination), 2023. Article Number: 104620. Date of Publication: June 2023.	Mou Z. Han L. Cai L. Luo W. Du Q. Zhang Y. Kong L. Lang Y. Lin X.	Investigation on marital status of patients with neuromyelitis optica spectrum disorders in China	Background: Neuromyelitis optica spectrum disorders (NMOSD) may have a great impact on patients' marriage, and marital status may also affect patients' compliance and prognosis. We investigated the marital status of 494 NMOSD patients in China to explore the mutual influence between them. Method(s): A cross-sectional survey was conducted by the online questionnaires or telephone follow-up. Basic information of all respondents was analyzed from NMOSD-database of West China hospital. All 444 married respondents finished self-assessment of NMOSD's effect on marriage and over 80% of them	Outcomes

Wang X.

Shi Z.

Chen H.

Zhou H.

accepted Marital Cumulative Damage Score (MCDS). Result(s): The proportion of unmarried male patients is higher than female (23.1% vs. 9.0%), especially in youth stage (44.0% vs. 20.2%). However, the females reported bigger impacts on their marriage among married NMOSD patients (97.5% vs. 70.7%). Compared to married patients, divorced patients costed more in hospital every time (29,857.1 CNY vs. 15,577.2 CNY), received longer education (12.75 years vs. 9.36 years), had longer duration of disease (117.16 vs. 93.62 months), more relapses (5.50 vs. 3.73) and higher EDSS score (3.58 vs. 2.59). EDSS scores are associated with MCDS (R2=0.267, P<0.0001), and divorced patients have higher MCDS (P<0.01). Decreased group activities (84.1%), declined working ability (73.7%) and alienation from friends (72.54%) are the first three factors in MCDS. Conclusion(s): NMOSD exerts cumulative damage for patients' marriage, and the progression of NMOSD is more likely to lead to marital breakdown. Healthy marriage may improve the prognosis of patients by providing the psychological support and improving treatment compliance.

Multiple Sclerosis. Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. London United Kingdom. 22(Supplement 3) (pp 96), 2016. Date of Publication: September 2016.	Orviz Garcia A. Valles Salgado M. Matias-Guiu Antem J. Gonzalez-Suarez I. Oreja-Guevara C.	Is cognitive impairment common in neuromyelitis optica spectrum disorders (NMOSD)?	Introduction and background: NMOSD and multiple sclerosis (MS) are both relapsing central nervous system (CNS) inflamatory disease with similar clinical features at the beggining. Cognitive decline is often present in MS, even since early stages, and seems to correlate with brain atrophy, therefore with a neurodegenerative process independent on number of relapses. Until now, there are very few and controversy evidences of cognitive impairmenti n NMOSD and not evidence of global axonal degeneration out of relapses. Method(s): NMOSD patients were recruited from a reference Multiple Sclerosis Center. Cross-sectional study was carried out. A wide batery of specific neuropsychological tests was used to evaluate every cognitive domain: concentration/attention (Verbal Span, PASAT), language (ACE-III subtest), basic and complex executive function (SDMT, A and B form of TMT, categorial and formal recall), memory (FCSR, FCRO), visuospatial and visuoperceptive function (VOSP, Benton JLO) and also depression and fatigue scales. Cognitive impairment was diagnosed when low scores were yielded in two tests for an specific domain (adjusted by level of	Outcomes

			education and age), at least in two different domains. Result(s): Ten patients were examined, with a median age of 40 years old (rank 21-69) and a disease duration of 4.42 years (rank 1.75-10.75). The mean EDSS was 3.0 (rank 1.0-6.0). Only one patient (female and 42 years old) meet criteria of cognitive impairment, showing deficiency in executive and visuoperceptive function. Two patients presented decline in frontal execution but no other domain, both associated with mild and moderate deppresion in Beck Inventary Scale (BIS). More than 50% patients showed high levels of fatigue. Conclusion(s): Despite long median disease duration of our patients, cognitive impairment was very rare. Mainly affected domains were frontal execution and visuoperceptive function. This results could reflect the absence or low degree of global progressive degeneration in NMOSD patients and could help us to distinguish from MS.	
Multiple Sclerosis. Conference: 8th Congress of the Pan Asian Committee for Treatment and Research in Multiple Sclerosis, PACTRIMS	Nakashima I. Harada N. Nakaya F.	Large-scale epidemiological survey of disability progression in japanese patients with multiple sclerosis and neuromyelitis optica	Background: Epidemiological data on disability and progression in Japanese patients with multiple sclerosis (MS) and neuromyelitis optica (NMO) is not well established. Objective(s): To evaluate disability, progression, and degree of severity based on the Patient Determined	Population

2015. Seoul South Korea. 21(6) (pp 824), 2015. Date of Publication: May 2015.	Disease Steps (PDDS) scale. Method(s): This survey used questionnaires mailed to patients through 3 Japanese MS patient associations. Patients were asked to provide demographic/clinical information and evaluate their own disability using the PDDS and 8-item Short-Form Health Survey (SF-8) quality of life scales. Result(s): Of 2823 patients with MS/NMO who received questionnaires, 1089 (38.6%) responded (74%, MS; 24%, NMO). Disability at or above gait disturbance (PDDS >=3) was reported by 45% and 58% of MS and NMO patients, respectively. Patients with NMO were older at onset, had greater disability, and were more often female than MS patients. In MS patients, the mean time from first symptoms to treatment initiation was 4.5 years and was longer for younger onset (<=29 years) than for older onset (>=40 years) patients (6.2 vs 2.2 years). MS patients whose current disabilities were reported as "early or late cane/bilateral support/ wheelchair/bedridden" often started treatment after gait disturbance. PDDS scores in MS patients correlated with SF-8 physical component scores, but not mental component scores; all SF-8 scores were lower than in the healthy

			Japanese population. Conclusion(s): The prevalence of disability among Japanese patients with MS/NMO is higher than previously thought. Treatment is often delayed, particularly among younger onset patients. Patients with severe disability often did not start treatment until after gait disturbance.	
Journal of the Neurological Sciences. Conference: World Congress of Neurology (WCN 2019). Dubai United Arab Emirates. 405(Supplement) (pp 286), 2019. Date of Publication: 15 October 2019.	Alvarenga R. Neri V.C. Catharino A.M.D.S. Airao A.R. Filho H.A. Siqueira H.H. Pereira A.B.C.D.G. Lucidi A.R. Alvarenga M.P. Bento C. Vasconcelos C.	Morbi mortality in Brazilian patients with recurrent neuromyelitis optica	Objective: The chronic form of Devic's disease with relapsing remitting course was only recognized in the 90's. Neuromyelitis optica (NMO) affect mainly Asian and African women. The aim of this study was to evaluate the long term prognosis and quality of life in NMO patients from Rio de Janeiro, where the majority of the population is Afro descendent. Method(s): In a cohort of 1444 patients followed in Hospital da Lagoa since 1990 (Figure 1) we selected NMO by 2006 criteria and analyzed long term disability, health quality of life by SF-36 and mortality. The classification of the NMOSD syndromes (2015) were applied. Result(s): 122 Recurrent NMO patients, 89.3% women, 70.55 % black, mean disease onset of 31.30 years (3 - 70 years), 18.9% pediatric forms (<18 years) were analyzed. 827 acute events were registered [TM (53%), ON (31%), [ON+TM] (9%), brainstem syndrome	Outcomes

			(4%), encephalopathy (3%), diencephalic syndrome (0.81%)]. Prevention treatment included azatioprin, micophenolato and rituximabe. At last assessment after the average of 12.7 years +/- 8.98 (1-40), 39 % of the patients had paraplegia and bilateral amaurosis (Devic like-syndrome), 83.6% severe bilateral dysfunction and 59.8% severe motor dysfunction. The SF-36 scores were under 50 in all domains. 46 patients died (38%) died, 9 unknown data. They were classified as SDNMO (2015) AQP4-Ab positive (40,2%), negative (23,8%) or unknown (36,1%). Conclusion(s): NMO represented 11% of all IIDD patients. Recurrent NMO patients developed severe disability, had a high reduction in quality of life and and high mortalily.Copyright © 2019	
Journal of Neuro-Ophthalmology. 36(4):356-362, 2016 12.	Brody J Hellmann MA Marignier R Lotan I Stiebel-Kalish H	Neuromyelitis Optica Spectrum Disorder: Disease Course and Long-Term Visual Outcome	BACKGROUND: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease that classically manifests as attacks of optic neuritis (ON) and transverse myelitis (TM). The prevalence, course, and severity of NMOSD vary considerably. Few studies report the neuro-ophthalmologic disease course and visual outcome. OBJECTIVE: We sought to describe the course and long-term visual outcome in a	Outcomes

cohort of NMOSD patients treated in a single tertiary referral center.

METHODS: The database was searched for all patients with NMOSD who were treated in our center from 2005 to 2014. Data collected included detailed visual outcome, grade of final visual disability, neuroimaging, and results of optical coherence tomography. Details on relapses, acute episodes, and maintenance therapies were recorded.

RESULTS: Of the 12 patients with NMOSD who were followed for a mean duration of 9.06 years, 10 (83%) were women. Mean age at presentation was 33.90 +/- 16.94 years. Patients with acute attacks were treated with high-dose intravenous methylprednisolone and offered immunosuppressive maintenance. ON occurred in 18 eyes of 12 patients, with a cumulative total of 37 ON episodes. At the end of the follow-up period, no patient had become legally blind and only 1 patient had lost her driver's license. Pain associated with acute ON was common (83%), whereas optic disc edema was a rare finding in our patient cohort (6%).

			CONCLUSIONS: In this retrospective series of 12 patients with NMOSD, followed for a mean of 9.06 years, acute-phase treatment was given within 8 days of relapse, followed by maintenance therapy. Functional visual outcome, as measured by the World Health Organization/International Classification of Diseases, Tenth Revision visual disability scale was better than reported in previous studies and driver's license was preserved in 11 of 12 patients. Pain accompanied 83% of ON attacks and may not aid differentiating multiple sclerosis from NMOSD-related ON.	
Multiple Sclerosis. Conference: 7th Congress of LACTRIMS. Rio de Janeiro Brazil. Conference Publication: (var.pagings). 18(12) (pp 1854), 2012. Date of Publication: December 2012.	Vanotti S. Eizaguirre B. Cores E.V. Melamud L. Villa A.	Neuromyelitis optica: Searching for a cognitive pattern	Objective: 1) To determine the pattern of Cognitive disorders in NMO patients 2) To analyze the visual imagery ability. Background(s): As NMO is a relatively new disease, little is known about its cognitive impairment pattern, frequency and its relationship with clinical variables. Considering patients' complaints, the search for a cognitive pattern is necessary. Design/Methods: Eighteen NMO patients were compared to 18 healthy controls. Mean age 36.39 (12.35); Female: 15; education 11.44 (2.95); EDSS: 4.31(2.59); disease evolution 7.87(4.50) years. Controls: age 36.56 (12.39), education 12.00 (3.62).	Outcomes

			Outcomes measures: 1) Brief Repeatable Neuropsychological Battery, including: Long Term Storage (LTS), Long Term Retrieval (LTR) and Consistent Long Term (CLT) and Delay Recall (DR SRT) of the Selective Reminding Test (SRT), Correct Response (CR) and Delay Recall (DR) of the 7/24 Visuospatial Test, PASAT and Verbal Fluency (VF); 2) Beck Depression Inventory II (BDI II); 3) Vividness of Visual Imagery Questionnaire (VVIQRV). Result(s): 44,4 (%) NMO patients had abnormal performance in two or more cognitive tests. Compared to controls was found significant impairment on VF (NMO: 21.36 SD15.12; Controls: 37.82 SD11.52; CLT (NMO: 29.6116.14; Controls: 41.00 SD15.02); DRSRT (NMO: 7.61 SD3.12; Controls: 9.72 SD2.02); DR7/24 (NMO: 28.07 SD4.43; Controls: 29.76 SD6.28); Evidence for the presence of depression: 13,9% mild, 5,6% moderate; 11,1% severe. No differences were found on VVIQRV between groups. Conclusion(s): Cognitive and neuropsychiatric domains decline in NMO patients.	
Multiple Sclerosis Journal. Conference: 37th Congress of the European Committee	Gholizadeh S. Exuzides A.	Novel assessment of disability vs cognition and pain in neuromyelitis optica spectrum	Introduction: Neuromyelitis optica spectrum disorders (NMOSD) comprise closely related autoimmune diseases of the central nervous system that may	Outcomes

for Treatment and Research in Multiple Sclerosis, ECTRIMS 2021. Virtual. 27(2 SUPPL) (pp 154), 2021. Date of Publication: October 2021.	Sinnott J. Palmer C. Waltz M. Rose J. Jolley A. Behne J. Behne M. Blaschke T. Smith T. Yeamen M. Lewis K. Cook L.	disorders: A CIRCLES cohort study	result in significant disability. Traditional disability assessments have focused on tangible, physical disability. However, less tangible cognitive or pain-mediated disabilities have received comparatively little attention regarding disease burden in NMOSD. Aim(s): To compare novel, distinct disability domains and a derived composite disability index with cognitive and pain measures in patients with NMOSD of the CIRCLES cohort in North America. Method(s): CIRCLES patients (N=198) were assessed for disability in mobility, vision or self-care domains, and a composite disability index integrating these domains. Statistical analyses tested for associations among disability, cognition (MoCA), pain (BPI severity or BPI interference) and demographic or clinical variables. Result(s): Disability, cognition and pain measures revealed significant correlates ($p<0.05$) among patient and disease variables. Worsened physical disability, cognition and pain correlated with race/ethnicity. Disease onset phenotype correlated with pain interference and approached significance relative to worsened selfcare, MoCA and pain severity. Domain analyses revealed that visual disability correlated with the broadest variables, including

	race/ethnicity, serostatus, time on study and seropositivity among patients >=18 years of age. Greater pain severity or interference uniquely correlated with female sex. Significant correlates were absent for mobility in this cohort. Conclusion(s): A novel assessment of distinct disability domains and their composite index compared physical disability with validated cognition and pain measures in NMOSD. Race/ethnicity appeared to be a unifying correlate of physical disability, worsened cognitive function and pain in NMOSD. Likewise, onset disease phenotype may have a greater impact on physical disability, cognition or pain than previously recognized. Further, domain-specific assessment may yield greater resolution of correlates than traditional disability indexes. Based on these initial data, the novel NMOSD disability assessment merits further investigation in the context of registries or clinical trials to assess sensitivity and specificity vs existing methods. Lastly, the results reinforce the need to better understand and address cognitive and pain issues as well as potential healthcare disparities in NMOSD.

Multiple Sclerosis Journal. Conference: 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2018. Berlin Germany. 24(2 Supplement) (pp 819-820), 2018. Date of Publication: October 2018.	Asseyer S. Schmidt F. Chien C. Scheel M. Ruprecht K. Bellmann-Strobl J. Brandt A.U. Paul F.	Pain in AQP4-ab-positive and MOG-ab-positive neuromyelitis optica spectrum disorders	Background: Pain is a frequent symptom in aquaporin-4-IgGpositive and antibody-negative neuromyelitis optica spectrum disorders (AQP4-NMOSD/ ABneg-NMOSD). Data on pain in MOG-IgG associated neuromyelitis optica spectrum disorders (MOG-NMOSD) are scarce. Objective(s): To investigate pain in MOG-NMOSD in comparison to AQP4- and ABnegNMOSD. Method(s): Forty-nine patients with MOG- (n=14), AQP4- (n=29), and ABneg- (n=6) NMOSD were included in this cross-sectional analysis from an ongoing observational study of patients with NMOSD and related disorders. We identified spinal cord lesions in MRI, assessed pain by PainDETECT and McGill Pain Questionnaire, quality of life by Short Form Health Survey, and depression by Beck's Depression Inventory. Result(s): Twelve MOG-NMOSD patients (86%), 24 AQP4- NMOSD patients (83%), and all ABneg-NMOSD patients (100%) suffered from pain. MOG-NMOSD patients had mostly neuropathic pain and headache; AQP4- and ABneg-NMOSD patients had mostly neuropathic pain. A history of myelitis was less frequent in MOG-NMOSD than in AQP4-NMOSD patients. Pain influenced quality of life in all	Outcomes

			patients. Thirty-six percent of patients with pain received pain medication; none of them were free of pain. Conclusion(s): Pain is a frequent symptom of patients with MOGNMOSD and as important as in AQP4- and ABneg-NMOSD. Despite its impact on quality-of-life, pain is insufficiently alleviated by medication.	
Frontiers in neurology [electronic resource].. 11:778, 2020.	Asseyer S Cooper G Paul F	Pain in NMOSD and MOGAD: A Systematic Literature Review of Pathophysiology, Symptoms, and Current Treatment Strategies [Review]	Neuromyelitis optica spectrum disorders (NMOSDs) and myelin oligodendrocyte glycoprotein-antibody-associated disease (MOGAD) are autoimmune inflammatory disorders of the central nervous system (CNS). Pain is highly prevalent and debilitating in NMOSD and MOGAD with a severe impact on quality of life, and there is a critical need for further studies to successfully treat and manage pain in these rare disorders. In NMOSD, pain has a prevalence of over 80%, and pain syndromes include neuropathic, nociceptive, and mixed pain, which can emerge in acute relapse or become chronic during the disease course. The impact of pain in MOGAD has only recently received increased attention, with an estimated prevalence of over 70%. These patients typically experience not only severe headache, retrobulbar pain, and/or pain on eye movement in optic neuritis but also neuropathic and	Study Design

			nociceptive pain. Given the high relevance of pain in MOGAD and NMOSD, this article provides a systematic review of the current literature pertaining to pain in both disorders, focusing on the etiology of their respective pain syndromes and their pathophysiological background. Acknowledging the challenge and complexity of diagnosing pain, we also provide a mechanism-based classification of NMOSD- and MOGAD-related pain syndromes and summarize current treatment strategies. Copyright © 2020 Asseyer, Cooper and Paul.	
Multiple Sclerosis Journal. Conference: 8th Joint ACTRIMS-ECTRIMS Meeting. Virtual. 26(3 SUPPL) (pp 472-473), 2020. Date of Publication: December 2020.	Ayzenberg I. Richter D. Henke E. Asseyer S. Paul F. Trebst C. Hummert M.W. Kumpfel T. Havla J.	Pain, depression and quality of life in nmosd: A crosssectional study of 166 aqp4-antibody seropositive patients in Europe	Background: Spinal pain, girdle-like dysesthesia, and painful spasms were noted already in earliest disease descriptions in the 18th century. Nowadays it has become clear that pain is a frequent and one of the most disabling symptoms in these patients. Due to the rarity of NMOSD most previous studies of pain and depression were relatively small or included a mixed population AQP4- IgG-seropositive and seronegative patients, while recent clinical trials clearly indicate that pathogenetic mechanisms are different in these forms. Objective(s): To evaluate prevalence, clinical characteristics and	Outcomes

Ringelstein M. Aktas O. Jarius S. Wildemann B. Hausler V. Stellmann J.-P. Senel M. Klotz L. Pellkoffer H. Weber M. Pawlitzki M. Rommer P. Berthele A. Hellwig K. Gold R. Kleiter I.	predictive factors of pain, depression and their impact on the quality of life (QoL) in a large European seropositive neuromyelitis optica spectrum disease (NMOSD) cohort. Method(s): We included 166 patients with aquaporin-4-seropositive NMOSD from 13 tertiary referral centers of Neuromyelitis Optica Study Group (NEMOS). Clinical data, including expanded disability status scale and localization of spinal lesions on MRI, were retrieved from the NEMOS database or local electronic patient records. Data on pain, depression and quality of life were captured by self-reporting questionnaires. Result(s): 125 (75.3%) patients suffered from chronic NMOSDassociated pain. Of these, 65.9% had neuropathic pain, 68.8% reported spasticity-associated pain and 26.4% painful tonic spasms. Number of previous myelitis attacks (OR 1.27, p=0.018) and involved upper thoracic segments (OR 1.31, p=0.018) were the only predictive factors for chronic pain. Interestingly, the latter was specifically associated with spasticity-associated (OR 1.36, p=0.002), but not with a neuropathic pain. 39.8% suffered from depression (moderate to severe in 51.5%). Pain severity (OR 1.81, p<0.001) and especially neuropathic

character (OR 3.44, P<0.001) were strongly associated with depression. 70.6% of patients with moderate or severe depression and 42.5% of those with neuropathic pain had no specific medications. 64.2% of those under symptomatic treatment still reported moderate to severe pain. Retrospectively, 39.5% of pain-sufferers reported improvement of pain after start of immunotherapy: 37.3% under rituximab, 40.0% under azathioprine, 33.3% under mycophenolate mofetil and 66.7% under tocilizumab. However, there was no difference in terms of pain prevalence or intensity in patients with different immunotherapies. Pain intensity, walking impairment and depression could explain 56% of the physical QoL variability, while depression was the only factor, explaining 46% of the mental QoL variability. Conclusion(s): Myelitis episodes involving upper thoracic segments are main drivers of pain in NMOSD. Although pain intensity was lower than in previous studies, pain and depression remain undertreated and strongly affect QoL. Interventional studies on targeted treatment strategies for pain are urgently needed in NMOSD.

