Medicinrådet

Bilag til Medicinrådets vurdering af ravulizumab til behandling af neuromyelitis optica spektrum

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. ravulizumab til NMOSD
2. Forhandlingsnotat fra Amgros vedr. ravulizumab til NMOSD
3. Ansøgers endelige ansøgning vedr. ravulizumab til NMOSD
4. Evt. øvrige bilag

Feedback to DMC Assessment Report on NMOSD

Relapses in NMOSD are unpredictable and often cause permanent disability; 76% of patients do not fully recover after relapse[1], and relapse prevention is the core treatment goal in clinical guidance[2]. For the assessment to accurately reflect clinical practice, we recommend DMC to:

- Recognize relapse prevention as an evidence-based driver of lower mortality and retain the dual-pathway model of disease to reflect NMOSD pathophysiology. If residual concerns of double counting persist, adjust the disability multiplier of mortality or per-relapse EDSS increase in sensitivity analyses. A realistic extrapolation function should also be used. Thereafter, validate base-case relapse, disability, and mortality projections against external NMOSD data to ensure external validation.
- Remove the non–evidence-based infection-related restriction on ravulizumab (Ravu) post-rituximab (RTX). With standard risk mitigation, absolute meningococcal risk under ravu is low and overall serious infection risk appears lower than with RTX. The risk-benefit assessment of treatment should be done by the treating physician, and not restricted beforehand.

Meningococcal infections: DMC asserts higher risks of meningococcal and other opportunistic infections with ravu versus other immunosuppressants (IST) and proposes restricting use after RTX discontinuation due to infection. No comparative evidence is cited; available evidence indicates the opposite.

Data show that RTX infection burden in NMOSD is substantial[3] and that a significantly lower rate of serious infection related adverse events was observed for C5 inhibitors compared to RTX, with an incidence rate ratio of 0.17 (95% CI 0.06–0.43, p=0.0002)[4].

Meningococcal infection is a monitored class risk of terminal complement inhibition, for which established risk mitigation measures are in place[5]. The published evidence of meningococcal infections suggests that the rate is low[6]. Long-term extension results showed no new safety signal, suggesting the safety profile remains consistent over time[7].

No evidence supports that patients who have had RTX prior to ravu treatment, and have discontinued RTX due to an infection, would be at higher risk of infection. Given distinct mechanisms of action (B-cell depletion vs complement inhibition), immunosuppression with RTX does not necessarily imply an increased or comparable infection risk with ravu, and the two agents' infection profiles should not be conflated.[8] Additionally, sub-group analyses have failed to identify any safety difference of C5 treatment between RTX-exposed and RTX-naïve patients[9], rather the opposite with decreased hospitalizations and comorbidities of C5 treatment post-RTX treatment[10].

Mortality: DMC applies the same SMR to ravu and SoC, effectively decoupling mortality from relapse prevention. This conflicts with evidence that mortality in NMOSD is largely relapse-driven, as shown in several studies[11]

In the model, mortality is linked to relapse reduction using treatment-specific mortality hazard ratios proportional to observed relapse reductions, with a cap so non-disabled ravu patients do not have lower-than-general-population mortality. Given near-elimination of adjudicated relapses with ravu and published relapse–mortality associations, this is clinically plausible.

A separate mortality uplift applies in the long-term disability state to reflect excess risk with high disability. If double-counting is a concern, set the disability multiplier to 1.0 while retaining relapse-linked mortality differences grounded in NMOSD pathophysiology and observed relapse effects.

Effect of comparator: DMC questions representability of PREVENT's placebo group where 33% received no IST and 9.5% corticosteroids alone, implying Danish practice would have lower relapse risk.

PREVENT placebo ARR (~0.35) was below historically observed ARR (due to event-driven design, adjudication, regression to the mean, placebo effect) and below real-world ARR (~0.8 in US)[12]. Across pivotal trials (eculizumab, inebilizumab, satralizumab) with differing IST policies, including where IST was mandated for all patients, placebo relapse was higher than in PREVENT [13]. In addition, PREVENT's event-driven design curtailed placebo follow-up (median 0.83 vs 1.71 years in eculizumab)[14], likely under-observing subsequent relapses and downstream disability in the control arm. In all, the evidence suggests that PREVENT placebo ARR is conservative even for Danish setting.

Extrapolation in the model: Multiple parametric fits are statistically acceptable over observed data; clinical plausibility for long-term relapse risk should therefore guide the selection. Clinical input supported the exponential model in the base case as a realistic scenario. If alternatives are desired, Weibull or Gamma provide more plausible long-run hazards than lognormal, which risks understating relapse risk.

Modelling of disease progression. DMC is concerned about double counting with both a 17.5% immediate transition to long-term disability per relapse and a +0.56 EDSS increment per relapse. NMOSD's natural history justifies two pathways: immediate disability from severe attacks[15] and cumulative permanent disability accrual across relapses[16], unlike MS's more gradual progression.

In the model, the +0.56 EDSS/relapse is not tied to QALY estimation, it is merely an alternative pathway to long term disability state. This estimate can be lowered if worry persists on double counting. Removing the immediate pathway to long-term disability would underestimate patient impact and contradict clinical experience of abrupt disability after severe relapses which is characteristic to NMOSD.

Patient characteristics: Starting age should reflect ravu-relevant populations for Danish AQP4+ post RTX patients (≈45)[17], and not be based on DMC unreferenced assumptions.

Quality of Life: Differential dropout does not inherently bias treatment effects; bias depends on the missing-data mechanism and handling. Disability utilities were sourced from literature using UK weights; Danish 2009 weights cited by DMC are outdated, and the 2021 Danish value set may not systematically produce higher values than UK. Given uncertainty and relevance of published mappings, use of UK weights is reasonable; impact can be tested in sensitivity analyses.

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31.03.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.04.2026
Leverandør	Alexion Pharma Nordic
Lægemiddel	Ultomiris (ravulizumab)
Ansøgt indikation	Til behandling af voksne patienter med neuromyelitis optica spektrum sygdom (NMOSD), som er anti-aquaporin 4 (AQP4)-antistofpositive.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Ultomiris (ravulizumab):

Tabel 1: Aftalepris

Lægemiddel	Styrke (Paknings-størrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Ultomiris	1.100 mg (1 stk.)	137.092,01	[redacted]	[redacted]
Ultomiris	300 mg (1 stk.)	37.388,73	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale på Ultomiris. Aftalen løber indtil den 31.10.2026 med mulighed for forlængelse i 12 måneder. [redacted]

Konkurrencesituationen

Der findes ingen anbefalet standardbehandling for NMOSD i Danmark. Rituximab gives off-label som forebyggende behandling efter et attak.

Medicinrådet har tidligere vurderet tre andre lægemidler til NMOSD; Enspryng (satralizumab), Soliris (eculizumab) og Uplizna (inebilizumab), men anbefaler ikke disse behandlinger til NMOSD.

Tabel 2 nedenfor viser de årlige lægemiddeludgifter til Ultomiris for en patient, der vejer mellem 60 og 100 kg, da størstedelen af patienterne forventes at ligge i dette vægtinterval, jf. Medicinrådets vurdering af ravulizumab til behandling af neuromyelitis optica spektrum sygdom.

Tabel 1: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Ultomiris	1.100 mg (1 stk.)	Støddosis: 2.700 mg, i.v. Vedligeholdelse*: 3.300 mg hver 8. uge, i.v.	[redacted]	[redacted]

*Første vedligeholdelsesdosis administreres 2 uger efter støddosis

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	Revurdering i gang	Link til status
England	Ansøgning tilbagetrukket		Link til status
Sverige	Ikke ansøgt		

Opsummering

[redacted]

Application for the assessment of Ravulizumab (Ultomiris) as an add-on to standard therapy for the treatment of adult patients with Neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
(yellow)	Confidential information

Contact information

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Abbreviations

Abbreviation	Meaning
ADA	Anti-Drug Antibodies
AE	Adverse Event
AIC	Akaike Information Criterion
AQP4	Aquaporin-4
ARR	Annualised Relapse Rate
ATE	Average Treatment Effect
ATT	Average effect of the treatment on the treated
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BSA	Body Surface Area
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
C5	Complement Component 5
DK	Denmark
DMC	Danish Medicines Council
DRG	Diagnosis Related Groups
DSA	Deterministic Sensitivity Analysis
EAN	European Academy of Neurology
EC	European Commission
EC	External Comparator
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	End of study
EQ-5D	EuroQol 5-Dimension Quality Of Life Questionnaire
EQ-5D-3L	EuroQoL 5-Dimension 3-Level Questionnaire
EQ-5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
FAS	Full Analysis Set
HAI	Hauser Ambulation Index
HCRU	Healthcare Resource Use
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life

Abbreviation	Meaning
HSUVs	Health State Utility Values
HTA	Health Technology Assessment
ICC	Intraclass Correlation
ICER	Incremental Cost-Effectiveness Ratio
IgG	immunoglobulin G
IPND	International Panel for NMO Diagnosis
IQR	Interquartile Range
IST	Immunosuppressive Therapy
IV	Intravenous
IVIg	Intravenous immunoglobulin
kg	Kilogram
KM	Kaplan-Meier
LETM	Longitudinally extensive transverse myelitis
LTD	Long-Term Disability
mAB	Monoclonal Antibody
MAC	Membrane Attack Complex
MOG	Myelin Oligodendrocyte glycoprotein
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
MS	Multiple Sclerosis
N/A	Not Applicable
NEMOS	Neuromyelitis Optica Study Group
NIH	National Institutes of Health
NMOSD	Neuromyelitis Optica Spectrum Disorder
NR	Not Reported
OCT	Optical Coherence Tomography
OLE	Open Label Extension
ON	Optic Neuritis
OSIS	Optic Spinal Impairment Score
PLEX	Plasma Exchange
PML	Progressive Multifocal Leukoencephalopathy
PNH	Paroxysmal Nocturnal Hemoglobinuria
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
QoL	Quality Of Life
RAC	Relapse Adjudication Comittee
RCT	Randomized Controlled Trial
RfA	Request for Assessment
SAE	Serious Adverse Event
SAT	Single-Arm Trial

Abbreviation	Meaning
SD	Standard Deviation
SE	Standard Error
SF-36	36-Item Short Form Health Survey
sIPTW	Stabilised Inverse Probability Treatment Weights
SLR	Systematic Literature Review
SMD	Standardized Mean Difference
SoC	Standard of Care
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organisation

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Ultomiris
Generic name	Ravulizumab
Therapeutic indication as defined by EMA	Ravulizumab is indicated in the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive
Marketing authorization holder in Denmark	Alexion Pharma Nordics AB
ATC code	L04AJ02
Combination therapy and/or co-medication	-
(Expected) Date of EC approval	Approved as extension of indications on May 10, 2023
Has the medicine 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	Ravulizumab is also indicated for: The treatment of adult and paediatric patients with a body weight of 10 kg or above with **paroxysmal nocturnal haemoglobinuria**: • in patients with haemolysis with clinical symptom(s) indicative of high disease activity • in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months. The treatment of adult and paediatric patients with a body weight of 10 kg or above with **atypical haemolytic uremic syndrome** who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab. Add-on to standard therapy for the treatment of adult patients with **generalised myasthenia gravis** who are anti-acetylcholine receptor (AChR) antibody-positive.

Overview of the medicine	
Other indications that have been evaluated by the DMC (yes/no)	**PNH** as part of "Behandlingsvejledningen" published in March 2025
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? There are no official guidelines across the Nordic countries except for Sweden. Is the product suitable for a joint Nordic assessment? **No** If no, why not? The market landscape differs across the Nordics; for example, ravulizumab is not available in Norway. In addition, ravulizumab has four approved indications managed differently in each country.
Dispensing group	**BEGR**
Packaging – types, sizes/number of units and concentrations	1 pack includes 1 vial of ravulizumab containing concentrate for IV infusion and is available in following sizes: 300 mg/3ml and 1,100 mg/11ml.

2. Summary table

Summary	
Indication relevant for the assessment	Adult patients with NMOSD who are AQP4 antibody-positive (AQP4+) with an Expanded Disability Status Scale (EDSS) score ≤ 7 and have experienced a relapse in the past 12 months and, who had received rituximab prior to any relapse, or are contraindicated for rituximab, or have experienced a serious adverse event requiring discontinuation of rituximab.
Dosage regimen and administration	**Dosage regimen:** The recommended dosing regimen consists of a loading dose followed by maintenance dosing. The doses are administered by intravenous infusion based on the patient's body weight. Maintenance dosing should be administered once every eight weeks, starting two weeks after the loading dose. <table><tr><th>Body weight</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)</th></tr><tr><td>≥ 40 to < 60 kg</td><td>2,400</td><td>3,000</td></tr><tr><td>≥ 60 to < 100 kg</td><td>2,700</td><td>3,300</td></tr><tr><td>≥ 100 kg</td><td>3,000</td><td>3,600</td></tr></table>**Administration:** Ravulizumab concentrate for solution for infusion is presented as 3 mL and 11 mL vials (100 mg/mL) and must be diluted to a final concentration of 50 mg/mL. Following dilution, ravulizumab is to be administered by intravenous infusion using

Summary	
	a syringe-type pump or an infusion pump over a minimal period of 0.17 to 1.3 hours (10 to 75 minutes) depending on body weight.
Choice of comparator	Standard of Care (Soc) is the comparator.
Prognosis with current treatment (comparator)	NMOSD typically follows a relapsing course, with around 80-90% of patients experiencing recurrent relapses (1-3). Due to the unpredictable and severe nature of relapses, NMOSD can cause blindness, paralysis, and increased overall mortality, and a significant reduction in health-related quality of life (HRQoL). The median life expectancy for AQP4+ NMOSD patients is 64 years (95% CI: 53-84) versus 83 years in the general Danish population, with a standardised mortality ratio (SMR) of 2.54 (95% CI: 1.47–4.09), indicating a higher mortality risk (4).
Type of evidence for the clinical evaluation	Phase 3 study, ALXN1210-NMO-307 (CHAMPION-NMOSD), which is an external placebo-controlled, open-label, multicentre trial (5).
Most important efficacy endpoints (Difference/gain compared to comparator)	<u>Endpoints for post-rituximab subgroup:</u> **Time to first adjudicated on trial relapse -** Hazard ratio of ravulizumab versus placebo: [redacted] **Annualised Relapse Rate (ARR) -** Adjusted ARR of ravulizumab: [redacted] **Change in ambulatory function from baseline as measured by Hauser Ambulation Index (HAI) -** Number of patients experiencing clinically important worsening in HAI score from baseline: [redacted] in ravulizumab versus [redacted] in placebo. **Clinically important worsening from baseline in EDSS score -** Number of patients experiencing clinically important worsening in EDSS score from baseline: [redacted] in ravulizumab versus [redacted] in placebo
Most important serious adverse events for the intervention and comparator	Treatment-emergent serious adverse events (TESAEs) were reported in [redacted] of ravulizumab patients vs. [redacted] for placebo. No TESAEs were reported in ≥5% of patients in the ravulizumab arm during the Primary Treatment Period. However, [redacted] of patients in the placebo arm reported NMOSD as a TESAE.
Impact on health-related quality of life	Clinical documentation: The impact on HRQoL was measured in CHAMPION-NMOSD with EQ-5D Index and EQ-5D VAS. Health economic model: The impact on HRQoL was measured in CHAMPION-NMOSD and PREVENT with EQ-5D index and EQ-5D VAS

Summary	
Type of economic analysis that is submitted	Cost-utility analysis based on a Markov cohort model
Data sources used to model the clinical effects	EDSS scores and time to relapse from CHAMPION-NMOSD and PREVENT
Data sources used to model the health-related quality of life	EQ-5D-3L data collected from the CHAMPION-NMOSD and PREVENT, mapped to EQ-5D-5L
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Hazard ratio between ravulizumab and standard of care, discount rate, relapse utility
Number of eligible patients in Denmark	Incidence: 4-5 patients per year Prevalence: 66 patients
Budget impact (in year 5)	[redacted]

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

3.1 The medical condition

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare, relapsing, demyelinating autoimmune disorder of the central nervous system (CNS) (1, 2, 6-8). It is a severely disabling disease with a poor prognosis, and can result in death (9). The vast majority of patients with NMOSD experience a relapsing disease course, with each relapse resulting in acute inflammation, further neurodegeneration and accumulating disability (1-3, 9, 10).

3.1.1 Aetiology and pathophysiology

NMOSD is characterised by uncontrolled complement activation triggered by anti-aquaporin 4 (AQP4) autoantibodies (11-15), but it is not known what initiates the immune reaction (16, 17). Aquaporins help transport water across plasma membranes of cells. In the CNS, they are responsible for maintaining neuroexcitatory processes and water homeostasis, or a balance between the blood, cerebrospinal fluid (CSF), and brain parenchyma (17, 18). When AQP4 function is impaired, it can lead to nerve damage and demyelination that most commonly affects optic nerves and the spinal cord (16, 17, 19).

3.1.1.1 Anti-AQP4 antibodies

The presence of immunoglobulin G (IgG) autoantibodies in the serum that binds to extracellular AQP4 is the main characteristic of NMOSD in anti-AQP4 antibody-positive (AQP4+) patients (16, 17). This antibody is found in 60% to 90% of patients with NMOSD (16, 18, 20-24). The underlying NMOSD pathology can be described as astrocytopathy as a result of antigen-targeted antibodies (19).

3.1.1.2 The role of complement in NMOSD

Uncontrolled complement activation triggered by anti-AQP4 antibodies is a major underlying mechanism of the disease (11, 12, 25, 26). NMOSD lesions are caused by complement induced cytotoxicity where inflammatory components infiltrate through an impaired blood-brain barrier (16). Peripheral lymphoid organs synthesise anti-AQP4 antibodies which bind to AQP4 found on astrocytic end-feet, and result in complement activation (14, 16-18, 27-29). Anti-AQP4 antibodies activate complement through the classical pathway (16). This involves complement component 1, 2, and 4 (C1, C2, and C4), with triggering of C3 convertase to cleave C3 into C3a and C3b (30). C3b triggers C5 convertase, resulting in the cleavage of C5 into C5a and C5b (30). C5b binds to C6, C7, C8, and C9 to form the membrane attack complex (MAC), which causes cell lysis/death (30).

3.1.2 Clinical features of NMOSD

NMOSD may present at any age; however, the median age of onset for those with a relapsing course has been estimated to be at 39 years (10). Often occurring over the course of a few days, an acute attack of NMOSD commonly includes visual disability (i.e., acute optic neuritis) and longitudinally extensive transverse myelitis (LETM), which can lead to severe weakness, impaired mobility, sensory and motor disability, loss of bowel and bladder function, and respiratory failure (29, 31). At disease onset, 17.5% of patients experienced a disabling attack and were either unable to walk without assistance or were left functionally blind in at least one affected eye up to one year post-attack (32); 76% of patients were unable to make a full recovery after their first NMOSD attack (e.g., experienced residual disability) (1). Up to 50% of patients experience at least 1 relapse per year (1, 33). These relapses are often severe and disabling.

Frequently reported symptoms, either NMOSD related or treatment-related, negatively impact many aspects of patients’ lives. Pain, either neuropathic or spastic, has been reported in up to 86% of patients with NMOSD (Qian 2012; Zhao 2014) and can be disabling (34). Moderate to severe fatigue has been reported in 55% of patients with NMOSD, and negatively affects sleep quality and depression severity (34, 35).

3.1.3 Diagnosis

According to the 2015 International Panel for NMO Diagnosis (IPND) diagnostic criteria for NMOSD, an NMOSD diagnosis can be made with the appearance of at least one of the core clinical characteristics, anti-AQP4 antibody seropositivity, and the exclusion of alternative diagnoses (8). The core clinical characteristics of NMOSD include: optic neuritis (ON); acute myelitis; area postrema syndrome (i.e., unexplained hiccups or nausea and vomiting); acute brainstem syndrome; symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic magnetic resonance imaging (MRI) lesions; and symptomatic cerebral syndrome with NMOSD-typical brain lesions (8).

Among patients with NMOSD, 60% to 90% are seropositive for anti-AQP4 antibodies (20-23). In the absence of anti-AQP4 antibodies, or if anti-AQP4 antibody status cannot be determined, at least two of the core clinical characteristics must be present, one of which must be either ON, acute myelitis with LETM, or area postrema syndrome, along with other supportive MRI characteristics, and exclusion of alternative diagnoses (8). The 2015 IPND diagnostic criteria is also currently in use in Denmark (4).

It is imperative that NMOSD is properly diagnosed in the early stages prior to treatment initiation. If NMOSD is misdiagnosed as MS and treated with interferon-β, natalizumab, or fingolimod, it can become worse as a result of treatment (8). Another related, but distinct, demyelinating disorder of the CNS is myelin oligodendrocyte glycoprotein (MOG)-antibody disease (36, 37). NMOSD should be differentiated from MOG antibody disease using tools such as MRI and optical coherence tomography (OCT) (36-38).