Multiple Sclerosis and Related Disorders. 46:102578, 2020 Nov.	Lotan I Bacon T Kister I Levy M	Paroxysmal symptoms in neuromyelitis optica spectrum disorder: Results from an online patient survey	BACKGROUND: Paroxysmal symptoms (PS), defined as short-lasting, recurrent, and stereotyped neurological symptoms, are frequently reported by patients with Neuromyelitis Optica Spectrum Disorder (NMOSD). Their prevalence and spectrum of presentations in NMOSD have not been fully characterized. METHODS: Patients with NMOSD, who were members of a closed international Facebook Group, were recruited to complete an anonymous survey on REDCap. Participants were queried regarding demographic and NMOSD-related characteristics and PS history. RESULTS: The sample consisted of 219 responders with self-reported NMOSD, of whom 134 (63.8%) reported testing positive for AQP4 Antibody. 156 responders (71.9%) reported >=1 type of PS during the disease course. The most common PS were intermittent tingling/numbness sensation (N=106, 67.9%), followed by involuntary muscle contractions/abnormal posture (N=95, 60.9%), hot/cold/burning sensations (N=87, 55.8%), and shock-like sensations along the spine or limbs (N=77, 49.4%). 150 responders (96% of those with PS)	Outcomes

reported that PS were painful; in 82 responders (54.6%), the pain intensity reached >= 8/10 and in 40 responders (26.0%) - 10/10 level. PS were most commonly aggravated by fatigue (105 responders, 70.0%), physical activity (N=86, 57.3%), and neck flexion (N=39 responders, 26.0%). 82 patients (52.5% of those with PS) reported having been prescribed one or more medications for PS. Less than 50% reported them to be 'very helpful.'

CONCLUSIONS: This survey highlights that PS occurs commonly in NMOSD patients. The symptomatology of PS is diverse. PS are often painful and not adequately treated. Our study represents a novel method to learn more about a rare disease from the patient's perspective. Given the fact that the study was conducted using an anonymous questionnaire and the diagnosis of NMOSD was self-reported by the survey participants, its' results should be regarded as a first step towards the understanding of PS in NMOSD, which should be further validated in a larger, controlled study.

Journal of the Neurological Sciences. 428:117546, 2021 09 15.	Fujihara K Hattori S Kleiter I Levy M Matsuda Y Mitsutake A Haramura M Palace J Yamamura T	Patient-reported burden of symptoms in neuromyelitis optica: A secondary analysis on pain and quality of life	INTRODUCTION: Relapses of neuromyelitis optica spectrum disorder (NMOSD) result in cumulative neurologic disabilities, are unpredictable, and are interspersed with remissions. Pain in NMOSD is often severe and intractable, with a significant impact on patient quality of life (QoL). We performed a more detailed analysis of previously published survey data on the association of pain and QoL, comparing patients who were seropositive and seronegative for antibodies against aquaporin-4 (AQP4-IgG). METHODS: We conducted a secondary analysis of questionnaire data from 193 NMOSD patients across North America. The study population was predominantly female (88.6%) and aged 19-76 years. Results were reported for three groups: AQP4-IgG-seropositive (61.1%), AQP4-IgG-seronegative and the total cohort including patients with unknown serostatus. We measured the strength of associations and interactions between pain and variables including QoL, patient satisfaction, frequency of hospital visits, and number of relapses versus other symptoms.	Outcomes

			RESULTS: Pain severity was the strongest negative predictor of QoL. In the total and AQP4-IgG-seropositive groups, pain was the most common symptom that patients wanted their physician to be concerned about; in the AQP4-IgG-seronegative group, this was fatigue. For all patients, frequent hospital visits and relapses were associated with more severe pain, but not frequency of NMOSD specialist visits. Patients without recent relapse still commonly reported moderate or severe pain (>25%). CONCLUSION: This study confirms the heavy burden of pain on NMOSD patients and its effect on QoL and healthcare utilization. Prevention or early treatment of relapses and more effective pain management may reduce this burden.	
Canadian Journal of Neurological Sciences. Conference: 46th Annual Congress of the Canadian Neurological Sciences Federation. Vancouver, BC Canada. Conference Publication:	Traboulsee A. Sadjadi R. Al-Thubaiti I. Kwon O. Kuan A.J.	Patient-reported outcome measures in neuromyelitis optica: UBC experience	Background: Neuromyelitis optica (NMO) is an uncommon, severe demyelinating central nervous system disease affecting the optic nerve and spinal cord. Unique clinical course and recent identification of a specific antibody biomarker differentiates NMO from other similar demyelinating diseases such as multiple sclerosis (MS). Limited population studies	Outcomes

(var.pagings). 38(3 SUPPL. 1) (pp S60), 2011. Date of Publication: May 2011.

describing clinical presentation and epidemiology of NMO have shown increased prevalence in non- Caucasian groups, particularly in Asian populations. An NMO clinic and research centre has been established at the University of British Columbia (UBC) to develop a patient registry, to provide patient support, and to investigate the emerging cases of NMO, which may be a reflection of the changing ethnic profile of the province. In this ongoing descriptive study, NMO patients self-characterize their illness perception, associations, and impact on well-being. Method(s): All new consecutive consenting NMO referrals aged 19 years or older prospectively assessed their symptom presentation and level of impairment via self-rated questionnaires, adapted from those used for MS. Psychometric properties of the questionnaires were described in NMO patients. Result(s): Level of impairment, quality of life, and mental well-being in those affected by NMO can be measured systematically by adapted self-rated questionnaires. Conclusion(s): Subjective assessments may help to confirm clinical severity of NMO and may assist in treatment management, but rating scales specific to NMO need to be developed in

			order to accurately track disease course and guide particular recommendations.	
Neurology. Conference: 73rd Annual Meeting of the American Academy of Neurology, AAN 2021. Virtual. 96(15 SUPPL 1) (no pagination), 2021. Date of Publication: May 2021.	Lallana J.M. Prefasi D. Casanova B. Diaz L.F. Saiz A. Calles C. Martinez-Gines M.L. Gonzalez-Suarez I. Boyero S. Pinel L.R. Sempere A.P. Lallana V.M. Querol L. Costa-Frossard L.	Perception ofstigma in people with neuromyelitis optica spectrum disorders (PERSPECTIVESNMO Study)	Objective: To assess the perception of stigma and its impact in neuromyelitis optica spectrum disorders (NMOSD). Background(s): The stigma associated with neurological disorders contributes to poor healthrelated quality of life outcomes. However, limited information is available in people with NMOSD. Design/Methods: A non-interventional, cross-sectional study was conducted in 13 neuroimmunology clinics in Spain. Patients with a diagnosis of NMOSD (2015 Wingerchuk criteria) were included. The 8-item Stigma Scale for Chronic Illness (SSCI-8), the Expanded Disability Status Scale (EDSS), the 29-item Multiple Sclerosis Impact Scale (MSIS-29), the Beck Depression Inventory-Fast Screen (BDI-FS), the Pain Effects Scale (MOS PES) and the Fatigue Impact Scale for Daily Use (D-FIS) were used to assess the perception of stigma, disability, health-related quality of life, mood, presence and impact of pain and fatigue, respectively. Associations between outcomes measures were analysed using Spearman's rank correlation and logistic	Outcomes

	De Castro-Trapiello H. Canal N. Maurino J.		regression (assessing the contribution of stigma to symptoms of depression [depressed, not depressed]). Result(s): Seventy-one subjects were studied (mean age= 47.4 years +/- 14.9, 81.7% female, mean time since diagnosis: 6.1 years +/- 3.9). The median EDSS score was 3.0 (interquartile range 1.5, 4.5). Stigma prevalence was 61.4% (n=43); mean SSCI-8 score=11.9 +/- 5.1. Thirty-one patients (44.3%) were classified as depressed. The SSCI-8 score showed a significant correlation with both physical (rho=0.576, p<0.0001) and psychological (rho=0.608, p<0.0001) MSIS-29 scales scores, EDSS score (rho=0.349, p=0.0033), MOS PES score (rho= 0.457, p<0.0001) , and D-FIS score (rho=0.556, p<0.0001). Stigma was found to positively predict concurrent depression (OR=1.32; 95% CI: 1.13-1.55, p=0.0004). Conclusion(s): Stigma is a common phenomenon in people with NMOSD. Identifying stigma may be crucial to implement specific educational intervention strategies.	
Value in Health. Conference: ISPOR Europe 2021. Virtual, Online. 25(1 Supplement) (pp S71),	Vicente C. Diles D. Di Maio D.	POSB56 Cost-Effectiveness of Satralizumab Compared to Eculizumab for the Treatment Neuromyelitis	Objectives: Until recently, the approach to preventing NMOSD relapses has been with unapproved, off-label immunosuppressant therapies (ISTs) potentially leaving patients at risk of	Outcomes

2022. Date of Publication: January 2022.	Damonte E. Wu J. Traboulsee A.	Optica Spectrum Disorders (NMOSD) in Adult and Adolescent Patients Who Are Anti-Aquaporin 4 (AQP4) Seropositive in Canada	experiencing poor outcomes. Satralizumab was recently approved in Canada based on a statistically and clinically meaningful reduction in the risk of relapse shown in the SAkuraSky and SAkuraStar (SAkura) trials. Eculizumab also demonstrated positive results; however, the high cost of therapy and requirement for access to an infusion center may limit its viability. Method(s): To understand the economic implications of the approved therapies from the societal perspective, a de novo, Markov model was developed to estimate the cost-effectiveness of satralizumab versus eculizumab. Health states were defined based on the Expanded Disability Status Scale (EDSS); transition probabilities were based on natural history of NMOSD (preventing patients from improving their EDSS) which is in line with Canadian payers preferred assumption on the NMOSD disease course. A Network Meta-Analysis (NMA) was performed to inform comparative treatment effects. Utilities were calculated from EQ-5D values collected during the SAkura trials. Life years, quality-adjusted life years (QALYs) and costs (reported as 2021 Canadian dollars) were discounted at an annual rate of 1.5%, over a life-time

			horizon. Result(s): Deterministic results demonstrated that satralizumab was the most cost-efficient treatment strategy. Over a life-time horizon, use of satralizumab results in substantially lower costs and slightly lower, but comparable, clinical outcomes relative to eculizumab. The base case ICER is $3.65M per QALY (the south-west quadrant with both negative costs and outcomes). Results were similar probabilistically, nearly all iterations showing satralizumab would be the cost-efficient therapy. Use of satralizumab would result in life-time, discounted savings of over $9.5M per patient. Conclusion(s): Satralizumab may be considered a cost-effective therapy in the treatment of NMOSD in adult and adolescent patients who are AQP4 seropositive.Copyright © 2021	
Neurology. Conference: 67th American Academy of Neurology Annual Meeting, AAN 2015. Washington, DC United States. Conference Publication: (var.pagings). 84(SUPPL. 14) (no pagination), 2015. Date	Ana A. Mealy M. Kaplin A. Levy M.	Processing speed and informant reports of executive functioning in neuromyelitis optica	Objective: This study sought to characterize cognitive functions among patients with neuromyelitis optica (NMO) through performance-based neuropsychological assessment and informant-reports of executive functions (EF), which have not been concurrently reported. Background(s): Limited research suggests that approximately half of patients with NMO demonstrate cognitive weaknesses in attention, verbal	Outcomes

of Publication: 06 Apr 2015.	fluency, memory, and processing speed that are exacerbated in the presence of depressive symptoms. Less is known about EF skills in everyday life of patients with NMO. Design/Methods: After consent, 31 patients (ages 15-69) with NMO/NMO spectrum disorder who attended an NMO informational meeting underwent assessment including 1) a task of nonmotor processing speed [Symbol Digit Modalities Test (SDMT-oral version)], and 2) informant-ratings of EF (Behavior Rating Inventory of Executive Function-BRIEF). They also completed a history questionnaire and questionnaires about life goals/quality. Patients were predominantly female (n=28) and Caucasian (n= 25). Result(s): For most, performance on the SDMT and BRIEF informant-ratings were average. Twenty-four percent of participants who completed the SDMT (n=29) performed below age-expectation (greater than one standard-deviation below the mean). Thirty-nine percent of patients with BRIEF informant-ratings (n=23) had at least one clinically-significant rating of EF difficulties. The most common clinically-significant ratings included emotional control (i.e., influence of EF on expression/regulation of emotions), and

			initiation (i.e., independently generating ideas/responses/problemsolving strategies). The influence of clinical variables such as disease duration, number of relapses, medication history, vision-status, and mood will be reported to better characterize these subsamples. Conclusion(s): Findings highlight the importance of monitoring of cognition, including processing speed and EF, in NMO. This study is the first to document cognitive concerns as rated by informants of daily behaviors in NMO and highlights questions surrounding central nervous system injury associated with cognition in NMO that may not be apparent on performance. Findings warrant further exploration of neuropsychological outcomes in NMO to inform intervention.	
Multiple Sclerosis Journal. Conference: 8th Joint ACTRIMS-ECTRIMS Meeting. Virtual. 26(3 SUPPL) (pp 613-614), 2020. Date of Publication: December 2020.	Wallenstein G. Costantino C. Kuenzel T. Stokmaier D. Damonte E. Klingelschmitt G. Von Budingen H.C.	Psychometric validation of the expanded disability status scale in neuromyelitis optica spectrum disorder	Background: The Expanded Disability Status Scale (EDSS) is an established measure of disability in multiple sclerosis (MS). Due to similarities in the clinical presentations of MS and neuromyelitis optica spectrum disorder (NMOSD), the EDSS is also widely used to assess disability in NMOSD but has yet to be validated for this purpose. Objective(s): To establish the psychometric reliability, validity, and responsiveness of the EDSS in NMOSD patients. Method(s): Analyses	Outcomes

were conducted in a pooled population of NMOSD patients (N=178) from the phase 3 SAkuraSky (NCT02028884) and SAkuraStar (NCT02073279) studies. EDSS was assessed at regular intervals. Reliability was evaluated using standardized Cronbach's alpha and test/re-test reliability. Convergent validity was assessed by comparison with the EuroQol Visual Analog Scale (EQ-VAS) and relevant outputs from the Short Form-36 (SF-36) health survey (Physical Functioning [PF], Rolefunctioning Physical [RP], and Physical Component Summary [PCS] domain scores). Discriminant validity was assessed against the Visual Analogue Scale for Pain (VAS-pain), and non-physical domains of the SF-36 (Vitality [VT], Mental Health [MH], Role-Emotional [RE], and Mental Component Score [MCS]). Criterion validity was assessed by comparison with the modified Rankin Scale (mRS). Responsiveness of the EDSS to changes in health status was assessed through a relative validity (RV) comparison of EDSS scores in patients who experienced an investigator-reported clinical relapse vs those without. Result(s): Cronbach's alpha coefficient was >0.6, suggesting reasonable internal

			consistency (alpha=0.67). The test/retest reliability coefficient was alpha=0.91, with scores >0.70 representing reasonable reliability. Assessment of convergent validity revealed moderateto- strong correlations between EDSS and other measures of physical functioning (EQ-VAS, rs -0.53; SF-36 PF, rs -0.61; SF-36 RP, rs -0.58; SF-36 PCS, rs -0.60). The EDSS showed strong discriminant validity against VAS-pain and non-physical SF-36 domains (VAS-pain, rs 0.31; SF-36 VT, rs -0.35; SF-36 MH, rs -0.27; SF-36 RE, rs -0.37; SF-36 MCS, rs -0.25). Strong criterion validity was observed in relation to the mRS (rs 0.68). The EDSS was found to be responsive to investigator-reported relapses (F-statistic=36.64, p<0.0001; RV=1.0). Conclusion(s): The EDSS demonstrated reliability, validity, and responsiveness as a measure of disability in patients with NMOSD. Further studies to corroborate these findings are warranted.	
Value in Health. Conference: ISPOR 20th Annual International Meeting Research. Philadelphia, PA United States. Conference Publication:	Likhar N. Dang A.	Quality of life in neuromyelitis optica: A systematic review	OBJECTIVES: Neuromyelitis optica (NMO) is an inflammatory CNS disease, that presents with severe optic neuritis and transverse myelitis. It is often accompanied by severe motor and sensory disability. In the past few years, NMO has gained lot of interest and	Study Design

(var.pagings). 18(3) (pp A287-A288), 2015.
Date of Publication: May 2015.

shares a controversial relationship with multiple sclerosis (MS). It is not yet known whether NMO differs in its effect on quality of life (QoL) when compared with MS. We aimed to evaluate the QoL in patients with NMO by conducting a systematic review of published peer-reviewed studies. METHOD(S): A literature search was performed in "MEDLINE" and "EMBASE" using search terms "quality of life", "neuromyelitis optica", and "Devic's". The search was limited to English language. All studies that got published before November 2014 were retrieved. Studies that included patients with NMO and reported use of validated QoL instrument were considered eligible for qualitative analysis. Two independent researchers were involved in study selection and data extraction. RESULT(S): A total of seven studies met the inclusion criteria. All the studies were conducted in different countries: The United states of America, United Kingdom, France, Japan, and Argentina. The number of patients included in the studies ranged from 18-50. The common QoL instruments used included: Short form-36 and different pain severity scores. Three studies used MS patients as the comparator while two

			compared the data with normal subjects. Most studies reported that QoL is lower in NMO patients as compared to the ones suffering from MS and is much worse than normal subjects. The lower QoL score corresponded with higher pain scores in NMO patients as compred to MS patients. CONCLUSION(S): Our review showed that NMO patients are associated with higher levels of pain and lower QoL scores than MS patients. However, available evidence seems to be insufficient and more research is warrented in this context.	
Journal of Neurology, Neurosurgery & Psychiatry. 80(10):1162-4, 2009 Oct.	Cabre P Gonzalez-Quevedo A Bonnan M Saiz A Olindo S Graus F Smadja D Merle H Thomas L	Relapsing neuromyelitis optica: long term history and clinical predictors of death	BACKGROUND: Relapsing neuromyelitis optica (RNMO) is an uncommon but devastating inflammatory disorder of the central nervous system. Long term history in a wide series of RNMO is required for better knowledge of the course of the disease and identification of patients at high risk of death. METHODS: Clinical features of patients with RNMO (88 women/eight men) obtained from the geographic Caribbean database (Cuba and French West Indies) were used to determine the progression of disability and to identify clinical predictors of death.	Outcomes

Cabrera-Gomez JA	RESULTS: Median age at onset of RNMO was 29.5 years (range 11-74). Median duration of disease was 9.5 years (1-40). Median relapse rate was 0.7 attack/patient/year (0.1-3). 66 patients experienced severe visual loss in at least one eye and 46 in both eyes. Median time from onset to unilateral and bilateral severe visual loss was 3 and 15 years, respectively. Median times to reach Kurtzke Disability Status Scale 3, 6 and 8 from onset of RNMO were 1, 8 and 22 years. There were 24 deaths (25%); within 5 years in 63% of cases. A higher attack frequency during the first year of disease ($p = 0.009$), blindness ($p = 0.04$) and sphincter signs at onset ($p = 0.02$) and lack of recovery of first attack ($p = 0.003$) were independently associated with a shorter time to death. CONCLUSION: RNMO is a very rapidly disabling disease affecting primarily young women. This study has identified clinical features that predict a poor outcome. These findings suggest that early and aggressive immunotherapy might be warranted in RNMO.

Multiple Sclerosis Journal. Conference: 3rd Annual Americas Committee for Treatment and Research in Multiple Sclerosis Forum, ACTRIMS 2018. San Diego, CA United States. 24(1 Supplement 1) (pp 77-78), 2018. Date of Publication: February 2018.	Stephens S. O'Driscoll V. Grover S. Berenbaum T. Finlayson M. Motl R.W. Yeh A.	Relationship between physical activity level, fatigue and depression in paediatric neuomyelitis optica spectrum dis-order and recurrent optic neuritis	Background: Moderate-to-vigorous physical activity (MVPA) has been associated with better psychosocial outcomes in pediat-ric multiple sclerosis, but has not been evaluated in youth with other recurrent demyelinating diseases such as neuromyelitis optica spectrum disorder (NMOSD) and recurrent optic neuritis (RON). Objective(s): To describe MVPA as it relates to fatigue and depression in children with NMOSD/RON as compared with healthy controls. We hypothesized that youth with NMOSD/RON would report higher depression and fatigue and lower MVPA levels compared to sex and age matched healthy controls. Method(s): This cross-sectional study included consecutive youth (<=18 yrs.) with NMOSD or RON who completed the Pediatric Quality of Life Multidimensional Fatigue scale, Center for Epidemiological Studies Depression Scale, the Godin Leisure Time Exercise Questionnaire at a Neuroinflammatory Clinic (Hospital for Sick Children, Toronto, ON). Previously collected healthy control data were used for comparison. NMOSD/RON outcomes were examined by antibody profile. Result(s): The sample included 30 NMOSD/RON patients (77% female,	Outcomes

		mean age 13.0 years, 24 NMOSD/6 RON, avg. EDSS=1.0) and 30 healthy controls (77% female, mean age 13.6 years.). MVPA in the NMOSD/RON group was similar to healthy controls (49.3 and 53.6 METs/week, respectively). Total fatigue (mean=69.6 and 70.6, respectively) and depression (mean=12.7 and 12.0, respectively) were similar between groups. Higher MVPA was associated with less total fatigue (r=0.420, p=0.026) in the NMOSD/RON group. AQP-4-ab positive youth (n=6) reported lower MVPA levels (mean=29.0 METs/week) and higher fatigue levels (mean=59.3) than MOG-ab positive (n=16, 56.8 METs/week, 72.7) or ab negative (n=8, 51.5 METs/week, 71.1) youth (NS p=0.129, p=0.338). Conclusion(s): Youth with NMOSD/RON report similar fatigue, depression and MVPA compared with healthy controls. AQP-4-ab positivity may confer increased risk for low MVPA, but larger studies are needed to confirm this finding. MVPA and total fatigue correlated moderately in youth with disease, suggesting MVPA may contribute to reduced fatigue in this group.

Quality of Life Research. Conference: 27th Annual Conference of the International Society for Quality of Life Research. Virtual. 29(SUPPL 1) (pp S55-S56), 2020. Date of Publication: October 2020.	Schwartz C. Stark R. Stucky B. Li Y. Rapkin B.	Response Shift , Response-shift effects in a Neuromyelitis Optica Spectrum Disorder clinical trial: A novel application of random-effects modeling and equating for small samples	Aims: Researchers have long posited that response-shift effects may obfuscate treatment effects but, to our knowledge, no one has yet empirically tested this hypothesis in clinical-trial data using multivariate statistical methods. The present work investigated possible response-shift effects in a recent clinical trial testing a new treatment for Neuromyelitis Optica Spectrum Disorder (NMOSD). This pivotal trial provided impressive support for the drug Eculizumab in preventing relapse (primary outcome) and for the more objective evaluative outcomes, but less strong or null results as the indicators became more subjective. This pattern of results suggests that response-shift effects are present. Method(s): This secondary analysis utilized data from a randomized, double-blind trial evaluating the impact of Eculizumab in preventing relapses in 143 people with NMOSD. Treatment arm and then relapse status were hypothesized 'catalysts' of response shift in two series of analyses. Because the study sample was too small for Oort structural-equation modeling, we devised a "de-constructed" version using random-effects models (REMs). Beginning by testing an omnibus response-shift	Outcomes

hypothesis, REMs then elucidate specific response-shift types by focusing on a global outcome (EQ-5D Visual Analogue Scale (VAS)) that is likely subject to response-shift effects. The predictors (SF36TMv2 mental and physical component scores (MCS and PCS)) helped us to detect response-shift effects in VAS. We then "back-translated" the VAS into the MCS and PCS scores that would have been observed if response shift had not been present. Result(s): The omnibus test revealed treatment- A nd relapse-related response shifts. REMs revealed recalibration and reconceptualization response-shift effects for treatment, and recalibration, reprioritization, and reconceptualization response-shift effects for relapse. Equating was done using raw scores from the VAS, MCS, and PCS, and for computing scores that removed response-shift effects. Correlation analysis and descriptive displays provided a more comprehensive examination of response-shift effects. Conclusion(s): This secondary analysis of clinical-trial data revealed that not receiving Eculizumab and, more specifically, the experience of relapse made people change their thinking about QOL. Thus, the QOL

			impacts of placebo/relapse on mental health in particular were under-estimated by the usual analyses. This novel application of REM and equating provides a smallsample method for better estimating treatment effects in clinical trials.	
Quality of Life Research. 30(5):1283-1292, 2021 May.	Schwartz CE Stark RB Stucky BD Li Y Rapkin BD	Response-shift effects in neuromyelitis optica spectrum disorder: estimating response-shift-adjusted scores using equating	BACKGROUND: In our companion paper, random intercept models (RIMs) investigated response-shift effects in a clinical trial comparing Eculizumab to Placebo for people with neuromyelitis optica spectrum disorder (NMOSD). RIMs predicted Global Health using the EQ-5D Visual Analogue Scale item (VAS) to encompass broad criteria that people might consider. The SF36 TMv2 mental and physical component scores (MCS and PCS) helped us detect response shift in VAS. Here, we sought to "back-translate" the VAS into the MCS/PCS scores that would have been observed if response shift had not been present. METHODS: This secondary analysis utilized NMOSD clinical trial data evaluating the impact of Eculizumab in preventing relapses (n = 143). Analyses began by equating raw scores from the VAS, MCS, and PCS, and computing scores that removed response-shift	Outcomes

effects. Correlation analysis and descriptive displays provided a more comprehensive examination of response-shift effects.

RESULTS: MCS and PCS crosswalks with VAS equated the scores that include and exclude response-shift effects. These two sets of scores had low shared variance for MCS for both groups, suggesting that corresponding mental health constructs were substantially different. The shared variance contrast for physical health was distinct only for the Placebo group. The larger MCS response-shift effects were found at end of study for Placebo only and were more prominent at extremes of the MCS score distribution.

CONCLUSIONS: Our results reveal notable treatment group differences in MCS but not PCS response shifts, which can explain null results detected in previous work. The method introduced herein provides a way to provide further information about response-shift effects in clinical trial data.

Annals of Indian Academy of Neurology. Conference: 27th Annual Conference of Indian Academy of Neurology, IANCON 2019. Hyderabad India. 22(SUPPL 1) (pp S132), 2019. Date of Publication: September 2019.	Nagpal T.	Restless leg syndrome in neuromyelitis optica	We studied 30 patients of Neuromyelitis optica (serpositive for aquaporin 4) and 30 age matched controls for symptoms of restless leg syndrome. We administered questionnaire for RLS consensus criteria, RLS severity score and Epworth Sleepiness Scale. The frequency of RLS, it's severity and impact on sleep health was found to be significantly higher in NMO patients than age matched controls who suffered from RLS.	Outcomes
Chinese Medical Sciences Journal. 36(4):316-322, 2021 Dec 31.	Zhang X Xu Y Pei LJ	Review of Neuromyelitis Optica Spectrum Disorder with Pain-Depression Comorbidity [Review]	Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disorder of the central nervous system predominantly targeting optic nerves and the spinal cord. The prevalence of the disease is much higher in Asia than in other parts of the world. Pain can be detected in more than 80% of NMOSD patients, with evoked pain mostly being caused by painful tonic muscle spasms and neuropathic pain as the most characteristic types. Depression is often comorbid with pain, and their comorbidity can severely influence quality of life. In recent years, studies have found considerable overlaps between the mechanisms of pain and depression; however, their association remains unclear. This article reviews the epidemiology, mechanism, evaluation and	Study Design

			treatment of pain-depression comorbidity in NMOSD patients.	
Pain Management Nursing. 20(6):580-591, 2019 12.	Mealy MA Kozachik SL Levy M	Review of Treatment for Central Spinal Neuropathic Pain and Its Effect on Quality of Life: Implications for Neuromyelitis Optica Spectrum Disorder [Review]	OBJECTIVES: Neuromyelitis optica spectrum disorder (NMOSD) causes disabling and persistent central neuropathic pain (NP). Because the pain syndrome in NMOSD is severe and often intractable to analgesic treatment, it interferes with quality of life in patients. No interventional trials have been published looking at response to interventions for pain in NMOSD. This is a synthesis of the literature surveying the impact on quality of life of interventions in all mechanisms of central spinal NP. This review has important implications for management of pain in NMOSD. METHODS AND DATA SOURCES: A systematic database search was conducted using PubMed, Embase, and CINAHL Plus with keywords including "spinal cord," "quality of life," and "neuropathic pain" in an attempt to identify original research that targeted spinal NP treatment and used quality of life as an outcome measure. Both pharmacologic and nonpharmacologic treatments were sought out.	Study Design

			RESULTS: Twenty-one studies meeting our eligibility criteria were identified and evaluated, 13 using pharmacologic treatments and 8 using nonpharmacologic interventions. Overall, sample sizes were modest, and effects on decreasing pain and/or improving quality of life were suboptimal. CONCLUSIONS: This review provides researchers with a foundation from which to start a more thorough and thoughtful investigation into the management of NP in NMOSD and underscores the importance of including quality of life as a clinically meaningful outcome measure.	
Medicine. 99(28):e21067, 2020 Jul 10.	Han M Chen Y Nong L Liu Z Hao L Wang Z	Safety and efficacy of plasma exchange for the treatment of optic neuritis in neuromyelitis optica spectrum disorders: A protocol for systematic review and meta-analysis	BACKGROUND: Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory and heterogeneous astrocyte disorder of the central nervous system (CNS), concerned because of its high pathogenicity, high risk of recurrence, and poor prognosis. Optic neuritis (ON) is the first manifestation in 30% to 50% of NMOSD patients, and eventually involved optic nerve in 70% of patients. The idiopathic ON associated	Study Design

with NMO is called NMO-associated ON(NMO-ON). There are substantial costs to the countries and individuals associated with treatment of NMO-ON. Intravenous corticosteroids (IVCSs), as the first-line therapy, leads to unsatisfactory outcomes for NMO-ON and is associated with potential adverse events (AEs). Emerging evidences have proved the important value and potential prospect of plasma exchange (PLEX) in NMO-ON. Although PLEX is increasingly used in NMO-ON, its therapeutic effect and safety are still controversial. There are no systematic reviews yet that evaluated the effects of PLEX against other therapies in patients with NMO-NO. It is therefore timely to perform a systematic review to assess the efficacy and safety of PLEX on current research for its potential use in clinical practice in treating NMO-ON.

METHODS: The systematic review will include all of the randomized controlled trials (RCT) on the efficacy and safety of PLEX for NMO-ON. A relevant literature search by sensitive search strategies was conducted using the following electronic databases from their inception to November 30, 2019: PubMed, Web of

Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and CBM. We will also search registers of clinical trials, potential gray literature, and conference abstracts. There are no limits on language and publication status. The literature screening, data extraction, and quality assessment will be conducted by 2 reviewers independently. The reporting quality and risk of bias will be assessed by other 2 researchers. Best-corrected visual acuity (BCVA), annualized relapse rate (ARR), the frequency and extent of adverse events (AEs) will be evaluated as the primary outcome. The secondary outcomes will include expanded disability status scales (EDSS), relapse-free rate, peri-papillary retinal nerve fibers layer (pRNFL) or macular volume, visual electrophysiology examinations, standard automated perimetry examinations, time to the next attack. Meta-analysis will be performed using RevMan5.3 software provided by the Cochrane Collaboration and Stata 12.0.

RESULTS: This study will provide a comprehensive review based on current

			evidence of PLEX treatment for NMO-ON in several aspects, including BCVA, ARR, the frequency and extent of adverse events (AEs), EDSS, relapse-free rate, etc. CONCLUSION : : The conclusion of this study will provide evidence to determine whether PLEX is an effective and safe intervention for patients with NMO-ON. ETHICS AND DISSEMINATION: It is not necessary to obtain ethical approval for this study, given that this protocol is for a systematic review. The systematic review will be published in a peer-reviewed journal, presented at conferences and will be shared on social media platforms. PROSPERO REGISTRATION NUMBER: PROSPERO CRD 42020162585.	
Multiple Sclerosis Journal. Conference: Pan-Asian Committee for Treatment and Research in Multiple Sclerosis Congress, PACTRIMS 2019. Singapore Singapore. 26(9) (pp NP50), 2020. Date of Publication: August 2020.	Lee H.J. Jeong W.K. Kwon S.W. Min J.H. Kim B.J.	Self-reported quality of life in multiple sclerosis (MS) and neuromyelitis optica spectrum disease (NMOSD) patients in a single center in Korea	Background: Both MS and NMOSD resultdisability and reduced quality of life through the attacks of optic nerves, brain, and spinal cord. Objective(s): The aim of this study is to assess the quality of life (QoL) of MS and NMOSD patients in Korea. Method(s): The study was a retrospective study performed in a single center in Korea (January 2006 to March 2019). TheEuroQol- 5-Dimensional (EQ-5D) and EuroQoL Visual Analogue Scale	Outcomes

(EQ-VAS) were assessed by a neurologist. Result(s): The study included the patients of MS (N=19, F:M 12:7, mean age 35.11+/-13.63 years, mean disease duration 64.21+/-64.02 months) andNMOSD (N=50, F:M8:42, mean age 41.58+/-14.48 years, mean disease duration 89.06+/-68.50 months). The EQ-5D score was significantly higher in the patients of NMOSD who had a cord lesion initially (3.328+/-3.087, p=0.015) and the patients with MSwho had acord lesion and optic neuritis (4.250+/-1.165, p<0.001). On the other hand, there was no difference in EQ-VAS depending on the lesion location. The patients with late onset NMOSD (onset age >40 years) had lower anxiety score (p=0.006). The patients with late onset MS had lower EQ-5D, especially in the domain of motility, usual activities, and pain/discomfort. Female patients with MS more struggled in self-care, pain/discomfort, and anxiety/depression. In a longitudinal study, there was meaningless change of EQ-5D and EQ-VAS, as the patients had performed the survey every 9 months. Conclusion(s): MS and NMOSD affects the QoL, especially the lesion at cord. Female patients with MS had more

			severity selfcare, pain/discomfort, anxiety/depression.	
JAMA Neurology. 72(1):81-7, 2015 Jan.	Flanagan EP Weinshenker BG Krecke KN Lennon VA Lucchinetti CF McKeon A Wingerchuk DM Shuster EA Jiao Y Horta ES Pittock SJ	Short myelitis lesions in aquaporin-4-IgG-positive neuromyelitis optica spectrum disorders	IMPORTANCE: Short transverse myelitis (STM; <3 vertebral segments) is considered noncharacteristic of neuromyelitis optica (NMO) spectrum disorders (NMOSDs). Nonappreciation of the potential for STM to occur in NMOSD may lead to increased disability from delay in diagnosis and appropriate treatment. OBJECTIVES: To determine the frequency of short lesions at the initial myelitis manifestation of NMOSD and to compare the demographic, clinical, and radiological characteristics of aquaporin-4-IgG (AQP4-IgG) seropositive and seronegative STM. DESIGN, SETTING, AND PARTICIPANTS: We reviewed the records and images of patients at the Mayo Clinic who were identified as AQP4-IgG positive from 1996 to 2014. Inclusion criteria were first STM episode, magnetic resonance imaging performed 90 days or less from symptom onset, spinal cord T2-hyperintense lesion less than 3 vertebral	Outcomes

segments, AQP4-IgG seropositivity, and a final diagnosis of NMO or NMOSD. Patients with an initial longitudinally extensive transverse myelitis were excluded (n = 151). Patients with STM who were seronegative for AQP4-IgG among an Olmsted County population-based cohort of inflammatory demyelinating disorders of the central nervous system were used as a control group.

MAIN OUTCOMES AND MEASURES: Delay to diagnosis in months, clinical and radiological characteristics, and disability measured by ambulatory status.

RESULTS: Twenty-five patients who were AQP4-IgG seropositive with an initial STM represented 14% of initial myelitis episodes among patients with NMOSD. The STM episode was defined as the first manifestation of NMOSD in 10 patients (40%) preceded by optic neuritis in 13 patients (52%) and preceded by a nausea and vomiting episode in 2 patients (8%). In comparison with the excluded patients with NMOSD who had an initial longitudinally extensive transverse myelitis, delay to diagnosis/treatment was greater when initial lesions were short (P

			= .02). In AQP4-IgG-positive STM cases, subsequent myelitis episodes were longitudinally extensive in 92%. Attributes more common in patients with AQP4-IgG-positive STM than in 27 population-based patients with AQP4-IgG-negative STM included the following: nonwhite race/ethnicity; tonic spasms; coexisting autoimmunity; magnetic resonance imaging (central cord lesions, T1 hypointensity, and a brain inconsistent with multiple sclerosis); and cerebrospinal fluid (oligoclonal bands lacking). CONCLUSIONS AND RELEVANCE: Short transverse myelitis is not uncommon in NMOSD and, when it is present, delays diagnosis and treatment. Clinical and radiological characteristics identified in this study may help select patients with STM who are at the highest risk for an NMOSD. Short transverse myelitis does not exclude consideration of AQP4-IgG testing or NMOSD diagnosis.	
International Journal of Ms Care. 24(3):124-131, 2022 May-Jun.	Eshtiaghi A Eapen-John D Zaslavsky K Vosoughi R	Sleep Quality in Neuromyelitis Optica Spectrum Disorder: A Systematic Review	Background: This review summarizes the literature on sleep quality in neuromyelitis optica spectrum disorder (NMOSD) and discusses these findings in the context of current knowledge of sleep physiology. Methods: A literature search was	Study Design

Murray BJ Margolin E	performed using Ovid MEDLINE, Embase, and Scopus from inception to September 3, 2020. All included studies reported at least 1 measure of sleep quality in individuals with NMOSD. Pittsburgh Sleep Quality Index (PSQI) scores of individuals from 4 studies were compared with those from a data set of controls. Results: Thirteen studies (1041 individuals with NMOSD) were included in the review. Disturbed sleep was demonstrated across subjective metrics based on patient surveys and objective metrics such as polysomnography. An estimated 70% of individuals with NMOSD can be classified as poor sleepers. Standardized mean difference between PSQI scores of 183 individuals with NMOSD and those of 9284 controls was 0.72 (95% CI, 0.57-0.86; P < .001). Decreased sleep quality was significantly associated with decreased quality of life and increased anxiety, depression, and disability status. Sleep disturbances in NMOSD were similar in severity to those in multiple sclerosis. Conclusions: Sleep disturbances are a major contributor to NMOSD disease

			burden and may arise from the disruption of sleep circuitry, in addition to physical and psychological complications. Multiple processes involved in sleep regulation may be affected, such as, but not limited to, neural circadian circuit disruption, direct effects of inflammation, aminergic projecting system abnormalities, glymphatic system impairment, and development of sleep disorders such as restless legs syndrome/sleep apnea. A better understanding of these mechanisms is necessary for developing effective therapies for NMOSD-associated sleep disturbances. Copyright © 2022 Consortium of Multiple Sclerosis Centers.	
European Journal of Neurology. Conference: 6th Congress of the European Academy of Neurology. Paris France. 27(Supplement 1) (pp 113), 2020. Date of Publication: May 2020.	Habek M. Andabaka M. Brecl Jakob G. Drulovic J. Fanciulli A. Leys F. Pekmezovic T.	Sudomotor dysfunction in people with neuromyelitis optica spectrum disorders	Background and aims: To analyze sudomotor function in people with neuromyelitis optica spectrum disorders (pwNMOSD). Method(s): We enrolled 41 NMO-IgG positive pwNMOSD (32 females, mean age 47.9+/-13.3, median EDSS 2.5, median disease duration 7 years) from Zagreb, Ljubljana and Belgrade. 27 patients had history of transverse myelitis, 30 optic neuritis and 7 area postrema/brainstem syndrome. Sudomotor function was evaluated with a validated questionnaire (COMPASS-31) and quantitative sudomotor axon reflex	Outcomes

Junakovic A. Krbot Skoric M. Wenning G.K. Deisenhammer F. Gabelic T. Barun B. Adamec I. Lazibat I.	test (QSART). Sweat volumes were determined on 4 sites (hand, proximal and distal leg and foot) on the right side of the body and interpreted in the form of sudomotor index (SI) of Composite Autonomic Scoring Scale (CASS). Result(s): Hypohidrosis and anhidrosis on the hand was present in 2 (4.9%) and 2 (4.9%), on the proximal leg in 4 (9.8%) and 4 (9.8%), on the distal leg in 2 (4.9%) and 5 (12.2%), and on the foot in 2 (4.9%) and 3 (7.35) pwNMOSD, respectively. Involvement of more than one site (hypohidrosis or anhidrosis) was present in 7 (17.1%) pwNMOSD. 2 participants reported reduced sweating in the COMPASS-31 questionnaire: 1 of them had hypo/anhidrosis on all sites, the other participant had normal QSART responses. The SI was pathological in 18 (43.9%) patients: sudomotor dysfunction was mild in 8 (19.5%), moderate in 6 (14.6%) and severe in 4 (9.8%) patients. Disease duration, EDSS, transverse myelitis or area postrema/brainstem syndrome were not associated with sudomotor dysfunction. Conclusion(s): Sweating is frequently impaired in pwNMOSD, with up to 25% of patients showing moderate to severe sudomotor dysfunction.