3.1.4 Disease progression and mortality

The symptoms of NMOSD ultimately translate into disease progression and mortality. Prognosis is generally poor because most relapsing patients do not recover fully after an attack, and neurologic impairments accumulate in a stepwise manner, resulting in severe disability (8, 39-41). Most patients (75.6%) do not achieve complete remission after the first attack, and fewer patients recover fully as the number of relapses increase (87% had an incomplete recovery after the second attack, and 100% by the sixth attack) (1).

Disease-specific mortality in NMOSD is primarily driven by relapses. Deaths from NMOSD are mostly due to respiratory failure after cervical myelitis attacks, (42) multi-organ failure, or as a result of long-term quadriplegia (43). Although contemporary estimates in NMOSD show an improved mortality rate compared to older studies, it may be attributable to earlier diagnosis and treatment (44). In a study conducted in a Danish NMOSD cohort followed from 2006 to 2021, the median life expectancy for AQP4+ NMOSD patients is 64 years (95% CI: 53-84) versus 83 years in the general Danish population, with a standardised mortality ratio (SMR) of 2.54 (95% CI: 1.47–4.09), indicating a higher mortality risk (4).

Without treatment, NMOSD is a disabling, sometimes fatal condition, with high annualised relapse rates and poor recovery after each attack (45). The scientific literature widely agrees that early diagnosis, aggressive treatment of acute relapses and early adoption of long-term preventive therapies is a necessary approach to reduce morbidity and mortality (8, 46, 47). However, there are currently no preventive treatment options reimbursed by DMC for patients with NMOSD aimed at reducing the frequency and severity of relapses (48-50). Therefore, several therapies are used off-label to reduce relapse risk in Denmark, with rituximab used by most patients. Nevertheless, a substantial proportion patients still experience disease progression and accumulating disability.

Patients who continue to relapse despite rituximab therapy, or who discontinue treatment due to adverse events or contraindications, represent a high-risk subgroup. Evidence suggests that there is considerable risk of relapses (51, 52) and serious adverse events with rituximab treatment (52). In one study, up to 30% of patients experienced relapses, most commonly within six months of initiating treatment or in the context of delayed retreatment and/or B-cell reconstitution (51). Furthermore, the off-label use of rituximab raises concerns regarding the consistency of long-term safety monitoring (53).

3.1.5 Quality of life

The unpredictable nature of NMOSD and the severity of symptoms have marked impact on activities of daily living, social relationships, and emotional health, and individuals can struggle to adjust to life after diagnosis (54, 55).

In a study of 193 participants, more than 70% reported that NMOSD greatly affected their quality of life (4.58 ± 1.41 overall; scale 1-6 [1 = least impact, 6 = greatest impact]) (54). The majority of patients reported strong negative impact of NMOSD on physical health (56), a finding consistent with the 65% of patients that reported activity impairment in a qualitative interview-based study (57). In health-related quality of life surveys, most patients (59%) with NMOSD were limited by their health in the type of work or other activities they could perform (34).

The cumulative impact of relapses is particularly concerning for patients who continue to relapse despite treatment with rituximab or who are contraindicated or discontinue due to adverse events. Even a single NMOSD relapse can worsen disability and HRQoL, underscoring the role of relapse prevention in AQP4+ NMOSD patients (58). In the PREVENT trial and its OLE (58), 27 patients with an adjudicated relapse experienced significantly worse disability (mRS; EDSS) and HRQoL (SF-36 mental and physical; EQ-5D-3L VAS; utility index scores). In 4 of 7 outcomes, clinically meaningful worsening was more likely for relapsing versus non-relapsing patients (n = 116). Extrapolating the effect of 2 relapses also predicted clinically meaningful worsening in almost all outcomes in relapsing versus non-relapsing patients. Therefore, this underscores the broader clinical relevance of relapse prevention, particularly in high-risk subgroups.

3.2 Patient population

In Denmark, a population-based study of NMOSD conducted by Papp et al. (2024) estimated that there were 78 Danish patients with AQP4+ NMOSD (4), which aligns with the expected prevalence from global data. Earlier epidemiological data from 2018 reported an incidence of 0.070 per 100,000 person-years and a prevalence of 1.09 per 100,000 persons for the Danish population (59). For the purposes of this application, latest prevalence estimates of 78 patients in 2024 was used, which aligns with the DMC assessment of inebilizumab (50). Furthermore, the DMC has estimated that 5 new patients are diagnosed yearly (50).

Table 1 Incidence and prevalence in the past 5 years

Year	2020*	2021*	2022*	2023*	2024
Incidence in Denmark	5	5	5	5	5
Prevalence in Denmark	58	63	68	73	78

*As incidence and prevalence data are not available, 2024 estimates were assumed to be applicable for 2020-2023

The patient population relevant for this assessment is a subgroup of AQP4+ NMOSD patients with an EDSS score ≤ 7 and have experienced a relapse in the past 12 months and, who had received rituximab prior to any relapse, or are contraindicated for rituximab, or have experienced a serious adverse event requiring discontinuation of rituximab. Hereafter, this subgroup will be referred to as the 'post-rituximab subgroup'. Rituximab is used as first-line treatment for NMOSD in Denmark (section 3.3 below), so when patients are unable to receive rituximab for various reasons, alternative treatment options must be considered. However, there are no available reimbursed therapies in Denmark today (50). Furthermore, patients with an EDSS score ≤ 7 represents a population that is generally ambulatory with or without assistance, i.e. a lower disease severity.

This patient population is reflective of the patient population in Denmark, based on an interview with a local expert clinician (60). The estimated number of patients eligible for treatment is based on DMC estimates that there would be 4-5 patients annually who experience treatment failure with rituximab (50), as seen 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	4-5	8-10	12-15	16-20	20-25

3.3 Current treatment options

While there are no national treatment guidelines for NMOSD in Denmark, clinical practice aligns with European recommendations. The European Academy of Neurology (EAN) (61) recommends use of the ‘Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) - revised recommendations of the Neuromyelitis Optica Study Group (NEMOS) (62, 63). In general, treatment for NMOSD can be categorised by acute treatment of relapses and prevention of future relapses.

3.3.1 Acute treatment

The outcome of NMOSD relapse is often poor without acute treatment, with full recovery observed in only a minority of patients. However, recovery can be improved by prompt initiation of therapy in acute attacks and early escalation (47). Acute treatment of NMOSD aims to supress acute inflammatory attack so as to reduce oedema and inflammation in the lesion, which may minimise CNS damage and have some mild to moderate immediate improvement in neurological functions (64). A single relapse can leave permanent damage and can lead to ongoing disability with every relapse: as such every relapse should be treated.

Typical treatment of an acute relapse involve high dose intravenous corticosteroids, which are used off-label (50). In severe cases, plasmapheresis is applied (50). As ravulizumab is a preventive treatment and will not be used in the acute setting, patients requiring ravulizumab will have been treated acutely during a relapse, before commencing preventive treatment with ravulizumab in the outpatient setting.

3.3.2 Preventive treatment

The main goal of NMOSD treatment is relapse risk reduction as relapses occur in 80-90% of NMOSD cases and can result in severe disability (6-8, 65). These relapses usually occur early, in clusters, and at unpredictable intervals (6). As they are the main drivers of cumulative neurological damage, preventing every relapse is essential to limit permanent disability (6). In Denmark, no relapse-preventive treatments are reimbursed for NMOSD, so most patients are managed using off-label treatments (48-50). Rituximab is used as the first-line, with the nonsteroidal immunosuppressive therapies (ISTs) azathioprine and mycophenolate mofetil also used (50). In addition, low-dose methylprednisolone can be used for several weeks to months, with tapering adjusted to the individual patient (50).

Based on the NEMOS guidelines, long-term immunotherapy must be offered to patients with AQP4+ NMOSD after the first attack, patients stable on off-label therapies without significant side effects do not need treatment switch, and that traditional ISTs are less effective than biological treatments. Additionally, in case of treatment failure with traditional ISTs, therapy should be switched to a monoclonal antibody, and in case of treatment failure with a monoclonal antibody, therapy should be switched to another monoclonal antibody, preferably with a different mode of action.

Patients who received rituximab in first-line would be switched to another monoclonal antibody such as ravulizumab following a relapse. Similarly, those patients who experience a serious adverse event (SAE) during treatment with rituximab, or were contraindicated for treatment with rituximab, would be treated with a different monoclonal antibody. Contraindications for rituximab include hypersensitivity to rituximab or murine proteins, serious active infection, or severely immunocompromised patients e.g.

hypogammaglobulinemia or where CD4 or CD8 levels are very low (66, 67). SAEs requiring discontinuation include progressive multifocal leukoencephalopathy (PML), severe pulmonary events, serious cardiac arrhythmias, toxic epidermal necrolysis or Stevens-Johnson syndrome (67).

An international panel of 24 clinical experts has recently published a Delphi consensus on the management of AQP4+ NMOSD, which focuses on recommendations for eculizumab, inebilizumab, and satralizumab (68). Key messages include that biological treatments should be started after the first attack, with monotherapy preferred but combination with ISTs is an option, and that comorbidities, mechanism of action and patient preference should lead the selection among biological treatments. Although these three monoclonal antibody therapies have been approved by the EMA for NMOSD, none of them are reimbursed in Denmark.

3.4 The intervention

Ravulizumab is a humanised monoclonal Ab (mAb) that specifically binds with high affinity to the human terminal C5, and provides immediate, complete, and sustained inhibition of terminal complement, thereby preventing the inflammatory consequences of terminal complement activation.

Table 3 Key descriptive information of ravulizumab

<table>
<tr><th colspan="2">Overview of intervention</th></tr>
<tr><td>Indication relevant for the assessment</td><td>Adult patients with AQP4+ NMOSD with an EDSS score ≤ 7 and have experienced a relapse in the past 12 months and, who had received rituximab prior to any relapse, or are contraindicated for rituximab, or have experienced a serious adverse event requiring discontinuation of rituximab.</td></tr>
<tr><td>ATMP</td><td>N/A</td></tr>
<tr><td>Method of administration</td><td>Intravenous infusion</td></tr>
<tr><td>Dosing</td><td>The recommended dosing regimen consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient’s body weight, as shown in the table below. Maintenance dosing should be administered once every eight weeks, starting two weeks after the loading dose.
<table>
<tr><th>Body weight</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)</th></tr>
<tr><td>≥ 40 to < 60 kg</td><td>2,400</td><td>3,000</td></tr>
<tr><td>≥ 60 to < 100 kg</td><td>2,700</td><td>3,300</td></tr>
<tr><td>≥ 100 kg</td><td>3,000</td><td>3,600</td></tr>
</table></td></tr>
<tr><td>Dosing in the health economic model (including relative dose intensity)</td><td>Relative dose intensity is 100%.</td></tr>
</table>

Overview of intervention	
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Considering that NMOSD is a chronic disease, there is no criteria for discontinuing treatment with ravulizumab. According to the SmPC, patients benefiting from ravulizumab treatment who discontinue treatment should be monitored for symptoms of NMOSD relapse. If symptoms of NMOSD relapse occur after discontinuation, consider restarting treatment with ravulizumab (69).
Necessary monitoring, both during administration and during the treatment period	Patients treated with traditional ISTs for NMOSD undergo regular monitoring for signs of toxicity specific to their treatment regimen. The addition of ravulizumab is not expected to increase the frequency of regular monitoring in these patients. All patients should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics (69).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Assessment of AQP4-IgG status for diagnosing patients with NMOSD has been a common practice in Denmark since December 2007 (59). Patients are also required to have a level of disability demonstrated by an EDSS score of ≤ 7. The EDSS is a widely used method of quantifying physical disability in neurology (70). The EDSS is currently used in Danish neurological practice, as validated by a Danish clinical expert (60).
Package size(s)	1 pack includes 1 vial of ravulizumab containing concentrate for IV infusion and is available in following sizes: 300mg/3ml and 1,100mg/11ml.

Abbreviations: AQP4-IgG, Aquaporin-4 Immunoglobulin G; AQP4+, Aquaporin-4-Positive; ATMP, Advanced Therapy Medicinal Product; EDSS, Expanded Disability Status Scale; ISTs, Immunosuppressive Therapies; IV, Intravenous; N/A, Not Applicable; NMOSD, Neuromyelitis Optica Spectrum Disorder.

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

The primary goal of NMOSD treatment is to prevent relapses, prevent permanent functional disability, and improve patients' quality of life (48). As previously described in section 3.3.2, there is limited evidence of the effectiveness of traditional ISTs in NMOSD relapse prevention, and safety implications of long-term use. As mentioned by the DMC, treatment alternatives are extremely limited when patients experience side effects, contraindications, or insufficient response to the above agents.

Growing evidence indicates that rituximab treatment in NMOSD is associated with a significant risk of both serious infectious events and relapses (52, 71). Over 30% of NMOSD patients eventually experience a relapse with long-term rituximab use (72-77). A Swedish retrospective cohort study (n=42) reported that 46% of rituximab-treated patients experienced serious infectious events (SIEs), with a mean annual incidence rate of 0.32 (range: 0–3.3) (52). The most common SIEs included urinary tract infections (54.2%), upper respiratory tract infections (41.7%), pneumonia (29.2%), bacterial skin infections (29.2%), and sepsis (20.8%) (52). Equally concerning is the persistence of disease activity, as 37.5% of patients relapsed during follow-up, with a median annualised relapse rate (ARR) of 0.21 (IQR 0–0.5) (52). Importantly, relapse risk re-emerged after more than six relapse-free years, indicating that long-term control is not assured even in patients who initially respond well to the treatment (52). This dual burden leads to a high rate of treatment discontinuation. Nearly one third of AQP4+ patients (29%) stopped rituximab, because of new disease activity, anti-rituximab antibodies, infectious complications, or other factors such as advancing age (52). Therefore, there is an unmet clinical need for patients who experience relapse or develop adverse effects while receiving treatment with rituximab.

Based on the results of the CHAMPION-NMOSD study, the EMA indication, and Danish clinical practice, ravulizumab is expected to be second-line treatment for patients who fail rituximab, are contraindicated for rituximab or experience SAEs that require discontinuation of rituximab or are contraindicated for rituximab treatment.

Ravulizumab and rituximab will not be administered in combination, due to incompatibility between their mechanisms of action. Specifically, rituximab selectively depletes B cells, via complement-dependent cytotoxicity (78), and in the presence of C5 inhibitors such as ravulizumab, B-cell lysis is inhibited by up to 90% (79). Patients who meet the proposed eligibility criteria for ravulizumab would require cessation of rituximab prior to the commencement of ravulizumab.

Ravulizumab may be used as monotherapy, or in combination with Standard of Care (SoC), which comprises elements from traditional ISTs (azathioprine, MMF, oral corticosteroids), plasma exchange (PLEX) or intravenous immunoglobulin (IVIg). A supplemental dose of ravulizumab is required if PLEX or IVIg is used (i.e., in acute management of relapse) (80).

Therefore, ravulizumab does not substitute for any existing therapies.

3.5 Choice of comparator

The relevant comparator for ravulizumab is SoC. Ravulizumab may be used as monotherapy, or in combination with SoC, and in the proposed indication does not substitute directly for any currently used therapies. In Denmark, SoC comprises primarily traditional ISTs and oral corticosteroids for preventive treatment. As ravulizumab may be used in conjunction with these therapies, the comparator is represented by SoC in the clinical evaluation.

3.6 Cost-effectiveness of the comparator(s)

As outlined in section 3.5, the primary comparator is SoC. Given the absence of alternative approved treatments for NMOSD in Denmark, SoC is considered the most appropriate comparator for this assessment.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Time to first relapse, annualised relapse rate (ARR) and clinically important change from baseline in Hauser Ambulation Index (HAI) are the most relevant outcomes for this assessment.

Table 4 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Time to first adjudicated on-trial relapse (CHAMPION-NMOSD; PREVENT)	2.25 years	On-trial relapses are acute attacks that occur during the trial. On-trial relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persists for >24 hours as confirmed by the treating physician. The signs and symptoms must be attributed to NMO (that is, not attributed to an identifiable cause such as infection, excessive exercise, or excessively high ambient temperature). Isolated changes on MRI or other imaging investigation with no related clinical findings are not considered an on-trial relapse. The relapse must be preceded by ≥30 days of clinical stability. Defined as number of days from first dose to onset of first on-trial relapse in the Study Period; or number of days observed in the Study	On-trial relapses will be monitored throughout the study. The Investigator or a qualified designee will review the signs and symptoms of a potential relapse with the patient in detail at each visit. Patients will be educated on the potential signs and symptoms of NMOSD relapse and will be instructed to contact the study site at the first sign or symptom of a potential relapse. Patients should be evaluated within 24 hours (and no later than 48 hours) of notification of signs or symptoms suggestive of a potential relapse. On-trial relapses will be independently reviewed by the RAC, which consists of 3 physicians who have particular expertise in NMOSD and will conduct independent reviews of all on-trial Relapses. The Committee will decide by majority vote whether each reported on-trial relapse meets the objective criteria for an on-trial relapse.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		Period with no on-trial relapse	
Adjudicated on-trial ARR (CHAMPION-NMOSD)	2.25 years	Defined as number of adjudicated on-trial relapses during the Study Period divided by the patient years in the Study Period.	The adjudicated on-trial ARR will be presented showing the ravulizumab treatment group estimate and 95% CI from a Poisson regression model in which the log of time in the Study Period will be used as the offset variable and historical ARR will be a covariate in the model. This endpoint will be considered statistically significant if the 2-sided p-value is ≤ 0.05, and if the adjudicated on-trial ARR < 0.25 or if 0 relapses are observed.
Clinically important change from baseline in HAI (CHAMPION-NMOSD; PREVENT)	2.25 years	The HAI is a rating scale developed to assess mobility by evaluating the time and degree of assistance required to walk 25 feet (81). The examiner records the time and type of assistance (e.g., crutches) needed. The time that the patient takes to walk is utilised in conjunction with other factors to rate the patient on an ordinal scale with 10 gradations (82).	Patients were assessed for change in HAI scores from baseline into 3 categories (clinical improvement, stable, clinical worsening). Analysed using a proportional odds model including treatment group and baseline HAI as a covariate.
Clinically important worsening from baseline in EDSS score (CHAMPION-NMOSD; PREVENT)	2.25 years	The 10-point Neurostatus EDSS (modified Kurtzke EDSS) is widely used and accepted as a valid tool for quantifying disability and monitoring changes in disability over time (70). The EDSS scale ranges from 0 to 10.0 in 0.5 unit increments.	Change from baseline in the EDSS score to the 6-week post-relapse/EOPT Period analysis time point. This change from baseline will be categorised into clinically important worsening (no worsening, clinical worsening). This endpoint will be analysed using a logistic regression model including treatment

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			group and baseline EDSS as a covariate.

Abbreviations: ARR, Annualized Relapse Rate; CI, Confidence Interval; EDSS, Expanded Disability Status Scale; EOPT, End of Primary Treatment Period; HAI, Hauser Ambulation Index; MRI, Magnetic Resonance Imaging; NMO, Neuromyelitis Optica; NMOSD, Neuromyelitis Optica Spectrum Disorder; RAC, Relapse Adjudication Committee.

Note: *Time point for data collection used in analysis (follow up time for time-to-event measures)

Note: Patients in the ravulizumab arm who did not experience an adjudicated On-trial Relapse were censored at the end of the study period. The end of the study period is the earlier of the following dates: (i) the data cutoff date; and (ii) the last dose date + 63 days, and (iii) the final disposition date for patients who left the study before the data cutoff date. The End of Study Period was similar for the placebo group: The earlier of the last dose date + 16 days and the last date observed in the PREVENT study. If a patient in the placebo group was followed longer than any of the patients in the ravulizumab arm, then that patient was censored at the longest ravulizumab follow-up time.

Note: The on-trial ARR from the CHAMPION-NMOSD is tested against the null hypothesis of 0.25 (1 relapse in 4 patient-years). This comparison was selected, as opposed to a comparison to placebo, because of differences in study design between the CHAMPION-NMOSD and PREVENT studies that result in differences in follow-up time for patients following a relapse. The comparator rate was chosen to represent a conservative ARR that may be experienced in the NMOSD patient population.

Validity of outcomes

Time to first adjudicated on-trial relapse, adjudicated on-trial ARR, and EDSS scores are considered to be reliable and relevant for this submission and have previously been used by the DMC for the assessment of inebilizumab in NMOSD (50). The HAI has been developed for use in patients with multiple sclerosis (81).

4. Health economic analysis

4.1 Model structure

The economic impact of ravulizumab vs. SoC was evaluated using a Markov model in Microsoft Excel®. The model structure is illustrated in Figure 1 and Figure 2.