Multiple Sclerosis Journal. Conference: 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2019. Stockholm Sweden. 25(Supplement 2) (pp 936), 2019. Date of Publication: September 2019.	Xu Y. Su X. Jiang H. Lu X. Zhang M. Wang W. Ding D. Quan C. Zhou L. Zhangbao J.	The mediating effect of health-related hardiness on the degree of physical disability and perceived stress in Chinese female patients with neuromyelitis optica spectrum disorder	Introduction: The characteristics and main symptoms of recurrent Neuromyelitis optica spectrum disorder (NMOSD) lead to an increase in psychological stress and accelerate a decline in the patients' quality of life.The incidence of NMOSD in the Chinese population is much higher than that for other countries and the majority of NMOSD patients are female. In general, there are sex differences in the perception and management of stress, with females experiencing higher levels of perceived stress than males. Thus, we should be concerned about the psychological issues experienced by Chinese female NMOSD patients. Objectives and Aims: Health-related hardness (HRH) is a psychological adjustment factor.This study aimed to investigate the mediation effect of HRH on physical disability and perceived stress in Chinese female NMOSD patients. Method(s): Participants were 68 female patients with NMOSD treated at the Department of Neurology, Huashan Hospital, Fudan University, China, between March and September 2018. Patients were evaluated for their degree of physical disability, perceived stress, and health-related hardiness. Measures included the Expanded Disability Status	Outcomes

Scale (EDSS), Perceived Stress Scale (PSS), and Health-related Hardiness Scale (HRHS). Pearson's correlation analyses, stepwise multiple linear regression analysis and structural equation model were used. Result(s): Findings indicated EDSS, PSS and HRH were significantly correlated with each other. After adjusting for the confounding factors, the EDSS was found to have a positive predictive effect on the PSS (beta =2.743, P=0.000), and the HRHS was found to have a negative predictive effect on the PSS (beta =-0.152, P=0.04). Mediation analysis showed a direct effect of the EDSS on the PSS, and as a mediating variable for health-related hardiness (alpha =-1.928, b =-0.152, c = 2.743, c' = 2.481), which was statistically significant (P < 0.05). The mediating effect of healthrelated hardiness accounted for 10.68% of the total effect. Conclusion(s): A high level of HRH is beneficial in reducing psychological stress caused by physical disability in NMOSD patients. HRH in this study was related to each individual's control of psychological stress. Therefore, investigations focusing on the development of psychological interventions for stress in NMOSD patients aiming to reduce negative

			emotions, as well as the evaluation of these in improving the HRH of NMOSD patients, remain important avenues for future research.	
Archives of Neurology. 61(9):1401-5, 2004 Sep.	Pirko I Blauwet LA Lesnick TG Weinshenker BG	The natural history of recurrent optic neuritis	BACKGROUND: Optic neuritis (ON) may occur in isolation or may herald multiple sclerosis (MS) or neuromyelitis optica (NMO). Occasionally, ON may recur many times without intervening evidence of dissemination in space. OBJECTIVE: To define the clinical course and prognosis of patients with recurrent ON. DESIGN: Retrospective medical record review and telephone follow-up survey. SETTING: Clinic-based practice in a large tertiary referral institution. MAIN OUTCOME MEASURES: Survival analysis of conversion to MS and NMO and final visual impairment. We studied the association of clinical and demographic factors, the presence of brain lesions on magnetic resonance images, and the use of corticosteroid treatment at the time of the first ON occurrence with conversion to MS and NMO.	Population

RESULTS: We identified 1274 patients with ON between 1994 and 2000 and selected 72 (5.7%) with recurrent ON without intervening symptoms of a disseminated demyelinating condition for further analysis. The 5-year conversion rate to NMO was 12.5% and to MS, 14.4%. Among 5 patients with 2 or more lesions consistent with MS on brain magnetic resonance images, 2 (40.0%) converted to MS and none to NMO, while among 11 patients without such lesions, none converted to MS and 2 (18.2%) converted to NMO (P =.16). Conversion to MS occurred in 7 (19.4%) of 36 individuals treated for their first ON episode with corticosteroids vs 4 (44.4%) of 9 untreated individuals (P =.19). There was no difference in the conversion rate to MS between those treated with intravenous steroids (4 [16.7%] of 24) vs oral steroids (3 [25.0%] of 12) (P =.33). Conversion to NMO occurred earlier than conversion to MS (2.3 +/- 1.6 vs 5.3 +/- 4.3 years, respectively; P =.01). Women tended to convert to NMO more frequently than men (female-male ratio for NMO converters, 7:1; MS converters, 2:1; nonconverters, 2:1; P =.56), as did those with a higher annual frequency of ON

			episodes (NMO converters, 2.0 +/- 1.3; MS converters, 1.0 +/- 1.0; nonconverters, 0.6 +/- 0.5; P =.04). The number of ON events in the first 2 years following the first ON episode was higher in the NMO group (NMO converters, 2.4 +/- 0.9; MS converters, 1.9 +/- 1.1; nonconverters, 1.7 +/- 0.7; P =.04). The final visual impairment was greatest in the NMO group (P =.02). CONCLUSIONS: Patients with rapid succession of severe ON events are more likely to develop a generalized demyelinating disease. Patients with NMO had a worse visual outcome.	
Multiple Sclerosis and Related Disorders. 37 (no pagination), 2020. Article Number: 101484. Date of Publication: January 2020.	Milewska M. Grabarczyk K. Dabrowska-Bender M. Jamroz B. Dziewulska D. Staniszewska A. Panczyk M. Szostak-Wegierek D.	The prevalence and types of oral- and pharyngeal-stage dysphagia in patients with demyelinating diseases based on subjective assessment by the study subjects	Background: Studies show that dysphagia is a common problem in patients with demyelinating diseases. However, there are no published studies on dysphagia in this group of patients, which would include the individual phases or the safety and effectiveness of the swallowing process. Objective(s): The main objective of this study was to assess the prevalence of swallowing disorders and to characterize them based on subjective assessment by the study subjects with multiple sclerosis and Devic's syndrome. Method(s): The study included 72 patients (47 F, 25 M). Patients at risk of dysphagia	Population

			were identified using the DYMUS, EAT-10 and SDQ questionnaires. To assess the type of oral- and pharyngeal-stage dysphagia, questions in the questionnaires were classified into groups according to symptoms typical of each stage. Result(s): The risk of dysphagia and the need for instrumental examination were identified in 37.5% of the study subjects. Pharyngeal-stage dysphagia (repeated swallowing, increased effort of swallowing, cough, a feeling of food sticking in the throat) was reported to occur at a significantly higher frequency. However, no differences were found between difficulty in swallowing liquids and difficulty in swallowing solid food. Conclusion(s): There is a need for further research, which should include a detailed dysphagia-oriented diagnosis, with a view to gaining a detailed insight into the pathophysiology of deglutition in this group of patients.Copyright © 2019 The Author(s)	
Dysphagia. Conference: 6th European Society for Swallowing Disorders Congress, ESSD 2016. Milan Italy. 32(1) (pp 170), 2017. Date of	Milewska M. Grabarczyk K. Czernicki T. Dziewulska D.	The prevalence of pharyngeal swallowing disorders in patients with demyelinating diseases	Introduction: Dysphagia in demyelinating diseases usually receives limited attention. It is commonly known that swallowing disorders can lead to aspiration pneumonia, dehydration and malnutrition. Material(s) and Method(s): In total, 72 consecutive patients (64 with	Outcomes

Publication: February 2017.	Panczyk M. Jamroz B. Chmielewska J.	multiple sclerosis (MS) and 8 with Devic's Syndrome) admitted to a Neurological Unit of Public Central Teaching Hospital Medical University of Warsaw. Participants receiving enteral or parenteral nutrition were excluded. The assessment of swallowing disorders was taken by the Dysphagia Multiple Sclerosis (DYMUS) and Eating Assessment Tool 10 (EAT-10) questionnaire. Dysphagia was defined as having >= 3 points in both scales. The results were analyzed using SPSS version 17.0. Result(s): Among 72 patients, 34.7% were classified as having dysphagia (35.9% of MS patients and 50% of Devic's Syndrome). The mean age was 44.2 +/- 10.6 years and mean duration of disease-9.9 +/-7.4 years. Analysis of regression did not show correlation neither between duration of disease nor age and dysphagia. Swallowing disorders were more prevalent in women than in man (respectively 38.3% vs.28%, NS). The necessity of multiple swallows of solid food (80%), pills and solid foods swallowing difficulties (72%) and coughing during swallowing liquids (68%) were the most common observed problems. Increased efforts during swallowing coexisted with cough (p <=

			0.001). Dysphagic patients had a significantly increased length of meals then patients without dysphagia (p <= 0.001), risk of malnutrition and aspiration pneumonia was detected in 22.2%, however the differences between mentioned groups were not statistically significant. Conclusion(s): Swallowing problems were relatively common in patients with demyelinating diseases and occurred independently of duration of disease. These results emphasize the importance of screening dysphagia assessment in patients with demyelinating diseases.	
Current Opinion in Ophthalmology. 31(6):462-468, 2020 Nov.	Holroyd KB Manzano GS Levy M	Update on neuromyelitis optica spectrum disorder [Review]	PURPOSE OF REVIEW: Neuromyelitis optica spectrum disorder is an autoimmune disease that causes optic neuritis and transverse myelitis. Attacks can cause severe neurological damage leading to blindness and paralysis. Understanding of the immunopathogenesis of this disease has led to major breakthroughs in diagnosis and treatment. In the past 18 months, three successful phase 3 clinical trials have been published using targeted approaches to preventing relapses. RECENT FINDINGS: Updates in epidemiology, imaging, quality of life and	Study Design

			treatment for acute relapse and prevention have been published in the past 18 months. Epidemiology studies are distinguishing patients based on their antigen specificity for aquaporin-4 and myelin oligodendrocyte glycoprotein, which are increasingly recognized as separate immunological conditions. Imaging by MRI and optical coherence tomography continue to be developed as tools to distinguish neuromyelitis optica spectrum disorders (NMOSD) from other diseases. This is especially relevant as the recent clinical trials showed differences in response between aquaporin-4 seropositive and seronegative patients. The three drugs that were tested for prevention of NMOSD relapses were eculizumab, inebilizumab, and satralizumab. All of the trials were worldwide, placebo-controlled, double-masked studies that demonstrated a clear benefit with each approach. SUMMARY: Recent research in NMOSD has resulted in improved diagnosis and approved treatments.	
Multiple Sclerosis. Conference: 26th Congress of the European Committee	Apostolos Pereira S. Carvalho F.	Urinary tract dysfunction in women with Neuromyelitis optica	Background: Neuromyelitis optica (NMO) is an autoimmune inflammatory demyelinating disorder characterized by recurrent attacks of optic neuritis and	Population

for Treatment and Research in Multiple Sclerosis, ECTRIMS, 15th Annual Conference of Rehabilitation in MS, RIMS. Gothenburg Sweden. Conference Publication: (var.pagings). 16(10 SUPPL. 1) (pp S225-S226), 2010. Date of Publication: October 2010.	Gomes C. Adoni T. Trigo Rocha F. Bissoni J. Lino A. Callegaro D. Marchiori P. Bruschini H.	longitudinally extensive transverse myelitis(LETM). Lower urinary tract symptoms (LUTS) such as voiding dysfuntion are disturbing in LETM patients and has not been studied in this specific population. Objective(s): Evaluate the LUTS and urodynamic findings in women with NMO. Method(s): 13 women that fulfilled Wingerchuk's criteria for NMO were assessed by the Expanded Disability Status Scale (EDSS), NMO IgG status, presence of LUTS, Bristol Female Lower Urinary Tract Symptoms (BFLUTS, Overactive Bladder V8 (OAB V8) questionnaires. Result(s): Mean age was: 41.5 (range 22-70), mean duration of disease: 3,35 years (range 0,5-11), mean EDSS score: 5.3 (range 1-8). NMO IgG Status was positive in 10 patients and was not correlated with severity of urinary symptoms. The most common urinary complaints were incomplete emptying in 8 (61.5%) patients and urodynamic alterations was detrusor overactivity (DO) with sphincteric dyssinergia (DESD) in 5 (38.5%). Three (23.1 %) patients used diapers. The mean BFLUTS score was 26.5 (range 3 - 64), the mean OAB V8 score was 16.0(range 0-40). Voiding dysfunction increased with disease duration and degree of neurological

			impairment (Spearman's rho =0.663, p =0.013; r =-0,583, p =0.036, respectively). Conclusion(s): Women with NMO have a high prevalence of LUTS, with DESD and DO as the main urodynamic findings. The severity of the neurological disease is associated with a higher chance of voiding dysfunction unregard of NMO IgG status.	
Journal of Aapos: American Association for Pediatric Ophthalmology & Strabismus. 23(3):157.e1-157.e7, 2019 06.	Waldman AT Yeshokumar AK Lavery A Liu G Pineles SL Repka MX Adang L Narula S Liu GT	Validation of a symptom-based questionnaire for pediatric CNS demyelinating diseases	PURPOSE: Optic neuritis is a manifestation of numerous neuroinflammatory disorders. Recognition of current and prior symptoms may facilitate identification of an underlying multifocal neurologic disease. The purpose of this study was to determine whether a symptom-based questionnaire could inform clinical decision making by identifying children with visual complaints who may have a systemic demyelinating disorder. METHODS: Children with visual changes from non-demyelinating disease were compared with patients with confirmed pediatric-onset multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD). Participants completed a 21-item questionnaire to capture their recent (<30 days) and remote (>30 days) symptoms of neurologic dysfunction. The	Population

questionnaire scores were compared using t tests, and the 95% confidence interval for each group was used to determine a threshold score suggesting demyelinating disease.

RESULTS: We enrolled 51 participants (30 females [59%]) with a mean age of 14.6 years (range, 4-21): 25 in the non-demyelinating disease group and 26 with MS/NMOSD. The mean questionnaire score for the non-demyelinating group was 5.0 points (95% CI, 3.3-6.9); for the MS/NMOSD group, 9.4 points (95% CI, 7.4-11.4) for the MS/NMOSD group (P < 0.002). Questionnaire results were dichotomized using a score of >=7 as indicative of demyelinating disease, with 69% sensitivity and 72% specificity. An abbreviated questionnaire, using 8 questions that differed between groups, had a sensitivity of 65% and specificity of 92%.

CONCLUSIONS: A symptom-based questionnaire is sensitive and specific for identifying children with CNS demyelinating disease and may be useful as a screening tool for children with vision complaints and possible demyelination.

		for Pediatric Ophthalmology and Strabismus. Published by Elsevier Inc. All rights reserved.	
Canadian Agency for Drugs and Technologies in Health. CADTH Common Drug Reviews2021 06	Anonymous	CADTH undertook reanalyses of the sponsor's economic models for satralizumab administered as monotherapy and in combination with immunosuppressive therapies (IST) to address some of the identified limitations. In both models, CADTH's base-case reanalysis included a definition of relapse that is more reflective of clinical practice and removed caregiver disutilities. In addition, in the economic model for satralizumab plus IST compared with IST alone, CADTH further assumed no differences in the frequency of adverse events between groups. CADTH's findings remained aligned with the sponsor, such that satralizumab is not cost-effective at a $50,000 per quality-adjusted life-year (QALY) willingness-to-pay (WTP) threshold as monotherapy or in combination with IST. The incremental cost-effectiveness ratio (ICER) for satralizumab monotherapy versus no treatment was $337,535 per QALY gained, and the ICER for satralizumab plus IST versus IST alone was $752,179 per QALY gained. Price-reduction	Outcomes

analyses suggest that, for satralizumab to achieve an ICER below $50,000 per QALY gained, reductions in the price by 80% when administered as monotherapy, and 89% when administered in combination with IST, would be required. Relapse was incorporated into the model as the main treatment-effectiveness measure to define progression and movement within the sponsor's economic model. As such, the model results were primarily driven by the definition of relapse. The incremental benefit ofsatralizumab as monotherapy or as an add-on therapy to IST was minimal over the trial's observed period, while the majority (approximately 98%) of the incremental benefits were achieved over the remainder of the extrapolated time horizon under the assumption of persistent treatment effects over time. CADTH was further unable to address the inherent limitations with the conceptualization of the economic model and the uncertainties resulting from the overestimation of life-years. Given the lack of comparative clinical information, the cost-effectiveness of satralizumab compared with IST, and compared with eculizumab, is unknown.

		2021 Canadian Agency for Drugs and Technologies in Health.	
Canadian Agency for Drugs and Technologies in Health. CADTH Common Drug Reviews2020 10	Anonymous	CADTH's findings remained aligned with the sponsor's: the addition of eculizumab to standard of care (SOC) is not a cost-effective option at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY). CADTH accounted for some limitations, including changing the model's relapse definition, selecting an alternate parametric distribution for time to first relapse, assuming lifelong treatment, capturing costs associated with administration and vaccination, and assuming eculizumab would be administered in outpatient clinics. In CADTH's base case, eculizumab plus SOC was associated with an incremental cost-effectiveness ratio (ICER) of $1,508,152 per QALY gained compared with SOC alone in neuromyelitis optica spectrum disorder (NMOSD) patients who are anti-aquaporin-4 (AQP4) antibody positive. A price reduction of 96% would be required for eculizumab plus SOC to achieve an ICER below a WTP threshold of $50,000 per QALY. The results of CADTH's reanalysis are highly dependent on the	Outcomes

		treatment effects of eculizumab plus SOC compared to SOC alone. Several limitations were associated with the PREVENT trial (e.g., the absence of relevant outcomes related to subsequent relapses after the first relapse; high rates of major protocol deviation) that could not be addressed by CADTH. In the submitted model, the majority of the incremental clinical benefits were found to occur beyond the trial observed period; there is high uncertainty associated with this extrapolation. The cost-effectiveness of eculizumab compared to rituximab, mitoxantrone, or intravenous immunoglobulin (IVIG) is unknown in the absence of both direct and indirect treatment comparisons. Interpretation of the economic results therefore warrants careful consideration. Copyright © 2020 Canadian Agency for Drugs and Technologies in Health.	
Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH). NIPH Systematic Reviews, Report from the Norwegian Institute of Public Health No. 2016-23.2016 02	Couto E Hamidi V Ringerike T Odgaard-Jensen J Harboe I	This Health Technology Assessment was commissioned by the "National system for the introduction of new health technologies within the specialist health service". The aim of this report was to assess the effect and cost-effectiveness of the disease modifying medicines used in Norway for patients with relapsing remitting multiple sclerosis (dimethyl	Outcomes

	Klemp M	fumarate, teriflunomide, interferon beta, peg-interferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab). The key results are: We identified 37 randomised clinical trials. The quality of the available evidence ranged from very low to high. Alemtuzumab 12 mg had the best effect on annual relapse (for medicines we had evidence of high quality). Dimethyl fumarate 240 mg twice daily and fingolimod oral 0.5 mg were the most effective against disability progression (for medicines we had evidence of high quality). Our results indicated that interferon beta-1a 44 mcg and peg-interferon beta-1a were associated with more withdrawal due to adverse events than placebo. The examined treatments had no effect on mortality compared to placebo. Our health economic analysis, examining all multiple sclerosis treatment alternatives, indicated that alemtuzumab was more effective (in terms of quality-adjusted life-years (QALY)) and less costly than the other treatment alternatives. We did several scenario analyses and the cost-effectiveness results were robust to variations in the model assumptions. The results of a scenario analysis that excluded

alemtuzumab (the dominant strategy), showed that three treatment alternatives (interferon beta-1b (Extavia), peg-interferon beta-1a and natalizumab) could be cost-effective depending on the willingness-to-pay (WTP) per QALY. Assuming a WTP below NOK 1,000,000, interferon beta-1b (Extavia) was 40% likely to be the most cost-effective treatment, followed by peg-interferon beta-1a (30% likely). The results of our model analysis showed that there is some degree of uncertainty regarding the input parameters. More research on efficacy and epidemiological data would have the greatest impact on reducing decision uncertainty. Our budget impact analysis based on the results of our cost-effectiveness analysis, the drugs' adverse events profile, and current clinical practice showed that there is a substantial potential for cost saving.

Table 95 Quality assessment of studies included in humanistic SLR

Study	A priori hypotheses	Rationale for instrument choice	Psychometric properties*	Cultural validity	Adequacy of domains	Instrument administration	Timing of assessments	Compliance	Missing data	Clinical significance	Presentation of results in general
Hümmert, 2022	Not applicable	Yes	No	No	No	No	Not applicable	Yes	Not applicable	Yes	Yes

I.1.3 Unpublished data

Not applicable, as no unpublished data was included in the SLR.

Appendix J. Literature searches for input to the health economic model

External literature for input to the health economic model

J.1.1 Ex. Systematic search for […]

Table 96 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

J.1.2 Ex. Targeted literature search for [estimates]

Table 97 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Abbreviations:

Not applicable.

Appendix K. Summary of ongoing inebilizumab and rituximab trials

Table 98 summarizes ongoing inebilizumab trials within NMOSD, IgG4-related disease, and Generalized Myasthenia Gravis, and rituximab trials within NMOSD.