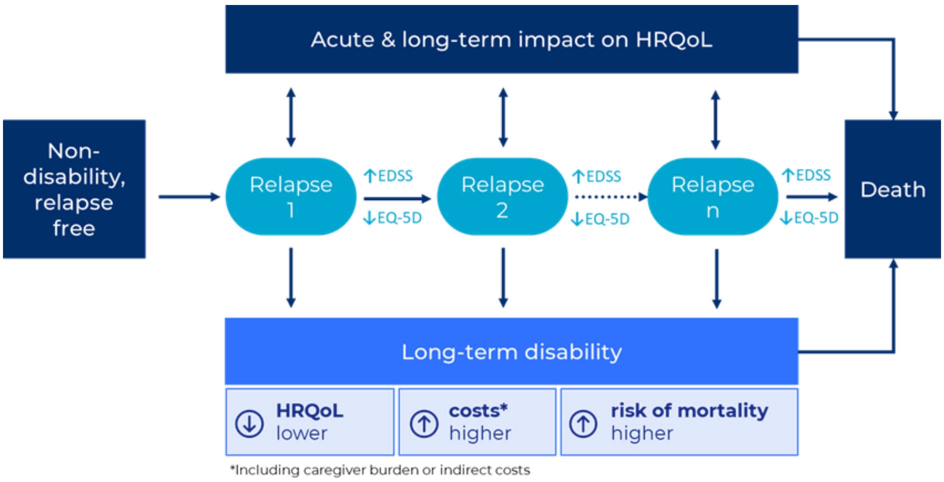
A Markov cohort model was used to structure the health state movement. Patients entered the model in the relapse-free health state, without long-term NMOSD-related disability, defined as a Kurtzke EDSS score of 5.5 or higher (consistent with disability definitions in MS literature) (83). There is currently a lack of literature on the disability level related to EDSS score in NMOSD, therefore MS literature is used as a proxy. This corresponds to disability severe enough to preclude full daily activities, with patients only being ambulatory without aid or rest for about 100 meters. Patients incurred costs over time, both direct medical costs associated with NMOSD disease and one-time costs at relapse. Baseline HRQoL was based on EQ-5D utilities at CHAMPION-NMOSD and PREVENT trial baseline, and varies over time based on experience of relapse, as described below. Mortality estimates were based on observed real-world evidence of NMOSD patients.

In each model cycle, patients can experience a relapse, with the probability of relapse determined by the treatment arm and informed by data from CHAMPION-NMOSD. As relapses occur stochastically, NMOSD patients remain at risk of relapse and therefore, in the base case, the risk of relapse is consistent over time. The impact of a relapse event on HRQoL includes a temporary component that only occurs during the first 50 days following the event and a permanent component, reflecting irreversible health effects, based on analysis of HRQoL outcomes over time from the CHAMPION-NMOSD and PREVENT trials. As relapses occur, patients become eligible for subsequent relapses, with patients eligible to experience up to 20 relapses over the time horizon. The base case analysis assumed that the active treatment is continued for the entire time horizon despite experiencing relapses, consistent with advice from local experts.

For every relapse, patients can remain in a non-disability substate or transition to a disability substate (via either a single disabling relapse or a progression of disability over multiple relapse events). With each relapse, there is a 17.5% risk of immediately entering the long-term disability state, based on published NMOSD relapse data. Additionally, patients have the potential to steadily increase their EDSS score to 5.5 or greater (hence entering the long-term disability state) via progressive increases in EDSS with successive relapses. With each relapse, EDSS is assumed to permanently increase by 0.56 (based on PREVENT trial data), with the number of relapses required to reach a threshold of 5.5 dependent on baseline EDSS value. The distribution of patients across EDSS scores at baseline in the CHAMPION-NMOSD trial is used to represent the cohort, with the risk of permanent disability per each relapse varying according to the baseline score. Whether patients enter the long-term disability state via either a single disabling relapse or a progression of disability over multiple relapses, they then remain in the long-term disability state for the remainder of their life.

While in the long-term disability states, patients continue to be at risk for relapse events based on their treatment arm and incur higher costs associated with the complexity of managing additional disability, have an increased risk of mortality, and decreased HRQoL.

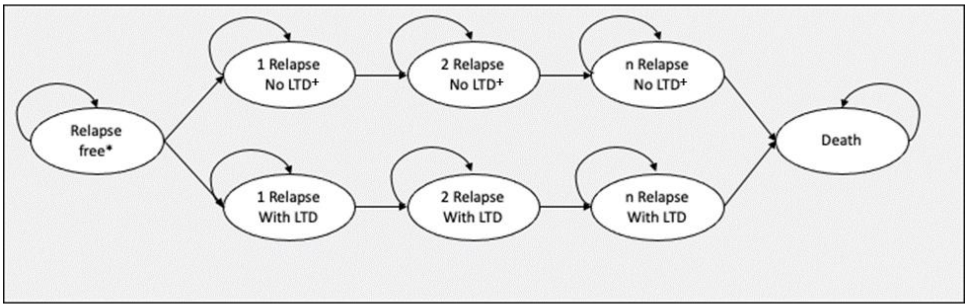
Figure 1 Model Structure: Model overview



Abbreviations: EDSS, Expanded Disability Status Scale; HRQoL, Health Related Quality of Life.

Note: *caregiver burden and indirect costs are not included in the base case economic evaluation.

Figure 2 Model Structure: Markov Cycles



Abbreviations: LTD, Long-Term Disability.

Note: *Relapse free state can apply to either to patients with or without LTD depending on EDSS score at the start of the model. + Patients without LTD may enter in the LTD states after a relapse.

4.1.1 Health state specific assumptions

Four primary health states are applied and are described as below:

- Relapse-free: All patients enter the model in this state and are at risk of first relapse or death each cycle. Patients exit this state on first relapse, or on death. Utility weight equivalent to non-disability state (0.6671). Treatment costs applied. Direct medical costs applied in a weighted manner per proportion disabled at baseline per EDSS. The proportion of patients disabled is derived from EDSS distribution at baseline in the CHAMPION-NMOSD study.
- (Post-relapse) No long-term disability: Patients are at risk of relapse or death each cycle. For every relapse, patients can remain in a non-disability substate or transition to a disability substate (via either a single disabling relapse or a progression of disability over multiple relapse events). Acute costs and impact on quality of life are applied for each relapse. Treatment costs applied. Utility weight (0.6671) and background costs are for the non-disability state, irrespective of the relapse count.
- (Post-relapse) Long-term disability: Patients are at risk of relapse or death each cycle. Once patients enter a disability substate, they then remain in the disability state for the remainder of their life. Acute costs and impact on quality of life are applied for each relapse. Treatment costs applied. Utility weight and background costs are for the disability state, irrespective of the relapse count.
- Death: Background mortality applies to all health states in each cycle, and has been adjusted for NMOSD mortality, and for treatment arm. No additional cost is applied to death events.

Within the Non-disability and Disability states are (up to) 20 substates according to model features. The substates are based on EDSS scores, which stretch from 0 to 9 with a 0.5 score increment, thus up to 20 substates in total.

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with NMOSD who are AQP4+ with an EDSS	N/A

Model features	Description	Justification
	score ≤ 7 and have experienced a relapse in the past 12 months and, who had received rituximab prior to any relapse, or are contraindicated for rituximab, or have experienced a serious adverse event requiring discontinuation of rituximab	
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (53 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the Danish population (53 years). Validated by Danish clinical expert
Cycle length	30 days	Consistent with length of treatment cycle (day 1 every 30 days)
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Ravulizumab	
Comparator(s)	SoC	No specific national guidelines. Validated by clinical experts.
Outcomes	Time to first relapse, OS	

Abbreviations: AQP4+, Aquaporin-4-Positive; DMC, Danish Medicines Council; EDSS, Expanded Disability Status Scale; N/A, Not Applicable; NMOSD, Neuromyelitis Optica Spectrum Disorder; OS, Overall Survival; SoC, Standard of Care.

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was conducted in April 2024 and updated in August 2025, the full details of which is provided in Appendix H. Comprehensive electronic and manual searches of the medical literature were undertaken to identify all controlled trials of ravulizumab in adults with AQP4+ NMOSD.

In summary, 17 publications were identified from the clinical SLR, which included 16 citations for CHAMPION-NMOSD and 1 for PREVENT. Therefore, the CHAMPION-NMOSD study (5) was the most appropriate to describe the efficacy of ravulizumab for NMOSD patients. The publication for the placebo-controlled trial PREVENT (84), from which the external comparator arm (placebo) of CHAMPION-NMOSD was sourced, was also included. The study designs between these two trials were similar with generally the same inclusion criteria, with modifications including using the most recently updated NMOSD diagnostic criteria. Table 6 shows the trials from the SLR that were most relevant to include for this submission in order to inform the efficacy and safety.

Table 6 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Pittock SJ, Barnett M, Bennett JL, Berthele A, de Sèze J, Levy M, et al. Ravulizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. Annals of neurology. 2023;00. (5)	ALXN1210-NMO-307 (CHAMPION-NMOSD)	NCT04201262	Start: 10/12/2019 Completion: 01/11/2024 Data cut-off: 15/03/2022	Ravulizumab vs. external comparator (placebo group from the ECU-NMO-301 trial) for patients with AQP4+ NMOSD
Pittock SJ, Berthele A, Fujihara K, Kim HJ, Levy M, Palace J, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(7):614-25. (84)	ECU-NMO-301 (PREVENT)	NCT01892345	Start: 11/04/2014 Completion: 17/07/2018 Data cut-off: 17/07/2018	Eculizumab vs. placebo for patients with AQP4+ NMOSD

Abbreviations: AQP4+, Aquaporin-4-Positive; NMOSD, Neuromyelitis Optica Spectrum Disorder.

Note: *In this submission, PREVENT is the trial used as the external comparator arm for CHAMPION-NMOSD.

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

The assessment of HRQoL in relation to health states is based on the CHAMPION-NMOSD and PREVENT trials. Disutility values in relation to adverse events were sourced from Sullivan et al., 2006 due to its comprehensive EQ-5D utility catalogue and widespread acceptance in economic evaluations, such as in Australia and Canada. A comprehensive systematic search of the medical literature for a global SLR was originally conducted on 24 November 2021, and the same search was re-run on 12 April 2023 and 4 November 2024. For the current application, the SLR relevant to the health-related quality-of-life was updated on 11 August 2025, the full details of which is provided in Appendix I.

Table 7 Relevant literature included for (documentation of) health-related quality of life (See section 9.2)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Pittock SJ, Barnett M, Bennett JL, Berthele A, de Sèze J, Levy M, et al. Ravulizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. Annals of neurology. 2023;00. (5)	Health utilities per EDSS score and relapses (ravulizumab)	10.2.1
Pittock SJ, Berthele A, Fujihara K, Kim HJ, Levy M, Palace J, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(7):614-25. (84)	Health utilities per EDSS score and relapses (placebo)	10.2.1
Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Medical decision making: an international journal of the Society for Medical Decision Making. 2006;26(4):410-420. (85)	All disutilities	10.2.3

Abbreviations: EDSS, Expanded Disability Status Scale, EQ-5D, EuroQol 5-Dimension Quality Of Life Questionnaire.

5.3 Literature used for inputs for the health economic model

No literature was used in sourcing the inputs for the health economic model. The healthcare resource use (HCRU) costs were sourced from the previous DMC assessment on eculizumab the result of a grey literature search (86).

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of ravulizumab compared to standard of care for adult patients with AQP4+ NMOSD with an EDSS score ≤ 7 and have experienced a relapse in the past 12 months and, who had received rituximab prior to any relapse, or are contraindicated for rituximab, or have experienced a serious adverse event requiring discontinuation of rituximab

6.1.1 Relevant studies

The Phase 3 study CHAMPION-NMOSD (ALXN1210-NMO-307; NCT04201262), an external placebo-controlled, open-label, multicentre trial evaluated the efficacy and safety of ravulizumab in adult patients with AQP4+ NMOSD. In this study, ravulizumab was assessed against an external placebo comparator derived from the PREVENT trial of eculizumab in AQP4+ NMOSD (ECU-NMO-301; NCT01892345). The primary treatment period of the ravulizumab study is complete (data cut-off: 15 March 2022), with the long-term extension phase ongoing.

An overview of the ravulizumab and placebo studies is presented in Table 9. Further study details and the overall study results are provided in Appendix A.

Table 9 Overview of study design for studies included in the comparison

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
A Phase 3, External Placebo-Controlled, Open-Label, Multicentre Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with NMOSD, ALXN1210-NMO-307 (CHAMPION-NMOSD), NCT04201262, Pittock et al. 2023 (5)	Phase 3, external placebo-controlled, open-label, multicentre study	The study was initiated in December 2019. The primary treatment period was completed in March 2022. The long-term extension period is ongoing.	Patients with AQP4+ NMOSD diagnosed per 2015 international consensus criteria, ≥18 years of age, with ≥1 attack or relapse in the past 12 months, and an EDSS score ≤7	Ravulizumab at a weight-based IV loading dose on Day 1, followed by weight-based IV maintenance doses on Day 15 and every 8 weeks thereafter until the end of the long-term extension period. Transition from 10 mg/mL to 100 mg/mL formulation during the long-term extension period, with no change to the dosing regimen.	External comparator: placebo group from the PREVENT trial of eculizumab in AQP4+ NMOSD (ECU-NMO-301)	• Time to first adjudicated on-trial relapse [Time frame: baseline up to 2.25 years (end of the primary treatment period)] • Adjudicated on-trial ARR [Time frame: baseline up to 2.25 years (end of the primary treatment period)] • Clinically important changes from baseline in ambulatory function as measured by HAI [Time frame: baseline up to 2.25 years (end of the primary treatment period)] • Change from baseline in EQ-5D index score [Time frame: baseline up to 2.25 years (end of the primary treatment period)] • Change from baseline in EQ-5D VAS score [Time frame: baseline up to 2.25 years (end of the primary treatment period)] • Clinically important worsening from baseline in EDSS score [Time frame: baseline up to 2.25 years (end of the primary treatment period)]
A Randomised, Double-Blind, Placebo-	Randomised, placebo-controlled, multicentre, parallel-group, Phase 3 study with quadruple	The study was initiated in April 2014. The primary	Patients with AQP4+ NMOSD, diagnosed per 2006/2007 criteria,	Eculizumab (SOLIRIS) ± IST. Administered intravenously.	Placebo ± IST. Administered IV. Induction phase: 900 mg	• Time to first adjudicated on-trial relapse [Time frame: baseline, up to 211 weeks (end of study)]

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
Controlled, Multi-Centre Trial to Evaluate the Safety and Efficacy of Eculizumab in Patients with Relapsing NMO, ECU-NMO-301, NCT01892345 Pittock et al. 2019 (84)	blinding (participant, care provider, investigator, and outcomes assessor) of eculizumab versus placebo.	treatment period was completed in July 2018.	aged ≥18 years, with ≥2 relapses in the previous 12 months or ≥3 relapses in the previous 24 months (with at least 1 relapse in the 12 months prior to the screening) and an EDSS score ≤7.	Induction phase: 900 mg IV weekly for 4 weeks, followed by 1200 mg IV for the fifth dose. Maintenance phase: 1200 mg IV every 2 weeks.	IV (placebo) weekly for 4 weeks, followed by 1200 mg IV (placebo) for the fifth dose. Maintenance phase: 1200 mg IV (placebo) every 2 weeks.	• Adjudicated on-trial ARR [Time frame: baseline, up to 211 weeks (end of study)] • Change from baseline in EDSS at end of study [Time frame: baseline, up to 211 weeks (end of study)] • Change from baseline in mRS score at end of study [Time frame: baseline, up to 211 weeks (end of study)] • Change from baseline in HAI score at end of study [Time frame: baseline, up to 211 weeks (end of study)]

Abbreviations: AQP4+, Aquaporin-4-Positive; ARR, Annualised Relapse Rate; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol 5-Dimension Quality Of Life Questionnaire; HAI, Hauser Ambulation Index; IST, Immunosuppressive Therapy; IV, Intravenously; mRS, Modified Rankin Scale; NMO, Neuromyelitis Optica; NMOSD, Neuromyelitis Optica Spectrum Disorder; VAS, Visual Analog Scale.

6.1.2 Comparability of studies

Patients in the ravulizumab arm were part of a single-arm trial (SAT) (CHAMPION-NMOSD) that used the placebo arm from the PREVENT trial as an external comparator. The PREVENT trial was a randomised controlled trial (RCT), in which participants were randomised to receive either eculizumab or placebo. The study designs were generally similar, with largely overlapping inclusion criteria and some protocol modifications. One difference was in the relapse inclusion criteria, as the placebo group required participants to have experienced ≥2 relapses in the previous 12 months or ≥3 in the previous 24 months (including at least 1 within 12 months before screening), whereas the ravulizumab group allowed enrolment of participants with ≥1 relapse in the past 12 months, including those with a first-time attack. Diagnostic criteria were also updated in the ravulizumab group to reflect the 2015 IPND guidelines, compared to the 2006/2007 criteria used in the placebo group. Baseline MRI and OCT assessments (contrast optional) were included in the ravulizumab group but not in the placebo group. Additionally, patient disposition following relapse differed, since in the placebo group, participants exited the study upon relapse, whereas in the ravulizumab group, patients remained in the trial. Finally, dosing regimens varied, as patients in the placebo study received a fixed-dose schedule with biweekly maintenance dosing after induction, while those in the ravulizumab study received weight-based regimen with maintenance dosing every eight weeks.

As patients in the ravulizumab study were not randomly allocated to the ravulizumab or placebo arms, there was a potential for imbalance between treatment groups in covariates that could affect efficacy outcomes. It was therefore important to consider differences in patient characteristics between the two groups, in particular with regards to effect modification. Treatment effect modifiers are study design or patient characteristics that influence the efficacy of the treatment, resulting in different relative treatment effect estimates, for example, different hazard ratios for relapse (87). In the context of AQP4+ NMOSD, anti-AQP4 antibody serological status and background IST were considered treatment effect modifiers. As both the ravulizumab and the placebo study included patients with AQP4+ NMOSD, there were no differences in serological status between treatment groups, and this variable was not considered a source of bias. However, there were potential differences in the use of background IST between patients in the ravulizumab and placebo arms; to account for these differences and evaluate whether they influenced treatment effect estimates, subgroup and sensitivity analyses were conducted. Treatment effects for ravulizumab and placebo were determined for a subgroup of patients without IST use at baseline, and propensity scores were used to evaluate differences in baseline characteristics between the ravulizumab and the placebo treatment group (88). The results of sensitivity analyses stratified by propensity score and using stabilized inverse probability of treatment weight (sIPTW) analysis indicate that any differences in baseline characteristics due to the trial design did not confound the results of the primary analysis (88).

In rare diseases and highly targeted patient populations, traditional RCTs often present ethical and practical challenges. In these situations, there is justification for using non-RCT designs, such as SATs (89, 90). To contextualise findings from an SAT, external comparator

(EC) data are collected from patient cohorts outside the SAT (e.g., real-world evidence or previous clinical trial data in a similar population) (90).

There are circumstances in which the use of an external control design is considered appropriate (91), especially when it is not possible or ethical to conduct a placebo-controlled study, when the treatment effect is large or dramatic, when there is a strong temporal association with administration of the investigational product, and when the external control population closely resembles the treatment group (89, 91). Ravulizumab for treatment of AQP4+ NMOSD meets the majority of criteria for which the use of an external control design is considered acceptable (89), which is also stated in the EMA assessment report for ravulizumab (92). The below summary outlines the appropriateness of using an external placebo-controlled design in the ravulizumab study.

1. In the EMA assessment report, the use of an external placebo control arm was deemed to have a reasonable framework for exceptional acceptance from the scientific advice procedures in 2019.
2. This was given that ravulizumab and eculizumab differ only slightly in molecular structure, share the same mechanism of action, and that the biological rationale for C5 inhibition in preventing complement-mediated damage is well established, together with the demonstrated non-inferiority of ravulizumab versus eculizumab in two pivotal phase 3 trials in PNH (considered supportive despite the different indication) (92).
3. In addition, it was noted that acceptability depended on the ravulizumab study including a similar population, operational procedures and endpoints in order to get results as comparable as possible (92).
4. Comparison of ravulizumab to eculizumab (being approved for use in NMOSD) under a non-inferiority hypothesis was considered unfeasible in terms of required sample size in a rare condition (92).
5. Despite not being a randomised design, the rigor of the external placebo-controlled design of the ravulizumab study provides credible evidence on the efficacy of ravulizumab.
6. Propensity score matching and weighting using patient data (complete datasets from PREVENT and CHAMPION-NMOSD available to Alexion Pharmaceuticals) were performed to ensure any differences in baseline characteristics due to the trial design did not confound the results of the primary analysis.
7. Externally controlled trials have increasingly been used for regulatory approvals and HTA evaluations. Robust statistical methods enhance the reliability of comparisons between external control arms and treatment groups.

6.1.2.1 Comparability of patients across studies

Demographics and baseline characteristics for the subgroup of patients who had received rituximab prior to any relapse are summarised in Table 10. Subgroup patients from both the ravulizumab and placebo groups were adults with AQP4+ NMOSD and with a history of relapsing disease.

Pre-specified subgroup analysis of key characteristics confirms a consistent treatment effect for ravulizumab across these groups, including age, gender, and race (88). A post hoc subgroup analysis of the ravulizumab group was conducted to align with the proposed population for reimbursement. Although specific data is not available for those patients who are unable to be treated with rituximab due to an adverse event or contraindication, these patients may be considered part of the broader group of patients enrolled in CHAMPION-NMOSD, which included patients with a variety of prior treatment exposure to ISTs and rituximab.