Table 98 Summary of ongoing inebilizumab and rituximab trials

Intervention	Sponsor	Trial identifier	Trial name	Objective	Indication	Trial design	Population	Status	Start and planned end date
Inebilizumab	Amgen	VIB0551.P2.S2, NCT05549258 (129)	An Open-Label Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Inebilizumab in Pediatric Subjects With Neuromyelitis Optica Spectrum Disorder	Pharmacokinetic/pharmacodynamic, safety	NMOSD	Phase II, open-label multicenter 15 patients planned	Pediatric subjects 2 to <18 years of age with recently active NMOSD who are seropositive for autoantibodies against AQP4	Enrolling	Start; 25 August 2022 Completion: 13 April 2027
Inebilizumab	Amgen	HZNP/UPL-401, NCT06180278 (130)	Long-term, Open-label, Safety Study of Inebilizumab in Neuromyelitis Optica Spectrum Disorder	Long-term safety	NMOSD	Phase IV, global open-label long-term safety study	Subjects who have completed at least 2 years in the OLP of the N-MOmentum study (including those who have	Ongoing	Start: 02 April 2024 Completion: June 2028

Intervention	Sponsor	Trial identifier	Trial name	Objective	Indication	Trial design	Population	Status	Start and planned end date
			(NMOSD) (N-MOmentum LT)				since discontinued inebilizumab) or who are newly initiating inebilizumab treatment at participating sites.		
Inebilizumab	Amgen	VIB0551.P4.S4 NCT05909761 (131)	An Observational Pregnancy Safety Study in Women With Neuromyelitis Optica Spectrum Disorder (NMOSD) Exposed to UPLIZNA® (Inebilizumab-cdon) During Pregnancy	Monitor female patients exposed to inebilizumab during pregnancy	NMOSD	Observational study	Patient who have been exposed to inebilizumab during pregnancy	Recruiting	Start: 17 July 2023 Completion: August 2032
Inebilizumab, rituximab	Feng Jinzhou	NCT06068829 (132)	A Multicentric, Retrospective, Real-Word Study to Evaluate the Efficacy and Safety of Inebilizumab Compare With	To compare the safety and efficacy of Inebilizumab and Rituximab in neuromyelitis optica	NMOSD	Observational study	Patients with NMOSD	Not yet recruiting	Start: 20 October 2023 (estimated) Completion: 30 July 2025

Intervention	Sponsor	Trial identifier	Trial name	Objective	Indication	Trial design	Population	Status	Start and planned end date
			Rituximab in Neuromyelitis Optica Spectrum Disorders	spectrum disorders (NMOSD) patients.					
Inebilizumab, oral immunosuppressant	Xuanwu Hospital, Beijing	NCT05891379 (133)	Effectiveness and Safety of Inebilizumab in the Acute Phase of Neuromyelitis Optica Spectrum Disorders-a Multicentric, Prospective, Real Word Study	To observe the effectiveness and safety of inebilizumab in the acute phase of NMOSD	NMOSD	Observational study	NMOSD patients with acute attacks	Not yet recruiting	Start: 20 July 2023 (estimated) Completion:31 July 2024
Inebilizumab, placebo	Amgen	2090BVIB0551.P3.S1 (MINT), NCT04524273 (134)	A Randomized, Double-blind, Multicenter, Placebo-controlled Phase 3 Study With Open-label Period to Evaluate the Efficacy and Safety of Inebilizumab in Adults With Myasthenia Gravis (MINT)	Efficacy, safety, tolerability	Myasthenia Gravis	Phase III, randomized, double-blind, placebo-controlled, parallel-group study with optional open-label extension.	Adult myasthenia gravis patients	Active, not recruiting	Start: 30 August 2020 Completion: 29 November 2027

Intervention	Sponsor	Trial identifier	Trial name	Objective	Indication	Trial design	Population	Status	Start and planned end date
Inebilizumab, placebo	Amgen	2091BVIB0551.P3.S2 (MITIGATE), NCT04540497 (135)	A Phase 3, Randomized, Double-blind, Multicenter, Placebo Controlled Study of Inebilizumab Efficacy and Safety in IgG4-Related Disease (MITIGATE)	Efficacy, safety, tolerability	IgG4-related disease	Phase III, Randomized, double-blind, placebo-controlled, parallel-group study with optional open-label extension	Adult patients with IgG4-realted disease	Active, not recruiting	Start: 26 October 2020 Completion: October 2028

Appendix L. Parameters included in Scenario analysis

Table 99 Parameters included in the Scenario analysis

Parameters
Treatment discontinuation
Hazard ratio
EDSS decrement associated with an attack
Healthcare resource use associated with stable disease
Utility decrement associated with an attack
Adverse event, events per 100 person-years
Healthcare resource use associated with NMOSD attack
Discount rate
Start age
Time horizon
Half-cycle correction
Adverse events, event per person for rituximab
Alternative utility set
Extrapolation of NMOSD attack
Analysis method of change in EDSS score associated with an NMOSD attack

Appendix M. Protocol-defined Criteria for an NMOSD Attack

The primary efficacy endpoint was time (days) from Day 1 to onset of an AC-determined NMOSD attack on or before Day 197. The definition of an NMOSD attack is the presence of a new symptom(s) or worsening of an existing symptom(s) related to NMOSD that meets at least one of the protocol-defined criteria for an NMOSD attack. For the primary analysis, only AC-determined attacks were used.

At the time the N-MOmentum trial was designed (and at the time of the CSR), there exists no widely accepted set of criteria for diagnosis of an NMOSD attack. With its primary efficacy endpoint of time to NMOSD attack, this study required the development of objective attack criteria to ensure the uniform and consistent diagnosis of attacks, despite heterogeneity among participating sites and investigators in terms of attack diagnostic practices. The Sponsor, working closely with a panel of NMOSD disease experts and with input from the FDA, developed a set of NMOSD attack criteria with the following characteristics:

- Clinically meaningful
- Objective
- Quantifiable
- Able to be used worldwide

The NMOSD attack criteria developed and used in this study are presented in Table 100. The attack criteria recognize attacks in all domains affected by NMOSD (ON, myelitis, brain, and brainstem) and include criteria based exclusively on substantial clinical manifestations, as well as criteria that augment more modest clinical findings with the use of MRI.

Table 100 Protocol-defined Criteria for an NMOSD Attack

Example Symptoms of an NMOSD Attack[a]	Attack Type[b]	Protocol-defined Attack Criteria
Blurred vision Loss of vision Eye pain	ON	1. > 15-character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in a previously affected eye and no other ophthalmological explanation 2. ≥ 2-step drop[c] in CF to NLP from last visit as measured in a previously affected eye and no other ophthalmological explanation 3. ≥ 7-character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye 4. ≥ 7-character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured

		in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye 5. ≥ 5-character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye 6. ≥ 5-character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye 7. ≥ 1-step drop[d] in CF to NLP from last visit as measured in a previously affected eye AND a new RAPD in affected eye 8. ≥ 1-step drop[d] in CF to NLP from last visit as measured in a previously affected eye AND loss of a previously documented RAPD in fellow eye 9. ≥ 7-character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new gadolinium (Gd)-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve[f] 10. ≥ 5- or more character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve[f] 11. ≥ 1-step drop d in CF to NLP from last visit as measured in a previously affected eye AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve[f]
Deep or radicular pain Extremity paresthesia Weakness Sphincter dysfunction Lhermitte's sign (not in isolation)	Myelitis[e]	12. ≥ 2-point worsening in 1 or more of the relevant (pyramidal, bladder/bowel, sensory) FSS compared to last visit 13. ≥ 1-point worsening in EDSS score compared to last visit if previous EDSS score is 5.5 or more 14. ≥ 1-point worsening in 2 or more of the relevant (pyramidal, bladder/bowel, sensory) FSS compared to last visit when the last visit score was 1 or greater AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord 15. ≥ 0.5-point worsening in EDSS score compared to last visit if previous EDSS score is

		5.5 or more AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord
Nausea Intractable vomiting Intractable hiccups Other neurological signs[g]	Brainstem	16. Isolated (not present at last visit) intractable nausea, vomiting, and/or hiccups lasting for greater than 48 hours AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem 17. ≥ 2-point worsening in 1 or more of the relevant (brainstem,[b] cerebellar) FSS compared to last visit AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem
Encephalopathy Hypothalamic dysfunction	Brain	18. ≥ 2-point worsening in 1 or more of the relevant (cerebral, sensory, pyramidal) FSS (with a score of 3 or more at the current visit) compared to last visit AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brain consistent with the clinical presentation

Abbreviations: CF: cCounting fingers; EDSS: Expanded Disability Status Scale; FSS: Functional System Scores; Gd:= Gadolinium; HM: Hand motion; LP: Light perception; MRI: Magnetic resonance imaging; NLP: No light perception; NMOSD: Neuromyelitis optica spectrum disorder; ON: Optic neuritis; RAPD: Relative afferent pupillary defect

[a]The symptoms listed are examples and are not inclusive of all NMOSD symptoms.

[b]Four major areas of the body may be affected by an attack: the optic nerve, resulting in ON; the spinal cord, resulting in myelitis; the brainstem, resulting in a number of outcomes; and the brain.

[c]At least 2-step drop can be any of the following worsening: on Landolt C Broken Rings Chart to HM, LP, or NLP; CF to LP or NLP; HM to NLP.

[d]At least 1-step drop can be any of the following worsening: on Landolt C Broken Rings Chart to CF, HM, LP, or NLP; CF to HM or LP or NLP; HM to LP or NLP; LP to NLP.

[e]Note: A 1-point change in a single FSS without a change in the EDSS, with or without a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord, is not considered a clinically significant change and will not count as an attack per this protocol.

[f]Lesions seen in the optic chiasm also count toward these criteria.

[g]Other neurological signs may include: double vision, dysarthria, dysphagia, vertigo, oculomotor palsy, weakness, nystagmus, or other cranial nerve abnormality.

Source: Clinical study report (10)

Appendix N. Literature search for real-world evidence

Due to the lack of a head-to-head between rituximab and inebilizumab, the estimation of adverse events for rituximab relied on estimates from the literature. Details on the approach taken are described in section 9.2. below, the SLR used to identify the studies for rituximab from is described. This appendix documents the details of the SLR on real world evidence. It aimed to identify any studies on the safety of relevant comparators in NMOSD as identified in real-world evidence (RWE) studies.

Real-world evidence search

The objective of this SLR was to identify studies on the clinical effectiveness and safety of inebilizumab and relevant comparators in NMOSD as identified in real-world evidence (RWE) studies.

The SLR was designed to meet the standards of most health technology assessment (HTA) bodies. The SLR was performed in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Intervention,(136) guidance from the Centre for Reviews and Dissemination (CRD) for undertaking reviews in healthcare,(137) and guidance from the National Institute for Health and Care Excellence (NICE).(126) The results for the SLR have been presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(126)

Electronic database searches for the SLR were carried out in May 2023. Electronic searches for both the initial SLR and SLR updated were conducted in Embase, Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic reviews (CDSR) as well as the Database of Abstracts and Reviews of Effects (DARE).

These data sources were selected in accordance with the list of databases suggested by the HTA organizations of interest, such as NICE, the Canadian Agency for Drugs and Technologies in Health (CADTH), Pharmaceutical Benefits Advisory Committee (PBAC), and the Scottish Medicines Consortium (SMC), as well as the Institute for Clinical and Economic Review (ICER; a non-profit organization). Database search strategies were devised for each database.

Table 101 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	1974 – 23.05.2023	23.05.2023
Medline	Ovid	1946 – 23.05.2023	23.05.2023

Database	Platform/source	Relevant period for the search	Date of search completion
Cochrane Central Register of Controlled Trials (CENTRAL)	Ovid	1991 to May 2023	23.05.2023
Cochrane Database of Systematic reviews (CDSR)	Ovid	2005 to 23.05.2023	23.05.2023
Database of Abstracts and Reviews of Effects (DARE)*	Ovid	1991 to March 2015	23.05.2023

*DARE wasdiscontinued and only the archived versions are available

Trial registration websites were searched in parallel with the Ovid search. Information from clinical trial registries was used as a quality assurance tool to ensure all relevant studies were identified in the SLR, as well as to supplement information on study and treatment characteristics where needed (e.g., for the purposes of the network meta-analysis/indirect treatment comparison feasibility study). Baseline characteristics and results were extracted from clinical trial registries. Search terms used on the website included: "Neuromyelitis Optica," "Neuromyelitis Optica Spectrum Disorder," and "NMOSD."

Table 102 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov		"Neuromyelitis Optica" OR "Neuromyelitis Optica Spectrum Disorder" OR "NMOSD"	05.06.2023-28.08.2023
WHO ICTRP		"Neuromyelitis Optica" OR "Neuromyelitis Optica Spectrum Disorder" OR "NMOSD"	05.06.2023-28.08.2023
EU Clinial Trials Rregister		"Neuromyelitis Optica" OR "Neuromyelitis Optica Spectrum Disorder" OR "NMOSD"	05.06.2023-28.08.2023

Source name	Location/source	Search strategy	Date of search
Health Canada's Clinical Trials Database		"Neuromyelitis Optica"	05.06.2023-28.08.2023

Abbreviations: EU, European Union; ICTRP, International Clinical Trials Registry Platform; WHO, World Health Organization

All conference abstracts indexed via Ovid were searched. In addition, proceedings from the last three editions of selected conferences and congresses were manually reviewed to retrieve the latest abstracts and results not yet published in journals as full-text articles, or to supplement the results of previously published studies.

Table 103 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ACTRIMS 2021-2023	https://www.abstractsonline.com/pp8/#!/10822	Manual search	"Neuromyelitis", "NMOSD"	31.05.2023
CMSC 2021-2023	https://cmsc.confex.com/cmsc/2022/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1&searchterm=neuromyelitis	Manual search	"Neuromyelitis", "NMOSD"	01.06.2023
CONy 2021-2023	https://cony.comtecmed.com/e-posters/	Manual search	"Neuromyelitis", "NMOSD"	01.06.2023
ECTRIMS 2021-2023	https://journals.sagepub.com/doi/full/10.1177/13524585209749 37	Manual search	"Neuromyelitis", "NMOSD"	01.06.2023
JNLF 2021-2023	https://mediatheque.jnlf.fr	Manual search	"Neuromyelitis", "NMOSD"	31.05.2023
NANOS 2021-2023	https://collections.lib.utah.edu/search?sort=az_ti	Manual search	"Neuromyelitis", "NMOSD"	31.05.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	tle+asc&year_start=2020&year_end=2022&facet_setname_s=ehsl_novel_nam			

Abbreviations: ACTRIMS, Congress of the American Committee for Treatment and Research in Multiple Sclerosis; CMSC, Consortium of Multiple Sclerosis Centers Annual Meeting; CONy, World Congress on Controversies in Neurology; ECTRIMS, Congress of the European Committee for Treatment and Research in Multiple Sclerosis; JNLF, Journees de Neurologie de Langue Francaise; NANOS, North American Neuro-Ophthalmology Society Annual Meeting;

Additionally, the bibliographies of systematic reviews and meta-analyses identified through the database searches were used to identify studies that met PICOS criteria for the SLR. Furthermore, bibliographies from selected studies were also reviewed to identify relevant studies. This process ensured that papers and articles not picked up in the initial search were included in the review.

N.1.1 Search strategies

The search strategies include a combination of free-text and controlled vocabulary terms specific to each database (e.g., Emtree terms for Embase or Medical Subject Headings in MEDLINE). The search strings are presented in Table 104, Table 105, Table 106, Table 107 and Table 108.

Available (validated) search filters are available from key HTA bodies for study design and outcomes, not for population terms. Internal search terms were used to identify relevant literature. These have been cross-checked with key publications to ensure search identifies most relevant studies. Relevant interventions were identified through reviews and clinicaltrials.gov screening (114-119). Search strategies for RCTs, non-randomised clinical trials and single arm trials were based on SIGN and NICE. Language restrictions were based on standard limits in Ovid.

Table 104 of search strategy table for RWE SLR in Embase

#	Search terms	Search hits
1	exp myelooptic neuropathy/	12307
2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	11376
3	1 or 2	13593
4	immunosuppressive agent/	86704

5	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn.	951978
6	exp mycophenolate mofetil/ or (mycophenolic acid mofetil or mycophenolate mofetil or "cell cept" or cellcept or cellmune or cellsept or munoloc or myclausen or myfenax).ti,ab,kw,kf,rn.	45421
7	exp methotrexate/ or (methotrexat* or methopterine* or abitextrate* or adx 2191 or adx2191 or amethopterin* or ametopterine* or antifolan* or biotrexate* or brimexate* or canceren* or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate* or emthexat* or farmitrexat* or farmitrexate* or farmotrex* or folex* or ifamet* or imeth* or jylamvo* or lantarel* or ledertrexate* or lumexon* or maxtrex* or metatrexan* or methoblastin* or methotrate* or metoject* or metotrexat* or mexate* or mpi 2505 or mpi2505 or neotrexate* or nordimet* or novatrex* or nsc 740 or nsc740 or otrexup* or r 9985 or r9985 or rasuvo* or reditrex* or reumatrex* or rheumatrex* or texate* or tremetex* or trexall* or trexeron* or wr 19039 or wr19039 or xaken* or xatmep* or zexate* or zlatal*).ti,ab,kw,kf,rn.	213687
8	exp cyclophosphamide/ or (cyclophosphamid*2 or alkyroxan or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo-cell or cycloblastin*2 or "cyclofos amide " or cyclofosfamid#2 or cyclophar or cyclophosphan*2 or cylostin or cycloxan or cyrevia or cytophosphan*2 or cytoxan or endoxan*2 or endocyclo or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid).ti,ab,kw,kf,rn.	270481
9	exp mitoxantrone/ or (mitoxantron*2 or "cl 232,315 " or "cl 232315 " or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxantrona or mitoxgen or mitozantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or "now 85 34 " or "now 8534 " or now8534 or "nsc 279836 " or "nsc 301739 " or "nsc 301739d " or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ravenova).ti,ab,kw,kf,rn.	26453
10	exp rituximab/ or (rituximab or "abp 798 " or apb798 or blitzima or "ct p10 " or ctp10 or "gp 2013 " or gp2013 or halpryza or "hlx 01 " or hlx01 or "ibi 301 " or ibi301 or "idec 102 " or "idec c2b8 " or idec102 or idecc2b8 or mabthera or "mk 8808 " or mk8808 or "pf 05280586 " or "pf 5280586 " or pf05280586 or pf5280586 or "r 105 " or r105 or reditux or "rg 105 " or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294 " or ro452294 or "rtxm 83 " or rtxm83 or ruxience or truxima or "tuxella ").ti,ab,kw,kf,rn.	110539

11	exp eculizumab/ or (eculizumab or abp 959 or abp959 or bcd 148 or bcd148 or elizaria or soliris).ti,ab,kw,kf,rn.	9423
12	exp inebilizumab/ or (inebilizumab or "medi 551 " or medi551 or "mt 0551 " or mt0551 or uplizna or "vib 0551 " or vib0551).ti,ab,kw,kf,rn.	394
13	exp tocilizumab/ or (toclizumab or actemra or atlizumab or "bat 1806 " or bat1806 or lusinex or "msb 11456 " or msb11456 or "r 1569 " or r1569 or "rg 1569 " or rg1569 or "ro 4877533 " or ro4877533 or roactemra).ti,ab,kw,kf,rn.	26601
14	exp satralizumab/ or (satralizumab or enspryng or "rg 6168 " or rg6168 or "ro 5333787 " or ro533787 or "sa 237 " or sa237 or sapelizumab).ti,ab,kw,kf,rn.	322
15	exp orelabrutinib/ or (orelabrutinib or "icp 022" or icp022 or innobruka).ti,ab,kw,kf,rn.	107
16	exp Ublituximab/ or (Ublituximab or Briumvi or "emab 6" or emab6 or "lfb r 604" or "lfb r603" or lfbr603 or "tg 1101" or tg1101 or "tgtx 1101" or tgtx1101 or utuxin).ti,ab,kw,kf,rn.	399
17	(NBP-01 or NBP01).ti,ab,kw,kf,rn.	7
18	(telitacicept or RC18 or RC-18).ti,ab,kw,kf,rn.	89
19	exp Belimumab/ or (belimumab or benlysta or "gsk 1550188" or gsk1550188 or "hgs 1006" or hgs1006).ti,ab,kw,kf,rn.	3999
20	exp daratumumab/ or (daratumumab or dalinvi or darasarex or darzalex or "hlx 15" or hlx15 or "jnj 54767414" or jnj54767414).ti,ab,kw,kf,rn.	6312
21	exp Ravulizumab/ or (ravulizumab or "alxn 1210" or "alxn 1810" or alxn1210 or alxn1810 or ultomiris).ti,ab,kw,kf,rn.	636
22	exp ofatumumab/ or (ofatumumab or arzerra or "gsk 1841157" or gsk1841157 or HuMaxCD20 or kesimpta or "omb 157" or omb157).ti,ab,kw,kf,rn.	4041
23	exp zanubrutinib/ or (zanubrutinib or "bgb 3111" or bgb3111 or brukinsa).ti,ab,kw,kf,rn.	910
24	exp batoclimab/ or ("hbm 9161" or hbm9161 or "hl 161" or "hl 161 bkn" or "hl 161bkn" or "hl 61" or "hl161 hl161 bkn" or hl161bkn or hl61 or "imvt 1401" or "imvt1401" or "rvt 1401" or rvt1401).ti,ab,kw,kf,rn.	48
25	exp edralbrutinib/ or (edralbrutinib or "ebi 1459" or ebi1459 or "shr 1459" or shr1459 or "tg 1701" or tg1701).ti,ab,kw,kf,rn.	24
26	mil62.ti,ab,kw,kf,rn.	4

27	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw,kf,rn.	983044
28	prednisone/ or prednisolone/ or meprednisone/ or methylprednisolone/ or betamethasone/ or (prednisone or prednisolone or meprednisone or methylprednisone or methylprednisolone or betamethasone).ti,ab,kw,kf,rn.	436453
29	exp ocrelizumab/ or (ocrelizumab or "pro 70769" or pro70769 or ocrevus or "pr 070769" or "r 1594" or r1594 or "rg 1594" or rg1594 or "rhumab 2H7" or "ro 4964913" or ro4964913).ti,ab,kw,kf,rn.	4083
30	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw,kf,rn.	512962
31	exp tacrolimus/ or (tacrolimus or advagraf or astagraf or envarsus or "fk 506" or fk506 or "fr 900506" or fr900506 or fugimycin or graceptor or hecoria or "l 679934" or l679934 or "mld 987" or mld987 or modigraf or "mtd 2019" or mtd219 or "mustopic oint" or prograf or prograft or protopic or protopy or "rtu 007" or rtu007 or tac-lac or tacforius or tsukubaenolide).ti,ab,kw,kf,rn.	102240
32	BAT4406F.ti,ab,kw,kf,rn.	0
33	immunoglobulin G/ or "immunoglobulin G".ti,ab,kw,kf,rn.	221359
34	plasmapheresis/ or plasma exchange/ or (plasmapheresis or (plasma adj exchange)).ti,ab,kw,kf,rn.	55448
35	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	2825510
36	3 and 35	7330
37	exp Randomized Controlled Trial/ or exp randomization/	860131
38	exp double blind procedure/ or exp single blind procedure/	259986
39	exp clinical trial/ or exp controlled clinical trial/ or exp phase 4 clinical trial/ or exp phase 3 clinical trial/ or exp phase 2 clinical trial/	1846871

40	exp Multicenter Study/	377820
41	exp placebo/	403321
42	exp crossover procedure/	75221
43	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or dumm* or mask*)).tw,ti,ab,hw,kf.	366225
44	exp "controlled clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/	441619
45	random*.ti,ab,kw. or randomi?ed controlled trial*.tw. or rct.tw.	1984478
46	(random* adj2 allocat*).tw.	54689
47	blind*.ti,ab,kw.	506134
48	(placebo* or assign* or allocat* or volunteer* or sham).ti,ab,kw.	1387932
49	prospective study/	877274
50	(parallel* or factorial* or crossover* or cross over*).ti,ab,kw.	595315
51	trial.ti.	402863
52	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	351235
53	(nonrandom* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	70267
54	('double-blind' or 'double-blinded').tw,af. or (open label or open-label).af.	395787
55	(single arm or single group).ti,ab,hw,kf.	33904
56	(basket adj2 trial*).ti,ab,hw,kf.	768
57	observational study/	328404
58	cross-sectional study/	563468
59	cohort analysis/	1037107
60	longitudinal study/	193609
61	prospective study/	877274

62	retrospective study/	1469001
63	follow up/	2050765
64	exp case control study/	224500
65	quasi experimental study/	11286
66	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	349164
67	cohort*.ti,ab,kf.	1476111
68	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	816003
69	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	271051
70	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	495791
71	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	1151543
72	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	214583
73	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	704
74	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	354035
75	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	166037
76	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	5816
77	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	575621
78	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3609
79	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	25337
80	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	2373
81	((uncontrolled or non randomi#ed or nonrandomi#ed or pragmatic) adj1 (study or studies)).ti,ab,kf.	16763

82	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81	9811833
83	36 and 82	3520
84	case report/	2904053
85	(animal* not human*).sh,hw.	4844367
86	(book or chapter or conference review or editorial or erratum or letter or note or short survey or tombstone).pt.	3749414
87	84 or 85 or 86	11067395
88	83 not 87	2803
89	limit 88 to english language	2738
90	abstract.pt.	4769353
91	limit 90 to yr="1883 - 2019"	3841769
92	89 not 91	1993

Table 105 Search strategy for RWE SLR in Medline

#	Search terms	Search hits
1	exp neuromyelitis optica/	4248
2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	6263
3	or/1-2	6263
4	immunosuppressive agents/	104299
5	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn.	721391

6	exp mycophenolate mofetil/ or (mycophenolic acid mofetil or mycophenolate mofetil or "cell cept" or cellcept or cellmune or cellsept or munoloc or myclausen or myfenax).ti,ab,kw,kf,rn.	14566
7	exp methotrexate/ or (methotrexat* or methopterine* or abitextrate* or adx 2191 or adx2191 or amethopterin* or ametopterine* or antifolan* or biotrexate* or brimexate* or canceren* or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate* or emthexat* or farmitrexat* or farmitrexate* or farmotrex* or folex* or ifamet* or imeth* or jylamvo* or lantarel* or ledertrexate* or lumexon* or maxtrex* or metatrexan* or methoblastin* or methotrate* or metoject* or metotrexat* or mexate* or mpi 2505 or mpi2505 or neotrexate* or nordimet* or novatrex* or nsc 740 or nsc740 or otrexup* or r 9985 or r9985 or rasuvo* or reditrex* or reumatrex* or rheumatrex* or texate* or tremetex* or trexall* or trexeron* or wr 19039 or wr19039 or xaken* or xatmep* or zexate* or zlatal*).ti,ab,kw,kf,rn.	60657
8	exp cyclophosphamide/ or (cyclophosphamid*2 or alkyroxan or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo-cell or cycloblastin*2 or "cyclofos amide " or cyclofosfamid#2 or cyclophar or cyclophosphan*2 or cylostin or cycloxan or cyrevia or cytophosphan*2 or cytoxan or endoxan*2 or endocyclo or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid).ti,ab,kw,kf,rn.	84447
9	exp mitoxantrone/ or (mitoxantron*2 or "cl 232,315 " or "cl 232315 " or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxantrona or mitoxgen or mitozantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or "now 85 34 " or "now 8534 " or now8534 or "nsc 279836 " or "nsc 301739 " or "nsc 301739d " or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ravenova).ti,ab,kw,kf,rn.	6781
10	exp rituximab/ or (rituximab or "abp 798 " or apb798 or blitzima or "ct p10 " or ctp10 or "gp 2013 " or gp2013 or halpryza or "hlx 01 " or hlx01 or "ibi 301 " or ibi301 or "idec 102 " or "idec c2b8 " or idec102 or idecc2b8 or mabthera or "mk 8808 " or mk8808 or "pf 05280586 " or "pf 5280586 " or pf05280586 or pf5280586 or "r 105 " or r105 or reditux or "rg 105 " or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294 " or ro452294 or "rtxm 83 " or rtxm83 or ruxience or truxima or "tuxella ").ti,ab,kw,kf,rn.	30576
11	(eculizumab or abp 959 or abp959 or bcd 148 or bcd148 or elizaria or soliris).ti,ab,kw,kf,rn.	2529
12	(inebilizumab or "medi 551 " or medi551 or "mt 0551 " or mt0551 or uplizna or "vib 0551 " or vib0551).ti,ab,kw,kf,rn.	92
13	(toclizumab or actemra or atlizumab or "bat 1806 " or bat1806 or lusinex or "msb 11456 " or msb11456 or "r 1569 " or r1569 or "rg 1569 " or rg1569 or "ro 4877533 " or ro4877533 or roactemra).ti,ab,kw,kf,rn.	121
14	(satralizumab or enspryng or "rg 6168 " or rg6168 or "ro 5333787 " or ro533787 or "sa 237 " or sa237 or sapelizumab).ti,ab,kw,kf,rn.	100
15	(orelabrutinib or "icp 022" or icp022 or innobruka).ti,ab,kw,kf,rn.	25

16	(Ublituximab or Briumvi or "emab 6" or emab6 or "lfb r 604" or "lfb r603" or lfbr603 or "tg 1101" or tg1101 or "tgtx 1101" or tgtx1101 or utuxin).ti,ab,kw,kf,rn.	66
17	(NBP-01 or NBP01).ti,ab,kw,kf,rn.	6
18	(telitacicept or RC18 or RC-18).ti,ab,kw,kf,rn.	48
19	(belimumab or benlysta or "gsk 1550188" or gsk1550188 or "hgs 1006" or hgs1006).ti,ab,kw,kf,rn.	1004
20	(daratumumab or dalinvi or darasarex or darzalex or "hlx 15" or hlx15 or "jnj 54767414" or jnj54767414).ti,ab,kw,kf,rn.	1472
21	(ravulizumab or "alxn 1210" or "alxn 1810" or alxn1210 or alxn1810 or ultomiris).ti,ab,kw,kf,rn.	153
22	(ofatumumab or arzerra or "gsk 1841157" or gsk1841157 or HuMaxCD20 or kesimpta or "omb 157" or omb157).ti,ab,kw,kf,rn.	754
23	(zanubrutinib or "bgb 3111" or bgb3111 or brukinsa).ti,ab,kw,kf,rn.	259
24	("hbm 9161" or hbm9161 or "hl 161" or "hl 161 bkn" or "hl 161bkn" or "hl 61" or "hl161 hl161 bkn" or hl161bkn or hl61 or "imvt 1401" or "imvt1401" or "rvt 1401" or rvt1401).ti,ab,kw,kf,rn.	10
25	(edralbrutinib or "ebi 1459" or ebi1459 or "shr 1459" or shr1459 or "tg 1701" or tg1701).ti,ab,kw,kf,rn.	2
26	mil62.ti,ab,kw,kf,rn.	0
27	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw,kf,rn.	343187
28	Prednisone/ or Prednisolone/ or Methylprednisolone/ or Betamethasone/ or (prednisone or prednisolone or meprednisone or methylprednisone or methylprednisolone or betamethasone).ti,ab,kw,kf,rn.	134930
29	Prednisone/ or Prednisolone/ or Methylprednisolone/ or Betamethasone/ or (prednisone or prednisolone or meprednisone or methylprednisone or methylprednisolone or betamethasone).ti,ab,kw,kf,rn.	134930
30	(ocrelizumab or "pro 70769" or pro70769 or ocrevus or "pr 070769" or "r 1594" or r1594 or "rg 1594" or rg1594 or "rhumab 2H7" or "ro 4964913" or ro4964913).ti,ab,kw,kf,rn.	860
31	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw,kf,rn.	290736
32	exp tacrolimus/ or (tacrolimus or advagraf or astagraf or envarsus or "fk 506" or fk506 or "fr 900506" or fr900506 or fugimycin or graceptor or hecoria or "l 679934" or l679934 or "mld 987" or mld987 or modigraf or "mtd 2019" or	28748

	mtd219 or "mustopic oint" or prograf or prograft or protopic or protopy or "rtu 007" or rtu007 or tac-lac or tacforius or tsukubaenolide).ti,ab,kw,kf,rn.	
33	BAT4406F.ti,ab,kw,kf,rn.	0
34	Immunoglobulins/ or immunoglobulin G.ti,ab,kw,kf,rn.	188880
35	Plasmapheresis/ or Plasma Exchange/ or (plasmapheresis or (plasma adj exchange)).ti,ab,kw,kf,rn.	24280
36	or/4-35	1709527
37	3 and 36	2271
38	exp Randomized Controlled Trial/ or exp Random Allocation/	683908
39	exp Double-Blind Method/ or exp Single-Blind Method/	206888
40	exp clinical trial/ or exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp controlled clinical trial/	970864
41	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt.	80508
42	exp controlled clinical trials as topic/ or exp Randomized Controlled Trials as Topic/ or exp clinical trials as topic/	382288
43	exp Multicenter Study/	334049
44	exp Placebos/	39464
45	exp Cross-Over Studies/	55118
46	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or dumm* or mask*)).tw,ti,ab,hw,kf.	269475
47	randomized controlled trial.pt.	593290
48	controlled clinical trial.pt.	95312
49	random*.ti,ab,kw. or randomi?ed controlled trial*.tw. or rct.tw.	1425879
50	(random* adj2 allocat*).tw.	43461
51	blind*.ti,ab,kw.	346763
52	(placebo* or assign* or allocat* or volunteer* or sham).ti,ab,kw.	1018668
53	prospective studies/	659188
54	(parallel* or factorial* or crossover* or cross over*).ti,ab,kw.	488045
55	trial.ti.	285696
56	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	160835
57	(nonrandom* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	54277
58	('double-blind' or 'double-blinded').tw,af. or (open label or open-label).af.	272439
59	(single arm or single group).ti,ab,hw,kf.	17548
60	(basket adj2 trial*).ti,ab,hw,kf.	334
61	observational study/	142095
62	observational studies as topic/	8751
63	clinical studies as topic/	783
64	controlled before-after studies/	724

65	cross-sectional studies/	466978
66	historically controlled study/	227
67	interrupted time series analysis/	1826
68	cohort studies/	328533
69	longitudinal studies/	165035
70	prospective studies/	659188
71	retrospective studies/	1118854
72	follow-up studies/	691542
73	case-control studies/	327840
74	single-case studies as topic/	98
75	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	218004
76	cohort*.ti,ab,kf.	850373
77	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	529912
78	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	168727
79	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	343864
80	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	674788
81	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	158585
82	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	637
83	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	231712
84	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	108379
85	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	4906
86	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	431778
87	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3258
88	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	20159
89	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	1695
90	((uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic* or noninterventional or non interventional or pragmatic) adj1 (study or studies)).ti,ab,kf.	110105
91	or/38-90	6838757
92	37 and 91	929
93	case reports/	2336806
94	(animal* not human*).sh,hw.	5079797
95	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift	5038793

	or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	
96	or/93-95	9980459
97	92 not 96	821
98	limit 97 to english language	783
99	(conference or congress).pt.	67273
100	limit 99 to yr="1860 - 2019"	66241
101	98 not 100	783

Table 106 Search strategy for RWE SLR in CENTRAL

#	Search terms	Search hits
1	exp neuromyelitis optica/	75
2	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).mp.	456
3	or/1-2	456
4	immunosuppressive agents/	5869
5	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw.	44658
6	exp mycophenolate mofetil/ or (mycophenolic acid mofetil or mycophenolate mofetil or "cell cept" or cellcept or cellmune or cellsept or munoloc or myclausen or myfenax).ti,ab,kw.	3407
7	exp methotrexate/ or (methotrexat* or methopterine* or abitextrate* or adx 2191 or adx2191 or amethopterin* or ametopterine* or antifolan* or biotrexate* or brimexate* or canceren* or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate* or emthexat* or farmitrexat* or farmitrexate* or farmotrex* or folex* or ifamet* or imeth* or jylamvo* or lantarel* or ledertrexate* or lumexon* or maxtrex* or metatrexan* or methoblastin* or methotrate* or metoject* or metotrexat* or mexate* or mpi 2505 or mpi2505 or neotrexate* or nordimet* or novatrex* or nsc 740 or nsc740 or otrexup* or r 9985 or r9985 or rasuvo* or reditrex* or reumatrex* or rheumatrex* or texate* or tremetex* or trexall* or	12242

	trexeron* or wr 19039 or wr19039 or xaken* or xatmep* or zexate* or zlatal*).ti,ab,kw.	
8	exp cyclophosphamide/ or (cyclophosphamid*2 or alkyroxan or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo-cell or cycloblastin*2 or "cyclofos amide " or cyclofosfamid#2 or cyclophar or cyclophosphan*2 or cylostin or cycloxan or cyrevia or cytophosphan*2 or cytoxan or endoxan*2 or endocyclo or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid).ti,ab,kw.	13209
9	exp mitoxantrone/ or (mitoxantron*2 or "cl 232,315 " or "cl 232315 " or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxantrona or mitoxgen or mitozantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or "now 85 34 " or "now 8534 " or now8534 or "nsc 279836 " or "nsc 301739 " or "nsc 301739d " or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ravenova).ti,ab,kw.	1439
10	exp rituximab/ or (rituximab or "abp 798 " or apb798 or blitzima or "ct p10 " or ctp10 or "gp 2013 " or gp2013 or halpryza or "hlx 01 " or hlx01 or "ibi 301 " or ibi301 or "idec 102 " or "idec c2b8 " or idec102 or idecc2b8 or mabthera or "mk 8808 " or mk8808 or "pf 05280586 " or "pf 5280586 " or pf05280586 or pf5280586 or "r 105 " or r105 or reditux or "rg 105 " or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294 " or ro452294 or "rtxm 83 " or rtxm83 or ruxience or truxima or "tuxella ").ti,ab,kw.	5660
11	(eculizumab or abp 959 or abp959 or bcd 148 or bcd148 or elizaria or soliris).ti,ab,kw.	440
12	(inebilizumab or "medi 551 " or medi551 or "mt 0551 " or mt0551 or uplizna or "vib 0551 " or vib0551).ti,ab,kw.	87
13	(toclizumab or actemra or atlizumab or "bat 1806 " or bat1806 or lusinex or "msb 11456 " or msb11456 or "r 1569 " or r1569 or "rg 1569 " or rg1569 or "ro 4877533 " or ro4877533 or roactemra).ti,ab,kw.	183
14	(satralizumab or enspryng or "rg 6168 " or rg6168 or "ro 5333787 " or ro533787 or "sa 237 " or sa237 or sapelizumab).ti,ab,kw.	75
15	(orelabrutinib or "icp 022" or icp022 or innobruka).ti,ab,kw.	13
16	(Ublituximab or Briumvi or "emab 6" or emab6 or "lfb r 604" or "lfb r603" or lfbr603 or "tg 1101" or tg1101 or "tgtx 1101" or tgtx1101 or utuxin).ti,ab,kw.	54
17	(NBP-01 or NBP01).ti,ab,kw.	0
18	(telitacicept or RC18 or RC-18).ti,ab,kw.	35

19	(belimumab or benlysta or "gsk 1550188" or gsk1550188 or "hgs 1006" or hgs1006).ti,ab,kw.	336
20	(daratumumab or dalinvi or darasarex or darzalex or "hlx 15" or hlx15 or "jnj 54767414" or jnj54767414).ti,ab,kw.	554
21	(ravulizumab or "alxn 1210" or "alxn 1810" or alxn1210 or alxn1810 or ultomiris).ti,ab,kw.	158
22	(ofatumumab or arzerra or "gsk 1841157" or gsk1841157 or HuMaxCD20 or kesimpta or "omb 157" or omb157).ti,ab,kw.	307
23	(zanubrutinib or "bgb 3111" or bgb3111 or brukinsa).ti,ab,kw.	100
24	("hbm 9161" or hbm9161 or "hl 161" or "hl 161 bkn" or "hl 161bkn" or "hl 61" or "hl161 hl161 bkn" or hl161bkn or hl61 or "imvt 1401" or "imvt1401" or "rvt 1401" or rvt1401).ti,ab,kw.	17
25	(edralbrutinib or "ebi 1459" or ebi1459 or "shr 1459" or shr1459 or "tg 1701" or tg1701).ti,ab,kw.	6
26	mil62.ti,ab,kw.	4
27	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw.	44793
28	Prednisone/ or Prednisolone/ or Methylprednisolone/ or Betamethasone/ or (prednisone or prednisolone or meprednisone or methylprednisone or methylprednisolone or betamethasone).ti,ab,kw.	22788
29	(ocrelizumab or "pro 70769" or pro70769 or ocrevus or "pr 070769" or "r 1594" or r1594 or "rg 1594" or rg1594 or "rhumab 2H7" or "ro 4964913" or ro4964913).ti,ab,kw.	305
30	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw.	29342
31	exp tacrolimus/ or (tacrolimus or advagraf or astagraf or envarsus or "fk 506" or fk506 or "fr 900506" or fr900506 or fugimycin or graceptor or hecoria or "l 679934" or l679934 or "mld 987" or mld987 or modigraf or "mtd 2019" or	5435

	mtd219 or "mustopic oint" or prograf or prograft or protopic or protopy or "rtu 007" or rtu007 or tac-lac or tacforius or tsukubaenolide).ti,ab,kw.	
32	BAT4406F.ti,ab,kw.	0
33	Immunoglobulins/ or immunoglobulin G.ti,ab,kw.	2911
34	Plasmapheresis/ or Plasma Exchange/ or (plasmapheresis or (plasma adj exchange)).ti,ab,kw.	1507
35	or/4-34	150937
36	3 and 35	284
37	(animal* not human*).sh,hw.	2747
38	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	21469
39	37 or 38	24207
40	36 not 39	282
41	limit 40 to english language	278

Table 107 Search strategy table for RWE SLR in Cochrane Database of Systematic Reviews

#	Search terms	Search hits
1	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).ti,ab,kw.	0

Table 108 Search strategy table for RWE SLR in Database of Abstracts of Reviews of Effects

#	Search terms	Search hits

1	(neuromyelitis optica or devic*2 disease or devic*2 syndrome or myeloopticoneuropathy or myeloptico neuropathy or myelopticoneuropathy or neuromyelitis optica spectrum disorder or NMOSD).ti,ab,kw.	0

N.1.2 Systematic selection of studies

The Population, Intervention, Comparator, Outcomes, and Study design (PICOS) eligibility criteria are outlined in Table 109. Selection of studies was guided by the PICOS criteria and followed a 2-stage process: (1) title and abstract screening, and (2) full text review. All records were screened by two independent reviewers, with conflicts resolved by a third, independent reviewer. Following the article selection process, a list of included and excluded studies (with reasons for exclusion) for each step was generated.

In some instances, studies included a broader patient population than the target population of these SLRs. Based on guidance from the Institute for Quality and Efficiency in Health Care (IQWiG) (120), studies were included if at least 80% of the study population met the PICOS criteria outlined below or if relevant subgroup data were available.

Neither geographic nor time limit restrictions were applied in the initial search. The SLR update was limited to studies published since the initial search for the inclusion of any new studies. Records were not extracted if they only reported on subgroups that were not of interest.

Title/Abstract review

All records were screened at the title/abstract level by two independent reviewers with disagreements resolved by a third, independent researcher. All papers included by the reviewers at the end of this stage were retained for Step 2. Papers excluded at this level were disregarded and the rejection reason was recorded for use in the PRISMA flow diagram.

In the SLR update, citations for title and abstract screening were retrieved from two sources:

3. SLR update: Citations identified during electronic searches were downloaded using EndNote (at which point most duplicates were identified and removed) into a Microsoft Excel spreadsheet.

4. Re-screening: Citations that were not RCTs and were excluded at title and abstract screening with the exclusion category “study design” during original SLR were eligible for re-screening. Included citations from both screenings were cross-checked for duplicates.

Full-text review

The publications included after abstract review were obtained for a full review of the text. Two independent reviewers screened all citations and full-text articles and any

discrepancies in their decisions were resolved by a third, independent reviewer. All papers included after the full-text review were retained for data extraction. A record was kept of papers excluded at this stage along with a clear justification for their exclusion; this was reported in table format in the Excel report as per the NICE guidance (121). The details for the inclusion/exclusion criteria were consulted throughout this step to assist with data collection. This ensured that all decisions regarding the inclusion and exclusion of studies were consistent throughout the review process. Specific exclusion reasons as per the PICOS criteria were recorded at the full-text screening stage. The study selection process was reported in a PRISMA flow diagram.