A total of [redacted] of 58 patients [redacted] in the ravulizumab group and [redacted] of 47 patients [redacted] in the placebo group met the subgroup criteria. The mean time from the last dose of rituximab to the first study dose was [redacted] in the ravulizumab group and [redacted] in the placebo group.

Within the subgroup, [redacted] of patients in the ravulizumab group were [redacted] compared to [redacted] in the placebo group, with a [redacted]

Table 10 Demographics and baseline characteristics of subgroup patients with prior rituximab use prior to any relapse in the ravulizumab and placebo groups

	Ravulizumab (N=21)	Placebo (N=20)
Female, n (%)	20 (95.2)	18 (90.0)
Mean age (±SD), years		
At first receipt of trial agent	48.2 ± 13.38	43.0 ± 14.93
At initial clinical presentation	43.9 ± 14.47	35.9 ±15.06
Age group, n (%)		
<45 years	7 (33.3)	10 (50.0)
≥45 years	14 (66.7)	10 (50.0)
Region		
Americas	14 (66.7)	10 (50.0)
Europe	4 (19.0)	8 (40.0)
Asia-Pacific	3 (14.3)	2 (10.0)
Race, n (%)		
Asian	2 (9.5)	2 (10.0)
Black or African American	4 (19.0)	7 (35.0)
White	13 (61.9)	11 (55.0)
Other or unknown	2 (9.5)	0
Mean BMI (± SD), kg/m2	27.47 ± 7.34	28.13 ± 5.66
EDSS score*		
Mean (± SD)	3.76 ± 1.84	4.00 ± 1.62
Median (range)	3.50 (0.0 to 6.5)	4.00 (1.0 to 6.5)
EQ-5D index score†		
Mean (± SD)	0.67 ± 0.26	0.69 ± 0.22

Median (range)	0.77 (0.08 to 1.00)	0.77 (0.27 to 1.00)
EQ-5D VAS score¶		
Mean (± SD)	71.1 ± 16.91	62.9 ± 20.57
Median (range)	75.0 (40 to 97)	66.0 (20 to 95)
HAI score§		
Mean (± SD)	1.5 ± 1.44	2.2 ± 1.47
Median (range)	1.0 (0 to 5)	2.0 (0 to 6)
Proportion of patients on concomitant ISTs (%)#	4 (33.3)	13 (65.0)
Steroids alone	2 (9.5)	3 (15.0)
Azathioprine subgroup	0 (0.0)	4 (20.0)
Azathioprine alone	0 (0.0)	3 (15.0)
Azathioprine + Steroids	0 (0.0)	1 (5.0)
Mycophenolate mofetil subgroup	1 (4.8)	5 (25.0)
Mycophenolate mofetil alone	0 (0.0)	3 (15.0)
Mycophenolate mofetil + Steroids	1 (4.8)	2 (10.0)
Other ISTS(s)	2 (9.5)	1 (5.0)
Other IST(s) alone	2 (9.5)	0 (0.0)
Other IST(s) + Steroids	0 (0.0)	1 (5.0)

Abbreviations: ARR, Annualised Relapse Rate; BMI, Body Mass Index; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index; ITT, Intention-To-Treat; SD, Standard Deviation; VAS, Visual Analog Scale.

Notes: * EDSS scores ranged from 0 (no disability) to 10 (death)

† EQ-5D index scores range from 0 (with 0 being the value of a health state equivalent to dead) to 1 (the value of full health)

¶ EQ-5D VAS scores range from 0 (the worst imaginable health) to 100 (the best imaginable health)

§ HAI scores range from 0 to 9, with higher scores indicating decreased independent ambulation

ISTs are defined as those therapies used for relapse prevention.

Source: Alexion Pharmaceuticals, Inc. (88)

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

Table 11 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (4)	Value used in health economic model (reference if relevant)
Age at onset, years, median (IQR)	48 (28–60)	[redacted]
Gender, female, %	89.4%	[redacted]
Patient weight	Not reported	[redacted]

EDSS, mean (SD)	4.6 (2.2)	[redacted]

Abbreviations: EDSS, Expanded Disability Status Scale; IQR, Interquartile Range; SD, Standard Deviation

Source: Alexion Pharmaceuticals, Inc. (88)

6.1.4 Efficacy – results per CHAMPION-NMOSD

The following section presents key efficacy findings from the CHAMPION-NMOSD study based on the primary treatment period, with a data cut-off date of 15 March 2022. Detailed results for the outcomes and method for each analysis are provided in Appendix B.

The overall results demonstrated efficacy of ravulizumab for the treatment of adult patients with AQP4+ NMOSD (5). The outcomes presented below are for the subgroup of patients who had received rituximab prior to any relapse. This subgroup included [redacted]patients overall, with [redacted] in the ravulizumab group and [redacted] in the placebo group. All subgroup patients received at least one dose of study drug and were included in both the full analysis set (FAS) and safety set (SS). In addition, data on the outcomes for the ITT population are provided in Appendix B, and results from the long-term extension for both the ITT and post-rituximab subgroup are provided in Appendix K.

Time to first adjudicated on-trial relapse

In the post hoc analysis, all patients in the ravulizumab group were relapse-free at [redacted] [redacted] (median follow-up time of [redacted]) compared to [redacted] of patients in the placebo group (median follow-up time of [redacted]). [redacted]

In the subgroup, the hazard ratio for ravulizumab compared to placebo was[redacted], representing a [redacted] in the risk of relapse. [redacted] The Kaplan-Meier (KM) curves are shown in **Error! Reference source not found.**.

[redacted]

[redacted]

Abbreviations: CI, Confidence Interval.

Notes: *The placebo group data were collected as part of the PREVENT trial. Patients who did not experience an adjudicated on-trial relapse were censored at the earlier of the end of the study period and 35 days after a missed or >35-day delayed dose due to the COVID-19 pandemic. If a patient in the placebo group was followed longer than any of the patients in the ravulizumab arm, then that patient was censored at the longest ravulizumab follow-up time. (1) Based on the Kaplan-Meier product limit method, (2) Based on the complementary log-log transformation, (3) Based on the log-rank test, (4) Based on a Cox proportional hazards model, with Firth's adjustment if no relapses observed in a treatment arm, (5) Wald confidence interval or Profile Likelihood Confidence Limits, if no relapses observed in a treatment arm, (6) Constructed as a risk ratio: A tipping point analysis quantifying the level of confounding which could compensate the estimated treatment effect.

Source: Alexion Pharmaceuticals, Inc. (88)

Table 12 Number of patients censored at each timepoint per arm

Arm /Weeks	0	12	24	36	48	60	72	84	96	108	117
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The numbers provided indicate the number of patients censored between the current and the previous time-point.

Source: Alexion Pharmaceuticals, Inc. (88)

Adjudicated on-trial annualised relapse rate (ARR)

In the pre-defined subgroup analysis, ravulizumab demonstrated [redacted] in the adjudicated on-trial ARR compared to a conservative estimate of ARR in the NMOSD population of 0.25 (1 relapse in 4 patient-years). The adjusted ARR in the ravulizumab group was [redacted], [redacted]

Clinically important changes from baseline in ambulatory function as measured by Hauser Ambulation Index (HAI)

Mobility-related functional decline, assessed using the HAI (88), showed [redacted] outcomes for subgroup patients treated with ravulizumab. A clinically important worsening in HAI was observed in [redacted] in the ravulizumab group compared to [redacted] in the placebo group. [redacted]

Change from baseline in EDSS at end of study

[redacted]

Table 13 Comparison of key secondary endpoints for ravulizumab and placebo for subgroup

Change from baseline to end of study Variable	Statistic	Placebo (N = [redacted])	Ravulizumab (N = [redacted])	p-value
ARR*	Adjusted ARR (95% upper CI)	[redacted]	[redacted]	[redacted]

HAI†	No Clinically Important Worsening	[redacted]	[redacted]	[redacted]
	Clinically Important Worsening			
EDSS Score†	No Clinically Important Worsening	[redacted]	[redacted]	[redacted]
	Clinically Important Worsening			

Abbreviations: ARR, Annualised Relapse Rate; CI, Confidence Interval; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index; NA, Not Applicable; P-value, Probability Value.

Notes: * On-trial ARR from the CHAMPION-NMOSD study is compared to a conservative estimate of ARR in the NMOSD population of 0.25. Based on a Poisson regression adjusted for historical ARR in the 24 months prior to screening. 95% CI could not be estimated when the ARR or the rate ratio was 0.

† p value from logistic regression model adjusted for baseline score

Source: Alexion Pharmaceuticals, Inc. (88)

Sensitivity analyses using propensity scores

Propensity scores were utilised to evaluate any differences in baseline characteristics between the ravulizumab group and the placebo treatment group. The variables considered included region, gender, age at first dose, background IST use, baseline EDSS, and historical ARR within the 24 months prior to screening. Sensitivity analyses for the efficacy endpoints were performed to balance these baseline covariates between treatment groups and further reduce potential bias introduced through an external control. Two approaches were used: stratification by propensity score, and use of propensity scores in a weighted analysis (88). These analyses were done for the post-rituximab subgroup population.

The median propensity scores were [redacted] for the ravulizumab group and [redacted] for the placebo group (88). Within the post-rituximab subgroup, following stratification on median propensity score, [redacted] of patients in the ravulizumab group and [redacted] of patients in the placebo group had a propensity score that was above the median, [redacted]

The analysis of baseline characteristics across propensity score strata showed that, [redacted], the majority of covariates included in the propensity score calculation had a standardized mean difference (SMD) [redacted], [redacted]

As another approach to balance the baseline covariates between treatment groups and more closely match the patients between treatment groups, sIPTW, derived from propensity scores, were applied in the summary of baseline characteristics. Following this method of weighting, the SMD for all covariates included in the propensity score calculation was [redacted] (93). This method of weighting also balanced on covariates not included in the propensity score calculation, including HAI score and EQ-5D index.

7. Comparative analyses of efficacy

Placebo was included in the CHAMPION-NMOSD trial as the external comparator. Hence, this section is irrelevant for this comparator and only Table 14 presents data from the study.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

The results from the CHAMPION-NMOSD and PREVENT trials for the post-rituximab subgroup are presented in Table 14 below. ITT results can be found in Appendix B.

Table 14 Results from the comparative analysis of ravulizumab vs. placebo in the post-rituximab subgroup

Outcome measure	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI) for time to first adjudicated on trial relapse, ravulizumab/placebo, at 96 weeks		[redacted]	[redacted]
Adjusted ARR* (95% CI). Measured at end of primary treatment period	[redacted]	[redacted]	[redacted]
Clinically important worsening in change in ambulatory function from baseline as measured by HAI†, n (%) Measured at end of primary treatment period	[redacted]	[redacted]	[redacted]
Clinically important worsening in change in ambulatory function from baseline as	[redacted]	[redacted]	[redacted]

Outcome measure	XXXXXXXXXXXX	XXXXXXXXXXXX	XXXXXXXXXXXX
measured by EDSS Score†, n (%) Measured at end of primary treatment period			

Abbreviations: ARR; Annualised Relapse Rate; CI, Confidence Interval; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index; P-value, Probability Value.

Notes: * On-trial ARR from the CHAMPION-NMOSD study is compared to a conservative estimate of ARR in the NMOSD population of 0.25. Based on a Poisson regression adjusted for historical ARR in the 24 months prior to screening. 95% CI could not be estimated when the ARR or the rate ratio was 0.

† p value from logistic regression model adjusted for baseline score

Source: Alexion Pharmaceuticals, Inc. (88)

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

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

As presented in Section 4, the cost-effectiveness analysis relied on a Markov cohort model. The long-term extrapolation of time to relapse data and the calculation of the transition probabilities is described in this section.

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of Relapse-free rate

The CHAMPION-NMOSD and PREVENT data (adjudicated on-trial relapse) were used to calculate time to relapse events, using Kaplan-Meier and parametric time-to-event analytic methods. Based on the trial design, time to first on-trial relapse could be assessed, with the assumption within the economic model that these estimates would then "reset" and apply to subsequent relapse events. The external placebo-controlled CHAMPION trial was used to describe ravulizumab data, while SoC was based on the placebo arm in the PREVENT trial. Because patients were being combined across multiple trials with some variation in inclusion criteria, sensitivity analyses based on propensity scores were conducted in addition to the base case naïve (or unmatched) comparison consistent with the analyses reported in the clinical study report (CSR). Thus, two types of weighting for the sensitivity analyses were considered: average treatment effect (ATE) for all individuals across the two trials, and average effect of the treatment on the treated (ATT) for the target CHAMPION population. The respective weights were calculated using the function *mnps()* from R package "twang". Analyses were conducting using the *Flexsurv* package within R.

Estimation of Kaplan-Meier curves and parametric survival distributions using the individual patient failure time data from the CHAMPION and PREVENT trials was performed. The following parametric distributions were considered: Exponential, Weibull, Log-logistic, Log-normal, Gompertz, and Gamma, and used to estimate long-term probabilities of relapse.

Given the absence of events in the ravulizumab arm, it was not feasible to obtain uncertainty estimates from the parametric models. Therefore, it was assumed that the risk of having a relapse for patients receiving ravulizumab is proportional to SoC and appropriately captured by the HR reported in the CSR (HR = 0.049; standard error = 1.08).

Choice of statistical distribution was according to NICE DSU guidelines (94) and based on several factors: (i) statistical assessment via Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC), (ii) visual inspection of curve fit and consideration of face validity given clinical knowledge of NMOSD, and (iii) feasibility considerations within a Markov model.

(i) Statistical assessment (via AIC/BIC) and visual inspection/consideration of face validity were used to select the most appropriate distributions: log-normal and exponential (Table 15). Of these two distributions, the exponential was preferred for statistical reasons as it accommodates a proportional hazards assumption which is required to apply a HR for ravulizumab (preferred approach given the lack of relapse events in the CHAMPION trial as described above), while lognormal represents an accelerated failure time model.

(ii) In addition to statistical diagnostics, consideration was given to plausibility of resulting curves, both short- and long-term projections. During the period of observed data, all curves fit relatively well (Figure 3), while wider variation was observed in long-term projections during the period with no data available to validate against (Figure 3). Given that NMOSD is a disease characterised by periodic relapse (without spontaneous recovery in patients treated with SoC), and the PREVENT trial (from which the CHAMPION placebo arm was taken) required several relapses within the prior two years, it was considered that the exponential distribution, which was associated with the greatest long-term probability of relapse for SoC patients, was the most plausible. Further, given the "unpredictable" nature of relapse and the fact that they can occur at any point in time, the exponential curve was also considered to be a clinically appropriate selection given its "memoryless" property for which the risk of relapse is independent of prior history and time since the last relapse.

(iii) Finally, consideration was given to Markov model properties; while flexibility is available for distributional assumptions of the first relapse, the memoryless property requires that subsequent relapses follow an exponential distribution, to avoid a prohibitive number of tunnel states. Thus, while the model includes multiple distributional options for the first relapse, only the exponential distribution is included for subsequent relapses. Given the general preference for exponential as described in points above, the exponential distribution was thus included as the base case selection for all relapse events (first and subsequent) in the model.

Table 15 summarises the assumptions associated with extrapolation. Figure 3 provides the parameterisation curves for long term extrapolations.

Table 15 Summary of assumptions associated with extrapolation of the relapse free rate

Method/approach	Description/assumption
Data input	CHAMPION-NMOSD, PREVENT
Model	Partition survival model
Assumption of proportional hazards between intervention and comparator	Yes, see reasoning above
Function with best AIC fit	Log-normal
Function with best BIC fit	Exponential
Function with best visual fit	Exponential
Function with best fit according to evaluation of smoothed hazard assumptions	Exponential
Validation of selected extrapolated curves (external evidence)	No study available
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Exponential
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: N/A, not applicable.

Figure 3 Long-term extrapolation parametric and Kaplan-Meier analysis of time to adjudicated on-trial relapse – SoC and ravulizumab

[redacted]

[redacted]

Abbreviations: KM, Kaplan-Meier, SoC, Standard of Care.

Note: For ravulizumab, all parametric models overlap.

8.1.2 Calculation of transition probabilities

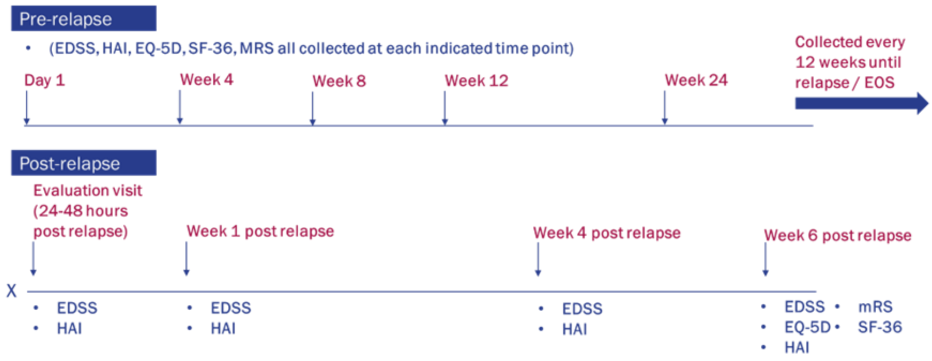
As described in Section 4, there are two channels through which patient will reach the long-term disability state. Patients can either transition directly into the long-term disability state, or they can reach the disability state by increasing EDSS scores through relapses. With each relapse, there is a 17.5% risk of immediately entering the long-term disability state, based on published NMOSD relapse data (32). For the EDSS score increasing channel, the transition probabilities are derived from patient-level data from CHAMPION-NMOSD and PREVENT (95, 96).

The health states described in Section 4.1.1 are categorised by patients' EDSS scores, and the EDSS scores are increased when patients have a relapse. The transition probabilities, therefore, are estimated with the EDSS scores. The following sections describe the estimation of EDSS score increase at the event of a relapse.

The data of the PREVENT trial was used to measure the primary outcome of the trial (i.e., time to first adjudicated on-trial relapse). The Intraclass Correlation (ICC) calculated using PREVENT was equal to 0.9, emphasising the need to use a mixed effect model to produce more accurate results by accounting for this high level of correlation. BIC statistics also confirmed that a mixed effect model fits the data better than the OLS specification.

The results below include a post-relapse indicator coefficient for all combinations of data sources pre- and post-relapse using mixed effect models (Figure 4). Results are presented for PREVENT, including data on eculizumab and placebo patients in Table 16.

Figure 4 Timing of Measurement Collection – Pre-Relapse and Post-Relapse Data Points



Abbreviations: EDSS, Expanded Disability Status Scale; EOS, End of Study; EQ-5D, EuroQol 5-Dimension Quality Of Life Questionnaire; HAI, Hauser Ambulation Index; mRS, Modified Rankin Scale; SF-36, 36-Item Short Form Health Survey.

Table 16 Mixed Effect Regression EDSS Scores Accounting for the Impact of Relapses on Patients' Disability Score, PREVENT

Parameter	Coefficient (SE)
Intercept (relapse free EDSS)	4.06 (0.14)
EDSS increment post-relapse	0.56 (0.08)
Model summary	
N patients	143
N observations	1555

Abbreviations: BIC, Bayesian Information Criteria; EDSS, Expanded Disability Status Scale; SE, Standard Error.

Table 17 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

As presented in Table 16, with each relapse, EDSS is assumed to permanently increase by 0.56 using mixed effect models.

To summarise, with each relapse, there is a 17.5% risk of immediately entering the long-term disability state. Additionally, patients have the potential to steadily increase their EDSS score to 5.5 or greater (hence entering the long-term disability state) via progressive increases in EDSS with successive relapses. With each relapse, EDSS is assumed to permanently increase by 0.56 (based on PREVENT trial data), with the number of relapses required to reach a threshold of 5.5 dependent on baseline EDSS value. These estimates are based on the trial data and the most accurate representation of the Danish setting.

Figure 5 and Figure 6 present the health state occupancy throughout the horizon of the model (53 years).

Figure 5 Ravulizumab health states per year

[redacted]

Figure 6 SoC health states per year

[redacted]

Abbreviations: SoC, Standard of Care.

Ravulizumab discontinuation

It was assumed in the model that patients would discontinue ravulizumab at time of first relapse. Patients receiving ravulizumab were assumed to transition to usual care after first relapse and thereafter stop accruing costs of ravulizumab. After ravulizumab discontinuation, it was assumed that there was no residual effect.

No patients discontinued treatment with ravulizumab in the post-rituximab subgroup. However, it is assumed that in clinical practice some patients may discontinue treatment, therefore an annual discontinuation rate was calculated based on the patients who discontinued in the ITT population. An annual discontinuation rate for patients on ravulizumab was estimated at 11.12%. The rate was derived from trial data on discontinued patients, i.e., [redacted] The reasons for discontinuation were either adverse event-related or physician decision. The proportion of discontinued patients was divided by the patient years [redacted] obtained from the median follow up time of the primary treatment period [redacted] of CHAMPION-NMOSD. The annual discontinuation rate affects both costs and effects.