In the SLR update, similarly to title and abstract screening articles were retrieved from two sources:

3. Full texts of publications included during screening were included for full text review.
4. Re-assessment: In addition to publications included during re-screening, publications excluded at full text review in the original SLR (exclusion category: “study design”) were included for full text review.

Data extraction

Once the list of SLRs for inclusion was finalized, data extraction was carried out using a pre-defined Microsoft Excel®-based data extraction template (DET), ensuring that data were extracted uniformly and that the extracted data were comparable across studies. Data were extracted by two independent reviewers and independently checked by a third, senior reviewer in accordance with CRD guidance (122). In the event of a discrepancy, a consensus-based discussion or a third reviewer was consulted to make the final decision.

In the updated SLR, data from the included studies were extracted into the DET from the initial SLR to capture publication, study, patient, and treatment characteristics, as well as outcome data of interest. The DET was slightly modified during the SLR update (i.e., additional columns were added to capture e.g., age at onset).

The following subgroups were defined as subgroups of interest:

- AQP4+ population
- EDSS score at baseline
- Subgroups by prior therapy
    - Prior immunosuppressant (e.g., AZA, MMF)
    - Prior B-cell depleting therapy (e.g., rituximab)
    - Treatment-naïve population
- Regional/ethnical subgroups
- Age (added during SLR update)
- Age on onset (added during SLR update)

An additional assessment was performed on publications that met the PICOS inclusion/exclusion criteria before proceeding to data extraction. During the additional

assessment data cross-check for publications reporting results from studies already identified in the original SLR was performed. Publications were not selected for extraction if: (1) data were already present in the original DET; (2) more recent data were already present in the original DET; (3) data were reported only for subgroups that were not listed as subgroup of interest; (4) no outcomes of interest were presented.

The data were extracted by one reviewer, and a second reviewer assessed the entries to ensure consistency and accuracy against the source article as a validation step.

Relevant SLRs, network meta-analyses (NMAs), and indirect treatment comparisons (ITCs) reporting study types of interest included, but not submitted for data extraction. Instead, their reference lists were reviewed for relevant articles that had not been identified through the above searches. The citations were retrieved with citationschaser from Lens.org (123) and the titles were screened for relevant articles using keywords “neuromyelitis” or “NMOSD” or “NMO”.

Table 109 Inclusion and exclusion criteria for the RWE SLR used for the assessment of studies

Inclusion		Exclusion
Population		
Patients with NMOSD		• Disease other than NMOSD • Non-human • Healthy volunteers
Interventions		
Monoclonal antibodies *B-cell depleting agents* • Inebilizumab (anti-CD19) • Rituximab (anti-CD20) • Ublituximab (anti-CD20) • Ravulizumab (C5 inhibitor) • Belimumab (BAFF inhibitor) • Daratumumab (anti-CD38) • Ofatumumab (anti-CD20) • Ocrelizumab (anti-CD20) • Mil62 (anti-CD20) • BAT4406F (anti-CD20) *Interleukin-6 signaling blocking agents* • Satralizumab • Tocilizumab *Complement blocking agents* • Eculizumab *FcRn inhibitors* • Batoclimab (HBM9161)	*Bruton’s tyrosine kinase inhibitors* • Orelabrutinib • Zanubrutininb • Edralbrutinib (SHR1459) *Other immunosuppressants* • Azathioprine • Mycophenolate mofetil • Cyclophosphamide • Tacrolimus • Telitacicept (RC18) • Glucocorticoids • Methotrexate • Cyclosporin A • Mitoxantrone *Others* • NPB-01 (Human immunoglobulin G) • Intravenous immunoglobulin G • Plasmapheresis	Studies not including at least one of the interventions listed in the inclusion criteria
Comparisons		

• Any included intervention • Any non-included intervention	None
Outcomes*	
• Time to NMOSD attack/relapse • NMOSD attack/relapse rate • Changes in disability scores (i.e., EDSS) • Change visual acuity scores • Number of active MRI lesions • Number of patients with positive anti-drug antibodies (ADAs) • Safety outcomes • Disease-related PROs (i.e., MSIS-29, pain scores etc) • Disease-related HRQoL	No limitations
Study design	
• Prospective observational studies • Retrospective studies • Cross-sectional studies • Database and registry analyses • Systematic reviews and meta-analyses (for cross-checking only)	• Non-human, pre-clinical studies • Reviews, Editorials, Notes, Comments, Letters • Case reports/case series • Interventional studies (Phase 1 Dose finding study or PK study, RCTs, single-arms, non-randomized trials)
Additional limits	
Language	
English language	Full-text articles not published in English

Abbreviations: EDSS, Expanded Disability Status Scale; HRQoL, health-related quality of life; MSIS-29, Multiple Sclerosis Impact Scale; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; PK, pharmacokinetic; PRO, patient-reported outcome ; RCT, randomized controlled trial; RWE, real-world evidence; SLR, systematic literature review.

The search of specified databases from inception to May 23, 2023 identified 3,054 records for screening. Following the title and abstract screening of citations, 1,663 records were excluded. Of the 504 potentially relevant records, 503 full-text reports were obtained for more detailed evaluation. Following full-detail examination of the reports, 331 reports were excluded. Reasons for exclusion at the full-text review stage included PICOS categories population (n=55), intervention (n=30), outcomes (n=161), and study design (n=83). Other reasons for exclusion of reports included duplicates (n=2). Following the grey literature search, 3 relevant reports from the congress review and 7 from the bibliographic search met the inclusion criteria. In total, 182 reports from 180 original studies were included in the SLR. The flow of the SLR is presented in the PRISMA diagram in Figure 22.

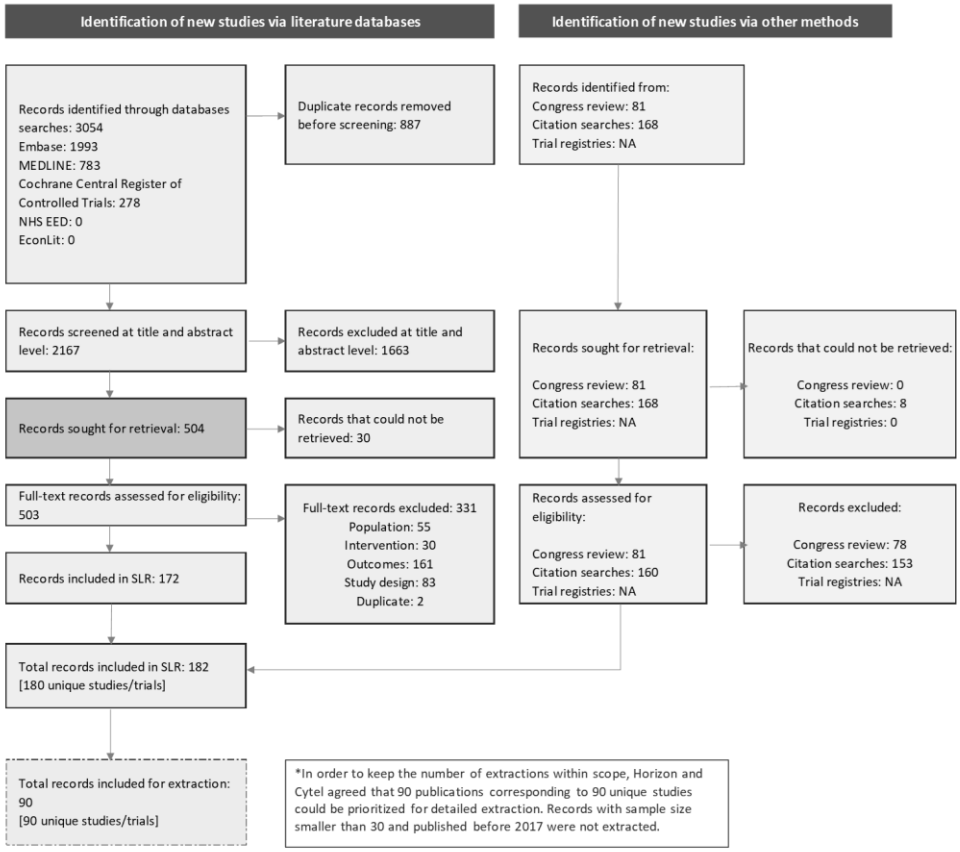

Figure 22 PRISMA diagram for RWE SLR

Table 110 Overview of study design for RWE studies included in the analysis

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Annovazzi et al. 2016	To contribute to better define the role of rituximab in a large cohort of patients with NMO, and to determine whether the different schedules of treatment can influence the clinical outcome	Retrospective study	NMO	Rituximab (n=73)	ARR (Mean follow-up: 35.6 months)	Relapse-free analysis, relapse-free survival safety (Mean follow-up: 35.6 months)
Bedi et al. 2011	To assess the impact of rituximab on the relapse rate and progression of disability in NMO	Retrospective longitudinal clinical review	NMO	Rituximab (n=23)	ARR and EDSS (Median treatment time: 32.5 months)	Safety, treatment withdrawal (Median treatment time: 32.5 months)
Cabre et al. 2018	To evaluate the clinical and neuroradiological effectiveness of rituximab on active forms of NMO	Prospective, multicenter study	NMOSD	Rituximab (n=32)	ARR (follow-up: 2 years)	EDSS, levels of AQP4 antibodies, safety (follow-up: 2 years)
Correa-Diaz et al. 2021	To evaluate the impact of rituximab on the effectiveness and safety in a cohort of Ecuadorian patients with NMOSD	Retrospective study	NMOSD	Rituximab (n=23)	Change in ARR and EDSS before and after treatment (mean follow-up on treatment: 40 months)	Brain MRI lesions, safety (mean follow-up on treatment: 40 months)

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Gomez-Figueroa et al. 2020	To explore the efficacy of rituximab in patients with NMOSD with positive AQP4-IgG serostatus	Retrospective, single center study	AQP4+ NMOSD	Rituximab (n=15)	ARR before and after treatment (Median follow-up: 8.12 years)	Safety (Median follow-up: 8.12 years)
Kim et al. 2015	To assess the long-term clinical efficacy and safety of rituximab treatment in patients with NMOSD and the influence of fragment c gamma receptor 3A (FCGR3A) polymorphisms on rituximab response.	Retrospective review	NMOSD	Rituximab (n=100)	ARR (Median treatment: 67 months)	EDSS score, proportion of patients who were relapse free, and safety of rituximab (Median treatment: 67 months)
Lin et al. 2018	To probe an effective and beneficial regime of rituximab for NMOSD patients	Retrospective, single center study	NMOSD	Rituximab (n=14) Non-rituximab (n=23)	ARR and EDSS before and after treatment (mean follow-up in rituximab/non-rituximab group: 20.5/9.6 months)	Time to next relapse, safety (mean follow-up in rituximab/non-rituximab group: 20.5/9.6 months)
Lu et al. 2020	To present our experience of treating adult Chinese patients having NMOSD with low-dose rituximab, and to further investigate its efficacy and safety in a long-term follow-up	Retrospective, observational study	NMOSD	Rituximab (n=20)	Change in EDSS and ARR (median follow-up: 29.5 months)	Relapse and dosage, re-infusion interval, CD19 + B cell monitoring, safety (median follow-up: 29.5 months)

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Radaelli et al. 2016	To assess the long-term benefit-risk profile of repeated courses of rituximab in Caucasian patients affected by NMO and related disorders, in everyday clinical practice.	Prospective, observational study	NMO	Rituximab (n=21)	ARR (Mean follow-up: 48 months)	EDSS, safety (Mean follow-up: 48 months)
Shaygannejad et al. 2019	To assess the long-term safety and efficacy in NMOSD patients receiving maintenance therapy with B-cell-depleting agent rituximab for more than 2 years	Prospective, single center study	NMOSD	Rituximab (n=44)	Safety (mean observation period: 31.6 months)	ARR and EDSS
Seyed Ahadi et al. 2020	To evaluate the efficacy and safety of rituximab treatment as the second line therapy, in patients with refractory NMOSD, based on ARR and EDSS, and proposed treatment protocol based on CD19+ B cell detection.	Non-randomised, prospective, open-label clinical trial	NMOSD	Rituximab (n=17)	EDSS and ARR (mean follow-up period: 12.7 months)	Safety (mean follow-up period: 12.7 months)
Uzunkopru et al. 2021	To evaluate the efficacy of rituximab as monotherapy in NMOSD and to determine whether the efficacy varies depending on the presence of antibodies in this cohort.	Retrospective, multicenter study	NMOSD	Rituximab (n=85)	ARR (mean time on treatment: 28.27 months)	EDSS score in the remission period and AE occurring during therapy (mean time on treatment: 28.27 months)

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Xiao et al. 2020	To investigate the efficacy and safety of low-dose rituximab in the treatment of NMOSD patients	Retrospective, single center study	NMOSD	Rituximab (n=36)	Changes in ARR, EDSS and VFSS score before and after treatment, length of spinal cord lesion (mean follow-up: 19.83 months)	Safety (mean follow-up: 19.83 months)
Zhang et al. 2017	To evaluate efficiency, safety of this treatment, and compared the clinical efficiency of azathioprine and rituximab in two groups of patients with NMO in which the clinical characteristics were similar.	Retrospective, single center study	NMOSD	Rituximab (n=31) Azathioprine (n=34)	ARR and EDSS score variation before and after therapy (mean treatment duration rituximab/azathioprine: 27.45/31.32)	Safety (mean treatment duration rituximab/azathioprine: 27.45/31.32)

Abbreviations: ARR: annualised relapse rate, AE: Adverse event, EDSS: Expanded Disability Status Scale, NMO: Neuromyelitis optica, NMOSD: Neuromyelitis optica spectrum disorder; VFSS: Visual function system scale

N.1.3 Quality assessment

Both the initial and updated SLRs were undertaken utilizing a rigorous methodology to minimize potential limitations, adhering to established guidelines by leading organizations such as the Centre for Reviews and Dissemination and the Cochrane Collaboration Handbook (110), and key HTA organizations (110, 112, 113), and was designed to satisfy the requirements of the majority of HTA organizations. The SLRs encompassed multiple databases and grey literature searches to ensure robust inclusion of publications containing evidence for NMOSD. The PICOS approach allowed for strict criteria to identify included studies. Two reviewers were involved at every stage of the SLRs (title/abstract review, full-text review, data extraction, and analysis) to ensure quality. Specific studies were identified that focused on NMOSD through a search strategy that was well balanced for specificity and sensitivity. The SLRs followed a transparent search strategy whereby the results can be reproduced using the same search terms and databases. There was no restriction on the timeframe for the clinical efficacy and effectiveness SLRs ensuring that all studies on NMOSD could be captured since database inception.

However, this SLR is not without limitations. Conclusions of the SLR were based on the included publications only. Some data were reported exclusively in conference abstracts, providing a limited context for interpretation. Sources of confounding within the dataset included, but were not limited to, country differences, sample size, treatment, severity of disease, and comorbidities. Moreover, publication bias is an inherent limitation to every SLR and cannot be avoided, despite a rigorous methodology. It may happen when pertinent studies, either ongoing or completed, remain unpublished. Studies included in these SLRs were limited by outcomes of interest at the data extraction phase; studies without relevant outcomes of interest were excluded. Included studies may be biased toward achieving a positive result. Differences between the study characteristics of the included studies were observed and may introduce bias into the conclusions of these studies, and therefore the conclusions of these SLRs. Additionally, despite implementing vigorous and accepted systematic review methods to mitigate bias the outcomes of SLRs, including this one, are restricted by the quality and quantity of evidence derived from the incorporated studies. A significant limitation of the available evidence from SATs studies is the inclusion of small numbers of patients in many studies. Furthermore, the search strings were limited to treatments of interest, increasing the risk of overlooking relevant evidence if treatment was not indexed or mentioned in the title or abstract. Finally, in the SLR update, only studies excluded based on "study design" were reassessed, potentially omitting relevant single-arm trials that were misclassified.

N.1.4 Unpublished data

Not applicable, as no unpublished data was included in the SLR.

Appendix O. Supporting information on the medical background

Disease description

Neuromyelitis optica spectrum disorder (NMOSD; also known as Devic's syndrome) is a rare, chronic, autoimmune, inflammatory disorder of the central nervous system (CNS) that often follows a relapsing course (2, 3). NMOSD was originally thought to be a variant of multiple sclerosis (MS) but is now recognized as a distinct disease (138). NMOSD is a severely disabling and potentially life-threatening condition, characterized by recurrent inflammatory attacks that manifest as optic neuritis, myelitis, and certain brain and brainstem syndromes (139). Approximately 60-80% of patients with NMOSD have autoantibodies to aquaporin 4 (AQP4-immunoglobulin G [IgG]) (140, 141) and AQP4-IgG-seropositive (AQP4+) NMOSD has a high female to male ratio (up to 9:1) (15, 29, 142, 143). The prevalence and prognosis of NMOSD varies between patients of different ethnicities; for example, the prevalence of NMOSD is higher and the age at disease onset is lower for Afro-Caribbean and East Asian populations than for Caucasian populations (143). To provide the most relevant evidence in terms of prognosis and patient characteristics, this dossier focuses on studies in Caucasian populations, primarily from Scandinavia.

Pathophysiology

The pathophysiology of NMOSD is complex with B-cells playing a fundamental role; consequently, B cells are a key target of some NMOSD therapies. A subpopulation of B cells that have differentiated into plasmablasts/plasma cells are responsible for the production of pathogenic IgG autoantibodies against AQP4, which are highly specific to NMOSD and are detected in the majority of patients (38, 141). CD19 is expressed on a wider lineage of B cells than CD20, including plasmablasts and some plasma cells (37, 38), and the number of CD19+ B cells has been shown to be increased in the blood of AQP4+ individuals with NMOSD, with the highest levels observed during an attack (5, 144).

AQP4 is the most abundant water channel expressed on the plasma membrane of astrocytes throughout the CNS. AQP4 autoantibodies are pathogenic because they bind to AQP4, causing astrocyte cell death and inflammation through complement dependent and independent mechanisms (3, 5, 145). Complement activation downstream of AQP4-IgG binding triggers recruitment of immune cells and astrocyte cell death via complement-dependent cytotoxicity (145). Independent of the complement system, AQP4 autoantibodies activate effector cells, such as natural killer cells, that cause antibody-dependent cellular cytotoxicity (ADCC). AQP4 autoantibody targeting of astrocytes leads to the subsequent degeneration of oligodendrocytes, secondary demyelination, and neuronal damage (3, 5, 146). Finally, autoreactive B cells are also involved in the activation of T-cells, which produce proinflammatory cytokines such as interleukin (IL)-6. These cytokines then recruit leukocytes to CNS lesions, potentiating the inflammatory response and neuronal damage (3, 144).

Clinical presentation

The clinical presentation of NMOSD depends on the location of the lesions and the resulting symptoms. Attacks are classified as optic neuritis, resulting in loss of vision or blindness, or transverse myelitis, resulting in severe motor impairment, loss of the ability to walk, sensory impairment, and bowel/bladder dysfunction. Attacks may also affect the brain stem, leading to refractory nausea, vomiting, and burping (area postrema syndrome), or cerebrum, leading to cognitive impairment, language dysfunction, and drowsiness (147, 148).

NMOSD attacks typically progress over days and about 76% of patients do not recover fully from the first attack. Patients who are AQP4+ are more likely to experience severe attacks than AQP4-IgG-negative (AQP4-) patients (149). At least 90% of patients with NMOSD experience recurrent attacks (6), which can lead to the accumulation of neurodegeneration and morbidity over time, with many individuals developing permanent

visual and motor disabilities, including wheel-chair dependency (4, 140, 149). Consequently, many patients with NMOSD are dependent on care provided by professional or informal caregivers (150).

Appendix P. [redacted] Validity of outcomes

The primary aim of NMOSD treatment is to prevent further attacks, in order to prevent disability worsening (4, 140, 149). Based on discussions with the U.S. Food and Drug Administration (FDA), the primary endpoint in N-MOmentum of time to first attack was considered a valid endpoint (28, 92, 151).

Disability in NMOSD and changes over time are measured using the EDSS, a tool used to evaluate disability in MS (152). The EDSS and functional system scores (FSS) were adopted from MS to measure disability in NMOSD. Nevertheless, some dimensions, such as visual function, pain, fatigue, depression, cognition, and function of upper limbs are not adequately captured by the EDSS (14). However, due to the lack of a validated scale for assessing disability in NMOSD, and the similarities between NMOSD and MS, the EDSS is used in this study as well as other key trials in NMOSD (153-156). The scale ranges from 0 to 10, with 0 being full function and 10 being dead (156). The EDSS score has been accepted as a measure of disease disability in the DMC assessments for eculizumab and satralizumab (28, 92).

Appendix Q. Supporting information for health economic analysis

Q.1.1 Additional information on the model structure

Treatment allocation

Patients were allocated to one of the included treatments in the model. During each cycle, patients faced the risk of discontinuing their current treatment at the beginning of the model cycle. If patients discontinued treatment, they received placebo (as per the N-MOmentum trial, see section 6.1) for the remainder of the time horizon.

Stable disease/NMOSD attack

In each model cycle, patients faced a treatment-specific risk of experiencing an NMOSD attack. Patients with stable disease were defined as patients who did not experience an attack. Details on inputs are provided in section 7. In the model, the risk of experiencing the first or subsequent attacks was estimated based on data on time to first adjudicated attack from the N-MOmentum trial on inebilizumab. This was extrapolated beyond the duration of the N-MOmentum trial, and an exponential parametric model was fitted to data (for details, please see Section 8.1.1.1).