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

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

The average and median time to relapse in the model are provided in Table 18.

Table 18 Estimates of the time to relapse in the model

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

Abbreviations: SoC, Standard of Care.

Table 19 provides the modelled average treatment length and time in the modelled health states.

Table 19 Overview of modelled average treatment length and time in the health states, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]	Relapse free [years]	(Post-relapse) no long-term disability [years]	(Post-relapse) long-term disability [years]
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC, Standard of Care.

9. Safety

9.1 Safety data from the clinical documentation

Safety outcomes are reported for the post-rituximab subgroup. Results from the long-term extension period for the ITT population are provided in Appendix K.

To ensure comparability across treatment arms, the CHAMPION-NMOSD study was prespecified to account for differences in follow-up time between the studies. Specifically, if a patient in the SoC group was followed longer than any of the patients in the ravulizumab group, then that patient's follow-up time ended at the longest ravulizumab follow-up time.

The safety data from the first administration of ravulizumab in the Primary Treatment Period (cutoff: 15 March 2022), encompassing [redacted], is summarised below.

9.1.1 Overview of adverse events

The safety population included post-rituximab subgroup patients who received at least one dose of study treatment, with [redacted] patients in the ravulizumab group and [redacted] in the placebo group.

Adverse events are reported as treatment-emergent adverse events (TEAEs). In the Primary Treatment Period, TEAEs were reported in [redacted] in the ravulizumab group. Most TEAEs were not related to study drug and were mild in severity. TESAEs were reported in [redacted] in the ravulizumab group.

Notably, [redacted] in the ravulizumab group experienced 1 event of meningococcal infection. The patient was promptly treated and recovered with no sequelae. No patients in the ravulizumab group discontinued treatment or died during the study and, overall, ravulizumab was well tolerated.

An overview of all TEAEs through the Primary Treatment Period for ravulizumab and the corresponding analysis period for the placebo arm is presented in Table 20.

Table 20 Overview of safety events

	Ravulizumab XXXXX	Placebo XXXXX	Difference, % (95 % CI)
Number of adverse events, n	[redacted]	[redacted]	Not available
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	Not available
Number of serious adverse events*, n	[redacted]	[redacted]	Not available
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted]	[redacted]	Not available
Number of CTCAE grade ≥ 3 events, n	Not available	Not available	Not available
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	Not available	Not available	Not available
Number of adverse reactions, n	Not available	Not available	Not available
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	Not available	Not available	Not available
Number and proportion of patients who had a dose reduction, n (%)	Not available	Not available	Not available
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	Not available

	Ravulizumab [redacted]	Placebo [redacted]	Difference, % (95 % CI)
Number and proportion of patients who discontinue treatment due to adverse events†, n (%)	[redacted]	[redacted]	Not available

Abbreviations: CI, Confidence Interval; CTCAE, Common Terminology Criteria for Adverse Events.

Notes: * A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, 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.

† For one patient, the reason for discontinuing was 'Adverse Event'; this event (invasive lobular breast carcinoma) is not included in this row, because it was reported as dose not changed. The patient remained on study for approximately 6 months after AE onset.

Data cutoff date: 15 Mar 2022

Source: Alexion Pharmaceuticals, Inc. (88).

9.1.1.1 Serious adverse events

During the Primary Treatment Period, there were no TESAEs reported in ≥5% of patients in the ravulizumab arm. However, [redacted] of patients in the placebo arm reported NMOSD as a TESAE. TESAEs occurring in the ravulizumab and placebo arms for the primary analysis timepoint of 15 March 2022 are presented in Table 21.

Table 21 Serious adverse events with a frequency of ≥ 5%

Adverse events	Ravulizumab (N=58)		Placebo (N=47)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
NMOSD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NMOSD, Neuromyelitis Optica Spectrum Disorder.

Note: * A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.

Data cutoff date: 15 Mar 2022

Source: Alexion Pharmaceuticals, Inc. (88).

9.1.1.2 Safety data used in the health economic model

Table 22 presents the adverse events and their frequencies that are used in the health economic model.

Table 22 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)				
Pneumonia	1.72%	0	CHAMPION-EDSS	From the trial
Sepsis	1.72%	0	CHAMPION-EDSS	From the trial
Encephalitis meningococcal	1.72%	0	CHAMPION-EDSS	From the trial

Abbreviations: NMOSD, Neuromyelitis Optica Spectrum Disorder.

Source: CHAMPION-NMOSD (97).

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

Not applicable

Table 23 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			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	N/A	N/A	N/A

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

In the CHAMPION-NMOSD and PREVENT trials, EQ-5D Index, EQ-5D VAS, and SF-36 were measured for the subgroup patients. The EQ-5D is the only instrument informing health state utilities, thus the only outcome described in this chapter.

Table 24 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L	CHAMPION-NMOSD (Median follow-up time of 73.5 weeks; DCO 15 Mar 2022); PREVENT (Median follow-up: 36.0 weeks; DCO 17 July 2018)	The EQ-5D outcomes were used to directly estimate Danish values

Abbreviations: EQ-5D, EuroQol 5-Dimension Quality Of Life Questionnaire; EQ-5D-3L, EuroQoL 5-Dimension 3-Level Questionnaire
Sources: CHAMPION-NMOSD (88); PREVENT (95).

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The instrument European Quality of Life Health 5-dimension Questionnaire (EQ-5D) was considered to be the most transferable and informative for the decision problem. The EQ-5D is a widely accepted measure of HRQoL and is a validated, standardised, appropriate measurement in the management of NMOSD.

The EQ-5D-3L is a self-assessed, standardised instrument to measure health-related QoL, which has been used in a wide range of health conditions, including NMOSD. The EQ-5D consists of 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system is a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each level is rated on a 3-level scale that describes the degree of problems in that area. The VAS asks a patient to mark on a scale from 0 to 100 (0 being worst health imaginable, and 100 best health imaginable), of how their overall health is that day. Per protocol the EQ-5D was to be administered prior to other study procedures at each visit.

10.1.2 Data collection

The EQ-5D was included in the trial protocol to capture the patient's overall health-related quality of life at the time of relapse. The Treating Physician administered the EQ-5D survey during relapse assessments. The data collection for EQ-5D was performed regularly during the PREVENT and CHAMPION-NMOSD trials, although with different frequency (Table 25).

Overall, there were very low levels of missing data in the trial. Missing data for the primary analysis of EQ-5D scores at the end of the primary treatment period was handled as follows: if the assessment 6 weeks after the first on-trial relapse was missing or if a non-relapse patient is missing the end of primary treatment period score (for the ravulizumab treatment group) or the end of study score (for the placebo treatment group), the last observed score from a protocol scheduled visit will be used. If a patient has no post-baseline assessments, the baseline value will be used. If a patient experiences a second on-trial relapse during the 6-week recovery phase after the initial relapse, the last score prior to the second attack will be used for the analysis. This approach was also consistent with the PREVENT study.

Table 25 Pattern of missing data and completion in the post-rituximab subgroup

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQoL, Health-Related Quality of Life.
Sources: CHAMPION-NMOSD (88), PREVENT (95).

10.1.3 HRQoL results

The HRQoL EQ-5D-3L summary statistics, with the baseline results and end of study results, are shown in Table 26. It showed a favourable treatment effect for ravulizumab compared to placebo for change from baseline in EQ-5D Index Score (calculated using Danish weights) and EQ-5D VAS, though these effects were not statistically significant. Figure 7 and Figure 8 respectively show the mean EQ-5D Index and VAS scores over time among patients in the post-rituximab subgroup.

Figure 7 Mean EQ-5D Index over time in the post-rituximab subgroup

[redacted]

Abbreviations: CI, confidence interval; EQ-5D, EuroQol 5-Dimension Quality of Life Questionnaire.

Figure 8 Mean EQ-5D VAS over time in the post-rituximab subgroup

[redacted]

Abbreviations: CI, Confidence Interval; EQ-5D, EuroQol 5-Dimension Quality of Life Questionnaire, VAS; Visual Analogue Scale.

Table 26 HRQoL EQ-5D-3L summary statistics in the post-rituximab subgroup

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value
			EQ-5D Index		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, Confidence Interval; EQ-5D, EuroQol 5-Dimension Quality Of Life Questionnaire; EQ-5D-3L, EuroQoL 5-Dimension 3-Level Questionnaire; HRQoL, Health-Related Quality of Life; VAS, visual analogue scale.

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

10.2.1 HSUV calculation

A regression model was fitted to the trial-based utility data (pooled trials ALXN1210-NMO-307 (CHAMPION-NMOSD), ECU-NMO-301 (PREVENT)). The model included time-varying covariates for the cumulative number of prior relapse events and a binary indicator variable equal to 1 if a relapse had occurred within the 50 days preceding the EuroQol five-dimension assessment (EQ-5D) and 0 otherwise. No explicit treatment-effect term was included, under the assumption that HRQoL is determined by relapse history and that any treatment effect on HRQoL operates through relapse prevention. The utility values have been age-adjusted following section 7.3 of the DMC methods guide (98).

The specification of the regression equation described below reflected the premise that relapses exert both an initial (acute) impact on HRQoL, which partially resolves over time, and a residual cumulative long-term effect. The long-term component acknowledges that the acute impact is unlikely to fully resolve and that multiple relapses produce a persisting decrement in chronic HRQoL. This conceptual framework was validated through interviews in November 2019 with two clinical experts in NMOSD: Dr. Dalia Rotstein (University of Toronto) and Dr. Mark Freedman (University of Ottawa) (99). The acute window was set at 50 days to maximise the number of observations within this period, consistent with the trial protocol specifying EQ-5D collection at 6 weeks post-relapse. The short-term effect may be underestimated because few EQ-5D assessments occurred within 1–2 weeks of relapse, when the impact is expected to be greatest. In preliminary analyses, varying the acute window from 25 to 100 days had minimal influence on the estimated regression coefficients.

The model was fitted using 2,632 longitudinal observations from 201 individuals. During follow-up, 175 individuals (2,252 observations) experienced 0 relapses, 24 individuals (347 observations) experienced 1 relapse, 1 individual (15 observations) experienced 2 relapses, and 1 individual (18 observations) experienced 3 relapses. For 25 individuals (35 observations), an EQ-5D value was recorded within 50 days of a relapse, so the indicator variable equalled 1 for those observations.

The utility values applied the economic model were calculated based on the following equation:

$$E\left[Y_{ij}\right] = \beta_0 + \beta_1 X_{1ij} + \beta_2 X_{2ij}$$

Where: - $E\left[Y_{ij}\right]$ is the expected value of the outcome for subject i. β_0 is the intercept. - β_1 and β_2 are the coefficients for the predictors. - X_{1ij} and X_{2ij} are the values of the predictors.

10.2.1.1 Mapping

The original mapping study was conducted to enable the estimation of EQ-5D-5L utilities in studies where only EQ-5D-3L data were available. This was essential due to the broader adoption of the EQ-5D-5L instrument, which offers improved sensitivity and reduced ceiling effects compared to the EQ-5D-3L. The mapping allows continuity in health economics evaluations without needing to collect new 5L data retrospectively. The mapping was based on a crosswalk developed by van Hout et al. (100), which aimed to provide a robust interim solution. The mapping was performed on all the patients available with no censor.

Following the mapping from 3L to 5L, the interim UK crosswalk value set (based on time trade-off and discrete choice experiments) was initially applied to derive utility values. To adapt these to the Danish context, UK-based values were subsequently converted using the Danish EQ-5D-5L value set, developed by Jensen et al. (101). This value set reflects Danish societal preferences and uses a hybrid valuation approach.

The conversion was done by re-applying the mapped 5L health states to the Danish tariff, ensuring that the utility values aligned with local health economic evaluation standards. Linear interpolation was used.

10.2.2 Disutility calculation

The disutility due to disability is applied to patients in the "permanent disability" health states in the model. The calculations on the utility tab estimate this disutility by taking a weighted average of utilities published by Hughes et al. by EDSS class (weighted by the number of people in each EDSS class in the Hughes et al. cohort) (102). The relative change in utilities for individuals with EDSS <5.5 is compared to those >5.5 to understand the impact of disability status on HRQoL. This proportional change in utility is then used to calculate an absolute decrement of -0.2387 that is applied to all health state utilities, once individuals enter the permanent disability state in the model. The model's "Permanent disability" state is characterized specifically by blindness and/or loss of ambulation. Therefore, the EDSS=5.5 threshold from Hughes et al. does not perfectly correspond to the model's definition of permanent disability (102). However, it was assumed to be a reasonable proxy, and the associated difference in utility from Hughes et al. was used to estimate the impact of blindness or loss of ambulation on HRQoL

Disutilities associated with AEs are included in the model but as they are derived from the literature, they are presented in 10.3.4.

10.2.3 Disutilities associated with AEs are included in the model but as they are derived from the literature, they are presented in 10.3.4. HSUV results

Table 27 summarises the utilities used in the model.

Table 27 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Number of patients (observations)	Comments
HSUVs					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, Confidence Interval; DK, Danish Kroner; EQ-5D-5L, EuroQol 5-Dimension 5-Level Questionnaire; N/A, Not Applicable.

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

N/A

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

To account for disutilities associated with adverse events, existing literature was used to inform decrements in the CEM. The 30-day disutility associated with each Grade 3/4 adverse event is presented Table 28. These disutilities are multiplied by the duration of each adverse event to calculate the total disutility incurred by each event.

Table 28 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Disutilities				
Pneumonia	0.0428 [0.0424, 0.0432]	EQ-5D-5L	US	Sullivan 2006 (85) - ICD-9 518 Other Lung Diseases. Duration 15 days.
Sepsis	0.0190 [0.0188, 0.0192]	EQ-5D-5L	US	Sullivan 2006 (85) - ICD-9 427 Cardiac Dysrhythmias. Duration 15 days.
Encephalitis meningococcal	0.0190 [0.0188, 0.0192]	EQ-5D-5L	US	Assumed to be the same as Sepsis.

Abbreviations: CI, Confidence Interval; EQ-5D-5L, EuroQol 5-Dimension 5-Level Questionnaire; N/A, Not Applicable, US, United States

Table 29 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

The recommended dosing regimen for ravulizumab consists of a loading dose followed by maintenance dosing. The doses are administered by intravenous infusion based on the patient's body weight. For adult patients (≥ 18 years of age), maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration.

Patients in both arms use concomitant background therapies, i.e., ISTs, however, patients in the SoC arm of the post-rituximab subgroup have a higher incidence of said treatments (section 6.1.2.1). It was conservatively assumed that the costs associated with the ISTs were zero. During the LTE period of 228 weeks, it was shown that the majority of ravulizumab patients (63.0%) taking IST at baseline decreased or stopped ≥ 1 therapy as of the end of the LTE period (103). No patients increased dosage or started a new IST for the prevention of NMOSD relapses (103).

The packages used in the model are the packages with the lowest price per unit. When vial sharing is not assumed (base case analysis), the ravulizumab cost per dose is derived with consideration to minimising wastage, based on the distribution of patients' weight from the CHAMPION-NMOSD study, and assuming the maximum dose for each weight interval.

Table 30 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Ravulizumab	See section 3.4	100%	One loading dose, then maintenance dose once every 8 weeks	No
Meningococcal vaccine	One time	100%	One time before the first cycle	No

Source: CHAMPION-NMOSD (104).Source: CHAMPION-NMOSD (105).

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

The ravulizumab administration cost is estimated using the cost per IV infusion. The cost of IV infusion was estimated using the Danish Health Data Authority's website Interactive DRG (106). The administration cost for the comparator basket is assumed to be zero, since all the drugs are orally administered.

Table 31 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV administration cost	Once for the loading dose, then once every 8 weeks for the maintenance dose	2,012	01MA98, MDC01 1-dagsgruppe, pat. min. 7 år	DRG 2025

Abbreviation: DRG, Diagnosis Related Groups; IV, intravenous.

11.4 Disease management costs

11.4.1 Relapse management

In the event of relapse, patients need to receive treatment. The cost of treating a relapse was based on data from CHAMPION-NMOSD for on-trial relapse as determined by the Treating Physician, as this could better represent clinical management. No adjudicated on-trial relapses were reported for patients receiving ravulizumab in CHAMPION-NMOSD. However, 3 patients had an on-trial relapse as determined by the Treating Physician that was adjudicated negatively by the Relapse Adjudication Committee. None required hospitalisation. In the PREVENT placebo arm, 29 patients had an on-trial relapse as determined by the Treating Physician, of which 9 were adjudicated negatively. Fifteen patients from this group were hospitalised. Overall, 15 (46.9%) of the 32 on-trial relapses required hospitalisation for management, and 10 (31.3%) were managed with PLEX, for a mean number of 5 sessions (Table 32).

Patients who receive PLEX while on ravulizumab treatment require a supplemental dose of 0.5 times the maintenance dose (104, 105), both the costs of PLEX and supplemental ravulizumab have been accounted for in the cost of treating a relapse. The weighted average cost of managing a relapse is therefore calculated accounting for hospitalisation, outpatient management and use of PLEX, with the supplementary use of ravulizumab added for the ravulizumab arm only (Table 33). The cost of a hospital admission is based on the Danish DRG 01MA15, "Andre specifikke sygdomme i nervesystemet, pat.mindst 18 år". The cost of PLEX is also sourced from the DRG (16PR01: Transfusion af plasma og/eller behandlet blod). The cost of supplementary ravulizumab is estimated at 0.5 times the cost of a maintenance dose.

In CHAMPION-NMOSD, PLEX/PP or IVIg was allowed at the discretion of the Treating Physician for treatment of an on-trial relapse. Two patients received supplemental infusions of ravulizumab; 1 supplemental infusion in 1 patient and 3 supplemental infusions in the other patient (104).(105). The use of supplementary ravulizumab during plasma exchange may vary significantly in practice and, according to the Australian evaluation of ravulizumab, would likely occur in admitted patients (107).

The estimated cost per relapse is DKK 33,010.

Table 32 Relapse management

Relapse management in CHAMPION-NMOSD /PREVENT	SoC/ Placebo n=47	Ravulizumab n=58	Overall n=105	Proportion
Patients with on-trial relapse (by treating physician)	29*	3*	32	30.5%
Patients with on-trial relapse requiring hospitalisation	15	0	15	46.9%
PLEX	10	1	11	34.4%
Mean number of PLEX sessions	5	5	5	-

Abbreviation: PLEX, Plasma Exchange.

Note: *9/29 PBO and 3/3 Ravulizumab relapses per treating physician were adjudicated negatively.

Source: CHAMPION-NMOSD CSR(104) 15 July 2022, Table 8Source: CHAMPION-NMOSD CSR(105) 15 July 2022, Table 8

Table 33 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Hospital admission	At relapse	40,649	01MA15	DRG 2025
Outpatient/non-patient setting	At relapse (assume 2 visits)	2,012	01MA98	DRG 2025
PLEX	At relapse	6,876	16PR01	DRG 2025

Abbreviation: DRG, Diagnosis Related Groups; PLEX, Plasma Exchange.

11.4.2 Disease management costs related to EDSS scores

Background medical costs are applied to patients based on disability status. The economic evaluation defines disability status by EDSS score, with a score of ≥5.5 defined as 'disability', and scores of <5.5 defined as 'non-disability'.

The data source relied on for costings is the eculizumab appraisal from DMC (48). To account for the inflation in Denmark between the end of 2021 and April 2025 (the latest available data), the Danish inflation rate from Danmarks Statistik (108) was applied to the final cost.

For the economic evaluation, only direct medical costs are included, and the costs of prescription medicines is excluded. As the categories of disability severity applied by do not perfectly align with the definitions in the model, the categories are re-allocated to EDSS scores with the assumption that respondents were evenly distributed across an EDSS range to allow them to be re-categorised according to definitions in the model (Table 35 and Table 36). The resultant costs applied in the model are presented in Table 34.

Table 34 Background medical costs

Average annual background medical costs	Costs from the eculizumab appraisal (DMC) (48)	Costs inflated to 2025
Patients without disability	29,137.16	33,768.23
Patients with disability	41,596.37	48,207.72

Abbreviations: DMC, Danish Medicinrådet.

Table 35 Direct costs per person according to disability severity - Non-disability health state, 2021

Definitions per CUA	No disability										
EDSS	*0*	*0.5*	*1*	*1.5*	*2*	*2.5*	*3*	*3.5*	*4*	*4.5*	*5*
N	52	52	20	20	20	20	20	20	35	35	35
Hospital costs (kr)	6,866	6,866	6,866	6,866	6,866	6,866	6,866	17,754	17,754	17,754	17,754
Ambulance costs (kr)	989	989	989	989	989	989	989	943	943	943	943
Consultations (kr)	10,231	10,231	10,231	10,231	10,231	10,231	10,231	14,595	14,595	14,595	14,595
Tests (kr)	3,542	3,542	3,542	3,542	3,542	3,542	3,542	8,226	8,226	8,226	8,226
Total	21,628	21,628	21,628	21,628	21,628	21,628	21,628	41,518	41,518	41,518	41,518

Abbreviations: CUA, Cost-Utility Analysis; EDSS, Expanded Disability Status Scale.

Table 36 Direct costs per person according to disability severity - Disability health state, 2021

Definitions per CUA	Disability								
EDSS	*5.5*	*6*	*6.5*	*7*	*7.5*	*8*	*8.5*	*9*	*9.5*
N	35	35	13	13	13	13	13	13	13

Hospital costs (kr)	17,754	17,754	26,579	26,579	26,579	26,579	26,579	26,579	26,579
Ambulance costs (kr)	943	943	1,832	1,832	1,832	1,832	1,832	1,832	1,832
Consultations (kr)	14,595	14,595	12,289	12,289	12,289	12,289	12,289	12,289	12,289
Tests (kr)	8,226	8,226	958	958	958	958	958	958	958
Total	41,518	41,518	41,658	41,658	41,658	41,658	41,658	41,658	41,658

Abbreviations: CUA, Cost-Utility Analysis; EDSS, Expanded Disability Status Scale.

11.5 Costs associated with management of adverse events

The adverse events included in the model are presented in Table 37. The frequencies of the adverse events included as input in the model are presented in Section 0. All unit costs were applied as one-off costs at the beginning of the time horizon. The unit costs are sourced from the Danish Health Data Authority's website Interactive DRG (106).

Table 37 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff (DKK)
Pneumonia	04MA98	1,330
Sepsis	18MA01	53,670
Encephalitis meninggococcal	01MA15	40,649

Abbreviations: DRG, Diagnosis Related Groups.

11.6 Subsequent treatment costs

Not applicable.

Table 38 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

Transportation (DKK 140.00 per visit) and patients costs (DKK 188.00 per hour) are included in the economic analysis as indicated in the DMC guidelines with unit cost sourced from the DMC's catalogue of unit costs (109). The inputs regarding number of trips and time spent in relation to treatment are shown in Table 39.

Table 39 Patient costs used in the model

Activity	Time spent [hours]
IV administration	Assumed 1.98 average hours for the infusion + 1 hour observation afterwards and trips to and from the hospital

Abbreviations: IV, Intravenous.

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

Not applicable.

12. Results

12.1 Base case overview

Table 40 Base case overview

Feature	Description
Comparator	SoC
Type of model	Markov model
Time horizon	53 years (lifetime)
Treatment line	2nd line after rituximab treatment. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L in CHAMPION-NMOSD (104). Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Hospital costs Costs of adverse events Patient and travel costs
Dosage of medicine	Based on weight
Average time on treatment	[redacted]
Parametric function for Time to relapse	Intervention: Exponential Comparator: Exponential
Average time in model health state Relapse free: [redacted] (Post-relapse) no long-term disability: [redacted] (Post-relapse) long-term disability: [redacted]	

12.1.1 Base case results

The base case results are presented in Table 41. The QALY gain compared to SoC is around [redacted] years, which is significant. The main benefit comes from the fact that patients who receive ravulizumab stay in the relapse-free state much longer than the SoC group. The base case ICER stands at [redacted]

Table 41 Base case results, discounted estimates

	Ravulizumab	SoC	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Background cost	[redacted]	[redacted]	[redacted]
Relapse cost	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (relapse-free)	[redacted]	[redacted]	[redacted]
Life years gained (no disability)	[redacted]	[redacted]	[redacted]
Life years gained (disability)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (relapse-free)	[redacted]	[redacted]	[redacted]
QALYs (no disability)	[redacted]	[redacted]	[redacted]
QALYs (disability)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]

	Ravulizumab	SoC	Difference
QALYs (relapse)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The following table describes the five most influential factors that affect the results. The results are stable in variation of the inputs, except for change in hazard ratio of ravulizumab vs. SoC. The tornado graph is presented in Figure 9.

Table 42 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
Hazard ratio for relapse (compared to Standard of care) - Ravulizumab	[redacted]	Upper end of a 95% confidence interval	[redacted]	[redacted]	[redacted]
	[redacted]	Lower end of a 95% confidence interval	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	[redacted]	+50%	[redacted]	[redacted]	[redacted]
	[redacted]	-50%	[redacted]	[redacted]	[redacted]
Discount rate – costs	[redacted]	+50%	[redacted]	[redacted]	[redacted]
	[redacted]	-50%	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Relapse free utility	[redacted]	Upper end of a 95% confidence interval	[redacted]	[redacted]	[redacted]
	[redacted]	Lower end of a 95% confidence interval	[redacted]	[redacted]	[redacted]
Age at baseline	[redacted]	ITT population starting age	[redacted]	[redacted]	[redacted]
	[redacted]	-33%	[redacted]	[redacted]	[redacted]

Figure 9 Tornado Graph

[redacted]

Table 43 summarises the two scenarios. Using ATE and ATT population do not change the ICER by a significant amount.

Table 43 Scenario analysis

Scenario	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
ATE	[redacted]	[redacted]	[redacted]
ATT	[redacted]	[redacted]	[redacted]

Abbreviations: ATE, Average treatment effect; ATT, Average effect of the treatment on the treated.

[redacted]The variables included in the PSA are listed in the “Parameter” sheet in the model. From this sheet, the variables to include/exclude from the analysis and which distribution to select for each parameter can be set. The results of the PSA are presented in Table 44.

Table 44 Probabilistic results of economic analysis

Incr. cost per QALY gained, DKK	Probabilistic
Ravulizumab vs. SoC	[redacted]

Abbreviations: ICER, Incremental cost effectiveness ratio; QALY, Quality adjusted life year; SoC, Standard of care.

Figure 10 shows the cost effectiveness acceptability curve.

Figure 10 Cost effectiveness acceptability curve

[redacted]

Figure 11 presents the cost effectiveness plane including all the 1000 PSA iterations, which are located for the vast majority in the north-east quadrant of the plane. The convergence plot in Figure 12 indicates that stability is reached after approximately 100 iterations.

Figure 11 Scatter plot derived from PSA

[redacted]

Abbreviations: ICER, Incremental Cost Effectiveness Ratio; QALYs, Quality Adjusted Life Years.

Figure 12 Convergence plot

[redacted]

Abbreviations: ICER, Incremental Cost Effectiveness Ratio.

13. Budget impact analysis

Number of patients (including assumptions of market share)

The relevant patient numbers in the next five years are presented in Table 45. It is assumed that ravulizumab will take 20% of the market share if it is introduced and will continuously increase its market share by 10% annually in years two and three, followed by a 5%

increase in years four and five. The budget impact is summarised in Table 45 and is taking patient carry-over into account.

Table 45 Number of patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Ravulizumab	1	3	5	8	11
SoC	4	6	8	9	10
			Non-recommendation		
Ravulizumab	0	0	0	0	0
SoC	5	9	13	17	21

Budget impact

Table 46 Expected budget impact of recommending the medicine for the indication (DKK)

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

14. List of experts

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Appendix A. Main characteristics of studies included

Table 47 Main characteristic of studies included

Trial name: CHAMPION-NMOSD (ALXN1210-NMO-307)	NCT number: NCT04201262
Objective	This study was conducted to evaluate the efficacy and safety of ravulizumab in adult patients with AQP4+ NMOSD.
Publications – title, author, journal, year	Pittock SJ, Barnett M, Bennett JL, Berthele A, de Sèze J, Levy M, et al. Ravulizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. Annals of neurology. 2023 Jun;93(6):1053-68.
Study type and design	A Phase 3, open-label, multicentre study of ravulizumab in adult patients with AQP4+ NMOSD, using a single-arm design with an external placebo control derived from PREVENT trial of eculizumab in AQP4+ NMOSD.
Sample size (n)	Ravulizumab Arm: N = 58
Main inclusion criteria	• Male or female patients ≥ 18 years of age, anti-AQP4 Ab-positive at screening, with a diagnosis of NMOSD as defined by the 2015 international consensus diagnostic criteria. A historically positive anti-AQP4 Ab test was acceptable if the test was performed using an acceptable, validated cell-based assay from an accredited laboratory. • History of at least 1 relapse in the last 12 months prior to the screening period. Patients with a single life-time attack were be considered to satisfy this inclusion criterion if the attack occurred in the last 12 months. • EDSS score ≤ 7 • Vaccinated against *Neisseria meningitidis* within 3 years prior to, or at the time of, initiating ravulizumab; administration of a 14-day course of prophylactic antibiotics if fewer than 14 days elapsed between vaccination and study treatment initiation • Stable doses of background immunosuppressive therapies were permitted. Patients who entered the trial receiving supportive treatment for relapse prevention, either in combination or as monotherapy, had to be on a stable dosing regimen for an adequate duration prior to screening, with no plan to change the dose during the study. • Body weight ≥ 40 kg

Trial name: CHAMPION-NMOSD (ALXN1210-NMO-307)	NCT number: NCT04201262
	• Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. • Written informed consent
Main exclusion criteria	• Participation in PREVENT trial (ECU-NMO-301), regardless of the study drug received (eculizumab or placebo) • Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1 • Presence of fever ≥ 38°C within 7 days prior to study drug administration on Day 1 • History of *Neisseria meningitidis* infection, HIV or unexplained infections • Hypersensitivity to murine proteins or to 1 of the excipients of ravulizumab • Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the trial, poses any added risk for the patient, or confounds the assessment of the patient • Use of rituximab or mitoxantrone within 3 months prior to screening, use of IVIg within 3 weeks prior to screening, or previous or current treatment with a complement inhibitor • Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days of screening or 5 half-lives of the investigational drug, whichever is greater • Pregnant, breastfeeding, or intending to conceive during the course of the study • Patients who were being treated with a biologic medication that may affect immune system functioning at the time of screening or had stopped treatment with a biologic medication that may affect immune system functioning, and 5 half-lives of the medication had not elapsed by the time of the screening visit, unless otherwise specified in the protocol
Intervention	Ravulizumab, with weight-based IV loading dose on Day 1, followed by weight-based IV maintenance doses on Day 15 and every 8 weeks thereafter until the end of the long-term extension period.
Comparator(s)	External comparator. Placebo group from the PREVENT trial of eculizumab in AQP4+ NMOSD (ECU-NMO-301)
Follow-up time	Median follow-up of 73.5 weeks (range 13.7–117.7)

Trial name: CHAMPION-NMOSD (ALXN1210-NMO-307)	NCT number: NCT04201262
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	*Primary endpoint:* • Time to first adjudicated on-trial relapse and relapse risk reduction *Secondary endpoints*: • Adjudicated on-trial ARR • Clinically important change from baseline in HAI • Clinically important worsening from baseline in EDSS • Change from baseline in EQ-5D index score and EQ-5D VAS score • Incidence of TEAEs, TESAEs, and TEAEs leading to study drug discontinuation • Change in serum ravulizumab concentration over the study duration • Change in serum free C5 concentration over the study duration • Presence and titre of ADAs over the study duration *Exploratory endpoints* • Change from baseline in OSIS • Characterise the change from baseline in visual acuity, colour vision, and confrontational visual fields • Change from baseline in SF-36 • Change from baseline in vital signs, ECG parameters, and clinical laboratory assessments • Shifts from baseline in C-SSRS • Change from baseline in levels of biomarkers of complement dysregulation, neuroinflammation and neural injury • Blood and CSF NMO-Ig (AQP4 Ab) concentration
Method of analysis	All analyses were conducted after completion of the primary treatment period using SAS® (Version 9.4 or higher), with a two-sided 5% Type I error and no imputation for missing data unless specified. The primary efficacy endpoint, time to first adjudicated on-trial relapse, was compared between ravulizumab and placebo using a log-rank test; hazard ratios and risk reductions were estimated via a Cox proportional hazards model with Firth's adjustment. Kaplan-Meier curves and 95% CIs for relapse-free proportions at selected timepoints, via the

Trial name: CHAMPION-NMOSD (ALXN1210-NMO-307)	NCT number: NCT04201262
	complementary log-log method, were provided, and sensitivity analyses were conducted. The adjudicated on-trial ARR was analysed using a Poisson regression model with log time as the offset and historical ARR as a covariate, with significance defined as an upper 95% CI ≤ 0.25 relapses/year. Clinically important HAI changes were assessed using a proportional odds model, and EDSS worsening using logistic regression, both adjusted for baseline. Changes in EQ-5D index score and EQ-5D VAS were analysed using nonparametric ANCOVA, each adjusted for its respective baseline value. A closed testing procedure was applied to control the type I error across endpoints, with hierarchical testing of secondary endpoints; descriptive p-values and CIs were reported regardless of formal significance. Safety data was summarised using the SS. TEAEs, defined as AEs occurring on or after first ravulizumab dose, were reported by SOC, with TESAEs presented similarly. Demographics and baseline characteristics were summarised by treatment group. Patient disposition, including numbers screened, treated, completed, discontinued (with reasons), and included in analysis sets, was summarised. Medical/surgical and NMOSD history were coded using MedDRA (v21.0 or later).
Subgroup analyses	A post hoc subgroup analysis was conducted in adult AQP4+ NMOSD patients with a history of relapsing disease who had received rituximab prior to any relapse. This subgroup included 21 patients treated with ravulizumab and 20 patients from the placebo external control arm of the PREVENT trial. All patients received at least one dose of study drug and were included in both the FAS and SS. The analysis assessed treatment effects across both primary and secondary clinical endpoints, using the same statistical methods as the main study. The comparability of baseline characteristics with ITT population supports the interpretability and the relevance of this subgroup analysis.
Other relevant information	N/A

Abbreviations: ADA, Anti-Drug Antibodies; AQP4 Ab, Aquaporin-4 Antibody; ARR, Annualised Relapse Rate; C5, Complement Component 5; CI, Confidence Interval; CSF, Cerebrospinal Fluid; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, Electrocardiogram; EDSS, Expanded Disability Status Scale; EQ-5D, European Quality of Life Health 5-dimension Questionnaire; FAS, Full Analysis Set; HAI, Hauser Ambulation Index; HIV, Human

Immunodeficiency Virus; Ig, Immunoglobulin; IV, Intravenous; IVIg, Intravenous Immunoglobulin; NMO, Neuromyelitis Optica; NMOSD, Neuromyelitis Optica Spectrum Disorder; OSIS, Optic Spinal Impairment Score; SF-36, 36-Item Short Form Health Survey; SOC, System Organ Class; SS, Safety Set; TEAE, Treatment-Emergent Adverse Event; TESAE, Treatment-Emergent Serious Adverse Event; VAS, Visual Analog Scale.

Trial name: PREVENT (ECU-NMO-301)	**NCT number: NCT01892345**
Objective	This study was conducted to evaluate the efficacy and safety of eculizumab versus placebo in adult patients with AQP4+ NMOSD.
Publications – title, author, journal, year	Pittock SJ, Berthele A, Fujihara K, Kim HJ, Levy M, Palace J, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(7):614-25.
Study type and design	Randomised, double-blind, placebo-controlled, multicentre, parallel-group, Phase 3 study of eculizumab versus placebo.
Sample size (n)	Total: N = 143 • Eculizumab Arm: N= 96 • Placebo Arm: N= 47
Main inclusion criteria	• Male or female patients ≥ 18 years of age, anti-AQP4 Ab-positive at screening, with a diagnosis of NMO or NMOSD according to 2006 or 2007 criteria, respectively. AQP4-IgG–seropositive status confirmed using of a commercially available cell-binding kit assay (Euroimmun) and analysed centrally at Mayo Medical Laboratories. • History of at least 2 relapses in the last 12 months or 3 relapses in the last 24 months with at least 1 relapse in the 12 months prior to the screening • EDSS score ≤ 7 • Stable doses of background immunosuppressive therapies were permitted, as defined by the treating physician, prior to screening and must have remained on that dose for the duration of the study, unless the participant experienced a relapse. • Daily corticosteroid must be no more than prednisone 20 mg/day (or equivalent), if a patient enters the trial receiving oral corticosteroid(s) with or without other IST(s) • Vaccination against Neisseria meningitidis prior to receiving study treatment, unless prior vaccination provided adequate coverage; administration of a 14-day course of antibiotics if fewer than 14 days elapsed between vaccination and study treatment initiation • Negative pregnancy test (serum human chorionic gonadotropin) for female participants of childbearing potential, with agreement to use effective, reliable, and medically approved contraceptive regimen

Trial name: PREVENT (ECU-NMO-301)	NCT number: NCT01892345
	during the study and for up to 5 months after treatment discontinuation
Main exclusion criteria	• Use of rituximab or mitoxantrone within 3 months prior to screening • Use of IVIg within 3 weeks prior to screening • Receipt of prednisone doses > 20 mg/day or the equivalent of other glucocorticoids at screening • Presence of unresolved meningococcal disease or systemic bacterial or other infection considered to be clinically significant or not treated with appropriate antibiotics • Hypersensitivity to murine proteins or to 1 of the excipients of eculizumab • Previous treatment with eculizumab • Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the trial, poses any added risk for the patient, or confounds the assessment of the patient • Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days • Pregnant, breastfeeding, or intending to conceive during the course of the study
Intervention	Eculizumab IV. Induction Phase: 900 mg IV weekly for 4 weeks, followed by 1200 mg for the fifth dose; Maintenance Phase: 1200 mg IV every 2 weeks
Comparator(s)	Placebo. Induction Phase: matching placebo (900 mg) IV weekly for 4 weeks, followed by matching placebo (1200 mg) for the fifth dose; Maintenance Phase: matching placebo (1200 mg) IV every 2 weeks
Follow-up time	Median follow-up time of 36.0 weeks (range 1.86–208.57), for the placebo arm
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary endpoint: • Time to first adjudicated on-trial relapse Secondary endpoints: • Adjudicated on-trial ARR

Trial name: PREVENT (ECU-NMO-301)	NCT number: NCT01892345
	• Change from baseline in scores on the EDSS • Change from baseline in mRS • Change from baseline in HAI • Change from baseline in EQ-5D index score and EQ-5D VAS score
Method of analysis	At baseline (day 1), patients were randomly assigned in a 2:1 ratio to receive either eculizumab or placebo. The patients were stratified across sites according to their EDSS score on day 1 (≤2.0 or 2.5 to 7.0 on a scale ranging from 0 [no disability] to 10 [death]) and the use of concomitant IST (no previous immunosuppressive therapy, except for glucocorticoids alone; continuing the same immunosuppressive therapy after the last relapse before screening, although doses may have changed; or receiving new immunosuppressive therapy or discontinuing an existing therapy after the last relapse). Patients, site staff members, and the representatives of the sponsor (Alexion Pharmaceuticals) were unaware of the trial-group assignments, and trial agents and treatment kits appeared identical. The trial was designed to continue until 24 patients had a relapse of NMOSD, as adjudicated by an independent panel. After a review of blinded data, representatives of the sponsor terminated the trial after 23 patients had had an adjudicated relapse, given the uncertainty in estimating when the final event would occur. The patients who completed the trial could enter an extension trial and receive open-label treatment with eculizumab. The primary efficacy endpoint was time to first adjudicated on-trial relapse. Secondary endpoints included ARR and changes from baseline in scores on the EDSS, mRS, HAI, and EQ-5D index score and EQ-5D VAS score. Treatment effects for the key clinical endpoints were estimated using Kaplan-Meier method and Cox proportional hazards regression model, where applicable. Safety assessments included monitoring for adverse events, evaluation of vital signs, a physical examination, the performance of electrocardiography and clinical laboratory tests, and evaluation for the presence of suicidal ideation or behavior. Adverse event data were analysed both with and without inclusion of physician-determined NMOSD relapses that met the criteria for a serious adverse event. Investigators assessed the relationship between each adverse event and the trial regimen using predefined categories (not related and unlikely, possibly, probably, or definitely related).
Subgroup analyses	A post-hoc defined subgroup analysis of patients who received rituximab prior to any relapse was conducted.
Other relevant information	N/A

Abbreviations: Anti-AQP4 Ab, Anti-Aquaporin-4 Antibody ARR, Annualised Relapse Rate; EDSS, Expanded Disability Status Scale; EQ-5D, European Quality of Life Health 5-dimension Questionnaire; HAI, Hauser Ambulation Index; IST, Immunosuppressive Therapy; IV, Intravenous; IVIg, Intravenous Immunoglobulin; mRS, Modified Rankin Scale; NMO, Neuromyelitis Optica; NMOSD, Neuromyelitis Optica Spectrum Disorder; VAS, Visual Analog Scale.

Appendix B. Efficacy results per study

Results per study

Efficacy results of the CHAMPION-NMOSD trial are presented in the tables below, for both the ITT population (Table 48), and the post-rituximab subgroup (Table 49). All results are based on the data cut from 15th of March 2022.

Across both populations, ravulizumab demonstrated efficacy over placebo for the primary endpoint of time to first adjudicated on-trial relapse. In the ITT population, no adjudicated relapses occurred, corresponding to a hazard ratio of 0.014 (95% CI: 0.000,0.103; p < 0.0001). Similarly, in the post-rituximab subgroup, no adjudicated relapses were observed, with a hazard ratio of 0.085 (95% CI: 0.001, 0.708; p = 0.0202).

Secondary efficacy outcomes, including adjudicated ARR, clinically important worsening in HAI, and EDSS scores, consistently showed favourable outcomes for ravulizumab compared to placebo. These results were observed across both the ITT population and the post-rituximab subgroup.

Table 48 Results per study for ITT population

Results of CHAMPION-NMOSD (NCT04201262)											
				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		
Time to first adjudicated	Ravulizumab	58	1.000 (1.000, 1.000)	NA	NA	NA	HR: 0.014	0.000, 0.103	p<0.0001	The comparison of the treatment groups for the primary endpoint used a log-	Alexion Pharmaceuticals, Inc. (88)

Results of CHAMPION-NMOSD (NCT04201262)											
				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		
on-trial relapse **(Result shows estimated proportion of patients relapse-free, cumulative probability)**	Placebo	47	0.519 (0.341, 0.670)							rank test. The hazard ratio and risk reduction were estimated using a Cox proportional hazards model, with Firth's adjustment. 95% CIs were presented for the estimated proportion of patients that were relapse-free at various timepoints based on the complementary log-log. Kaplan-Meier curves for both treatment groups were produced.	Alexion Pharmaceuticals, Inc. (88)
ARR	Ravulizumab	58	0.00 (NA, 0.044)	NA	NA	NA	NA	NA	p < 0.0001	On-trial ARR from the CHAMPION-NMOSD study is compared to a conservative estimate of ARR in the NMOSD population of 0.25. Poisson regression adjusted for historical ARR in the 24 months prior to screening was used to descriptively present the	Alexion Pharmaceuticals, Inc. (88)
	Placebo	47	NA								Alexion Pharmaceuticals, Inc. (88)

Results of CHAMPION-NMOSD (NCT04201262)											
				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		
										ravulizumab treatment group estimate and 95% CI.	
HAI **(Result shows patients with clinically important worsening in HAI score from Baseline to End of Study Period)**	Ravulizumab	58	2, 3.4%	NA	NA	NA	Odds ratio: 0.155	0.031, 0.771	0.0228	Clinically important worsening was conditional on the baseline value	Alexion Pharmaceuticals, Inc. (88)
	Placebo	47	11, 23.4%							Worsening if the baseline HAI was 0 and there was at least 2-point increase, or if the baseline HAI was > 0 and there was at least 1-point increase; Improvement if the baseline value was at least 2 and there was at least 1-point decrease Stable if baseline was 0 or 1 and a 0- or 1-point increase or decrease or baseline was at least 2 and no change).	Alexion Pharmaceuticals, Inc. (88)

Results of CHAMPION-NMOSD (NCT04201262)											
				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		
										Logistic regression model adjusted for baseline HAI score was used to calculate p-value.	
EDSS Score **(Result shows patients with clinically important worsening in EDSS score from Baseline to End of Study Period)**	Ravulizumab	58	6, 10.3%	NA	NA	NA	Odds ratio: 0.332	0.106, 1.042	0.0588	Clinically important worsening was defined as an increase in EDSS score conditional on the baseline value If the baseline EDSS was 0 and there was at least 2-point increase If the baseline is 1 to 5, and at least 1-point increase; if the baseline is > 5 and at least 0.5 increase). Logistic regression model adjusted for baseline EDSS score was used to calculate p-value.	Alexion Pharmaceuticals, Inc. (88)
	Placebo	47	11, 23.4%								Alexion Pharmaceuticals, Inc. (88)

Abbreviations: ARR, Annualised Relapse Rate; CI, Confidence Interval; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index; HR, Hazard Ratio; NA, Not Available.

Table 49. Results per study for subgroup population

Results of CHAMPION-NMOSD (NCT04201262)											
				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		
Time to first adjudicated on-trial relapse **(Result shows estimated proportion of patients relapse-free, cumulative probability)**	Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The comparison of the treatment groups for the primary endpoint used a log-rank test. The hazard ratio and risk reduction were estimated using a Cox proportional hazards model, with Firth's adjustment. 95% CIs were presented for the estimated proportion of patients that were relapse-free at various timepoints based on the complementary log-log. Kaplan-Meier curves for both treatment groups were produced.	Alexion Pharmaceuticals, Inc. (88)
	Placebo	[redacted]	[redacted]								Alexion Pharmaceuticals, Inc. (88)
ARR	Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poisson regression adjusted for historical ARR in the 24 months prior to screening was used to	Alexion Pharmaceuticals, Inc. (88)

Results of CHAMPION-NMOSD (NCT04201262)											
				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		
		[redacted]								descriptively present the ravulizumab treatment group estimate and 95% CI.	
	Placebo	[redacted]	[redacted]								Alexion Pharmaceuticals, Inc. (88)
HAI **(Result shows patients with clinically important worsening in HAI score from Baseline to**	Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Clinically important worsening was conditional on the baseline value Worsening if the baseline HAI was 0 and there was at least 2-point increase, or if the baseline HAI was > 0 and there was at least 1-point increase;	Alexion Pharmaceuticals, Inc. (88)
	Placebo	[redacted]	[redacted]								Alexion Pharmaceuticals, Inc. (88)

Results of CHAMPION-NMOSD (NCT04201262)											
				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		
End of Study Period)		[redacted]								Improvement if the baseline value was at least 2 and there was at least 1-point decrease Stable if baseline was 0 or 1 and a 0- or 1-point increase or decrease or baseline was at least 2 and no change). Logistic regression model adjusted for baseline HAI score was used to calculate p-value.	
EDSS Score **(Result shows patients with clinically important worsening in EDSS score from Baseline to**	Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Clinically important worsening was defined as an increase in EDSS score conditional on the baseline value If the baseline EDSS was 0 and there was at least 2-point increase If the baseline is 1 to 5, and at least 1-point increase; if the	Alexion Pharmaceuticals, Inc. (88)
	Placebo	[redacted]	[redacted]								Alexion Pharmaceuticals, Inc. (88)

Results of CHAMPION-NMOSD (NCT04201262)											
				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		
End of Study Period)		[redacted] [redacted]								baseline is > 5 and at least 0.5 increase). Logistic regression model adjusted for baseline EDSS score was used to calculate p-value.	

Abbreviations: ARR, Annualised Relapse Rate; CI, Confidence Interval; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index; HR, Hazard Ratio; NA, Not Available.

Appendix C. Comparative analysis of efficacy

Placebo was included in the CHAMPION-NMOSD trial as the external comparator. Hence, this section is irrelevant for this comparator.

Table 50 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	Yes/No

Appendix D. Extrapolation

There is no event in the ravulizumab patient group in the trial (i.e. no relapses). Therefore, the following sections are not applicable.

D.1 Extrapolation of [effect measure 1]

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

All serious AEs are reported for the post-rituximab subgroup population in Table 51.

Table 51 Serious adverse events

Preferred term	Ravulizumab [redacted], n (%)	Placebo [redacted], n (%)
Overall	[redacted]	[redacted]
Meningococcal sepsis	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]
Adenocarcinoma	[redacted]	[redacted]
Neuromyelitis optica spectrum disorder	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]

Data cutoff date: 15 Mar 2022, Dictionary: MedDRA v25.0
Source: Alexion Pharmaceuticals, Inc. (88).

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

The parameters used for the PSA are listed in Table 52.

Table 52 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Clinical parameters				
Proportion of males	[redacted]	[redacted]	[redacted]	Beta
Probability of having a permanent disability after relapse	[redacted]	[redacted]	[redacted]	Beta
Weight at baseline	[redacted]	[redacted]	[redacted]	Normal
BSA at baseline	[redacted]	[redacted]	[redacted]	Normal
Hazard ratio mortality – standard of care	[redacted]	[redacted]	[redacted]	Normal
Hazard ratio for relapse (compared to Standard of care) - Ravulizumab	[redacted]	[redacted]	[redacted]	Normal
Hazard ratio mortality – ravulizumab with disability	[redacted]	[redacted]	[redacted]	Normal
Hazard ratio mortality – Standard of care with disability	[redacted]	[redacted]	[redacted]	Normal
EDSS change per relapse - Baseline EDSS higher than 5.5	[redacted]	[redacted]	[redacted]	Normal
EDSS change per relapse - Baseline	[redacted]	[redacted]	[redacted]	Normal

EDSS lower or equal to 5.5				
Probabilities, Adverse events				
Probability of having pneumonia - Ravulizumab	[redacted]	[redacted]	[redacted]	Beta
Probability of having sepsis - Ravulizumab	[redacted]	[redacted]	[redacted]	Beta
Probability of having encephalitis meningococcal - Ravulizumab	[redacted]	[redacted]	[redacted]	Beta
Utilities				
Disutility decrement %	[redacted]	[redacted]	[redacted]	Beta
Disutility due to disability	[redacted]	[redacted]	[redacted]	Beta
Relapse free utility	[redacted]	[redacted]	[redacted]	Beta
Temporary disability due to a relapse	[redacted]	[redacted]	[redacted]	Beta
Relapse duration (days)	[redacted]	[redacted]	[redacted]	Normal
Permanent disutility due to a relapse	[redacted]	[redacted]	[redacted]	Beta
Disutility due to pneumonia	[redacted]	[redacted]	[redacted]	Gamma
Disutility due to sepsis	[redacted]	[redacted]	[redacted]	Gamma
Disutility due to encephalitis meningococcal	[redacted]	[redacted]	[redacted]	Gamma
Duration (days) of pneumonia	[redacted]	[redacted]	[redacted]	Gamma

Duration (days) of sepsis	[redacted]	[redacted]	[redacted]	Gamma
Duration (days) of encephalitis meningococcal	[redacted]	[redacted]	[redacted]	Gamma

Abbreviations: BSA; Boday surface area; EDSS, Expanded disability status scale; HSUVs, Health State Utility Values.
*Uncertainty was characterised in the probabilistic sensitivity analysis using the standard error.

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator

Objective

A SLR was first conducted to support this submission for ravulizumab in April 2024 and updated in August 2025. The objective of the SLR was to identify all controlled trials of ravulizumab in adults with AQP4+ NMOSD.

Methods

Comprehensive electronic and manual searches of the medical literature were undertaken to identify all controlled trials of ravulizumab in adults with AQP4+ NMOSD. As it was known that the pivotal trial was not randomised, the searches were inclusive of non-randomised, but controlled, study designs.

These included:

- Electronic searches of relevant databases of published literature
- Electronic searches of public registers of randomized trials
- Electronic searches of the various Cochrane databases

The bibliographic databases presented in Table 53 were used to conduct the primary SLR. Embase, Medline and CENTRAL were searched on 11 August 2025.

Table 53 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Elsevier	1974 – 07.08.2025	11.08.2025
Medline	Ovid	1946 – 08.08.2025	11.08.2025
CENTRAL	EBM Reviews	Up to July 2025	11.08.2025

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials.

Table 54 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	www.clinicaltrials.gov – NIH, USA	Ravulizumab OR Ultomiris | neuromyelitis optica OR	03.09.2025

Source name	Location/source	Search strategy	Date of search
		NMOSD OR NMO OR optic neuromyelitis OR Devic Disease	
WHO – International Clinical Trials Registry Platform	apps.who.int/trialsearch/	(Ravulizumab OR Ultomiris) AND (neuromyelitis optica OR NMOSD OR NMO OR myelooptic neuropathy OR myelopticoneuropath* OR myeloptico neuropathy OR neuropticomyelitis OR optic neuromyelitis OR Devic OR Devic's OR Devics)	04.09.2025
EU Clinical Trials Register	www.clinicaltrialsregister.eu/ctr-search/search	(Ravulizumab OR Ultomiris) AND (neuromyelitis optica OR NMOSD OR NMO OR myelooptic neuropathy OR myelopticoneuropath* OR myeloptico neuropathy OR neuropticomyelitis OR optic neuromyelitis OR Devic OR Devic's OR Devics)	04.09.2025

Abbreviations: EU, European Union; NIH, National Institutes of Health; USA, United States of America, WHO, World Health Organisation.

Table 55 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NR	NR	NR	NR	NR

Abbreviations: NR, not reported.

H.1.1 Search strategies

The complete details of the literature searches and search strategy tables are provided in Table 56 to Table 58. The manual searches were designed as searches of inclusion rather than exclusion; any additional relevant studies identified from internal company databases, reference lists of the returned citations, conference abstracts or presentations, or otherwise known to the sponsor, were to be noted and included.

Table 56 of search strategy table for Cochrane

No.	Query	Results
1	exp Neuromyelitis Optica/	98
2	neuromyelitis optica spectrum disorder*.ti,ab,kw.	319
3	neuromyelitis optica*.ti,ab,kw.	389
4	nmosd*.ti,ab,kw.	308
5	nmo*.ti,ab,kw.	6434
6	("myel?optic neuropath*" or "myel?optico neuropath*").ti,ab,kw.	274
7	myel?opticoneuropath*.ti,ab,kw.	0
8	(neuropticomyelitis* or "neuro opticomyelitis*").ti,ab,kw.	0
9	"optic neuromyelitis*".ti,ab,kw.	3
10	(Devic* adj (disease or syndrome*)).ti,ab,kw.	100
11	Devic* Neuromyelitis Optica.ti,ab,kw.	3
12	or/1-11	6611
13	Ravulizumab.ab,kw,ti.	246
14	Ultomiris*.ab,kw,ti.	13
15	(ALXN-1210 or ALXN1210).ab,kw,ti.	58
16	(ALXN-1810 or ALXN1810).ab,kw,ti.	0
17	or/13-16	257
18	exp Random Allocation/	25199
19	random*.ab,kw,ti.	1387208
20	double-blind*.ab,kw,ti.	323486
21	placebo*.ab,kw,ti.	388240
22	or/18-21	1517273
23	12 and 17 and 22	21

Table 57 of search strategy table for Embase

No.	Query	Results
1	exp myelooptic neuropathy/	14825
2	neuromyelitis optica spectrum disorder*.ti,ab,kw.	6654
3	neuromyelitis optica*.ti,ab,kw.	12648
4	nmosd*.ti,ab,kw.	6281
5	nmo*.ti,ab,kw.	111579
6	("myel?optic neuropath*" or "myel?optico neuropath*").ti,ab,kw.	9
7	myel?opticoneuropath*.ti,ab,kw.	9
8	(neuropticomyelitis* or "neuro opticomyelitis*").ti,ab,kw.	0
9	"optic neuromyelitis*".ti,ab,kw.	127
10	(Devic* adj (disease or syndrome*)).ti,ab,kw.	561
11	Devic* Neuromyelitis Optica.ti,ab,kw.	124
12	or/1-11	117844
13	Ravulizumab.ab,kw,ti,du.	1300
14	Ultomiris*.ab,kw,ti,du,tn.	86
15	(ALXN-1210 or ALXN1210).ab,kw,ti,du.	73
16	(ALXN-1810 or ALXN1810).ab,kw,ti,du.	0
17	"1803171 55 2".rn.	1166
18	or/13-17	1302
19	12 and 18	125
20	limit 19 to humans	123
21	Double Blind Procedure/ or Randomized Controlled Trial/	1150168
22	20 and 21	8
23	random*.ab,kw,ti.	2479702
24	double-blind*.ab,kw,ti.	324518

No.	Query	Results
25	placebo*.ab,kw,ti.	473352
26	or/23-25	2644958
27	20 and 26	35
28	22 or 27	37
29	review.pt.	3399314
30	28 not 29	28

Table 58 of search strategy table for Medline

No.	Query	Results
1	exp Neuromyelitis Optica/	5005
2	neuromyelitis optica spectrum disorder*.ti,ab,kw.	3825
3	neuromyelitis optica*.ti,ab,kw.	6836
4	nmosd*.ti,ab,kw.	3144
5	nmo*.ti,ab,kw.	82776
6	("myel?optic neuropath*" or "myel?optico neuropath*").ti,ab,kw.	3
7	myel?opticoneuropath*.ti,ab,kw.	2
8	(neuropticomyelitis* or "neuro opticomyelitis*").ti,ab,kw.	2
9	"optic neuromyelitis*".ti,ab,kw.	79
10	(Devic* adj (disease or syndrome*)).ti,ab,kw.	379
11	Devic* Neuromyelitis Optica.ti,ab,kw.	85
12	or/1-11	85499
13	Ravulizumab.ab,kw,ti,du.	321
14	Ultomiris*.ab,kw,ti,du.	18
15	(ALXN-1210 or ALXN1210).ab,kw,ti,du.	19
16	(ALXN-1810 or ALXN1810).ab,kw,ti,du.	0
17	"1803171 55 2".rn.	0

No.	Query	Results
18	or/13-17	326
19	randomized controlled trial/	643703
20	Random Allocation/	108717
21	Double Blind Method/	185340
22	random*.ab,kw,ti.	1660803
23	double-blind*.ab,kw,ti.	184379
24	placebo*.ab,kw,ti.	270460
25	or/19-24	1937600
26	12 and 18 and 25	10

Table 59 of search strategy table for Clinicaltrials.gov

No.	Query	Results
1	Ravulizumab OR Ultomiris | neuromyelitis optica OR NMOSD OR NMO OR optic neuromyelitis OR Devic Disease	6

Table 60 of search strategy table for WHO Trials Register

No.	Query	Results
1	Ravulizumab OR Ultomiris) AND (neuromyelitis optica OR NMOSD OR NMO OR myelooptic neuropathy OR myeloopticoneuropath* OR myeloptico neuropathy OR neuropticomyelitis OR optic neuromyelitis OR Devic OR Devic's OR Devics	16

Table 61 of search strategy table for EU Clinical Trials Register

No.	Query	Results
1	Ravulizumab OR Ultomiris) AND (neuromyelitis optica OR NMOSD OR NMO OR myelooptic neuropathy OR myeloopticoneuropath* OR myeloptico neuropathy OR neuropticomyelitis OR optic neuromyelitis OR Devic OR Devic's OR Devics	2

H.1.2 Systematic selection of studies

Citation records were screened and reasons for inclusion/exclusion are summarised in Table 62. For each entry, the highest ranked exclusion criterion found definitively to apply was selected.

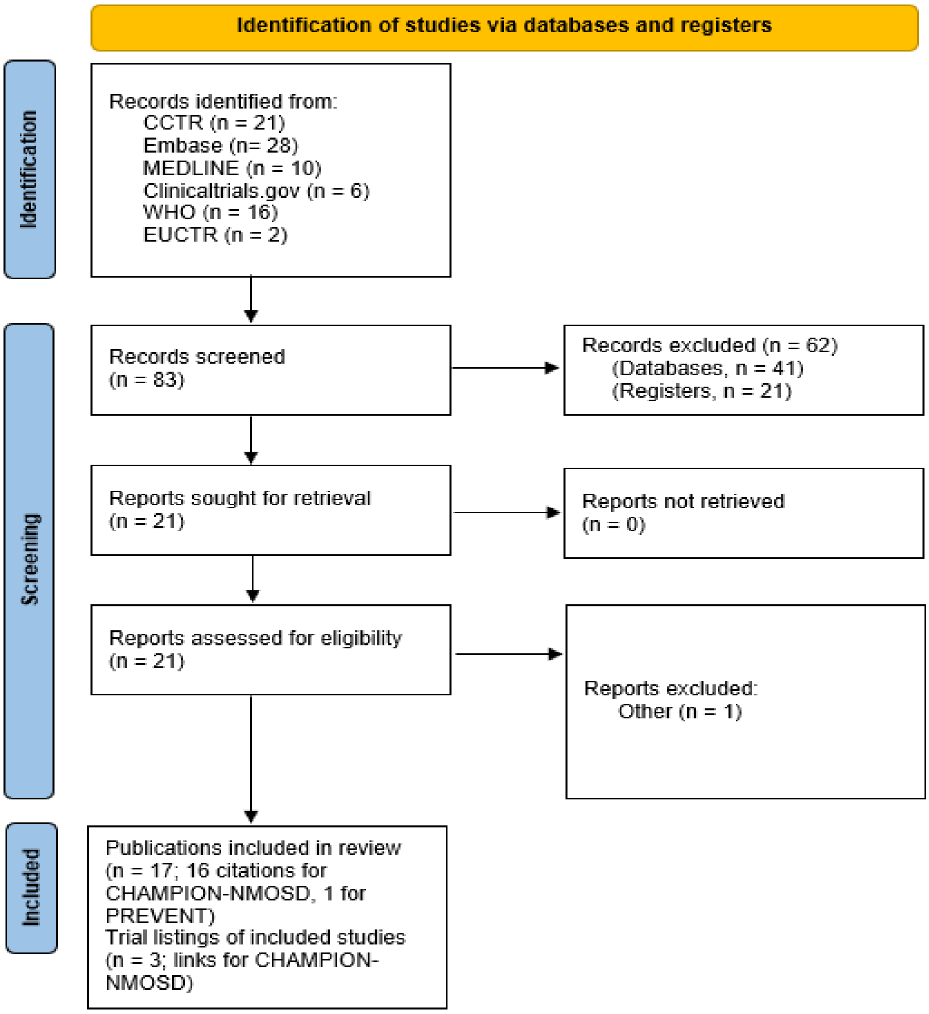
Table 62 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adult patients with AQP4+ NMOSD	Does not include the proposed population	NR
Intervention	Ravulizumab (Ultomiris)	Incorrect intervention	NR
Comparators	BSC (placebo)	Does not include the relevant comparator	NR
Outcomes	1. Relapse 2. Hauser Ambulation Index (HAI) 3. Expanded Disability Status Scale (EDSS) Score 4. EQ-5D 5. Adverse events (including treatment-emergent, treatment-related, serious) 6. Death	Other – i.e. trial incomplete/results not reported	NR
Study design/publication type	Controlled trials (randomised or non-randomised)	Not a [randomised] controlled trial;	NR
Language restrictions	English only	NR	NR

Abbreviations: AQP4+, Aquaporin-4 Antibody Positive; BSC, Best Supportive Care; Expanded Disability Status Scale, EDSS; Hauser Ambulation Index, HAI; NR, Not Reported; NMOSD, Neuromyelitis Optica Spectrum Disorder; RCT, Randomised Controlled Trial.

A PRISMA diagram reporting the summary results of the searches is in Figure 13.

Figure 13 PRISMA diagram for clinical SLR


Identification of studies via databases and registers
Identification
Records identified from:
CCTR (n = 21)
Embase (n= 28)
MEDLINE (n = 10)
Clinicaltrials.gov (n = 6)
WHO (n = 16)
EUCTR (n = 2)
Screening
Records screened
(n = 83)
Records excluded (n = 62)
(Databases, n = 41)
(Registers, n = 21)
Reports sought for retrieval
(n = 21)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 21)
Reports excluded:
Other (n = 1)
Included
Publications included in review
(n = 17; 16 citations for CHAMPION-NMOSD, 1 for PREVENT)
Trial listings of included studies
(n = 3; links for CHAMPION-NMOSD)

The results included one trial (CHAMPION-NMOSD) documenting the efficacy and safety of ravulizumab in adult patients with AQP4+ NMOSD, and one trial for the external comparator arm (placebo) of CHAMPION-NMOSD, which was sourced from the randomised placebo-controlled trial PREVENT. The overview of the included studies and the study designs is presented in Table 63.

Table 63 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Pittock et al., 2023 (CHAMPION, NCT0420126) (5)	Evaluate the efficacy and safety of ravulizumab in reducing relapse risk vs external placebo	Ongoing Phase 3, open-label, multicentre study, using a single-arm design with an external placebo control from PREVENT trial.	Adult patients with AQP4+ NMOSD	Ravulizumab (N=58); Placebo from PREVENT trial (N=47)	Primary outcome evaluated time to first adjudicated on-trial relapse and relapse risk reduction (median follow-up time of 73.5 weeks).	Secondary outcomes evaluated adjudicated on-trial ARR, clinically important changes in HAI, EDSS, EQ-5D index, and EQ-5D VAS, incidence of TEAEs, TESAEs, and TEAEs leading to discontinuation, changes in serum ravulizumab and free C5 concentrations, and presence and titre of ADAs over the study.
Pittock et al., 2019 (PREVENT, NCT01892345) (84)	Evaluate the efficacy and safety of eculizumab vs placebo	Randomised, double-blind, placebo-controlled, multicentre	Adult patients with AQP4+ NMOSD	Eculizumab (N=96); Placebo (N=47)	Primary outcome evaluated time to first adjudicated on-trial	Secondary outcomes evaluated adjudicated on-trial ARR,

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
	in adult patients with AQP4+ NMOSD.	, parallel-group, Phase 3 study.			relapse (median follow-up time of 36.0 weeks).	changes from baseline in HAI, EDSS, mRS, EQ-5D index, and EQ-5D VAS.

Abbreviations: ADA, Anti-Drug Antibodies; AQP4+, Aquaporin-4 Antibody Positive; ARR, Annualised Relapse Rate; C5, Complement Component 5; EDSS, Expanded Disability Status Scale; EQ-5D, European Quality of Life Health 5-Dimension Questionnaire; HAI, Hauser Ambulation Index; mRS, Modified Rankin Scale; NMOSD, Neuromyelitis Optica Spectrum Disorder; TEAE, Treatment-Emergent Adverse Event; TESAE, Treatment-Emergent Serious Adverse Event; VAS, Visual Analog Scale.

H.1.3 Excluded fulltext references

A list of excluded publications and trials in the SLR, including reason for exclusion, is provided in Table 64.

Table 64 List of excluded publications and trials

Author(s), year of publication or Trial	DOI/URL	Reason for exclusion
NCT06312644	https://ClinicalTrials.gov/show/NCT06312644	Not a controlled trial
NCT05346354	https://ClinicalTrials.gov/show/NCT05346354	Not a controlled trial
NCT06398158	https://ClinicalTrials.gov/show/NCT06398158	Not a controlled trial
NCT07010302	https://ClinicalTrials.gov/show/NCT07010302	Incorrect comparator
NCT06903130	https://ClinicalTrials.gov/show/NCT06903130	Not a randomised controlled trial
NCT06312644	https://clinicaltrials.gov/ct2/show/NCT06312644	Not a controlled trial
JPRN-jRCT2031220259	https://jrct.niph.go.jp/latest-detail/jRCT2031220259	Incorrect population
EUCTR2021-006075-42-DE	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-006075-42	Incorrect population

NCT05346354	https://clinicaltrials.gov/ct2/show/NCT05346354	Incorrect population
EUCTR2021-006075-42-ES	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-006075-42	Incorrect population
JPRN-jRCT2080225205	https://jrct.niph.go.jp/latest-detail/jRCT2080225205	Not a controlled trial
NCT04201262	https://clinicaltrials.gov/show/NCT04201262	Duplicate
NCT07010302	https://clinicaltrials.gov/ct2/show/NCT07010302	Incorrect comparator
NCT06903130	https://clinicaltrials.gov/ct2/show/NCT06903130	Not a controlled trial
DRKS00034631	http://drks.de/search/en/trial/DRKS00034631	Not a controlled trial
NCT06398158	https://clinicaltrials.gov/ct2/show/NCT06398158	Not a controlled trial
CTIS2023-508534-33-00	https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-508534-33-00	Incorrect population
JPRN-jRCTs031230647	https://jrct.mhlw.go.jp/latest-detail/jRCTs031230647	Not a controlled trial
EUCTR2021-006075-42-FR	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-006075-42	Incorrect population
NCT04201262	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-003352-37	Duplicate
Alexion Pharmaceuticals, Inc., 2022	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-006075-42	Incorrect population
Anonymous, 2019	https://onderzoekmetmensen.nl/en/node/49042/pdf	Other: Trial listing/brief protocol (no results reported)

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

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

I.1 Health-related quality-of-life search

Objective

A global SLR was conducted to identify relevant publications to the clinical evidence, burden and epidemiology of NMOSD. For this submission, the HRQoL SLR was updated in August 2025. The objective of the SLR was to identify HRQoL of ravulizumab in adults with AQP4+ NMOSD.

Methods

A comprehensive systematic search of the medical literature for a global SLR was originally conducted on 24 November 2021, and the same search was re-run on 12 April 2023 and 4 November 2024. For the current application, the SLR relevant to the health-related quality-of-life was updated on 11 August 2025.

A comprehensive systematic search of the medical literature was conducted on 11 August 2025 using the MEDLINE and Embase databases, as presented in Table 65 below.

Table 65 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 – 07.08.2025	11.08.2025
Medline	Ovid	1946 – 08.08.2025	11.08.2025

I.1.1 Search strategies

A customised search strategy was developed that included terms related to NMOSD, study designs, and outcomes of interest. The search strategy used a combination of free text words, indexing terms (e.g., MeSH, EMTREE terms) and keywords, tailored to each database.

Table 66 Search strategy for EMBASE search

No.	Query	Results
1	exp Neuromyelitis Optica/	14825
2	exp myelitis/	97890
3	exp optic neuritis/	15695

4	(neuromyelitis optica? or NMO or NMOSD or ((Devic? or Devic's) adj2 (syndrome or disease? or neuromyelitis optica?)) or myelooptic? neuropathy or transverse myelitis).mp.	21575
5	or/1-4	110695
6	quality adjusted life year/	41529
7	quality of life.ab,ti.	750772
8	quality of life index/	3572
9	short form 12/ or short form 20/ or short form 36/ or short form 8/	61439
10	sickness impact profile/ or sickness impact profile.ti,ab.	3329
11	(quality adj2 well?being).ti,ab.	1114
12	disability adjusted life.ti,ab.	10101
13	patient? reported outcome?.ab,ti.	78385
14	(qal* or qtime* or qwb* or daly*).ti,ab.	42071
15	(euroqol* or eq5d* or eq 5d*).ti,ab.	38441
16	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.	161442
17	(health utility* or utility score* or disutilit*).ti,ab.	7691
18	(hui or hui1 or hui2 or hui3).ti,ab.	3739
19	health* year* equivalent*.ti,ab.	41
20	(hye or hyes).ti,ab.	217
21	rosser.ti,ab.	155
22	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.	20104
23	(sf?36 or short?form?36).ti,ab.	4653
24	(sf?20 or short?form?20).ti,ab.	97
25	(sf?12 or short?form?12).ti,ab.	1522
26	(sf?8 or short?form?8).ti,ab.	289
27	(sf?6 or short?form?6).ti,ab.	7497
28	or/6-27	882938
29	Case Study/	109506
30	case report.tw.	625174
31	abstract report/ or letter/	1391416
32	Conference proceeding.pt.	0
33	Conference abstract.pt.	5569281
34	Editorial.pt.	843644
35	Letter.pt.	1371429
36	Note.pt.	1016176
37	(letter or comment*).ti.	261587
38	or/29-37	9496214
39	5 and 28	4646

40	39 not 38	3511
41	limit 40 to english language	3349
42	limit 41 to human	3285
43	limit 42 to yr="2024-Current"	941

Table 67 Search strategy for Medline search

No.	Query	Results
1	exp Neuromyelitis Optica/	5005
2	exp myelitis/	27578
3	exp optic neuritis/	11457
4	(neuromyelitis optica? or NMO or NMOSD or ((Devic? or Devic's) adj2 (syndrome or disease? or neuromyelitis optica?)) or myelooptic? neuropathy or transverse myelitis).mp.	10295
5	or/1-4	41927
6	quality-adjusted life years/	18184
7	sickness impact profile/ or sickness impact profile.ti,ab.	8124
8	(quality adj2 (wellbeing or well-being)).ti,ab.	3787
9	disability adjusted life.ti,ab.	8219
10	(qal* or qtime* or qwb* or daly*).ti,ab.	25212
11	(euroqol* or eq5d* or eq 5d*).ti,ab.	20568
12	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.	88297
13	(health utility* or utility score* or disutilit*).ti,ab.	4331
14	(hui or hui1 or hui2 or hui3).ti,ab.	2246
15	health* year* equivalent*.ti,ab.	41
16	(hye or hyes).ti,ab.	78
17	rosser.ti,ab.	112
18	(willingness to pay or time?trade?off or tto or standard gamble*).ti,ab.	12881
19	(sf?36 or short?form?36).ti,ab.	1598
20	(sf?20 or short?form?20).ti,ab.	71
21	(sf?12 or short?form?12).ti,ab.	629
22	(sf?8 or short?form?8).ti,ab.	174
23	(sf?6 or short?form?6).ti,ab.	3896
24	quality of life.ab,ti.	452533
25	patient? reported outcome?.ab,ti.	45320
26	or/6-25	521318
27	Case Study/	2495901
28	case report.tw.	471357
29	abstract report/ or letter/	1305044
30	editorial/	733539
31	news/	231512

32	exp historical article/	416866
33	anecdotes as topic/	4748
34	comment/	1054436
35	(letter or comment*).ti.	216940
36	(case* adj2 report*).tw.	797252
37	(case* adj2 stud*).tw.	362808
38	(case* and series).tw.	261670
39	or/27-38	5949616
40	5 and 26	419
41	40 not 39	366
42	limit 41 to english	340
43	limit 42 to humans	295
44	limit 43 to yr="2024-Current"	38

I.1.2 Systematic selection of studies

Selection criteria included the patient population, interventions/comparators, outcome measures, and study design as summarised in Table 68.

Table 68 Inclusion and exclusion criteria used for assessment of studies

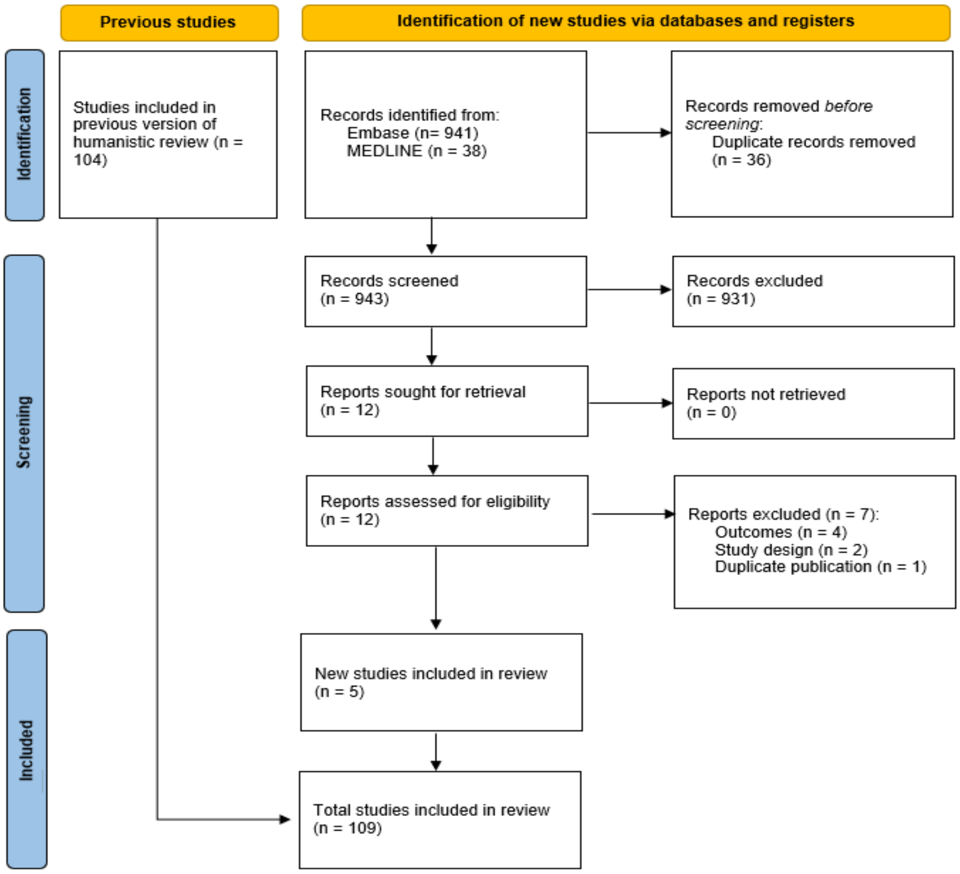
Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adult patients with AQP4+ NMOSD	Does not include the proposed population	NR
Intervention	Any intervention	Incorrect intervention	NR
Comparators	Any comparator	Does not include the relevant comparator	NR
Outcomes	1. Health-related quality of life 2. Health state utilities	Other – i.e. trial incomplete/results not reported	NR
Study design/publication type	1. Prospective observational study 2. Retrospective observational study 3. Cross-sectional study	Not a study	NR

Language restrictions	English only	NR	NR

Abbreviations: AQP4+, Aquaporin-4 Antibody Positive; NR, Not Reported; NMOSD, Neuromyelitis Optica Spectrum Disorder.

A PRISMA diagram reporting the summary results of the searches is in Figure 14.

Figure 14 PRISMA diagram for HRQoL SLR



The results included one trial (CHAMPION-NMOSD) documenting the efficacy and safety of ravulizumab in adult patients with AQP4+ NMOSD, and one trial for the external comparator arm (placebo) of CHAMPION-NMOSD, which was sourced from the randomised placebo-controlled trial PREVENT. The overview of the included studies and the study designs is presented in Table 63.

Table 69 Overview of studies included in the SLR

Study/ID	Study design	Patient population	HRQoL measure
Pittock et al., 2023 (CHAMPION, NCT0420126) (5)	Ongoing Phase 3, open-label, multicentre study, using a single-arm design with an external placebo control from PREVENT trial.	Adult patients with AQP4+ NMOSD	EQ-5D index, EQ-5D VAS, SF-36
Pittock et al., 2019 (PREVENT, NCT01892345) (84)	Randomised, double-blind, placebo-controlled, multicentre, parallel-group, Phase 3 study.	Adult patients with AQP4+ NMOSD	EQ-5D index and EQ-5D VAS

Abbreviations: AQP4+, Aquaporin-4 Antibody Positive; EQ-5D, EuroQol 5-Dimension Quality of Life Questionnaire; HRQoL, Health-Related Quality of Life; NMOSD, Neuromyelitis Optica Spectrum Disorder; SF-36, 36-Item Short Form Health Survey; VAS, Visual Analogue Scale.

I.1.3 Excluded fulltext references

A list of excluded publications and trials in the SLR, including reason for exclusion, is provided in

Table 70 List of excluded publications and trials

Author(s), year of publication or Trial	DOI/URL	Reason for exclusion
Afsharzadeh et al., 2024	NR	Duplicate publication
Correa-Diaz et al., 2025	NR	Incorrect outcomes
Etemadifar et al., 2024	NR	Incorrect outcomes
Khan et al., 2024	NR	Incorrect outcomes
Leng et al., 2024	NR	Incorrect outcomes
Lyou et al., 2024	NR	Duplicate publication
Silva et al., 2024	NR	Incorrect study design

Abbreviations: NR, Not Reported.

I.1.4 Quality assessment and generalizability of estimates

N/A

I.1.5 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A

J.1.1 Example: Systematic search for […]

N/A

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A			

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

N/A

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A			

Abbreviations:

Appendix K. Long-term extension outcomes

Results from the long-term extension of the ongoing phase 3 CHAMPION-NMOSD trial (data cutoff: 14 June 2024) provide updated efficacy and safety outcomes for ravulizumab in adults with AQP4+ NMOSD in the ITT population. As of the data cutoff on 23 January 2025, results from the long-term extension provide updated efficacy outcomes for ravulizumab in the post-rituximab subgroup. Overall, these findings demonstrate the long-term clinical benefit of ravulizumab in the prevention of relapses in patients with AQP4+ NMOSD, supported by a stable long-term safety profile.

K.1.1 Efficacy

Time to first adjudicated on-trial relapse

Across the primary treatment period and long-term extension, no patients had an adjudicated on-trial relapse during ravulizumab treatment (186.6 patient-years of follow-up), corresponding to a 98.9% reduction in the risk of relapse with ravulizumab versus placebo (log-rank p < 0.0001) (103). The median (range) follow-up duration was 170.3 weeks (11.0-233.9) for ravulizumab (N = 58) and 36.0 weeks (1.9-208.6) for placebo (N = 47) (103).

As of the data cut-off on 14 June 2024, the estimated HR for ravulizumab compared with placebo was 0.011 (95% CI: 0.000, 0.082, p < 0.0001), consistent with the results observed during the primary treatment period (103). KM curves are shown in Figure 15.

In the PREVENT-study, patients in the placebo group switched to eculizumab after week 120, which is likely the cause for the abrupt stop of relapse events from that point forwards.

These findings underscore ravulizumab's sustained efficacy in preventing relapses over extended treatment durations, highlighting its potential to provide long-term disease control in patients with AQP4+ NMOSD.

Figure 15 KM estimates for time to adjudicated on-trial relapse (14 June 2024)

[redacted]

Abbreviations: CI, Confidence Interval; PTP, Primary Treatment Period; PY, Patient-Years.
Source: Pittock S. J., 2025 (103).

As of the data cut-off on 23 January 2025, in the subgroup of patients who had received rituximab prior to any relapse, the estimated HR for ravulizumab compared with placebo in the subgroup was [redacted], consistent with the results observed during the primary treatment period. KM is shown in **Error! Reference source not found.**.

These findings indicate that ravulizumab maintains sustained efficacy in preventing relapses over extended treatment durations within the post-rituximab subgroup population.

[redacted]

[redacted]

Abbreviations: CI, Confidence Interval.

K.1.2 Safety

During the long-term extension period (data cut-off: 14 June 2024), no new safety signals were identified in the ravulizumab arm. A total of 593 TEAEs were reported in 55 patients (94.8%) (103). Of these, 60 TEAEs in 27 patients (46.6%) were considered related to the study drug (103). The majority of TEAEs (70.5%) were mild in severity and unrelated to ravulizumab (103). A total of three TEAEs leading to study drug discontinuation were reported, all occurring as part of the same clinical sequelae in a single patient (103).

Cumulatively as of 14 June 2024, 18 TESAEs were reported for 15 patients (25.9%), including 4 TESAEs in 4 patients (6.9%) considered related to the study drug (103). There was one death that occurred during the LTE, which was assessed by the investigator as unrelated to ravulizumab treatment (103).

These findings indicate that the long-term administration of ravulizumab has a safety profile consistent with the primary treatment period.

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