EDSS score progression

When patients experienced an NMOSD attack, they risked progressing in their EDSS score. Patients could progress more than one EDSS score each time they experienced an NMOSD attack. Details on inputs are provided in section 8.

Death

In each model cycle and during both 'stable disease' and 'NMOSD attack', patients were at risk of dying and transitioning to the 'Death' health state, whether due to general or NMOSD-related mortality.

Perspective

The health economic model takes on a limited societal perspective as per the DMC methods guide. This means that the model also includes costs related to transportation for the patient and patients' time spent in connection with treatment.

Time horizon and cycle length

The model estimates costs and health benefits expressed as QALYs over a lifelong time horizon. A lifelong time horizon was considered appropriate to ensure all relevant downstream benefits and costs were captured given the chronic nature of NMOSD. A maximum of 60 years was chosen in the model (i.e. patients are modelled until they die or turn 100 years), which sufficiently captures each patient's lifetime. The model applied a cycle length of 1 month to optimally fit the administration patterns of all relevant comparators.

Adverse events

The risk of adverse events (AEs) associated with inebilizumab and placebo were obtained from the N-MOmentum trial. AE risks for rituximab were extracted from identified studies and presented in section 0. Only AEs with an event rate above 5% are included in the model.

Model outcomes

Three outcomes of treatment effect are used in the model, as described above: time to NMOSD attack, EDSS score progression, and survival. Model transitions were based on the risk of experiencing an NMOSD attack.

Model validity

The model was validated internally: the internal validity and technical accuracy of the model at all stages of development were routinely checked by the health economists working on the model's development and by an independent health economist using an extensive quality checklist. Any errors identified by the quality check were addressed in the final model. An additional model validation was performed specifically to meet modelling requirements for the Danish setting.

Methods of addressing uncertainty

To assess the uncertainty associated with the parameters informing the model, various deterministic sensitivity analyses and a probabilistic sensitivity analysis (PSA) are performed.

Deterministic sensitivity analyses

Parameters included in the one-way sensitivity analyses (OWSAs) are listed in Table 72 (Appendix G). The OWSAs were conducted by varying the base case value by +/-10%. Table 72 in Appendix G presents the variables used in the OWSA. Scenario analyses were conducted as well, replacing the value applied in the base case with the lower- and upper-bound estimates usually according to the inner quartile range limits of the distributions used to inform the parameter. Additional scenario analyses were conducted with plausible alternative data where available. Included parameters are listed in Table 99 in Appendix L

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the parameter uncertainty simultaneously by ascribing distributions to all uncertain parameters (see Appendix G for details). The PSA conducts 1,000 such iterations, and the key result averages (life-years [LYs], QALYs, and incremental cost-effectiveness ratios [ICERs]) are presented in the PSA result. The key output of a PSA is a scatter plot of the ICERs within the cost-effectiveness (CE) plane. The plot is accompanied by a separate figure, the cost-effectiveness acceptability curve (CEAC), which presents the proportion of favorable results (i.e. considered cost-effective) at progressively higher CE thresholds.

Q.1.2 Supporting information for health economic analysis

EDSS score increments

When a patient experiences a NMOSD attack, the patient's EDSS score is at risk of changing. Changes in EDSS score associated with a NMOSD attack were based on a post-hoc analysis conducted in the patients with AQP4+ NMOSD from the N-MOmentum trial. Patients transition through the model across EDSS categories following an NMOSD attack.

An analysis of change in EDSS score associated with an attack by prior EDSS level was performed for two sub-samples: patients who undertook a follow-up visit (i.e. complete follow-up) and patients who had at least one visit after an NMOSD attack (i.e. nearest follow-up). Results from the post-hoc analysis are presented in Table 111 and Table 112.

Table 111 in presents the number of patients who experienced EDSS increments (or decrements) between -3.0 and +4.5 following a NMOSD attack. These patient counts were then grouped according to their EDSS score upon attack onset, and the table provides counts for both the complete- and nearest-follow up sub-samples. For example, in the complete follow-up sub-sample three patients who experienced a NMOSD attack with an EDSS score >2 and ≤4 experienced an EDSS score increase of 1.0.

The EDSS decrements applied in the model are presented in Table 111 in as the percentage of patients who will experience either an increase, a decrease, or no change in EDSS score following an NMOSD attack. The model assumed that the EDSS increment was the same for all patients regardless of EDSS score prior to the NMOSD attack. This assumption was made due to the small number of data points.

Table 111 Change in EDSS associated with an attack by prior EDSS level

Change in EDSS	Complete follow up sample					Nearest follow up sample				
	[0-2]	(2-4]	(4-6]	(6-8]	(8-10]	[0-2]	(2-4]	(4-6]	(6-8]	(8-10]
-3.0										
-2.5										
-2.0										
-1.5										
-1.0		■					■			
-0.5			■					■		
0.0	■	■	■	■		■	■	■	■	
0.5		■	■	■			■	■	■	
1.0	■	■		■		■	■	■	■	
1.5			■	■			■	■	■	
2.0		■					■			
2.5		■					■			
3.0										
3.5		■					■			
4.0		■					■			
4.5		■					■			

Abbreviations: EDSS: expanded disability status scale.
Source: Post hoc analysis of N-MOmentum data and own calculations.

Table 112 Different point changes in EDSS following an NMOSD attack (percent)

EDSS increment	Complete follow-up sample	Nearest follow-up sample
-3	[redacted]	[redacted]
-2.5	[redacted]	[redacted]
-2	[redacted]	[redacted]
-1.5	[redacted]	[redacted]
-1	[redacted]	[redacted]
-0.5	[redacted]	[redacted]
0	[redacted]	[redacted]
0.5	[redacted]	[redacted]
1	[redacted]	[redacted]
1.5	[redacted]	[redacted]
2	[redacted]	[redacted]
2.5	[redacted]	[redacted]
3	[redacted]	[redacted]
3.5	[redacted]	[redacted]
4	[redacted]	[redacted]
4.5	[redacted]	[redacted]

Abbreviations: EDSS: expanded disability status scale; NMOSD: myelitis optica spectrum disorder.

Transitions

Patients transition through the model across EDSS categories following an NMOSD attack. Patient transitions were modelled based on EDSS category prior to and following an NMOSD attack observed in the N-MOmentum trial. Table 113 presents the transition matrix applied in the model. The transition matrix illustrates the risk of changing an EDSS score (presented in the table's columns) by EDSS score prior to NMOSD attack (presented in the table's rows). If a patient has an EDSS score of 3 prior to an NMOSD attack, the patient has a [redacted] probability of retaining that EDSS score after the attack, while the patient has a [redacted] and [redacted] risk of transitioning to EDSS score 3.5 or 4.0, respectively. Patients might also transition to lower EDSS scores. In both ends of the matrix, EDSS 0 and EDSS 10 (after attack), the risk of transitioning to this score is equal to the cumulative probabilities. If a patient has an EDSS score of 8.5 before an attack, the risk of transitioning to an EDSS score 10 is [redacted], which is the sum of the risk of experiencing an EDSS increase of 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 scores.

An EDSS score of 10 is defined as death and is an absorbing state.

Table 113 Transition matrix: Transition across EDSS categories for patients experiencing an NMOSD attack, by EDSS category prior to attack

EDSS	EDSS score after attack																				
	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
0	[redacted]																				
0.5	[redacted]																				
1	[redacted]																				
1.5	[redacted]																				
2	[redacted]																				
2.5	[redacted]																				
3	[redacted]																				
3.5	[redacted]																				
4	[redacted]																				
4.5	[redacted]																				
5	[redacted]																				
5.5	[redacted]																				
6	[redacted]																				
6.5	[redacted]																				
7	[redacted]																				
7.5	[redacted]																				
8	[redacted]																				
8.5	[redacted]																				
9	[redacted]																				
9.5	[redacted]																				
10	[redacted]																				

Note: The table presents the transition of patients across EDSS categories (columns) by EDSS score prior to attack (rows).

Treatment discontinuation

In each model cycle in which treatment was administered, patients faced the risk of discontinuing their current treatment. This implied that patients treated with inebilizumab were allowed to discontinue treatment only every 6 months. Patients who discontinued treatment were assumed to receive placebo for the remaining model time horizon. This assumption was made to avoid adding additional uncertainty to the analysis, based on the lack of licensed treatments in this patient population and the lack of robust efficacy data for second line treatments. Patients who continued treatment with placebo faced the risk of a NMOSD attack and EDSS progression as estimated from N-MOmentum.

Data on treatment discontinuation was applied from the following clinical studies and converted to annual discontinuation rates.

Inebilizumab:
Four of 161 patients with AQP4+ NMOSD discontinued treatment with inebilizumab during the RCP in the N-MOmentum trial. This implied a discontinuation rate of 2.48% in the study period. Patients in this patient group were observed for a total of 74.1 patient-years (PY). The annual discontinuation rate was calculated to be 5.32% (95% CI: 1.85%-8.79%) (data on file).

Rituximab:
In the SLR, three studies including a total of 141 patients presented discontinuation rates for patients treated with rituximab. The weighted average discontinuation rate was [redacted] over a weighted average follow-up period of [redacted]. This implies a yearly discontinuation rate of [redacted](43–45).

[redacted] depicts the treatment distribution by treatment arm in the model. The average time on treatment for inebilizumab and rituximab in the model is [redacted] respectively.

[redacted]

[redacted]

Mortality

In each model cycle, patients can exit the model because of mortality. The model includes two sources of mortality:

- General mortality
- NMOSD-related mortality

General mortality is included in the model based on local input on age and gender-specific life tables. From the model, inputs on baseline patient characteristics and age-specific general mortality risk are calculated and applied uniformly across the study population irrespective of EDSS score. With cumulative NMOSD attacks, a patient's EDSS score gradually increases over time. Patients reaching an EDSS score of 10 exit the model due to NMOSD-related mortality. Therefore, although the model does not explicitly account for an excess mortality risk associated with NMOSD attacks, this is still captured as patients face the risk of exiting the model following an NMOSD attack that increases their EDSS to 10. [redacted] presents the simulated undiscounted survival for patients treated with inebilizumab and rituximab, respectively, along with the general mortality for a similar age group in Denmark.

Papp et al (8) estimated the median life expectancy for Danish patients with AQP4+ NMOSD to be 64.08 years, compared to 83.07 years for the general population. When comparing the modelled life expectancy for patients with the same diagnostic age (48 years) by adding the area under the curve (representative of the average remaining life-years in the model) to the model start age (48 years), the life expectancy in both the rituximab arm (63.4 years) and the general population (84.0) are very similar to the estimated life expectancy in Papp et al (8). The modelled rituximab arm is assumed to be representative of the patient population in the publication by Papp et al. Table 114 summarizes the comparison between real-life and modelled data.

Table 114 Comparing long-term with modelled survival in patients with AQP4+ NMOSD

Starting age	Survival data from CEM. Age of death			Average life expectancy In Denmark	Survival data NMOSD patient in Denmark
	General population	Rituximab	Inebilizumab	(89.4% female)	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CEM: cost-effectiveness model; N/A: Not applicable; NMOSD, Neuromyelitis optica spectrum disorder.
Source: Statistics Denmark, Papp et al 2024 (8)

Q.1.3 Additional information on quality of life data

Table 115 Pattern of missing data and completion – full details

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data are missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Inebilizumab				
Baseline (RCP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 (RCP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 28 (RCP)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline (OLP)*	[redacted]	[redacted]	[redacted]	[redacted]
Week 13 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 26 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 39 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 65 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 78 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 91 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 104 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 117 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 130 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 143 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 156 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 169 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 182 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 195 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 208 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo				
Baseline (RCP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 (RCP)	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 28 (RCP)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline (OLP)*	[redacted]	[redacted]	[redacted]	[redacted]
Week 13 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 26 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 39 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 65 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 78 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 91 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 104 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 117 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 130 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 143 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 156 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 169 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 182 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 195 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]
Week 208 (OLP)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQoL: Health-related quality of life; OLP: Open-label period; RCP, Randomized controlled period.
*Baseline OLP corresponds to Day 197 of the RCP.

Table 116 HRQoL SF-36 summary statistics – full details

	Intervention		Comparator		Intervention vs comparator
	N	Mean (95% CI)	N	Mean (95% CI)	Difference (95% CI) p-value
Mental component, SF-36v2, ITT APQ4+ population					
Baseline RCP (absolute value)	[redacted]				
Week 12 RCP					
Week 28 RCP					
Baseline OLP					
Week 13 OLP					
Week 26 OLP					
Week 39 OLP					
Week 52 OLP					
Week 65 OLP					
Week 78 OLP					
Week 91 OLP					
Week 104 OLP					
Week 117 OLP					
Week 130 OLP					
Week 143 OLP					
Week 156 OLP					
Week 169 OLP					
Week 182 OLP					
Week 195 OLP					
Week 208 OLP					
[redacted]					
Baseline RCP (absolute value)					
Week 12 RCP					
Week 28 RCP					

	Intervention	Comparator	Intervention vs comparator
Baseline OLP	[redacted]	[redacted]	[redacted]
Week 13 OLP	[redacted]	[redacted]	[redacted]
Week 26 OLP	[redacted]	[redacted]	[redacted]
Week 39 OLP	[redacted]	[redacted]	[redacted]
Week 52 OLP	[redacted]	[redacted]	[redacted]
Week 65 OLP	[redacted]	[redacted]	[redacted]
Week 78 OLP	[redacted]	[redacted]	[redacted]
Week 91 OLP	[redacted]	[redacted]	[redacted]
Week 104 OLP	[redacted]	[redacted]	[redacted]
Week 117 OLP	[redacted]	[redacted]	[redacted]
Week 130 OLP	[redacted]	[redacted]	[redacted]
Week 143 OLP	[redacted]	[redacted]	[redacted]
Week 156 OLP	[redacted]	[redacted]	[redacted]
Week 169 OLP	[redacted]	[redacted]	[redacted]
Week 182 OLP	[redacted]	[redacted]	[redacted]
Week 195 OLP	[redacted]	[redacted]	[redacted]
Week 208 OLP	[redacted]	[redacted]	[redacted]

Abbreviations: Not reported; OLP: Open-label extension period; RCP: Randomized controlled period; SE: Standard error

[redacted]

[redacted]

Appendix R. Supporting information from N-MOmentum trial

R.1.1 Exploratory/Post hoc

AAR - The **AAR** over the entire trial period (RCP and OLP) in the AQP4+ population receiving inebilizumab **was estimated to be 0.09** (10). This was based on 60 adjudication committee (AC)-determined attacks occurring over 667.513 person-years. In a post-hoc analysis of the N-MOmentum trial, **a decrease in the AAR with inebilizumab treatment could be observed over time**. From baseline to month 6, the AAR was 0.28, decreasing further to 0.07 after 0.5-1.5 years, 0.06 after 1.5-2.5 years, and 0.03 after ≥2-5 years (79). In the N-MOmentum end of study analysis, AAR was reduced to as much as 0.022 (adjusted) in AQP4+ patients treated continuously over 4-years with inebilizumab (81).

Post rituximab efficacy - A post-hoc analysis of the trial data assessed the efficacy and tolerability of inebilizumab in patients **previously treated with rituximab** (157). Out of 17 patients in the trial previously treated with rituximab, 13 were randomly assigned to inebilizumab. One of these patients experienced an attack in the RCP (HR vs all placebo: 0.16; 95% CI: 0.02-1.20; p = 0.07)**. During the OLP, two additional patients treated with inebilizumab experienced attacks, with an AAR of 0.08 (95% CI: 0.02-0.34) attacks/person-year. This AAR was similar to that of patients without prior rituximab use in the trial (0.10; 95% CI: 0.07-0.15).** Seven patients who had previously received rituximab had breakthrough attacks prior to enrollment in the N-MOmentum trial (AAR of 0.78 attacks/person-year) but did not experience any attacks during inebilizumab treatment (157). Based on this, it can be concluded that inebilizumab appears to be equally effective in rituximab pre-treated patients compared with untreated patients.

FCGR3A Status - Finally, a post-hoc analysis evaluated the impact of a highly prevalent FCGR3A mutation (V158F, by allelic status) (33) known to inhibit rituximab efficacy by 5.5 fold (158). This analysis included 142 patients (inebilizumab, n = 104; placebo, n = 38) who consented to *FCGR3A* polymorphism genotyping, of whom 14 (10%) were homozygous VV, 60 (42%) were heterozygous VF, and 68 (48%) were homozygous FF. There were no significant differences in the clinical metrics of NMOSD activity (AAR, relapse rate or EDSS) or B-cell depletion between V allele (VV and VF) and FF allele subgroups.

R.1.2 Patient-reported outcomes

SF-36 - HRQL was evaluated in patients with NMOSD using the 36-Item Short Form Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS). In the AQP4+ population in the RCP, the changes in PCS and MCS scores from baseline to week 28 were similar between the inebilizumab and placebo arms.

Changes from baseline in SF-36 MCS and PCS scores were similar in the OLP and no obvious trends were observed over time.

For patients with a baseline SF-36 pain score <40, there was a statistically significant improvement in median score at the end of the RCP compared with baseline for patients who received inebilizumab (median improvement of 3.6 [IQR 0.0, 8.1], p<0.001) (159). After 3 years of inebilizumab treatment, improvements in pain scores were reported in 78% (p<0.001) of patients with SF-36 pain score <40 at baseline (81).

NRS-11 - During the RCP, the average 11-point **Pain Numeric Rating Scale (NRS-11) score for the inebilizumab and placebo groups was similar**. In the AQP4+ population, a **trend towards a smaller mean increase in leg pain was observed in the inebilizumab versus the placebo group**. These results remained constant during the OLP (10). Fewer patients receiving inebilizumab than placebo reported a ≥3-point worsening in the pain score relative to baseline (OR: 2.6; 95% CI: 1.2-5.9) including in patients who experienced no attacks (OR: 0.56; 95% CI: 0.2-1.4) (159). Furthermore, a higher proportion of patients receiving inebilizumab were free of moderate (OR: 2.2; 95% CI: 1.0-5.6) and severe pain (OR: 2.3; 95% CI: 1.2-4.6) versus those receiving placebo.

R.1.3 Long-term efficacy

Inebilizumab demonstrated sustained long-term efficacy, as shown in a post-hoc analysis of the N-MOmentum trial (43). This analysis included the full study period (i.e. RCP and OLP) and included 75 patients with AQP4+ NMOSD who had received inebilizumab treatment for ≥4 years. Among these patients, 18 attacks occurred after initiation of inebilizumab, of which 12 (67%) occurred in the first year of treatment. Four of these attacks were rated as major in severity. In years 2-4, two attacks occurred each year, with only one attack rated as major in severity. **Of all 75 participants, 62 (83%) were attack-free throughout the whole study period (≥4 years) while on treatment with inebilizumab. After 1 year on inebilizumab treatment, the proportion of attack-free patients increased to 92% during the remaining study period**. Inebilizumab treatment also resulted in a robust depletion of CD20-positive B cells that was maintained throughout the whole study period, regardless of the originally assigned study arm during the RCP.

R.1.4 Adverse events experienced during open-label period

The adverse events experienced during the open-label period are presented in Table 117 and Table 118. Table 118 presents serious adverse events that occurred in more than 5% of the patients, in line with the adverse events reported in section 9.1.1.

Table 117 Overview of safety events (open label period)

	Inebilizumab/Inebilizumab (N = 154) (OLP, N-MOmentum trial)	Placebo/Inebilizumab (N = 47) (OLP, N-MOmentum trial)	Difference, % (95 % CI)
Number of adverse events, n	1,040	403	NR
Number and proportion of patients with ≥1 adverse events, n (%)	133 (86.4%)	41 (87.2%)	NR
Number of serious adverse events*, n	29	28	NR
Number and proportion of patients with ≥1 serious adverse events*, n (%)	17 (36.2%)	21 (13.6%)	NR
Number of CTCAE grade ≥3 events, n	90	36	NR
Number and proportion of patients with ≥1 CTCAE grade ≥3 events§, n (%)	30 (19.5%)	15 (31.9%)	NR
Number of adverse reactions, n	123	60	NR
Number and proportion of patients with ≥1 adverse reactions, n (%)	5 (3.2%)	4 (8.5%)	NR
Number and proportion of patients who had a dose reduction, n (%)	0	2 (4.3%)	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	32 (20.8%)	8 (17.0%	NR

	Inebilizumab/Inebilizumab (N = 154) (OLP, N-MOmentum trial)	Placebo/Inebilizumab (N = 47) (OLP, N-MOmentum trial)	Difference, % (95 % CI)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	3 (1.9%)	1 (2.1%)	NR

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; NR: Not reported; OLP: Open-label period; RCP: Randomized controlled period
* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
§ CTCAE v. 5.0 must be used if available.
Source: Clinical Study Report (10)

Table 118 Serious adverse events (open label period)

Adverse events	Inebilizumab/Inebilizumab (N = 154), OLP		Placebo/Inebilizumab (N = 47), OLP	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Urinary tract infection, n (%)	2 (1.3%)	0	6 (12.8%)	0

TAbbreviations: OLP: Open-label period; RCP: Randomized controlled period
* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Source: Clinical Study Report (10)

Appendix S. Checklist and test of CEM and BIM

tjekliste-og-test-til-su
ndhedsøkonomiske-m

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk