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CADTH COMMON DRUG REVIEW

Clinical Review Report

ECULIZUMAB (SOLIRIS)

Alexion Pharma Canada Corp.

Indication: Neuromyelitis optica spectrum disorder

Service Line:	CADTH Common Drug Review
Version:	Final (with redactions)
Publication Date:	October 2020
Report Length:	105 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
ARR	annualized relapse rate
AQP4	aquaporin-4
AQP4-IgG	aquaporin-4 antibody
CDR	CADTH Common Drug Review
CI	confidence interval
EDSS	Expanded Disability Status Scale
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels
EQ VAS	EuroQol Visual Analogue Scale
FAS	full analysis set
FSS	functional system score
HAI	Hauser Ambulation Index
HR	hazard ratio
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
IST	immunosuppressive therapy
ITC	indirect treatment comparison
IVIG	intravenous immunoglobulin
KFS	Kurtzke Functional System
LOCF	last observation carried forward
MCS	mental component score
MID	minimal important difference
mRS	modified Rankin Scale
MS	multiple sclerosis
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
OSIS	Optic-Spinal Impairment Scale
PCS	physical component score
PP	per-protocol
RAC	relapse adjudication committee
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
VAS	visual analogue scale

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Eculizumab (Soliris), 30 mL parenteral solution (10 mg/mL), for injection
Indication	For the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 antibody positive. Eculizumab is not intended for acute treatment of an NMOSD relapse.
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	September 24, 2019
Sponsor	Alexion Pharma Canada Corp.

NMOSD = neuromyelitis optica spectrum disorder; NOC = Notice of Compliance.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, immune-mediated demyelinating disorder of the central nervous system that primarily causes damage to the optic nerves and spinal cord of patients. NMOSD is distinct from multiple sclerosis (MS) despite overlapping clinical features.[1-3] NMOSD is a debilitating disease and is typically characterized by acute attacks or relapses of new or worsening signs and symptoms of optic neuritis and longitudinally extensive transverse myelitis, although additional clinical characteristics are now recognized.[2-4] Relapses result in the accumulation of irreversible damage to the optic nerve and spinal cord, causing neurological disability. Input from clinicians, patients, and their caregivers highlighted the debilitating nature of the damage caused by NMOSD relapses and the resulting impact on patients' vision and mobility that leads to a loss of independence, which alters every aspect of their daily life. The presence of the aquaporin-4 (AQP4) antibody is found in 70% to 90% of patients with NMOSD and is the defining criteria in this type of NMOSD.[1,2,4,5]

NMOSD disproportionally affects females and those with coexisting autoimmune diseases.[1,6] Systematic reviews based on data from several countries estimated the incidence and prevalence of neuromyelitis optica (NMO) to range from 0.053 to 0.40 per 100,000 people and 0.51 to 4.4 per 100,000 people, respectively.[7,8] No Canadian-specific estimates were identified in either study.

Eculizumab (Soliris) is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, which inhibits its cleavage into C5a and C5b and prevents the generation of the terminal complement complex C5b-9 and free C5a.[9] Eculizumab is the first drug with a Health Canada indication for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive.[9] Eculizumab is not intended for acute treatment of an NMOSD relapse.[9] Eculizumab is administered at 900 mg weekly for the first four weeks, followed by 1,200 mg for the fifth dose one week later, then 1,200 mg every two weeks thereafter.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of eculizumab 10 mg/mL intravenous infusion for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and by clinical experts consulted by CADTH for the purpose of this review.

Patient Input

One patient group, the Multiple Sclerosis Society (MS Society), responded to the call from CADTH to provide input on the topic. Through an online survey conducted in early 2020, patients with NMOSD and those affected by it expressed their concerns about how the diagnosis of NMOSD had impacted their lives, the debilitating nature of the damage caused by attacks, and the impact on their vision and mobility. Many of the patients declared using off-label agents such as azathioprine and rituximab. Patients stated that NMOSD, if untreated, leads to disability in all areas of a person's life, such as reduced employment stability, decreased family income, increased need for assistance or caregiving, loss of independence, isolation, cognitive decline, and increased mobility challenges. Patients remarked how eculizumab, as the first treatment targeted to people living with NMOSD, could fill a therapeutic gap that has been unmet in the treatment of NMOSD to date.

Clinician Input

In Canada, treatment for NMOSD differs by province and territory based on differential access to the drugs that are typically used to treat the disease, such as mycophenolate and rituximab. There are no formal treatment guidelines in Canada that specify which interventions should be used as first- or second-line therapies. In provinces with easier access to rituximab, it is generally used as first-line therapy for patients with NMOSD because it is considered more effective than other currently available preventive medications.

Treatment goals for NMOSD relate to three broad areas: prevention of relapses (disease modifying), treatment of relapses, and treatment of residual symptoms. Of these three areas, preventive treatment is of special interest because the goal of any intervention would be to reach the best possible effect for reducing relapses, as these are the major source of disability accumulation for patients with NMOSD. Currently available preventive treatment medications are considered only moderately effective, and patients may still experience relapses despite treatment; in addition, many of the available therapies are associated with serious adverse events (SAE).

The clinicians consulted by CADTH stated that the greatest unmet needs relate to patients with NMOSD who continue to experience relapses despite being on relapse prevention therapy; specifically, patients with very active relapses, patients who cannot tolerate current treatments such as mycophenolate, patients whose initial first episode is very severe, and patients who have not recovered from a past relapse are all less likely to recover to their previous level of functioning from subsequent relapse(s).

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One phase III, time-to-event randomized controlled trial (RCT) was included in this CADTH Common Drug Review (CDR). PREVENT (ECU-NMO-301) was a multi-centre, double-blind, placebo-controlled RCT conducted in 143 patients, 18 years of age and older, with a diagnosis of NMO or NMOSD. PREVENT included patients from North and South America, Europe, Australia, and Asia. No patients were recruited from Canada.

The primary objective of PREVENT was to assess the efficacy of eculizumab treatment, as compared with placebo, in relapsing NMOSD patients based on time to first relapse and relapse risk reduction. PREVENT also aimed to characterize the overall safety and tolerability of eculizumab compared with placebo in relapsing NMOSD patients.

The primary efficacy outcome in PREVENT was time to first adjudicated on-trial relapse, where adjudication of on-trial relapses was based on consensus of an independent relapse adjudication committee (RAC) consisting of two neurologists and one neuro-ophthalmologist. Secondary end points included adjudicated on-trial annualized relapse rate (ARR), change from baseline in Expanded Disability Status Scale (EDSS) score, modified Rankin Scale (mRS) score, EuroQol 5-Dimensions (EQ-5D) score, and Hauser Ambulation Index (HAI) score. While the outcomes assessed in the trials were relevant to the clinical population with NMOSD, outcomes related to productivity (e.g., attend school or work) were not assessed. Secondary outcomes were assessed according to a predetermined hierarchy to reduce the risk of type I error.

One long-term extension study of PREVENT assessed the safety and efficacy of eculizumab in [redacted] patients for up to 5.5 years (as of the last interim analysis) who had previously experienced an on-trial relapse (assessed by the treating physician) in PREVENT. The ARR, the EDSS score, the mRS score, the HAI score, the EQ-5D score, the visual Kurtzke Functional System (KFS) score, and harms were assessed. Other evidence considered in brief included a small (N = 14) open-label pilot study that assessed the effect and tolerability of eculizumab (using an alternative dose) and an indirect treatment comparison (ITC) of therapeutics for NMOSD excluding eculizumab.

Efficacy Results

In PREVENT, the hazard ratio [HR] for adjudicated on-trial relapse was 0.058 (95% confidence interval [CI], 0.017 to 0.197; P < 0.0001), in favour of eculizumab over placebo, which was considered to be clinically relevant by the clinical experts consulted by CADTH. This represented a 94.2% risk reduction (95% CI, 80.3 to 98.3) in favour of eculizumab. A post-hoc sensitivity analysis of the primary endpoint imputing all discontinuations in the eculizumab treatment group as adjudicated on-trial relapse events showed an attenuated, but statistically and clinically significant finding (HR = 0.297, 95% CI = 0.154 to 0.572, P = 0.0001) The adjusted adjudicated on-trial ARR ratio showed statistically and clinically significant results (ARR = 0.045; 95% CI, 0.013 to 0.151; P < 0.0001), representing a 95.5% reduction in ARR (95% CI, 84.9 to 98.7). Similar findings were observed in patients across all immunosuppressive therapy (IST) subgroups and when the outcomes were assessed by treating physicians instead of by the RAC. Exploratory analysis suggested that

treatment with eculizumab was associated with less severe relapses than treatment with placebo.

Reduction in disability caused by NMOSD was identified as an important outcome based on feedback from a patient group consulted for this review. The EDSS was used to assess disability in PREVENT; however, the difference between treatment arms was not statistically significant. This finding prevented the statistical and clinical interpretation of other secondary outcomes pre-specified in the statistical testing hierarchy related to disability, health-related quality of life (HRQoL), and symptoms. Input provided by patients with NMOSD and their caregivers indicated that the increasing disability associated with NMOSD impacts all areas of a person's life, including employment, independence, isolation, cognitive function, and mobility. The results of the trial (and the absence of an evaluation of outcomes related to the ability to work) prevent any conclusions being made about the efficacy of eculizumab in improving these outcomes that are important to patients.

The long-term extension study assessed the efficacy of continued use of eculizumab in patients who had previously experienced an on-trial relapse in PREVENT. Generally, the efficacy results of the extension were consistent with the results from PREVENT.

Harms Results

In PREVENT, 91.7% of patients in the eculizumab arm and 95.7% of patients in the placebo arm experienced an adverse event (AE). The most common AE was upper respiratory infection, which affected more patients in the eculizumab arm (29.2%) than in the placebo arm (12.8%). Serious adverse events (SAEs) occurred more often in patients treated with placebo; however, the difference in SAEs was largely eliminated when the SAE for worsening of NMOSD was excluded. Notable harms identified in the protocol for this review included the following: serious infusion reactions, serious infections (e.g., meningococcal or respiratory), and hemolysis or low hemoglobin. Infusion reactions occurred in 6.3% of patients in the eculizumab arm and 4.3% of patients in the placebo arm. No cases of meningococcal infections were reported in PREVENT. Respiratory-related serious infections occurred similarly between treatment arms. In PREVENT, one patient in the eculizumab arm died during the trial. The death of this patient was attributed to infectious pleural effusion and was considered by the investigator to be "probably related to the study drug."

Overall, the safety results were consistent with the safety profile of eculizumab for other indications for which it has already been approved.

The long-term extension study assessed safety associated with the continued use of eculizumab in patients who had previously experienced an on-trial relapse in PREVENT. In terms of AEs, treatment with eculizumab was well tolerated and safety results were consistent with the safety profile of eculizumab observed in PREVENT.

Table 2: Summary of Key Results From PREVENT

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Relapse		
Time to first adjudicated on-trial relapse (weeks)[a]		
Patients with a relapse, n (%)	3 (3.1)	20 (42.6)
Percent reduction (95% CI)	94.2 (80.3 to 98.3)	
Hazard ratio (95% CI)	0.058 (0.017 to 0.197)	
P value	< 0.0001	
Adjudicated on-trial annualized relapse rate[b]		
Total number of relapses	3	21
Adjusted ARR (95% CI)	0.016 (0.005 to 0.050)	0.350 (0.199 to 0.616)
Rate ratio (95% CI)	0.045 (0.013 to 0.151)	
P value	< 0.0001	
Disability progression		
Expanded Disability Status Scale[c]		
Baseline EDSS score, mean (SD)	4.15 (1.646)	4.26 (1.510)
Change from baseline, mean (SD)	–0.18 (0.814)	0.12 (0.945)
P value	0.0597	
Modified Rankin Scale[d,e]		
Baseline mRS score, mean (SD)	2.1 (1.14)	2.1 (0.98)
Change from baseline, mean (SD)	–0.2 (0.72)	0.1 (0.75)
P value	0.0154	
Health-related quality of life		
EQ-5D-3L VAS[d,e]		
Baseline EQ-5D-3L score, mean (SD)	63.6 (20.00)	59.1 (20.39)
Change from baseline, mean (SD)	7.76 (1.892)	1.33 (2.573)
P value	0.0302	
EQ-5D-3L index score[d,e]		
Baseline EQ-5D-3L score, mean (SD)	0.68 (0.196)	0.68 (0.196)
Change from baseline, mean (SD)	0.06 (0.021)	–0.03 (0.029)
P value	0.0075	
SF-36 physical component[d,e]		
Baseline SF-36 PCS, mean (SD)	38.587 (9.8261)	36.867 (10.8470)
Change from baseline, mean (SD)	3.357 (7.7264)	0.696 (8.2549)
P value	0.0210	
SF-36 mental component[d,e]		
Baseline SF-36 MCS, mean (SD)	47.029 (12.5485)	44.029 (11.4021)
Change from baseline, mean (SD)	0.453 (10.6063)	–0.057 (11.7945)
P value	0.2942	

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Symptoms		
Visual Kurtzke Functional System[d,f]		
Baseline visual KFS score, mean (SD)	3.2 (2.15)	2.7 (2.32)
Change from baseline, mean (SD)	–0.7 (1.15)	–0.3 (0.93)
P value	0.0884	
Hauser Ambulation Index Score[d,e]		
Baseline HAI score, mean (SD)	2.4 (2.17)	2.1 (1.40)
Change from baseline, mean (SD)	–0.4 (1.08)	0.5 (1.61)
P value	0.0002	
Harms, n (%)		
Adverse events	88 (91.7)	45 (95.7)
Serious adverse events	30 (31.3)	26 (55.3)
Patients who stopped treatment due to adverse events	0	2 (4.3)
Deaths	1 (1.0)	0
Notable harms, n (%)		
Infusion reactions	6 (6.3)	2 (4.3)
Meningococcal infections	0	0
Aspergillus infections	0	0
Serious cutaneous adverse reactions	0	0
Other serious infections	11 (11.5)	6 (12.8)
Sepsis	2 (2.1)	0
Low hemoglobin	NR	NR

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; HAI = Hauser Ambulation Index; KFS = Kurtzke Functional System; MCS = mental component score; mRS = modified Rankin Scale; NR = not reported; PCS = physical component score; SD = standard deviation; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

[a] Log-rank test including strata for the randomization stratification variable; based on a stratified Cox proportional hazards model; full analysis set. Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period. Stratified analyses are based on four randomization strata for EDSS and immunosuppressive therapy (IST): (1) low EDSS at randomization (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naive at randomization; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.

[b] Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to screening; full analysis set.

[c] P value from randomization-based nonparametric analysis of covariance (ANCOVA) adjusted for baseline score and stratified by randomization IST strata: (i) treatment naive at randomization, (ii) continuing on the same IST(s) since last relapse at randomization, (iii) changes in IST(s) since last relapse at randomization; full analysis set.

[d] P value from randomization-based nonparametric ANCOVA adjusted for baseline score and stratified by four randomization strata for EDSS and IST (see note [a]); full analysis set.

[e] Included in statistical hierarchy, but results are not statistically significant due to statistical significance not being achieved for higher-rank end points.

[f] P value has not been adjusted for multiple testing.

Source: Clinical Study Report for PREVENT.[10]

Critical Appraisal

Key limitations of PREVENT were the disproportionately higher percentage of patients who discontinued treatment prematurely in the eculizumab group compared with the placebo group, the likely underestimation of the ARR in both treatment groups related to censoring of patients after the primary outcome event (relapses after the first relapse), limited efficacy assessments based on clinically relevant subgroups, and inability to interpret findings

related to functional status and HRQoL because the hierarchical statistical analysis failed at a higher order comparison.

More patients discontinued treatment with eculizumab (n = 16; 16.7%) compared with placebo (n = 3; 6.7%). This difference was primarily attributed to “withdrawal by patient” from 12 patients (12.5%) receiving eculizumab. The most common reasons for withdrawal by patient included a geographical move (n = 3), and unknown cause (n = 3). The other discontinuations in the eculizumab group were from patients who were lost to follow-up (n = 3) and one patient who died (uncertain relation to eculizumab).

PREVENT was designed as a time-to-event trial, where patients completed the trial after having a relapse. This design inherently emphasizes the efficacy of eculizumab on the first relapse, but it is not designed to assess its efficacy pertaining to subsequent relapses. While ARR is a clinically relevant end point, it did not capture data on subsequent relapses (occurring after 30 days of the first relapse) in a meaningful way in PREVENT because patients were censored per the primary outcome analysis of time to relapse and therefore subsequent relapses would not have been captured, thereby likely underestimating the ARR. Therefore, the effectiveness of eculizumab on subsequent relapses remains largely unknown based on the results of PREVENT.

Subgroups of interest for this review — pre-specified with input from clinician experts — included disease severity at baseline, treatment experience, and primary system impairment at baseline (mobility related or vision related). Pre-specified subgroup analyses in PREVENT were limited to various IST groups at baseline. Data based on patients not receiving concomitant IST versus patients receiving concomitant IST were only available from a post hoc analysis in the 2019 Pittock[11] publication. No subgroup analyses were available for patients who had failed treatment with other therapeutics. The panel of clinical experts consulted by CADTH indicated that baseline disease severity is an important prognostic factor and that patients with a more severe first episode of NMOSD (e.g., requiring admission to an intensive care unit) or those with a higher frequency of relapses at presentation (i.e., patients with two or more relapses per year) would be particularly targeted for treatment with eculizumab. Therefore, the absence of data in these subgroups makes it difficult to determine the most efficient place in therapy for eculizumab and which patients are more likely to benefit from treatment with eculizumab.

Eculizumab did not demonstrate a statistically significant benefit on disability status (change in EDSS) versus placebo. The lack of a statistically significant difference for the change from baseline on the EDSS precluded conclusions being drawn on the effects of eculizumab on subsequent end points in the hierarchical testing sequence related to disability, HRQoL, and symptoms. Input provided by patients with NMOSD and their caregivers indicated that the increasing disability associated with NMOSD impacts all areas of a person’s life, including employment, independence, isolation, cognitive function, and mobility. The results of PREVENT preclude any conclusions from being made about the efficacy of eculizumab on these outcomes, which are important to patients.

Other Relevant Evidence: Long-Term Extension Study of the PREVENT Trial (ECU-NMO-302)

Description of Long-Term Extension Study

ECU-NMO-302, an open-label extension, phase III report[12] to determine the safety and efficacy of eculizumab in patients with relapsing NMOSD (from the PREVENT trial, ECU-NMO-301) was ongoing at the time of this review (NCT02003144; estimated completion date: June 2020). Therefore, only interim results were available to review.

The primary objective of this study is to evaluate the long-term safety of eculizumab in patients with relapsing NMOSD. This study was designed to provide patients who completed study ECU-NMO-301 to start (if they were originally randomized to placebo) or continue receiving eculizumab for up to 5.5 additional years and to provide information on the long-term safety and efficacy of eculizumab in patients with relapsing NMOSD. There are two phases in study ECU-NMO-302: the blind induction phase (to preserve the blinded nature of study ECU-NMO-301), followed by the open-label maintenance phase. The treatment groups were defined by the randomization assignments from study ECU-NMO-301.

Efficacy Results

Efficacy is analyzed through the change in the ARR by comparing it to a historical ARR from the 24 months prior to the initiation of the ECU-NMO-301 study in each patient. There was an overall median reduction in the ARR [redacted]

Harms Results

[redacted]

Critical Appraisal

There seems to be at least a moderate risk of selection bias due to the inclusion of a relatively small number of participants from the original randomized trial up until the cut-off date of the interim analysis, although blinding was preserved from the ECU-NMO-301 during the first (blinded) phase of this study, which could mitigate bias. There is low risk of misclassification bias or bias due to deviations from the intended interventions. The lack of a true comparator group and the use of a before-after design on top of the interim nature of the existing analyses make it difficult to draw any concrete conclusions from the results.

Conclusions

Eculizumab statistically and clinically significantly improves the time to first adjudicated on-trial relapse (primary end point) and adjudicated on-trial ARR (secondary end point) compared to treatment with placebo, regardless of concurrent IST use. Eculizumab may also reduce the severity of relapses that occur, but this analysis was only exploratory in the study. Eculizumab did not demonstrate a statistically significant benefit to disability status (change in EDSS) versus placebo. The lack of a statistically significant difference for the change from baseline on the EDSS precluded conclusions being drawn on the effects of eculizumab on subsequent end points in the hierarchical testing sequence, such as functional status and HRQoL. Adverse events for upper respiratory infection occurred more frequently for patients treated with eculizumab compared with placebo; no other important safety signals were observed in the main study.

The efficacy or safety results of the long-term extension study are difficult to interpret based on interim analysis available for patients treated with eculizumab.

Introduction

Disease Background

NMOSD is a rare, immune-mediated demyelinating disorder of the central nervous system that primarily causes damage to the optic nerves and spinal cord of patients. NMOSD is distinct from MS despite overlapping clinical features.[1-3] NMOSD is a debilitating disease and is typically characterized by acute attacks or relapses of optic neuritis and longitudinally extensive transverse myelitis, although additional clinical characteristics are now recognized.[2-4] Optic neuritis involves inflammation of the optic nerve; it causes eye pain and vision loss and can occur unilaterally or bilaterally. Transverse myelitis is inflammation of the spinal cord that may cause sensorimotor impairment, which may result in weakness in the arms and legs, numbness or tingling, pain and discomfort, and bladder and bowel dysfunction. The natural history of the disease is most often relapsing, where patients experience an episode and then may demonstrate some recovery, followed by further episodes and partial recovery while progressively accruing disability.[1-3] In some patients the first episode is severe enough to cause permanent disability. Most of the disability in NMOSD is incurred through relapses, rather than progression (as is the case with MS). Relapses in NMOSD can result in blindness, paraplegia, and increased overall mortality.[2,6] A relapse is defined as the development of new signs and/or symptoms that prompt a change or addition of treatments such as immunosuppressants, plasma exchange, or intravenous immunoglobulin (IVIG). The diagnosis of NMOSD now typically occurs during the first episode. In the past, when NMOSD was less recognized, the diagnosis may have been delayed or initially misclassified as MS. Input from patients and their caregivers highlighted the debilitating nature of the damage caused by NMOSD relapses and the resulting impact on their vision and mobility that leads to a loss of independence, which alters every aspect of their daily life.

NMOSD disproportionally affects females and those with coexisting autoimmune diseases.[1,6] Systematic reviews based on data from several countries estimated the incidence and prevalence of NMO to range from 0.053 to 0.40 per 100,000 people and 0.51 to 4.4 per 100,000 people, respectively.[7,8] No Canadian-specific estimates were identified in either study. It is unclear if these data are representative of NMOSD in Canadians, as the criteria for NMOSD are broader than those for NMO. People of Asian and African ancestry are at increased risk of NMOSD, and those with African ancestry have higher rates of mortality.[6,13] A recent study on overall mortality based on data from two large US clinics estimated the mortality rate to be 7%, which differs substantially from the mortality rate described in older studies (22% to 32%).[13]

NMOSD was previously referred to as Devic disease and until 2004 was suspected to be a severe form of MS.[1,6] The discovery of an AQP4 antibody (AQP4-IgG) was key in the understanding of the pathogenesis of NMOSD and was an important factor in distinguishing it from MS.[4,14] This antibody binds to AQP4, an abundant water channel in the central nervous system expressed on astrocytes.[4] AQP4-IgG is found in 70% to 90% of patients with NMOSD.[1,2,4,5] Other antibodies, such as myelin oligodendrocyte glycoprotein antibodies, may also be involved in the pathology of NMOSD; however, the evidence is limited compared with AQP4-IgG.[1,4]

In Canada, patients are typically diagnosed by a neurologist or physician with expertise in demyelinating disorders. The criteria currently used in Canada are based on the 2015 diagnostic criteria established by the International Panel for NMO Diagnosis. There are

separate criteria for patients who test positive for AQP4-IgG and for those who test negative for AQP4-IgG or whose status is unknown. A diagnosis of NMOSD for patients who test positive for AQP4-IgG involves one core clinical characteristic (i.e., optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical MRI lesions, or symptomatic cerebral syndrome with NMOSD-typical brain lesions) and the exclusion of alternative diagnoses.[1] As the testing for AQP4-IgG has evolved and become more available, it is now possible to identify a broader range of patients and to identify patients much earlier in the disease course, which allows for earlier treatment and possibly less disability. Few patients who are AQP4-IgG positive have the monophasic disease; this is more often seen in those who are AQP4-IgG negative. A diagnosis of NMOSD for patients who test negative for AQP4-IgG (or have an unknown AQP4-IgG status) requires more stringent clinical and MRI criteria.[1]

Standards of Therapy

Currently, there is no cure for NMOSD. In their input to CADTH, patients expressed that the currently available therapies for NMOSD only offered a temporary solution. Patients voiced the need for a new drug that reduces relapses and disability, as currently available therapeutics fail to do so.

In Canada, therapeutic management of NMOSD is not based on a specific clinical guideline. Prior to eculizumab, there were no Health Canada–approved drugs for the treatment of patients with NMOSD. Treatment of patients differs by province and territory within Canada based in part on differential access to drugs (e.g., mycophenolate mofetil and rituximab).

The goals of treatment relate to three broad areas: the prevention of relapses, the treatment of relapses, and the treatment of residual symptoms following an episode. The focus of this review is on the prevention of relapses based on the indication and place in therapy for eculizumab.

When available, the first choice for relapse prevention treatment is typically rituximab.[15] Alternative first-line therapies include immunosuppressants, such as azathioprine or mycophenolate mofetil. Other therapies that may be used to prevent relapses in NMOSD are tocilizumab, methotrexate, cyclophosphamide, mitoxantrone, cyclosporine, oral corticosteroids (prednisone), or bortezomib.

The evidence for the use of the aforementioned drugs in the prevention of relapses of NMOSD comes primarily from observational studies, except for one trial conducted with rituximab versus azathioprine.

Rituximab may exert its therapeutic effect on patients with NMOSD through B cell–mediated humoral immunity[16,17] and has been shown to be superior to azathioprine for NMOSD in one open-label RCT.[18]

Azathioprine is a purine analogue that interferes with DNA synthesis of rapidly proliferating cells. It has been widely used as a first-line immunosuppressant medication for autoimmune diseases.[17] Azathioprine was first studied in patients with NMOSD in 1998, where it was found to have a benefit on reducing disability.[17] Gastrointestinal and hematological side effects are associated with its use.

Mycophenolate mofetil was developed to be a specific immunosuppressive agent with limited side effects by targeting guanosine more than adenosine.[17] Mycophenolate mofetil is widely used as an immunosuppressant for the treatment of autoimmune diseases and NMOSD with fewer side effects than other therapies, such as azathioprine.[17]

Patients who provided input in this review stated that they tried alternative treatments, such as naturopathic treatments, natural supplements, acupuncture, cupping, and chiropractic adjustments, because they felt they were out of options.

Drug

Eculizumab (Soliris) is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, which inhibits its cleavage into C5a and C5b and prevents the generation of the terminal complement complex C5b-9 and free C5a.[9] The exact mechanism resulting in therapeutic effect is unknown; however, it is expected to relate to the inhibition of AQP4 antibody–induced terminal complement C5b-9 deposition and C5a-dependent inflammation.[9]

Eculizumab is indicated for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive.[9] Eculizumab is not intended for acute treatment of an NMOSD relapse.[9] In Canada, all patients with suspected NMOSD are tested for the presence of AQP4-IgG. Guidance from the 2015 diagnostic criteria established by the International Panel for NMO Diagnosis states that AQP4-IgG should be assessed using cell-based assay, which is considered to be the best available detection method.[1] A description and analysis of AQP4-IgG detection tests in patients with NMOSD is provided in Appendix 5.

The recommended dosage regimen of eculizumab consists of 900 mg weekly for the first four weeks, followed by 1,200 mg for the fifth dose one week later, then 1,200 mg every two weeks thereafter.[9] Supplemental dosing of eculizumab is required in the setting of concomitant support with plasmapheresis, plasma exchange, or fresh frozen plasma infusion.

Table 3 provides details regarding the mechanism of action, indication, route, dose of administration, and the key side effects of eculizumab and its relevant comparators.

Table 3: Key Characteristics of Eculizumab, Rituximab, Azathioprine, and Mycophenolate

	Eculizumab	Rituximab	Azathioprine	Mycophenolate
Mechanism of action	Monoclonal antibody that specifically binds to the complement protein C5	Monoclonal antibody that specifically binds to the transmembrane antigen CD20	Immunosuppressant	Immunosuppressant
Indication[a]	For the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive	No Health Canada indication for the treatment of NMOSD	No Health Canada indication for the treatment of NMOSD	No Health Canada indication for the treatment of NMOSD
Route of administration	IV	IV	Oral	Oral, IV
Recommended dose	900 mg weekly for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter	RA protocol: 1,000 mg IV infusion, followed 2 weeks later by the second 1,000 mg IV infusion Lymphoma protocol: 375 mg/m^2 IV infusion weekly for 4 weeks	2 to 3 mg/kg/day	Myfortic: 720 mg (four 180 mg or two 360 mg tablets) administered twice daily (1.440 g total daily dose) Cellcept: 1 g to 3 g daily, administered orally or intravenously twice a day
Serious adverse effects or safety issues	Serious or fatal meningococcal infections	Infusion reactions, progressive multifocal leukoencephalopathy, tumour lysis syndrome, hepatitis B virus, mucocutaneous reactions, infections, cardiovascular events.	Leukopenia, thrombocytopenia, macrophage activation syndrome, infection, carcinogenic, hepatotoxicity, fetal harm	Infection, lymphoma, fetal harm

AQP4 = aquaporin-4; NMOSD = neuromyelitis optica spectrum disorder; RA = rheumatoid arthritis.

[a] Health Canada–approved indication.

Source: Product monographs for Soliris,[9] Rituxan,[19] Imuran,[20] Myfortic,[21] and Cellcept.[22]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Groups and Information Gathered

One patient group responded to the call from CADTH to provide input on the topic: The MS Society of Canada, an organization that provides programs and services for people with MS and their families and that advocates for those living with MS.

The MS Society provides funding for research with the aim of improving the quality of life of people living with MS. Its mission is to connect and empower patients living with MS to improve outcomes and create positive change. The MS Society contributes to the production and dissemination of scientific information related to MS. Furthermore, the MS Society of Canada provides support and services to people living with allied diseases, including NMOSD.

Patient input used to inform this review was obtained through an online survey conducted between March 3 and March 13, 2020. The survey was posted on the MS Society website and social media platform (Facebook) in both English and French. The survey was targeted at people diagnosed with NMOSD and those affected by it. The respondents were asked to provide feedback related to their quality of life and experience with the drug being reviewed. In total, 11 responses were received. All respondents were female. Five were between the ages of 35 and 44, three between 55 and 64, two between 25 and 34, and one between 45 and 54. Eight respondents had been diagnosed with NMOSD; the remaining three respondents self-identified as caregivers. Four of the respondents reported living with NMOSD for two to four years, and two reported living with NMOSD for five to ten years. One respondent had been living with NMOSD for 11 to 20 years and one respondent was newly diagnosed and had been living with NMOSD for less than two years.

Disease Experience

NMOSD follows a relapsing-remitting disease course. With each attack, an individual living with NMOSD will accrue additional disability, with significant impact on every aspect of daily life, their family, community, employment, and ultimately society.

When asked how a diagnosis of NMOSD has impacted their lives, patients discussed the debilitating nature of the damage caused by attacks and the impact on their vision and mobility.

> "NMOSD has changed my life completely. I am no longer able to work as a nurse. I suffer from residual symptoms that affect my functioning on a daily basis. My husband no longer works. He gave up his job when I was diagnosed as I needed the help at home. My life will never be the same again."

Further descriptions included the following: "My life will never be the same," "Some days are just non-functional due to eye pain," and "It's almost impossible for me to leave my house because of the level of pain and injury I'm dealing with." The need for "more time off work for appointments" was also noted.

Experience With Treatment

None of the respondents had any experience with eculizumab. Prior to the approval of eculizumab, patients diagnosed with NMOSD were treated with off-label agents such as azathioprine and rituximab. The approval of eculizumab for NMOSD is a significant therapeutic advancement for the NMOSD community. Before that, standard treatment for NMOSD involved intravenous steroids, and IVIG or plasmapheresis or plasma exchange. In addition, immunosuppressants are used off-label to help prevent further attacks, though with varying levels of therapeutic benefit. Symptoms such as neuropathy, pain, stiffness, muscle spasms, and bladder and bowel control problems can be managed with various medications and therapies. When asked if the current therapies were effective, four respondents reported that they were effective, one reported no perceived effectiveness, and three did not know. The respondents declared that they had been trying other treatments, such as naturopathic treatments, natural supplements, acupuncture, cupping, and chiropractic adjustments, because they felt they were out of options. The overarching theme was that the currently available therapies for NMOSD only offer a temporary solution.

Improved Outcomes

The approval of eculizumab to the market is a significant milestone, as it is the first treatment targeted to people living with NMOSD. Untreated, the burden of disease and increasing disability impacts all areas of a person's life, resulting in challenges that may include decreased employment stability, decreased family income, increased need for assistance or caregiving, loss of independence, isolation, cognitive decline, and decreased mobility. Eculizumab may have the ability to reduce attacks and accrued disability and might fill a significant therapeutic gap that has been unmet in the treatment of NMOSD to date.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the eculizumab review, a panel of five clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel discussion is presented below.

Unmet Needs

In Canada, the approach to treatment for NMOSD differs by province and territory based on differential access to drugs such as mycophenolate mofetil and rituximab. There are no formal treatment guidelines in Canada that specify which interventions should be used as first- or second-line therapies. Treatment guidelines are still broad as a result of inconsistent availability of treatment and limited direct evidence related to the comparative efficacy of available treatments.

Rituximab is considered one of the most promising therapies for patients with NMOSD. However, its availability differs among provinces. When provinces have access to rituximab, it is generally used as first-line therapy for patients with NMOSD. If rituximab is not available, clinicians consider azathioprine or mycophenolate mofetil, with or without steroids, to be first-line therapy. Tocilizumab can be considered a first- or second-line therapy. Treatments such as azathioprine and mycophenolate mofetil are non-specific immunosuppressants used to prevent relapses, thereby preventing further accumulation of disability. Symptomatic treatments may include pharmacological therapies (i.e., those to help with pain) or non-pharmacological interventions (e.g., canes to help patients walk). High-dose corticosteroids and plasma exchange are interventions often used to treat relapses. The recovery from a relapse varies greatly among patients, with some taking more than a month to recover.

When treating patients with NMOSD, there are a series of treatment goals, which relate to three broad areas: prevention of relapses (disease modifying), treatment of relapses, and treatment of residual symptoms. Although ideal, it is unlikely that any single treatment would cover all three areas.

Of these three areas, disease-modifying or preventive treatment is of special interest because the goal of any intervention would be to reach the best possible effect for reducing relapses, as these are the major source of disability accumulation for patients with NMOSD. None of the therapies used for relapse prevention are expected to mitigate the existing symptoms. However, there are many downstream desirable effects of early prevention and control of the disease; these effects include better HRQoL, increased ability to maintain employment, increased independence, and less reliance on caregivers. It is also important to control NMOSD progression as early as possible, as damage (e.g., blindness) is irreversible.

Unfortunately, there are patients who still have relapses despite their current treatment regimens. Although treatment varies from province to province, all treatments (including the first-line option in some provinces, rituximab) have different rates of relapse. Current therapies are not considered particularly effective. Patients want, and need to be on, a therapy that effectively prevents relapses, which cause the greatest disability associated with NMOSD. Patients need a treatment that can impact and have a benefit to their quality of life as well as improve both safety and the burden associated with getting the treatment. Having access to a more effective treatment would make a huge difference in the lives of patients and their caregivers.

Place in Therapy

The panel indicated that eculizumab could become a first-line treatment for patients who are anti-AQP4 antibody positive but could also be used after inadequate response to ISTs. The panel acknowledged that comparative clinical data are not available at this time to optimally guide the position of eculizumab in the treatment algorithm.

Eculizumab could be used as a monotherapy or as an add-on to corticosteroids and other ISTs.

Patient Population

The clinical panel stated that the factors that weigh most in the decision regarding treatment of patients with NMOSD relate to the severity of the first episode (i.e., patients with a severe initial episode) and frequency of relapses (i.e., patients with two or more relapses per year).

The greatest unmet needs relate to patients with NMOSD who continue to experience relapses despite being on relapse prevention therapy. Specifically, subsets of patients who have the greatest unmet needs include patients whose initial first episode is severe (e.g., requiring admission to an intensive care unit); those with very active relapses (e.g., two or three in the first year); patients who cannot tolerate current treatments such as corticosteroids and other ISTs; patients who are unable to access rituximab and/or have serious adverse reactions to it (e.g., hypersensitivity); and patients who have not recovered from a past relapse or are unlikely to recover from a future relapse.

Assessing Response to Treatment

A clinically meaningful response to treatment relates to the reduction of the relapse rate and prolonged times to relapse. Although the absence of relapse is indicative of a clinically meaningful response, this may not be a realistic parameter for determining continuation of treatment reimbursement, as the number and severity of relapses patients experience differ widely on an individual level.

The determination of relapses is objective; assessment is based on a combination of patient reported symptoms, clinical exam, clinical tools, and patient history.

There is limited formal guidance on how often to assess treatment response. It would be reasonable to assess initial treatment response three months after the initial injection, then patients could be assessed every six months, or yearly for stable patients.

Discontinuing Treatment

Patients may need to discontinue a treatment if they experience a severe relapse (e.g., requiring intubation and support on a ventilator), two or more relapses within two years (assessed on a case-by-case basis), or SAEs while on treatment.

If eculizumab is being used as a monotherapy, the panel noted that clinicians may try adding other therapies (e.g., corticosteroids and/or other ISTs) before discontinuing eculizumab.

There are no specific guidelines or tools used to determine a severe relapse, but based on clinician judgment and patient input, it is important to refer to the severity of the relapse at its absolute worst and how much recovery is present (i.e., how much residual disability is left).

Prescribing Conditions

A neurologist (ideally one with expertise in demyelinating disorders) would be required for the diagnosis, treatment, and monitoring of patients based on the potential complexities around diagnosis and restrictions on who can order the diagnostic tests (e.g., AQP4-IgG).

It takes two to four weeks from ordering to receive the results of an AQP4-IgG test. During this time, patients would be set up with other aspects of care (e.g., education and vaccination). It is not expected that there would be an increase in demand for the AQP4-IgG test as it must be requested by neurologists. The AQP4-IgG test is currently covered by the provinces.

Additional Considerations

Patients living in rural areas travel to a clinic for initial diagnosis. Follow-up, education, and labs can be completed locally or by telehealth. Once patients start IV infusion medications, local clinics can be set up closer to patients to achieve a proper infusion administration of therapies, as patients prefer to receive treatment closer to home.

Clinical Evidence

The clinical evidence included in the review of eculizumab is presented in two sections. The first section, the systematic review, includes the pivotal study provided in the sponsor's submission to CADTH and Health Canada. The second section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review: Pivotal and Protocol Selected Studies

Objectives

To perform a systematic review of the beneficial and harmful effects of eculizumab 10 mg/mL intravenous infusion for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adult patients with NMOSD who are anti-AQP4 antibody positive Subgroups: • Severity of disease • Treatment experience • Mobility-related impairment vs. vision-related impairment
Intervention	Eculizumab 10 mg/mL intravenous infusion (900 mg weekly for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter) alone or in combination with other therapies
Comparators	• Rituximab[a] • Azathioprine[a] • Mycophenolate mofetil[a] • Tocilizumab[a] • Methotrexate[a] • Cyclophosphamide[a] • Mitoxantrone[a] • Cyclosporine[a] • Prednisone[a] • Bortezomib[a]

Outcomes	**Efficacy outcomes:** • Relapse (e.g., time to first relapse and relapse rate) • Disability progression[b] (e.g., worsening neurologic disability) • HRQoL[b] • Productivity[b] (e.g., attend school or work) • Symptoms[b] (e.g., pain, fatigue, bladder/bowel function, sexual dysfunction, and respiratory) **Harms outcomes:** • AEs, SAEs, WDAEs, mortality, serious infusion reactions, serious infections (e.g., meningococcal and respiratory), hemolysis/low hemoglobin
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; AQP4 = aquaporin-4; HRQoL = quality of life; NMOSD = neuromyelitis optica spectrum disorder; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus; WDAE = withdrawal due to adverse event.

[a] This drug does not have a Health Canada indication for the treatment of patients with NMOSD.

[b] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (cadth.ca/resources/finding-evidence/press).[23]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Soliris (eculizumab) and NMOSD. The US National Institutes of Health's clinicaltrials.gov clinical trial registry was searched.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on March 24, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on July 15, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters):[24] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

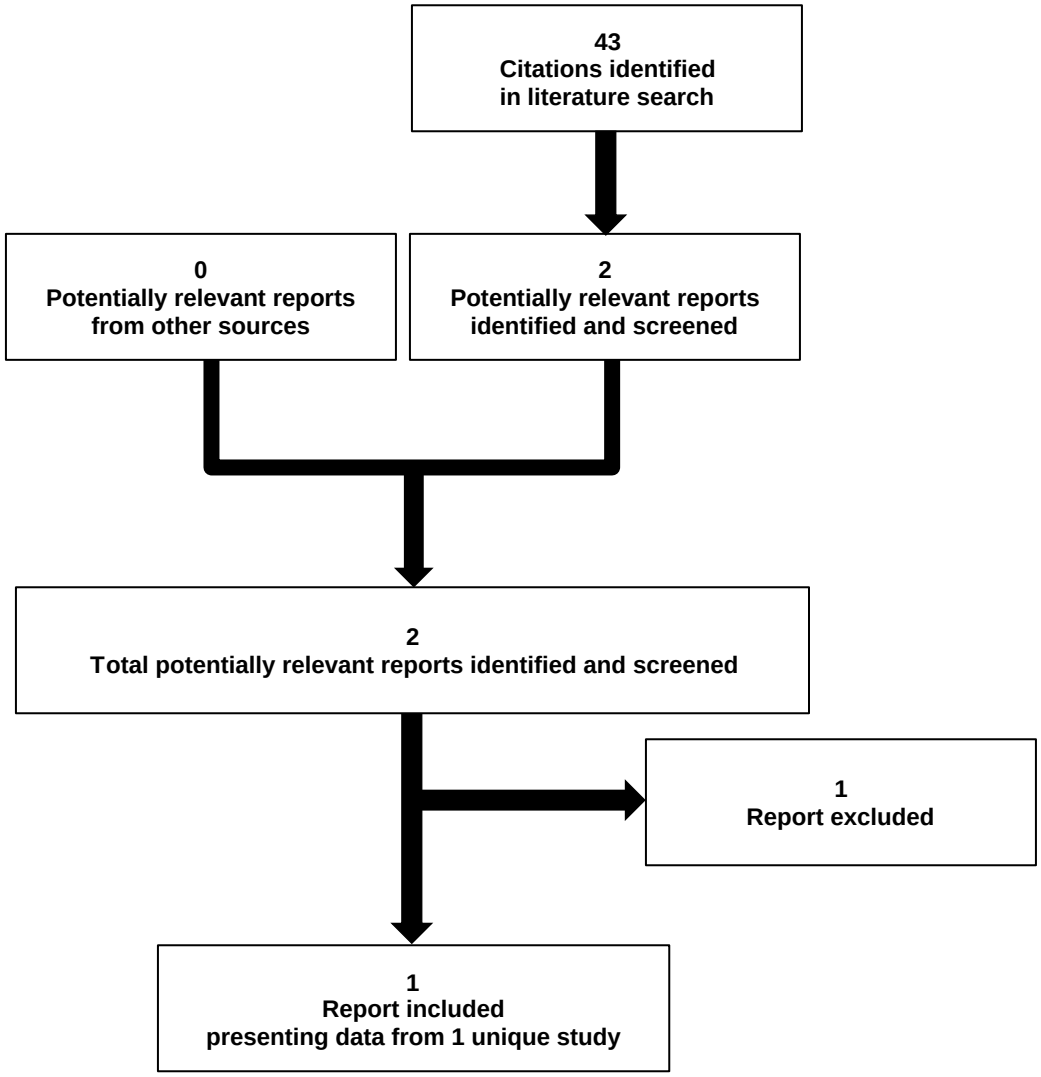


Table 5: Details of Included Studies

		PREVENT
Designs and Populations	**Study design**	Double-blind, placebo-controlled RCT
	Locations	North America, South America, Europe, Australia, Asia
	Randomized, N	143
	Inclusion criteria	• ≥ 18 years old • Diagnosis of NMO[a] or NMOSD[b] • Anti-AQP4 antibody seropositive • Historical relapse[c] of at least 2 relapses in last 12 months or 3 relapses in the last 24 months with at least 1 relapse in the 12 months prior to screening • EDSS score ≤ 7 • If a patient entered the study receiving IST(s) for relapse prevention, the patient must have been on a stable maintenance dose of IST(s) prior to screening
	Exclusion criteria	• Use of rituximab, mitoxantrone, or intravenous immunoglobulin 3 months prior to screening • If a patient entered the study receiving oral corticosteroid(s) with or without other IST(s), the daily corticosteroid dose must be no more than prednisone 20 mg/day (or equivalent) prior to the screening • Unresolved meningococcal disease • Any systemic bacterial or other infection that was clinically significant and had not been treated with appropriate antibiotics
Drugs	**Intervention**	Eculizumab • Induction phase: ○ 900 mg eculizumab (3 vials), intravenous, weekly for 4 weeks followed by ○ 1,200 mg eculizumab (4 vials), intravenous, once, 1 week later • Maintenance: ○ 1,200 mg eculizumab (4 vials), intravenous, every 2 weeks onward • Supplemental (if plasmapheresis/plasma exchange was given due to on-trial relapse): ○ 600 mg eculizumab (2 vials), intravenous within 1–2 hours after the end of plasmapheresis/plasma exchange session
	Comparator(s)	Placebo • Induction phase: ○ 3 vials of placebo, intravenous, weekly for 4 weeks, followed by ○ 4 vials of placebo, intravenous, once, 1 week later • Maintenance: ○ 4 vials of placebo, intravenous, every 2 weeks onward • Supplemental (if plasmapheresis/plasma exchange was given due to on-trial relapse): ○ 2 vials of placebo, intravenous, within 1–2 hours after the end of plasmapheresis/plasma exchange session
Duration	**Phase**	
	Run-in	Screening period of 1–6 weeks
	Double-blind	After 24 pre-specified adjudicated relapses
	Follow-up	8 weeks
Outcomes	**Primary end point**	Time to first adjudicated[d] on-trial relapse
	Secondary and exploratory end points	Secondary: • Adjudicated on-trial ARR • Change from baseline in EDSS score at the EOS • Change from baseline in mRS score at the EOS

		PREVENT
		• Change from baseline in ambulatory function (measured by HAI at the EOS) • Change from baseline in EQ-5D at the EOS Exploratory: • Change from baseline in ambulatory function (measured by HAI at the EOS) in patients with abnormal baseline ambulatory function • Change from baseline in visual function as measured by visual acuity at the EOS in all patients and patients with abnormal baseline visual function • Change from baseline in the SF-36 at the EOS • Change from baseline in the KFS scores (other than visual acuity) at the EOS • Types and severity of relapses using the OSIS • Changes from baseline to all the study collected time points after a relapse was summarized for EDSS, HAI, and visual acuity • On-trial relapses assessed by summarizing the number and rate of relapses requiring hospitalization and the number and rate of treatments for relapses by treatment group
NOTES	**Publications**	Pittock (2019)[11]

AQP4 = aquaporin-4; ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; EOS = end of study; EQ-5D = EuroQol 5-Dimensions; HAI = Hauser Ambulation Index; IST = immunosuppressive therapy; KFS = Kurtzke Functional System; mRS = modified Rankin Scale; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; OSIS = Optic-Spinal Impairment Scale; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey.

Note: Two additional reports were included: CDR submission[25] and Health Canada's reviewers report.[26]

[a] Diagnosis of NMO defined by Wingerchuk 2006 criteria.

[b] Diagnosis of NMOSD defined by Wingerchuk 2007 criteria.

[c] Historical relapse defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or MRI findings or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of existing neurologic symptoms that required treatment.

[d] Use of a central independent committee to adjudicate all on-trial relapses.

Source: Clinical Study Report for PREVENT.[10]

Description of Studies

One phase III, time-to-event RCT (PREVENT [ECU-NMO-301]) was identified and included in the systematic review. PREVENT included an open-label extension study (ECU-NMO-302) described in the "Other Relevant Evidence" section of the report. PREVENT was a multi-centre, double-blind, placebo-controlled RCT in patients 18 years of age and older with a diagnosis of NMO or NMOSD. The duration of PREVENT was designed to last until 24 patients experienced an on-trial adjudicated relapse.

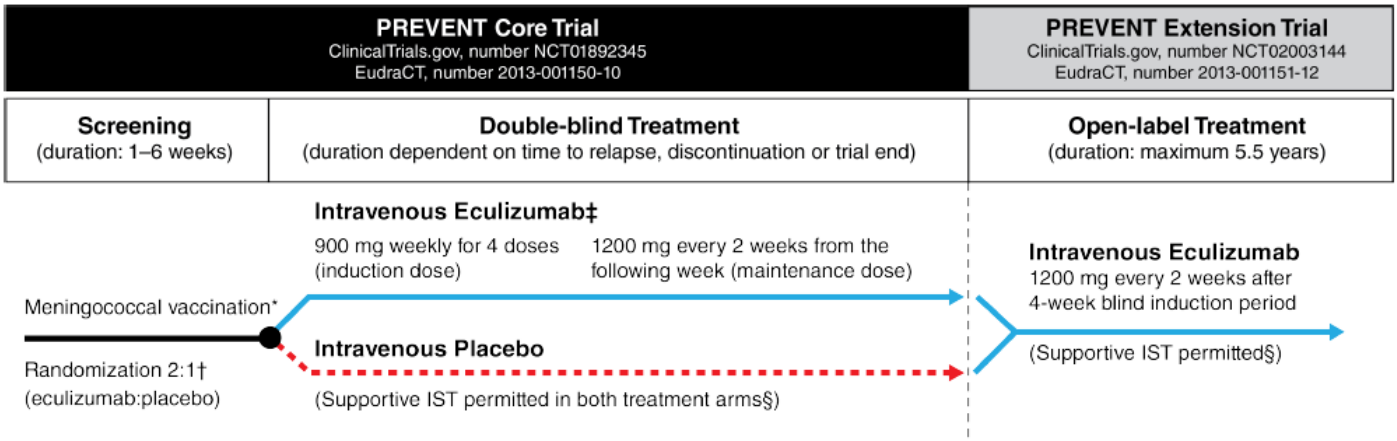
The primary objective of PREVENT was to assess the efficacy of eculizumab treatment, as compared with placebo, in relapsing NMOSD patients based on time to first relapse and relapse risk reduction. PREVENT also aimed to characterize the overall safety and tolerability of eculizumab compared with placebo in relapsing NMOSD patients. PREVENT took place between April 11, 2014, and July 17, 2018. Patients (N = 143) were centrally randomized 2:1 to receive eculizumab or placebo via an interactive voice response system. Patients received intravenous eculizumab at a dose of 900 mg weekly for the first four doses starting on day 1, followed by 1,200 mg every two weeks starting at week 4, or matched placebo. Randomization was stratified according to the EDSS score at randomization, as well as patients' prior supportive (i.e., for relapse prevention) IST and IST status at randomization, in the following strata: (1) low EDSS stratum at randomization (≤ 2.0); (2) high EDSS stratum (≥ 2.5 to ≤ 7) and treatment-naive patients at randomization; (3) high EDSS stratum (≥ 2.5 to ≤ 7) and patients continuing on the same IST(s) since last

relapse at randomization; and (4) high EDSS stratum (≥ 2.5 to ≤ 7) and patients with changes in IST(s) since last relapse at randomization. The minimum duration or dose of ISTs was not specified. Block sizes of three were used within strata.

PREVENT included patients from North and South America, Europe, Australia, Asia. The greatest proportion of patients were recruited from Europe (35.7%). No patients were recruited from Canada.

Figure 2 presents the study design of PREVENT. The screening period of PREVENT was one to six weeks in duration. Patients received treatment with eculizumab or placebo as part of PREVENT until they experienced an on-trial relapse (determined by the treating physician) or the trial ended. PREVENT was a time-to-event RCT that was designed to last until 24 patients experienced an on-trial adjudicated relapse. Patients could complete the trial earlier if they had a physician-determined relapse, whether positively adjudicated or not. Patients could enter an open-label extension study after completing PREVENT (extension study is ongoing). Patients who did not enter the extension or withdrew from PREVENT had a follow-up visit for safety assessments at eight weeks after the last dose of the study drug was received.

Figure 2: Study Design



IST = immunosuppressive therapy.

* Patients were vaccinated against *Neisseria meningitidis* before receiving a trial agent unless a previous vaccination provided adequate coverage; a 14-day course of antibiotics was administered if there were fewer than 14 days between vaccination and starting trial treatment.

† Randomization was stratified across sites by Expanded Disability Status Scale score on day 1 (≤ 2.0; 2.5 to 7.0) and use of supportive IST (IST; no previous IST; unchanged IST; changed IST). IST was considered to be unchanged if no therapy had been started or discontinued after the last relapse before screening, although doses may have changed; patients who had previously received only glucocorticoid therapy were considered to have received no previous IST. Block sizes of three were used within strata.

‡ Patients received 900 mg of eculizumab weekly for the first four doses in the trial; the following week, patients started the maintenance regimen, which was 1,200 mg every two weeks.

§ IST received at screening for the PREVENT core trial was continued unchanged unless treating physicians determined that a relapse had occurred or there was a compelling medical need for adjustment, whereas IST in use in the PREVENT extension trial could be changed at the discretion of the treating physician.

Source: The New England Journal of Medicine, Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder, 381(7):614-625. Copyright © (2019) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[11]

Populations

Inclusion and Exclusion Criteria

The study population in PREVENT consisted of patients 18 years of age and older with NMO or NMOSD based on the criteria defined by Wingerchuk et al. in 2006[27] and 2007,[2] respectively. Patients were anti-AQP4 antibody seropositive and had to have an EDSS score of 7 or less. Patients must have had at least two relapses in the last 12 months or three relapses in the last 24 months, with at least one relapse in the 12 months prior to screening.

If a patient entered the study receiving ISTs for relapse prevention, the patient must have been on a stable maintenance dose of ISTs prior to screening and must have remained on that dose for the duration of the study unless the patient experienced a relapse.

Patients were excluded from the trials if they used rituximab, mitoxantrone, or IVIG within three months of screening. Use of rituximab was not permitted because of incompatibility between its mechanism of action and that of the terminal complement inhibitor eculizumab. If a patient entered the study receiving oral corticosteroids with or without other ISTs, the daily corticosteroid dose could be no more than prednisone 20 mg/day (or equivalent) prior to the screening and must remain at that dose for the duration of the study or until the patient experiences a relapse.

All eligible patients were vaccinated against *N. meningitidis* if they had not already been vaccinated within the time period of active coverage.

Baseline Characteristics

The baseline characteristics were generally balanced between study arms (Table 6). In PREVENT, approximately 90% of patients were female. The study population consisted of 47.9% to 51.1% white patients and 31.9% to 38.5% Asian patients, with slightly more Asian patients in the eculizumab arm and slightly more black patients in the placebo arm. The mean age at NMOSD initial clinical presentation was 35.8 years in the eculizumab arm and 38.5 years in the placebo arm. Prior to the study, almost all patients had been treated with supportive IST, such as corticosteroids (70.8% to 63.8%), azathioprine (55.3% to 63.5%), and rituximab (27.1% to 42.6%).

Table 6: Summary of Baseline Characteristics

	PREVENT	
Characteristics	**Eculizumab N = 96**	**Placebo N = 47**
Age at first dose, years, mean (SD)	43.9 (13.32)	45.0 (13.29)
Sex, female, n (%)	88 (91.7)	42 (89.4)
Race, n (%)		
Asian	37 (38.5)	15 (31.9)
Black or African-American	9 (9.4)	8 (17.0)
White	46 (47.9)	24 (51.1)
Other or unknown	4 (4.2)	0
Region, n (%)		
Americas	29 (30.2)	15 (31.9)

Characteristics	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Europe	32 (33.3)	19 (40.4)
Asia-Pacific	35 (36.5)	13 (27.7)
Eye disorders, n (%)	33 (34.4)	15 (31.9)
Blindness unilateral	10 (10.4)	5 (10.6)
Baseline EDSS score, mean (SD)	4.15 (1.646)	4.26 (1.510)
Baseline HAI score, mean (SD)	2.4 (2.17)	2.1 (1.40)
Baseline mRS score, mean (SD)	2.1 (1.14)	2.1 (0.98)
Overall stratification group (4 strata), n (%)		
Low EDSS at randomization (≤ 2.0)	11 (11.5)	5 (10.6)
High EDSS (≥ 2.5 to ≤ 7) and treatment naive at randomization	12 (12.5)	5 (10.6)
High EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization	44 (45.8)	22 (46.8)
High EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization	29 (30.2)	15 (31.9)
Age at NMOSD initial clinical presentation, years, mean (SD)	35.8 (14.03)	38.5 (14.98)
Age at NMOSD diagnosis, years, mean (SD)	40.6 (14.00)	41.1 (14.36)
NMOSD grouped initial clinical presentation, n (%)		
Optic neuritis[a]	41 (42.7)	17 (36.2)
Transverse myelitis[b]	36 (37.5)	21 (44.7)
Optic neuritis and transverse myelitis[c]	12 (12.5)	2 (4.3)
Area postrema syndrome[d]	13 (13.5)	8 (17.0)
Other[e]	5 (5.2)	1 (2.1)
NMOSD diagnosis, n (%)		
Definitive NMO	69 (71.9)	38 (80.9)
NMOSD[f]	27 (28.1)	9 (19.1)
Longitudinally extensive transverse myelitis	14 (14.6)	5 (10.6)
Optic neuritis	8 (8.3)	2 (4.3)
Optic neuritis or longitudinally extensive myelitis coexisting with systemic autoimmune disease	3 (3.1)	1 (2.1)
Optic neuritis or transverse myelitis associated with brain lesions typical of NMO	1 (1.0)	1 (2.1)
Other	1 (1.0)	0
Time from initial clinical presentation to first dose of study drug, years, mean (SD)	8.156 (8.5792)	6.601 (6.5863)
Historical ARR (within the 24 months prior to screening), mean (SD)	1.94 (0.896)	2.07 (1.037)
Supportive IST for NMOSD used prior to study, n (%)		
Patients with any prior medications	88 (91.7)	45 (95.7)
Corticosteroids	68 (70.8)	30 (63.8)
Azathioprine	61 (63.5)	26 (55.3)
Rituximab	26 (27.1)	20 (42.6)
Mycophenolate mofetil	27 (28.1)	15 (31.9)
Cyclophosphamide	8 (8.3)	5 (10.6)

Characteristics	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Methotrexate	4 (4.2)	5 (10.6)
Cyclosporine and tacrolimus	3 (3.1)	3 (6.4)
Mitoxantrone and cladribine	3 (3.1)	3 (6.4)
IVIG	2 (2.1)	2 (4.3)
Mizoribine	1 (1.0)	2 (4.3)
Tocilizumab	2 (2.1)	0
Subgroup of supportive IST use at baseline, n (%)		
Corticosteroids alone	16 (16.7)	11 (23.4)
Azathioprine subgroup	37 (38.5)	13 (27.7)
Azathioprine alone	8 (8.3)	6 (12.8)
Azathioprine and corticosteroids	29 (30.2)	7 (14.9)
Mycophenolate mofetil subgroup	17 (17.7)	8 (17.0)
Mycophenolate mofetil alone	10 (10.4)	5 (10.6)
Mycophenolate mofetil and corticosteroids	7 (7.3)	3 (6.4)
Other ISTs	5 (5.2)	2 (4.3)
Other ISTs alone	1 (1.0)	0
Other ISTs and corticosteroids	4 (4.2)	2 (4.3)
No IST usage	21 (21.9)	13 (27.7)

ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; HAI = Hauser Ambulation Index; IST = immunosuppressive therapy; IVIG = intravenous immunoglobulin; mRS = modified Rankin Scale; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation.

Note: Full analysis set.

[a] Patients with optic neuritis but no transverse myelitis.

[b] Patients with transverse myelitis (ataxia, dysesthesia, paresthesia, transverse myelitis, or longitudinally extensive transverse myelitis) but no optic neuritis.

[c] Patients with both optic neuritis and transverse myelitis.

[d] Patients with area postrema syndrome (hiccoughs or intractable nausea or vomiting).

[e] Patients with any other presentations.

[f] NMOSD, as defined by Wingerchuk 2007 per the study protocol.

Source: Clinical Study Report for PREVENT.[10]

Interventions

In PREVENT, patients received treatment with intravenous eculizumab or placebo. The placebo, drug kit, and labels had an identical appearance to eculizumab. Treatments were divided into an induction phase and maintenance phase; the dosing regimens and schedules are described in Table 7. Each vial of study drug contained eculizumab 300 mg or placebo for intravenous administration.

If a patient experienced an acute relapse and required plasmapheresis or plasma exchange, then they received a supplemental dose of two vials, equivalent to 600 mg of eculizumab (or placebo), within one to two hours after the end of plasmapheresis or plasma exchange. If plasmapheresis or plasma exchange was administered on a day of regularly scheduled study drug administration, then the patients received the regularly scheduled number of vials of the study drug.

Table 7: Treatments Administered

PREVENT				
Dose period	**Frequency of study drug administration**	**Visits**	**Number of vials[a]**	**Equivalent eculizumab dose, mg**
Induction phase	Weekly (every 7 ± 2 days)	2 to 5	3	900
		6	4	1,200
Maintenance phase	Every 2 weeks (14 ± 2 days) from the sixth dose onward	7 to EOS/ET	4	1,200
Supplemental doses	If plasmapheresis/PE was given due to on-trial relapse, supplemental doses were administered preferably within 1–2 hours after the end of each plasmapheresis/PE session		2	600

EOS = end of study; ET = early termination; PE = plasma exchange.

[a] Vials contained eculizumab 300 mg or placebo for intravenous administration.

Source: Clinical Study Report for PREVENT.[10]

Patients were permitted to receive palliative and supportive care for "underlying" conditions. IVIG and plasma exchange were permitted only for the acute treatment of relapses. Patients could receive ISTs at the discretion of the treating physician. Use of corticosteroids (not exceeding prednisone 20 mg/day or equivalent), azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, or cyclophosphamide either in combination or as monotherapy were permitted if the patient was receiving it as a stable maintenance dose prior to randomization. Patients were not permitted to start new ISTs or to switch ISTs during the trial unless they had an on-trial relapse.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 8. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Table 8: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	PREVENT
Time to first adjudicated[a] on-trial relapse	Primary
Adjudicated[a] on-trial annualized relapse rate	Secondary
Severity of relapses	Exploratory
Change from baseline in EDSS	Secondary
Change from baseline in mRS	Secondary
Change from baseline in EQ-5D	Secondary
Change from baseline in the SF-36	Exploratory
Change from baseline in visual function (visual KFS)	Exploratory
Change from baseline in Hauser Ambulation Index	Secondary

EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions; KFS = Kurtzke Functional System; mRS = modified Rankin Scale; SF-36 = Short Form (36) Health Survey.

[a] Use of a central independent committee to adjudicate all on-trial relapses.

Relapse

Relapses were assessed as follows: time to first adjudicated on-trial relapse, adjudicated on-trial relapse rate, and severity of relapses. Relapses were also reported based on assessment by the treating physician.

The primary efficacy outcome in PREVENT was time to first adjudicated on-trial relapse. On-trial relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination (e.g., EDSS, KFS, mRS, visual acuity test [Snellen chart], HAI, and Columbia-Suicide Severity Rating Scale) that persists for more than 24 hours. The signs and symptoms had to be attributed to NMO. The relapse had to be preceded by at least 30 days of clinical stability. Adjudication of on-trial relapses was based on consensus of an independent RAC consisting of two neurologists and one neuro-ophthalmologist. The adjudication committee was blinded to treatment group and reviewed all cases of attending physician–determined relapses and possible relapses (cases of interest) retrospectively using the same criteria as the attending physician.

Adjudicated on-trial relapse rate was a secondary efficacy end point. It was computed for each group of patients based on the total number of relapses divided by the person-time in years.

Severity of relapses was assessed as an exploratory efficacy end point in PREVENT. The severity of a relapse was determined using the worst severity observed over all relapse visits based on the Optic-Spinal Impairment Scale (OSIS) where relapses were categorized as “major” or “minor.” The OSIS is a generic instrument that assesses visual acuity and motor, sensory, and urinary sphincter functions. No studies on validity or reliability for this scale were found in patients with either NMOSD or MS. No minimal important difference (MID) was identified in the literature for patients with NMOSD or MS.

Disability

Disability was assessed using the EDSS and the mRS.

Change from baseline in EDSS score was a secondary efficacy end point in PREVENT. The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. The EDSS assesses eight KFSs (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other) and ambulation. These are rated in the context of a standard neurological examination, and then these ratings (KFS scores) are used in conjunction with observations and information concerning the patient’s mobility, gait, and use of assistive devices to assign an EDSS score. Validity of the EDSS has been established, and it is used as the gold standard for evaluating new scales. Reliability has been assessed as being low to moderate, with inter-rater kappa values between 0.32 and 0.76 for EDSS and between 0.23 and 0.58 for the individual functional systems. For scores below 3.5, reliability is regarded as good. No MID specific for NMOSD was found. Indirect estimates can be obtained from patients with MS, for which one study found that a change of 1.5 points as a single score was considered enough deterioration from the patient perspective.[28] This was in agreement with a second study stating a 1.5-point increase from baseline 0 as important; from a baseline of 1 to 5.5, a 1-point increase was considered important, and from a baseline score greater than or equal to 6, a 0.5-point increase was considered important.[29]

Change from baseline in mRS was also a secondary efficacy end point in PREVENT. The mRS is a generic, commonly used clinician-reported scale for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. The scale ranges from 0 (no disability) to 6 (death). No studies on NMOSD or MS patients evaluating validity or reliability were identified; although the mRS has been validated in patients who suffered disability due to stroke.[30] No MID was identified in the literature for patients with NMOSD or MS.

Health-Related Quality of Life

Health-related quality of life was assessed using the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) instrument and the Short Form (36) Health Survey (SF-36).

Change from baseline in EQ-5D-3L was a secondary end point in PREVENT. The EQ-5D-3L is a generic preference-based HRQoL instrument, consisting of a visual analogue scale (VAS) and a composite index score of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension consists of three levels (some, moderate, and extreme problems), generating a total of 243 theoretically possible health states. Assessments were also made using the EQ-5D Visual Analogue Scale (EQ-5D VAS), which captures the self-rating of current health status using a visual "thermometer," with the end points of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. No studies assessing the validity or reliability of the EQ-5D were found in the literature for patients with NMOSD, although the EQ-5D-3L has been validated in patients with MS.[31] No MID was identified in the literature for patients with NMOSD or MS.

Change from baseline in SF-36 was an exploratory efficacy end point in PREVENT. The SF-36 is a generic self-reported questionnaire consisting of eight domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The SF-36 yields two summary measures of physical health (the physical component score [PCS] measure) and mental health (the mental component score [MCS] measure) derived from scale aggregates. Higher global scores are associated with better quality of life. No studies assessing the validity or reliability of the SF-36 were found in the literature for patients with NMOSD, although the SF-36 has been validated in patients with MS and neurological disabilities.[32] No MID studies were found for patients with NMOSD; however, indirect estimates have been obtained from patients with MS.[33]

Symptoms

Visual function was assessed using the visual KFS. Ambulation was assessed using the HAI.

Change from baseline in visual KFS was an exploratory efficacy outcome in PREVENT. The visual KFS is one of the functional domains included in the EDSS. Scores for the visual KFS range from 0 (normal) to 6 (grade 5 plus maximal visual acuity of the better eye of 20/60 or less). In terms of reliability, there was a fair agreement in visual KFS found in one study with a Cohen's kappa value of 0.39.[34] However, no values or assessment on validity directly related to the visual KFS were found. No MID can be calculated for visual acuity within the functional system score (FSS), and no further information could be obtained.

Change from baseline in HAI was a secondary efficacy outcome in PREVENT. The HAI evaluates gait and is used to assess the time and effort used by the patient to walk 8 m (28 ft). The scale ranges from 0 to 9, with 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst (restricted to wheelchair; unable to

transfer self independently). No studies assessing the validity or reliability of the HAI were found in the literature for patients with NMOSD, although the HAI has been validated in patients with MS. No MID studies were found for patients with NMOSD.

Other

The following CDR protocol–specified outcomes were not assessed in PREVENT: productivity (e.g., attend school or work).

Harms

The harms outcomes assessed included AEs, SAEs, withdrawals due to adverse events, and deaths.

Statistical Analysis

Primary Efficacy End Point for PREVENT

In PREVENT, 24 adjudicated on-trial relapse events in 24 distinct patients, based on a sample size of 132 patients (88 eculizumab and 44 placebo), were needed to achieve 90% power to detect a treatment difference in time to first relapse. The power calculation was based on a two-sided log-rank test at a 5% level of significance assuming a dropout rate of 10%, an accrual period of approximately 21 months, and an HR of 0.24, which corresponds to a relapse-free rate of 40% for the placebo arm and 80% for the eculizumab arm at 12 months. The sample size calculation was based on 2:1 randomization for treatment with eculizumab and placebo.

Time to first adjudicated on-trial relapse for the comparison between treatment arms was assessed using a stratified log-rank test. The randomization stratification was based on the EDSS score at day 1 (≤ 2.0 versus ≥ 2.5 to ≤ 7) and IST status at randomization for relapse prevention (treatment-naive patients, on the same IST(s) since the last relapse and with changes in IST(s) since last relapse). The HR and risk reduction from a stratified Cox proportional hazards model were summarized, including 95% CIs and P values. The primary objective was achieved if a statistically significant difference (P ≤ 0.05) was observed between the treatment arms.

For subgroups, a descriptive summary of adjudicated on-trial relapse was performed based on region, age group, sex, race, IST, and corticosteroid use. Baseline use of IST and corticosteroid, as well as baseline disease severity and primary disability (mobility-related impairment versus vision-related impairment), were subgroups of interest for this review; the latter two were not reported. No formal statistical tests were planned for the subgroup summaries.

The following sensitivity analyses were performed for the primary efficacy end point:

- stratified log-rank test using data from the per-protocol (PP) population
- unstratified log-rank test
- multivariate Cox proportional hazards model (with terms for treatment, baseline EDSS score dichotomized at median, historical ARR, and IST strata at baseline).

On-trial relapses were also assessed by the treating physician, including additional sensitivity analysis consistent with those for the primary efficacy end point.

All patients either experienced an adjudicated on-trial relapse or ended their participation without experiencing an adjudicated on-trial relapse. Patients who did not have an adjudicated on-trial relapse were censored based on their time from first dose to the end of the study period.

Secondary End Points for PREVENT

The following secondary end points were evaluated based on the following hierarchy:

- adjudicated on-trial ARR
- change from baseline in EDSS score at the end of the study
- change from baseline in mRS score at the end of the study
- change from baseline in ambulatory function as measured by HAI at the end of the study
- change from baseline in EQ-5D at the end of the study (VAS tested first; index score tested second).

If statistical significance was not achieved at an end point ($P \leq 0.05$), then end points of lower rank were not considered statistically significant. Regardless of the outcome of the testing procedure, CIs and P values were reported.

Adjudicated on-trial ARR was assessed using Poisson regression analysis with the following covariates: treatment group, randomization stratification variable, and historical ARR. The log of time in the study will be used as the offset variable. A sensitivity analysis based on treating physician–determined relapses was performed. Although the Poisson regression model has been recognized in the past as the standard analysis approach for relapse in MS, it is unknown whether the Poisson distribution assumption is satisfied with NMOSD, given that the disease is extremely rare. The Poisson distribution assumes that the mean and variance of data are equal or approximately equal.

A sensitivity analysis with a negative binomial model was used to handle the potential overdispersion in the distribution of infrequent relapses in NMOSD.

The change from baseline in EDSS score, mRS score, HAI score, EQ VAS score, and EQ-5D index score at end of the study were analyzed using a randomization-based nonparametric analysis of covariance (ANCOVA) adjusted for baseline score and stratified by randomization strata. Sensitivity analyses were performed for change from baseline at all scheduled visits using a mixed model for repeated measure (with covariates for baseline score, observed randomization strata, treatment group, and study visit); change from baseline at all scheduled visits after year 1 used a mixed model for repeated measure, with covariates for baseline score, observed randomization strata, treatment group, study visit, and study visit by treatment group interaction.

Change from baseline in ambulatory function as measured by the HAI was assessed in a subset of patients with abnormal baseline ambulatory function (HAI value of 1 to 9). Change from baseline in visual function, as measured by visual acuity, was assessed in a subset of patients with abnormal baseline visual function (KFS score for visual acuity of 1 to 6).

Missing data for the analysis of EDSS, EQ-5D, mRS, HAI, and visual acuity (Kurtzke FSS) at the end of the study were imputed based on the last observation carried forward (LOCF). If no post-baseline assessments were available, the baseline value was used. If a patient had a second relapse during the six-week recovery phase after the initial relapse, the last

score prior to the second attack was used for the analysis. Missing data for the SF-36 were handled according to the tool.

Analysis Populations

PREVENT had full analysis set (FAS), PP, and safety set populations.

- The FAS population consisted of all patients who were randomized to treatment and who had received at least one dose of the study drug (eculizumab or placebo treatment). Patients in this analysis set were compared for efficacy according to the treatment they were randomized to receive, irrespective of the treatment they actually received.
- The PP population consisted of all patients who had no major protocol deviations or key inclusion or exclusion criteria deviations that might potentially affect efficacy and who took at least 80% of the required treatment doses while they were in the double-blind study period.
- The safety set population consisted of all patients who received at least one dose of the study drug (eculizumab or placebo). Patients were compared for safety according to the treatment they actually received.

Results

Patient Disposition

Out of 213 patients screened for PREVENT, 70 (32.9%) failed screening, with the most common reasons attributed to being AQP4 antibody seronegative (n = 42) and not meeting the historical relapse criteria (n = 11). A total of 96 patients were randomized to treatment with eculizumab, and 47 were randomized to placebo. In the eculizumab arm, 16.7% patients discontinued the study, compared to 6.4% in the placebo arm. The most common reason for discontinuation was attributed to "withdrawal by patient" (12.5% versus 2.1% in eculizumab and placebo, respectively); the reason for withdrawal was unknown for most cases. Table 9 presents the patient disposition for PREVENT. Major protocol deviations occurred in 38.5% of patients in the eculizumab arm and 42.6% in the placebo arm; results are presented in Appendix 3, Table 28.

Table 9: Patient Disposition

	PREVENT	
	Eculizumab	Placebo
Screened, N	213	
Randomized, N (%)	96 (100.0)	47 (100.0)
Discontinued from study, n (%)	16 (16.7)	3 (6.4)
Adverse event	0	2 (4.3)
Death	1 (1.0)	0
Lost to follow-up	3 (3.1)	0
Withdrawal by patient	12 (12.5)	1 (2.1)
Full analysis set, N	96	47
PP, N	90	44
Safety, N	96	47
Enrolled in open-label extension study, n (%)	78 (81.3)	41 (87.2)

PP = per-protocol.

Source: Clinical Study Report for PREVENT.[10]

Exposure to Study Treatments

In PREVENT, patients in the eculizumab arm had a study duration of 172.8 patient-years, while patients in the placebo arm had a study duration of 53.1 patient-years. The overall treatment exposure was 170.0 patient-years, and the median treatment duration was 89.43 weeks for patients in the eculizumab group. In the placebo arm, the overall treatment exposure was 51.5 patient-years and the median treatment duration was 41.29 weeks. The median number of infusions with the full intended dose were 47 for the eculizumab arm and 25 for the placebo arm. Treatment compliance was similar between treatment arms (96.8% for patients in the eculizumab arm and 97.7% for patients in the placebo arm).

The concomitant use of stable ISTs used for NMOSD during the study are presented in Table 10.

Table 10: Concomitant Supportive IST for NMOSD During the Study

	PREVENT	
Characteristics	**Eculizumab N = 96**	**Placebo N = 47**
Patients with any IST treatment, n (%)	75 (78.1)	34 (72.3)
Azathioprine	37 (38.5)	13 (27.7)
Cyclosporine and tacrolimus	2 (2.1)	0
Corticosteroids	55 (57.3)	23 (48.9)
Cyclophosphamide	1 (1.0)	1 (2.1)
Methotrexate	1 (1.0)	1 (2.1)
Mizoribine	1 (1.0)	0
Mycophenolate mofetil	18 (18.8)	8 (17.0)

IST = immunosuppressive therapy; NMOSD = neuromyelitis optica spectrum disorder.

Source: Clinical Study Report for PREVENT.[10]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below (Table 11). See Appendix 3 for detailed efficacy data.

Relapse

In PREVENT, 3.1% (n = 3) of patients in the eculizumab arm experienced an adjudicated on-trial relapse compared with 42.6% (n = 20) of patients in the placebo arm. For the primary efficacy end point, the time to first adjudicated on-trial relapse, the HR for patients treated with eculizumab compared with patients treated with placebo was 0.058 (95% CI, 0.017 to 0.197; P < 0.0001) in favour of eculizumab. This difference corresponds to a 94.2% reduction in the risk of relapse and was determined to be clinically relevant according to clinical experts consulted for this review.

Figure 3 presents the Kaplan-Meier survival estimates for time to first adjudicated on-trial relapse.

Efficacy findings for time to first adjudicated on-trial relapse were consistent with those for time to first on-trial relapse as determined by the treating physician (Appendix 3, Table 30), although numerically greater relapse events were identified with the latter (14.6% in the eculizumab arm versus 61.7% in the placebo arm). Of the 45 on-trial relapses determined

by the treating physician, 24 (53.5%) on-trial relapses were adjudicated positively and 21 (46.7%) were adjudicated negatively. The kappa coefficient between treating physicians and the RAC was 0.44 (95% CI, 0.27 to 0.61), indicating moderate agreement.

A similar treatment effect of eculizumab as found in the primary analysis was observed in patients across all IST subgroups (baseline corticosteroids, baseline azathioprine, baseline mycophenolate mofetil, other ISTs, no IST use, and prior rituximab) (Appendix 3, Table 29). Post hoc analysis reported in the Pittock 2019[11] publication assessed time to first adjudicated relapse by patients not receiving concomitant IST versus patients receiving concomitant IST (Appendix 3,Figure 7. For patients who did not receive concomitant IST, 100% of patients in the eculizumab arm versus 20.2% of patients in the placebo arm were free from relapse at the end of the study. In comparison, for patients who received concomitant IST, 95.4% of patients in the eculizumab arm versus 55.0% of patients in the placebo arm were free from relapse at the end of the study.

Sensitivity analysis for time to first adjudicated on-trial relapse based on different analysis methods and analysis sets (i.e., PP set, unstratified log-rank test, and multivariate Cox proportional hazards model) showed results consistent with the primary analysis.

The adjusted adjudicated on-trial ARR for patients treated with eculizumab compared to patients treated with placebo was 0.045 (95% CI, 0.013 to 0.151; P < 0.0001), representing a 95.5% rate reduction in favour of eculizumab. Findings for this end point were determined to be clinically relevant according to clinical experts consulted for this review. Efficacy findings for adjudicated on-trial ARR were consistent with those for the on-trial ARR as determined by the treating physician (Appendix 3, Table 30). The sensitivity analysis with negative binomial model confirmed that the Poisson regression results were robust.

The severity of adjudicated relapse was greater in the placebo arm: 33.3% of patients in the eculizumab arm experienced a major relapse, compared to 65% of patients in the placebo arm.

Disability

The change from baseline in EDSS was –0.18 (standard deviation [SD] = 0.814) for the eculizumab arm and 0.12 (SD = 0.945) for the placebo arm (P = 0.0597).

The mean change from baseline in mRS was –0.2 (SD = 0.72) for the eculizumab arm and 0.1 (SD = 0.75) for the placebo arm (P = 0.0154). Statistical testing of the mRS violated the pre-specified hierarchial strategy.

Sensitivity analyses for EDSS and mRS using ANCOVA to report the difference in the least square means were consistent with the primary analysis (Appendix 3, Table 32).

Health-Related Quality of Life

The mean change from baseline in the EQ-5D-3L VAS was 7.76 (SD = 1.892) for the eculizumab arm and 1.33 (SD = 2.573) for the placebo arm (P = 0.0302). The mean change from baseline in the EQ-5D-3L index score was 0.06 (SD = 0.021) for the eculizumab arm and –0.03 (SD = 0.029) for the placebo arm (P = 0.0075). Statistical testing of the EQ-5D-3L violated the pre-specified hierarchical strategy.

The change from baseline in the SF-36 PCS was 3.357 (SD = 7.7264) in the eculizumab arm and 0.696 (SD = 8.2549) in the placebo arm (P = 0.0210). The change from baseline in

the SF-36 MCS was 0.453 (SD = 10.6063) in the eculizumab arm and –0.057 (SD = 11.7945) in the placebo arm (P = 0.2942).

Sensitivity analyses for EQ-5D and SF-36 using ANCOVA to report the difference in the least square means were consistent with the primary analysis (Appendix 3, Table 32).

Symptoms

The mean change from baseline in visual KFS was –0.7 (SD = 1.15) for the eculizumab arm and –0.3 (SD = 0.93) for the placebo arm (P = 0.0884). For the subset of patients with abnormal baseline visual function (visual KFS = 1 to 6), the mean change from baseline was –1.0 (SD = 1.02) in the eculizumab arm and –0.60 (SD = 0.87) in the placebo arm (P = 0.0002) (Appendix 3, Table 31).

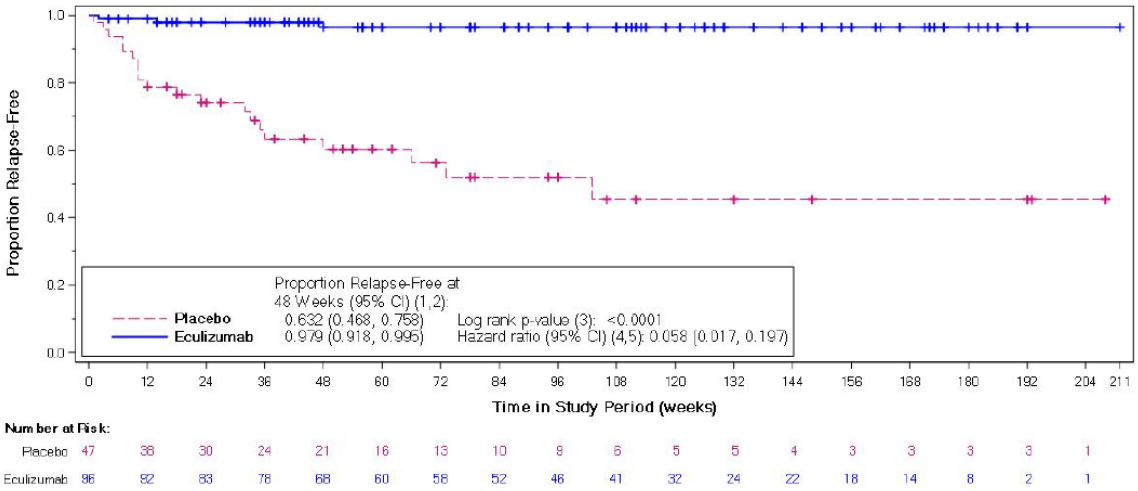
The mean change from baseline in HAI score was –0.4 (SD = 1.08) for the eculizumab arm and 0.5 (SD = 1.61) for the placebo arm (P = 0.0002). Statistical testing of the HAI violated the pre-specified hierarchial strategy. For the subset of patients with abnormal baseline ambulatory function (HAI value = 1 to 9), the mean change from baseline was –0.5 (SD = 1.11) in the eculizumab arm and 0.5 (SD = 1.65) in the placebo arm (P = 0.0002) (Appendix 3, Table 31).

Sensitivity analyses for visual KFS and HAI using ANCOVA to report the difference in the least square means were consistent with the primary analysis (Appendix 3, Table 32).

Other

Data for the following protocol-specified outcome were not available: productivity (e.g., attend school or work).

Figure 3: Kaplan-Meier Survival Estimates for Time to First Adjudicated On-Trial Relapse



CI = confidence interval.

Note: Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period. Stratified analyses are based on four randomization strata: (1) low Expanded Disability Status Scale (EDSS) at randomization (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naive at randomization; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same immunosuppressive therapies since last relapse at randomization; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in immunosuppressive therapies since last relapse at randomization. Full analysis set.

[1] Based on the Kaplan-Meier product limit method.

[2] Based on the complementary log-log transformation.

[3] Based on a stratified log-rank test.

[4] Based on a stratified Cox proportional hazards model.

[5] Wald confidence interval.

Source: Clinical Study Report for PREVENT.[10]

Table 11: Efficacy Outcomes

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Relapse		
Time to first adjudicated on-trial relapse[a]		
Number of patients contributing to the analysis	96	47
Patients with a relapse, n (%)	3 (3.1)	20 (42.6)
Follow-up time, weeks, median (min, max)	89.43 (2.57, 211.14)	36.00 (1.86, 208.57)
Estimated proportion of patients relapse-free at:		
48 weeks, cumulative probability (95% CI)	0.979 (0.918 to 0.995)	0.632 (0.468 to 0.758)
96 weeks, cumulative probability (95% CI)	0.964 (0.891 to 0.988)	0.519 (0.341 to 0.670)
114 weeks, cumulative probability (95% CI)	0.964 (0.891 to 0.988)	0.454 (0.262 to 0.628)
Percent reduction (95% CI)	94.2 (80.3 to 98.3)	
Hazard ratio (95% CI)	0.058 (0.017 to 0.197)	
P value	< 0.0001	
Adjudicated on-trial annualized relapse rate[b]		
Number of patients with a total relapse count of:		

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
0 relapses, n (%)	93 (96.9)	27 (57.4)
1 relapses, n (%)	3 (3.1)	19 (40.4)
2 relapses, n (%)	0	1 (2.1)
Total number of relapses	3	21
Total number of person-years in study period	171.32	52.41
Adjusted ARR (95% CI)	0.016 (0.005 to 0.050)	0.350 (0.199 to 0.616)
Rate ratio (95% CI)	0.045 (0.013 to 0.151)	
P value	< 0.0001	
Severity of relapse[c]		
Patients with an adjudicated on-trial relapse, n	3	20
Major, n (%)	1 (33.3)	13 (65.0)
Minor, n (%)	2 (66.7)	6 (30.0)
Unknown, n (%)	0	1 (5.0)
Disability progression		
Expanded Disability Status Scale[d]		
Number of patients contributing to the analysis	96	47
Baseline EDSS score, mean (SD)	4.15 (1.646)	4.26 (1.510)
End of study EDSS score, mean (SD)	3.97 (1.700)	4.37 (1.831)
Change from baseline, mean (SD)	–0.18 (0.814)	0.12 (0.945)
P value	0.0597	
Modified Rankin Scale[e,f]		
Number of patients contributing to the analysis	96	47
Baseline mRS score, mean (SD)	2.1 (1.14)	2.1 (0.98)
End of study mRS score, mean (SD)	1.9 (1.24)	2.2 (1.24)
Change from baseline, mean (SD)	–0.2 (0.72)	0.1 (0.75)
P value	0.0154	
Health-related quality of life		
EQ-5D-3L VAS[e,f]		
Number of patients contributing to the analysis	96	47
Baseline EQ-5D-3L score, mean (SD)	63.6 (20.00)	59.1 (20.39)
End of study EQ-5D-3L score, mean (SD)	69.0 (21.97)	59.7 (20.87)
Change from baseline, mean (SD)	7.76 (1.892)	1.33 (2.573)
P value	0.0302	
EQ-5D-3L index score[e,f]		
Number of patients contributing to the analysis	96	47
Baseline EQ-5D-3L score, mean (SD)	0.68 (0.196)	0.68 (0.196)
End of study EQ-5D-3L score, mean (SD)	0.73 (0.229)	0.64 (0.237)
Change from baseline, mean (SD)	0.06 (0.021)	–0.03 (0.029)
P value	0.0075	

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
SF-36 physical component[e,f]		
Number of patients contributing to the analysis	96	47
Baseline SF-36 PCS, mean (SD)	38.587 (9.8261)	36.867 (10.8470)
End of study SF-36 PCS, mean (SD)	41.945 (10.5831)	37.562 (10.6887)
Change from baseline, mean (SD)	3.357 (7.7264)	0.696 (8.2549)
P value	0.0210	
SF-36 mental component[e,f]		
Number of patients contributing to the analysis	96	47
Baseline SF-36 MCS, mean (SD)	47.029 (12.5485)	44.029 (11.4021)
End of study SF-36 MCS, mean (SD)	47.482 (12.1984)	43.972 (10.9411)
Change from baseline, mean (SD)	0.453 (10.6063)	–0.057 (11.7945)
P value	0.2942	
Symptoms		
Visual Kurtzke Functional System[e,g]		
Number of patients contributing to the analysis	96	47
Baseline visual KFS score, mean (SD)	3.2 (2.15)	2.7 (2.32)
End of study visual KFS score, mean (SD)	2.4 (1.65)	2.4 (2.08)
Change from baseline, mean (SD)	–0.7 (1.15)	–0.3 (0.93)
P value	0.0884	
Hauser Ambulation Index score[e,f]		
Number of patients contributing to the analysis	96	47
Baseline HAI score, mean (SD)	2.4 (2.17)	2.1 (1.40)
End of study HAI score, mean (SD)	2.0 (2.28)	2.7 (2.14)
Change from baseline, mean (SD)	–0.4 (1.08)	0.5 (1.61)
P value	0.0002	

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; HAI = Hauser Ambulation Index; KFS = Kurtzke Functional System; max = maximum; MCS = mental component score; min = minimum; mRS = modified Rankin Scale; PCS = physical component score; SD = standard deviation; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

[a] Log-rank test including strata for the randomization stratification variable; based on a stratified Cox proportional hazards model; full analysis set. Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period. Stratified analyses are based on four randomization strata for EDSS and immunosuppressive therapy (IST): (1) low EDSS at randomization (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naive at randomization; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.

[b] Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to screening; full analysis set.

[c] If a patient had more than one relapse, the relapse used for time to first relapse analysis is presented in the table. If the relapse includes more than one type of relapse, the worst severity is presented in the table. Severity of a relapse, as measured on the Optic-Spinal Impairment Scale, was only classified for optic neuritis and transverse myelitis relapses; patients with other types of relapses are reported as unknown; full analysis set.

[d] P value from randomization-based nonparametric analysis of covariance (ANCOVA) adjusted for baseline score and stratified by randomization IST strata: (i) treatment naive at randomization; (ii) continuing on the same IST(s) since last relapse at randomization; (iii) changes in IST(s) since last relapse at randomization; full analysis set.

[e] P value from randomization-based nonparametric ANCOVA adjusted for baseline score and stratified by four randomization strata for EDSS and IST (see note a); full analysis set.

[f] Included in statistical testing hierarchy but results not statistically significant as statistical significance was not achieved for higher-rank end points.

[g] P value has not been adjusted for multiple testing.

Source: Clinical Study Report for PREVENT.[10]

Harms

Only those harms identified in the review protocol are reported below. See Table 12 for detailed harms data.

Adverse Events

Adverse events occurred similarly in patients in the eculizumab arm (91.7%) and the placebo arm (95.7%) in PREVENT. The most common AE was upper respiratory infection, which affected more patients in the eculizumab arm (29.2%) than in the placebo arm (12.8%). Adverse events that occurred more often in the placebo arm than in the eculizumab arm were nausea (16.7% eculizumab; 25.5% placebo), worsening of NMOSD (7.3% eculizumab; 34% placebo), urinary tract infection (11.5% eculizumab; 21.3% placebo), and vomiting (10.4% eculizumab; 17.0% placebo).

Serious Adverse Events

In PREVENT, SAEs were reported in 31.3% of patients in the eculizumab arm and 55.3% of patients in the placebo arm. The most common SAE was worsening of NMOSD, which occurred in more patients in the placebo arm (34.0%) than in the eculizumab arm (7.3%).

Withdrawals due to AEs

Withdrawals due to AEs did not occur in any patients in the eculizumab arm but occurred in 4.3% of patients in the placebo arm. Withdrawals due to AEs were related to pancytopenia (2.1% placebo), pneumonia (2.1% placebo), and prerenal failure (2.1% placebo).

Mortality

In PREVENT, one patient in the eculizumab arm died during the trial. The death of this patient was attributed to infectious pleural effusion and was considered by the investigator to be “probably related to the study drug.”

One other death occurred approximately two weeks after the end of the study. This patient had been treated with placebo, and their death was attributed to pneumonia and myocardial ischemia.

Notable Harms

Notable harms identified in the protocol for this review included the following: serious infusion reactions, serious infections (e.g., meningococcal and respiratory), and hemolysis or low hemoglobin.

Serious adverse events related to infusion reactions occurred in 6.3% of patients in the eculizumab arm and 4.3% of patients in the placebo arm.

No cases of meningococcal infections were reported in PREVENT.

Respiratory-related serious infections occurred similarly between treatment arms: pneumonia (eculizumab 3.1%; placebo 2.1%), bronchitis (eculizumab 1.0%; placebo 2.1%), influenza (eculizumab 2.1%; placebo 0%), infectious pleural effusion (eculizumab 1.0%; placebo 0%), and viral upper respiratory tract infection (eculizumab 0%; placebo 2.1%).

Low hemoglobin was not reported in PREVENT.

Table 12: Summary of Harms

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Patients with ≥ 1 adverse event		
n (%)	88 (91.7)	45 (95.7)
Most common events,[a] n (%)		
Upper respiratory tract infection	28 (29.2)	6 (12.8)
Headache	22 (22.9)	11 (23.4)
Nasopharyngitis	20 (20.8)	9 (19.1)
Nausea	16 (16.7)	12 (25.5)
Neuromyelitis optica spectrum disorder	7 (7.3)	16 (34.0)
Urinary tract infection	13 (13.5)	10 (21.3)
Diarrhea	15 (15.6)	7 (14.9)
Pain in extremity	11 (11.5)	10 (21.3)
Back pain	14 (14.6)	6 (12.8)
Dizziness	14 (14.6)	6 (12.8)
Cough	11 (11.5)	7 (14.9)
Vomiting	10 (10.4)	8 (17.0)
Arthralgia	11 (11.5)	5 (10.6)
Influenza	11 (11.5)	2 (4.3)
Pharyngitis	10 (10.4)	3 (6.4)
Contusion	10 (10.4)	2 (4.3)
Fatigue	7 (7.3)	5 (10.6)
Patients with ≥ 1 serious adverse event		
n (%)	30 (31.3)	26 (55.3)
Most common events,[b] n (%)		
Neuromyelitis optica spectrum disorder	7 (7.3)	16 (34.0)
Pneumonia	3 (3.1)	1 (2.1)
Bronchitis	1 (1.0)	1 (2.1)
Cellulitis	2 (2.1)	0
Cholecystitis acute	1 (1.0)	1 (2.1)
Influenza	1 (1.0)	1 (2.1)
Sepsis	2 (2.1)	0
Urinary tract infection	2 (2.1)	0
Abdominal pain	0	1 (2.1)
Adenocarcinoma	0	1 (2.1)
Patients who stopped treatment due to adverse events		
n (%)	0	2 (4.3)
Pancytopenia	0	1 (2.1)
Pneumonia	0	1 (2.1)

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Prerenal failure	0	1 (2.1)
Deaths		
n (%)	1 (1.0)	0
Infectious pleural effusion	1 (1.0)	0
Notable harms, n (%)		
Infusion reactions	6 (6.3)	2 (4.3)
Meningococcal infections	0	0
Aspergillus infections	0	0
Serious cutaneous adverse reactions	0	0
Other serious infections	11 (11.5)	6 (12.8)
Pneumonia	3 (3.1)	1 (2.1)
Bronchitis	1 (1.0)	1 (2.1)
Cellulitis	2 (2.1)	0
Influenza	1 (1.0)	1 (2.1)
Urinary tract infection	2 (2.1)	0
Appendicitis	1 (1.0)	0
Bartholin abscess	1 (1.0)	0
Gallbladder empyema	1 (1.0)	0
Gastroenteritis viral	0	1 (2.1)
Herpes zoster	0	1 (2.1)
Infectious pleural effusion	1 (1.0)	0
Pneumococcal infection	0	1 (2.1)
Renal abscess	1 (1.0)	0
Viral upper respiratory tract infection	0	1 (2.1)
Sepsis	2 (2.1)	0
Low hemoglobin	NR	NR

NR = not reported.

[a] Frequency ≥ 10%.

[b] Frequency ≥ 2%.

Source: Clinical Study Report for PREVENT.[10]

Critical Appraisal

Internal Validity

Baseline disease and demographic characteristics were generally balanced across the treatment arms in PREVENT. It is noteworthy, however, that more patients in the eculizumab group were diagnosed with NMOSD based on the 2007 Wingerchuk criteria (28.1% versus 19.1%), while the majority of the patients were diagnosed with definitive NMO (71.9% versus 80.9%, eculizumab versus placebo, respectively). More patients had initial clinical presentation of optic neuritis (eculizumab 42.7%; placebo 36.2%) than transverse myelitis (eculizumab 37.5%; placebo 44.7%). The impact of these imbalances

on the treatment effect is unknown, but it may help to understand the observed imbalances in the use of supportive IST at baseline and during the study between the two treatment arms. Of note, more patients received concomitant supportive ISTs in the eculizumab group than in the placebo group during the study period; in particular there was greater use of corticosteroids (57.3% versus 48.9%) and azathioprine (38.5% versus 27.7%) in the eculizumab group. At baseline, a higher proportion of patients were on azathioprine plus corticosteroids in the eculizumab group than in the placebo group (30.2% versus 14.9%), but a lower proportion took corticosteroids alone (16.7% versus 23.4%) and azathioprine alone (8.3% versus 12.8%). It was unknown what the impact of these differences in the use of ISTs at baseline or during the study period would be on the assessment of efficacy.

PREVENT was conducted using double-blind methodology, where all study patients, investigational site personnel, sponsor staff, and all staff directly associated with the conduct of the study were blinded to the treatment assignments. Patients were treated with identical study drug kits, where the placebo had an identical appearance to eculizumab. Unblinding was only performed if it was deemed necessary by the investigators for safety reasons. There were no other factors (e.g., distinct AEs) that clearly contributed to unblinding.

The primary efficacy outcome was time to first adjudicated on-trial relapse. Relapse adjudication was performed by an independent, blinded RAC composed of three specialists for NMOSD (two neurologists and one neuro-ophthalmologist), who assessed all suspected relapses that occurred during the trial retrospectively. Use of adjudication is expected to increase the validity and objectivity of the outcome as it reduces inter-site variability in assessments and over-reporting bias that may have influenced attending physician–determined relapses, as the need for immediate treatment of relapses could impact the classification of an event as a relapse.

The dose schedule used in PREVENT for eculizumab was appropriate as it was consistent with the product monograph and was based on findings from quantitative modelling and simulation methodology using pharmacokinetics and pharmacodynamics data from five studies in patients with atypical hemolytic-uremic syndrome.

In PREVENT, 32.9% of patients failed screening, with the most common reasons attributed to being AQP4 antibody seronegative and not meeting the historical relapse criteria. The tests for the detection of AQP4 antibodies in patients with NMOSD has been shown to have moderate sensitivity (of around 75%) and high specificity (100%). While the impact is expected to be minimal, this introduces the possibility that in the study, some patients could have been screened out in error due to false negatives associated with the test.

The proportion of patients that discontinued PREVENT was greater in the eculizumab arm compared with the placebo arm (16.7% versus 6.4%, eculizumab versus placebo, respectively). The most common reason for discontinuation in the eculizumab group was attributed to “withdrawal by patient” (12.5% versus 2.1% with placebo). The reasons for withdrawal included a geographical move (n = 4), unknown cause (n = 3), and change in life situation (n = 2). One patient withdrew following hospital discharge for an unspecified treatment emergent AE, and another patient withdrew for an unspecified “unrelated” AE and difficult venous access. The other discontinuations in the eculizumab group were from patients who were lost to follow-up (n = 3) and one patient who died (uncertain relation to eculizumab). Sensitivity analysis of the primary end point, imputing all discontinuations in the eculizumab treatment group to be adjudicated on-trial relapse events, showed an

attenuated — but statistically and clinically significant — finding consistent with the primary analysis (post hoc sensitivity analysis: HR = 0.297; 95% CI, 0.154 to 0.572; P = 0.0001).

PREVENT was designed to end once there were 24 on-trial adjudicated relapses but was ended prematurely after 23 on-trial adjudicated relapses. The original end point at 24 on-trial adjudicated relapses was used in the sample size calculation and determination of 90% power. Using the end point of the 23 on-trial adjudicated relapses and the same assumptions used in the original power calculation, the revised calculation determined that the study would have power equal to or greater than 80%.

Major protocol deviations that could have impacted the overall integrity of the data occurred in approximately 40% of patients in each treatment arm; many of these deviations indicated poor conduct of the study (e.g., informed consent [failure to obtain, use of wrong form], randomization [errors in stratification or enrolment]). Sensitivity analysis using a PP population (excludes patients with major protocol deviations) was only performed for the primary efficacy end point, which was consistent with the main analysis population (FAS). Secondary end points were not assessed using the PP set.

Despite the limitations on the validity and test-retest reliability of outcome measures for patients' disability progression (i.e., EDSS), symptoms (i.e., KFS), and quality of life (i.e., EQ-5D), the findings on these patient-important outcomes generally showed a trend toward an improvement in favour of eculizumab. Due to the study design, more patients experienced their first relapse and concluded the study at an earlier phase in the placebo arm (42.6%) than in the eculizumab arm (3.1%). This resulted in there being more patients with less drug exposure in the placebo arm than in the treatment arm. However, using the LOCF approach, more patients used the assessments at earlier visits in the placebo arm than in the treatment arm, which would have skewed the results against the study drug, on the assumption that patients' disability and quality of life deteriorated continuously during the study period.

The impact on the results from differential missing data was not directly explored for the primary efficacy end point (time to first adjudicated on-trial relapse), which is unlikely to be a significant issue. Missing data on other questionnaire-based outcomes, such as EDSS and quality of life scores, applied a LOCF approach. A mixed model for repeated measure was used for the analysis of these types of data, which was deemed a suitable method in handling missing data with repeated measures over the study period. An ANCOVA model, with multiple adjustment of covariates at the baseline, was also helpful in improving the validity or precision of the findings. For the primary analysis, patients either had an adjudicated first relapse that ended their study participation or, without experiencing an adjudicated relapse, were censored at the end of the study. In this case, the Cox proportional hazards model was a suitable statistical model for the analysis of the primary end point of time to first relapse, and the proportional hazard assumption appeared to be met. The primary analysis results and the secondary analysis of the rate ratio based on ARR were similar, supporting the robustness of the findings on risk reduction of relapse. In fact, because of the study design, relapses that occurred after the first relapse (and time of censoring) would not have been captured, and therefore the rate ratio for ARR and the HR for time to first relapse would provide similar results. However, the ARR in PREVENT is likely underestimated because of the study design: What the impact of the treatment on the rate of relapses subsequent to the first on-treatment relapse would be is unknown. The long-term extension study (see "Other Relevant Evidence" section) does not provide clarity because of the limited results from an interim analysis and the way in which ARR was

analyzed. Lastly, ARR was analyzed using a Poisson model, which typically is appropriate for this type of data. However, it may not have been ideal for the analysis of ARR in PREVENT because of the study design and potential for statistical dispersion. Sensitivity analysis using a negative binomial model to correct for potential overdispersion found results consistent with the Poisson regression model in the analysis of ARR. Therefore, although the estimated ARR is likely an underestimate, the results appear to be statistically robust.

A multivariate Cox proportional hazards model with adjustment for baseline EDSS score, historical ARR, and IST strata at baseline further strengthened the robustness of the findings. This was particularly helpful when the use of supportive IST was found differential at baseline. Subgroup analyses, even though descriptive in nature, found no substantial differences between groups, but these analyses were limited by small sample size.

Although some analyses were performed by pre-specified IST subgroup, data based on patients not receiving concomitant IST versus patients receiving concomitant IST were only available from a post hoc analysis from the 2019 Pittock[11] publication. These subgroups and post hoc analyses were focused on clinically relevant groups; however, interpretation of the results is limited due to the small sample size and descriptive nature of the results. Subgroups based on severity of disease and mobility-related impairment versus vision-related impairment were not adequately assessed in the study. This would be particularly important given that the differences in the distribution of subtypes of NMOSD varied between the treatment groups and because the efficacy of eculizumab in these subgroups would have provided valuable information that would have helped to guide policy decisions on reimbursement.

External Validity

In PREVENT, 32.9% of patients failed screening, with the most common reasons attributed to being AQP4 antibody seronegative and not meeting the historical relapse criteria. The screening failures were reasonable as they pertain to appropriate study population restrictions that allow for the assessment of eculizumab. However, this may not represent the entire patient population in the real world; for example, patients with EDSS greater than 7 — a patient population with more severe disability — were excluded. Therefore, the observed drug effect in this trial represented mild to moderately severe patients and may not be generalizable to those patients with more severe disease.

PREVENT was a multi-centre, international study; however, none of the patients included were from Canada. Availability and preferred ISTs vary within Canada and internationally. The background usage of these medications was different than is seen in the Canadian clinical setting; for example, use of azathioprine and mycophenolate mofetil would be higher in the Canadian setting than was observed in the trial.

In this study, female patients made up approximately 90% of the study population. Approximately half of included patients were white, although slight differences in race distribution between arms was observed. Prior to the study, almost all patients had been treated with supportive IST, such as corticosteroids (70.8% to 63.8%), azathioprine (55.3% to 63.5%), and rituximab (27.1% to 42.6%). The clinical experts consulted by CADTH indicated that the baseline demographics and disease characteristics of the study population were consistent with patients seen in the Canadian clinical setting.

PREVENT was restricted to patients who were anti-AQP4 antibody seropositive, thereby preventing the extrapolation of results to the 10% to 30% of the clinical population who are anti-AQP4 antibody seronegative.[1,2,4,5]

The inclusion criteria of PREVENT created a study population that was likely to experience a relapse based on their historical relapses (at least two relapses in the last 12 months or three relapses in the last 24 months, with at least one relapse in the 12 months prior to screening). This is a practical point when designing an RCT in order to ensure the event of interest (in this case, relapse) occurs. Given the aforementioned limitations in calculating the ARR and the inclusion criteria, it is unclear how well the frequency of relapses in PREVENT reflect a broader NMOSD patient population in clinical practice.

PREVENT was a placebo-controlled trial. In Canada, patients are typically treated in clinic for NMOSD with drugs that do not have a Health Canada indication for NMOSD, such as azathioprine, mycophenolate, and rituximab. Most patients (> 70%) in both treatment groups were receiving concomitant ISTs, and therefore many patients randomized to placebo were not truly untreated. Nor can the design be considered a true comparative study. Therefore, determining the comparative effects of eculizumab and delineating the optimal place in therapy is challenging because of the design of the study.

PREVENT was originally designed to have a primary end point based on on-trial relapses as determined by the treating physician. Approximately midway through the study, a protocol change was enacted to change the primary end point to be based on adjudicated on-trial relapses. Adjudication of on-trial relapses was performed retrospectively and based on consensus of a blinded, independent RAC consisting of two neurologists and one neuro-ophthalmologist. While the use of adjudication is expected to increase the validity of relapse assessment, it is likely not consistent with clinical practice. In fact, physician-determined relapses were much more frequent (10% to 15%) than the committee-adjudicated relapses in both treatment arms, even though the overall effects were consistent.

PREVENT examined the effects of eculizumab treatment on several clinically relevant outcomes, including the primary outcome (time to first relapse). The clinical experts consulted by CADTH indicated that relapse prevention is a key goal of treatment of NMOSD because patients with NMOSD experience an accumulation of relapse-related irreversible neurologic disability. Therefore, time to first relapse is considered a clinically relevant primary efficacy outcome. While PREVENT used several end points that were consistent with outcomes identified as important to patients, the trial did not assess the impact on productivity (e.g., ability to attend school or work).

Other Relevant Evidence

This section includes long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

Long-Term Extension Study of the PREVENT Trial (ECU-NMO-302)

An open-label extension, phase III report[35] to determine the safety and efficacy of eculizumab in patients with relapsing NMOSD (from the PREVENT trial, ECU-NMO-301) was ongoing at the time of this review (NCT02003144; estimated completion date: June 2020). The sponsor provided data of the interim analyses up to a cut-off date of May 31, 2018. The first patient was enrolled on January 12, 2015.

As with its predecessor, this is a multi-centre study — of the 70 sites in 18 countries that were used in PREVENT, 33 sites in 15 countries had enrolled patients in ECU-NMO-302 as of the time of database cut-off on May 31, 2018.

The primary objective of this study is to evaluate the long-term safety of eculizumab in patients with relapsing NMOSD. Secondary objectives of the study include the evaluation of the long-term efficacy of eculizumab in patients with relapsing NMOSD as measured by the ARR and the evaluation of the long-term efficacy by additional efficacy measures such as disability, quality of life, and neurologic functions. A last secondary objective is to evaluate the pharmacokinetics and pharmacodynamics of eculizumab in this group of patients.

Methods

This study was designed to provide patients who completed the PREVENT study with the choice to continue receiving eculizumab for up to 5.5 additional years and to provide information on the long-term safety and efficacy of eculizumab in patients with relapsing NMOSD.

To enroll in this study, patients must have completed an end of study visit in the PREVENT study.

There were two phases in study ECU-NMO-302: the blind induction phase (to preserve the blinded nature of the PREVENT study), followed by the open-label maintenance phase (see the subsequent “Interventions” section). The treatment groups were defined by the randomization assignments from PREVENT.

Populations

Patients that completed the PREVENT study (i.e., finished either the week 6 follow-up relapse evaluation visit or the end of study visit) gave written, informed consent; were willing and able to comply with the protocol requirements; and were eligible to enter the open-label study. Patients of childbearing potential must have had a negative pregnancy test (serum human chorionic gonadotropin) and an effective, reliable, and medically approved contraceptive regimen. Exclusion criteria included those who withdrew from the PREVENT study as a result of an AE related to the study drug; patients who were pregnant, breastfeeding, or intended to conceive during the course of the study; and those with any medical condition that might interfere with the patient’s participation in the study, pose any added risk for the patient, or confound the assessment of the patients.

Patients who completed the PREVENT study were to have their first extension study visit no later than two weeks (14 ± 2 days) after the last dose of the study drug in PREVENT. Patients whose treatment assignment was unblinded in the PREVENT study were not eligible to enroll in ECU-NMO-302.

Baseline demographic characteristics were similar between groups, as shown in Table 13. As shown in the Table 15 of [redacted]

Table 13: Baseline Demographics and IST Use: ECU-NMO-302

Variable	Placebo/eculizumab (N = [redacted])	Eculizumab/eculizumab (N = [redacted])	Total (N = [redacted])
Age at first dose in study ECU-NMO-302, years, mean (SD)	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Race, n (%)			
Asian	[redacted]	[redacted]	[redacted]
Black or African-American	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Study ECU-NMO-302 baseline BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]
IST use at ECU-NMO-302 baseline			
Patients with any IST treatment	[redacted]	[redacted]	[redacted]
Azathioprine	[redacted]	[redacted]	[redacted]
Cyclosporine or tacrolimus	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]
Mycophenolate mofetil	[redacted]	[redacted]	[redacted]

BMI = body mass index; IST = immunosuppressive therapy; SD = standard deviation.

Source: ECU-NMO-302 study report.[35]

The previous history of NMOSD and the information about prior NMOSD relapses (up to 24 months prior to the screening to enter the PREVENT study) is presented in Table 14.

Table 14: History of Previous NMOSD and Prior NMOSD Relapses (FAS): ECU-NMO-302

Variable	Placebo/eculizumab (N = [redacted])	Eculizumab/eculizumab (N = [redacted])	Total (N = [redacted])
NMOSD history at baseline of ECU-NMO-302			
Age at NMOSD initial clinical presentation, years, mean (SD)	[redacted]	[redacted]	[redacted]
NMOSD grouped initial clinical presentation, n (%)			
Optic neuritis[a]	[redacted]	[redacted]	[redacted]
Transverse myelitis[b]	[redacted]	[redacted]	[redacted]
Optic neuritis and transverse myelitis[c]	[redacted]	[redacted]	[redacted]
Area postrema syndrome[d]	[redacted]	[redacted]	[redacted]
Other[e]	[redacted]	[redacted]	[redacted]

Variable	Placebo/eculizumab (N = [redacted])	Eculizumab/eculizumab (N = [redacted])	Total (N = [redacted])
NMOSD diagnosis			
Definitive neuromyelitis optica, n (%)	[redacted]	[redacted]	[redacted]
NMOSD[f]	[redacted]	[redacted]	[redacted]
Longitudinally extensive transverse myelitis	[redacted]	[redacted]	[redacted]
Optic neuritis	[redacted]	[redacted]	[redacted]
Optic neuritis or longitudinally extensive transverse myelitis coexisting with systemic autoimmune disease	[redacted]	[redacted]	[redacted]
Time from initial clinical presentation to first dose of study drug in study ECU-NMO-302, years, mean (SD)	[redacted]	[redacted]	[redacted]
History of previous NMOSD relapses			
Historical ARR (within the 24 months prior to study PREVENT screening), median (min, max)	[redacted]	[redacted]	[redacted]
Type of historical relapses 24 months prior to screening, n (%)			
Optic neuritis	[redacted]	[redacted]	[redacted]
Transverse myelitis	[redacted]	[redacted]	[redacted]
Brain stem symptoms	[redacted]	[redacted]	[redacted]
Cerebral symptoms	[redacted]	[redacted]	[redacted]
Other symptoms	[redacted]	[redacted]	[redacted]

ARR = annualized relapse rate; FAS = full analysis set; max = maximum; min = minimum; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation.

[a] Patients with optic neuritis but no transverse myelitis.

[b] Patients with transverse myelitis (ataxia, dysesthesia, paresthesia, transverse myelitis, or longitudinally extensive transverse myelitis) but no optic neuritis.

[c] Patients with both optic neuritis and transverse myelitis.

[d] Patients with area postrema syndrome (hiccoughs or intractable nausea or vomiting).

[e] Patients with any other presentations.

[f] NMOSD, as defined by Wingerchuk (2007), per the study protocol.

Source: ECU-NMO-302 study report.[35]

For the patients included in this extension study, the baseline values of the EDSS, HAI, and mRS of patients at the beginning of PREVENT and ECU-NMO-302 are presented in Table 15.

Table 15: Baseline NMOSD Disease Characteristics at Baseline of Both PREVENT and ECU-NMO-302

Variable		Placebo/eculizumab (N =)	Eculizumab/eculizumab (N =)	Total (N =)
EDSS	PREVENT baseline score, mean (SD)			
	Study ECU-NMO-302 baseline score, mean (SD)			
HAI	PREVENT baseline score, mean (SD)			
	Study ECU-NMO-302 baseline score, mean (SD)			
mRS	PREVENT baseline score, mean (SD)			
	Study ECU-NMO-302 baseline score, mean (SD)			

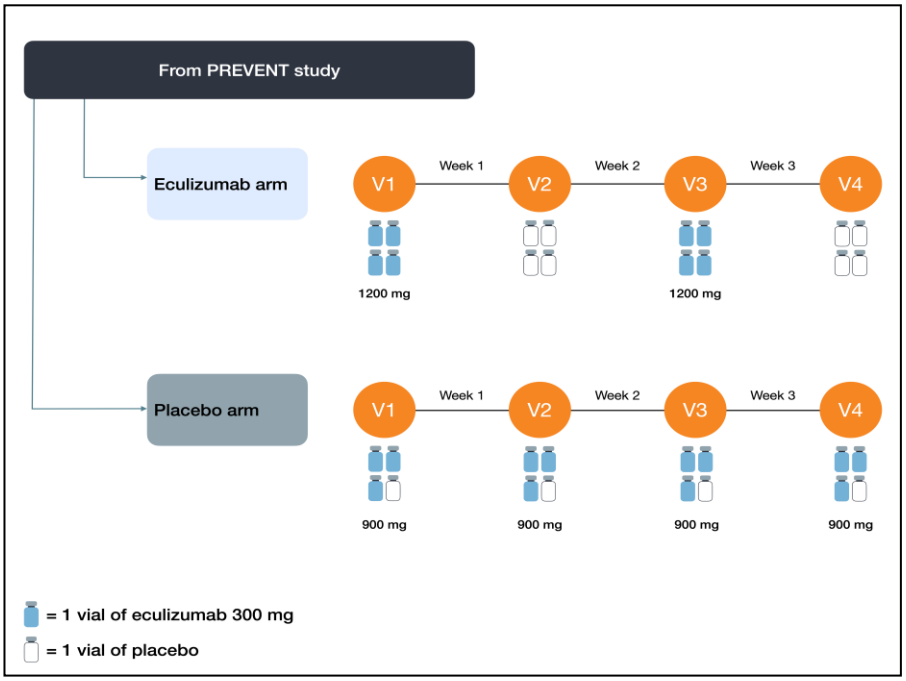
EDSS = Expanded Disability Status Scale; HAI = Hauser Ambulation Index; mRS = modified Rankin Scale; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation.

Source: ECU-NMO-302 study report.[35]

Interventions

The induction phase was a four-week period where placebo was administered to all patients regardless of their treatment group in PREVENT to allow proper induction for those switching from placebo in the PREVENT study to eculizumab and to maintain blinding. The study drug is administered weekly for four weeks during the blind induction phase. In the eculizumab-eculizumab group, four vials (300 mg in each vial or 1,200 mg in total) are administered in visit 1 and 3, plus four vials of placebo on visits 2 and 4. For the placebo-eculizumab group, four vials (three vials of eculizumab [900 mg] plus one vial of placebo) are administered on visits 1, 2, 3, and 4, as presented in Figure 4. For the open-label maintenance phase, all patients received four vials of eculizumab (equivalent to 1,200 mg) every two weeks at visit 5 and onward throughout the study. If plasmapheresis or plasma exchange were administered for on-trial relapse, a supplemental study drug or matching placebo was administered. Further ISTs (corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, or cyclophosphamide) were allowed during both phases if the clinicians deemed it necessary. However, rituximab, mitoxantrone, immunomodulatory drugs, IVIG, and plasma exchange were not allowed.

Figure 4: Study Drug Dosage and Administration During the Induction Phase: ECU-NMO-302



Source: ECU-NMO-302 study report.[35]

Outcomes

Efficacy

For this interim analysis, efficacy analyses were limited to the primary and secondary end points. Tertiary end points were not analyzed.

- Primary end point: ARR based on all on-trial relapses as determined by the treating physician and time in the study period. The ARR for each patient is computed as the number of relapses divided by the time in the study period.
- Secondary end points: Change from baseline in:
  - EDSS score
  - mRS score
  - HAI score in patients with abnormal baseline ambulatory function in the PREVENT study
  - EQ-5D score
  - visual KFS score in patients with abnormal baseline visual function in the PREVENT study.

The change in on-trial ARR compared with the historical ARR was used by the investigators as the primary analysis for efficacy, citing that it provides a numerical representation of the effect of eculizumab treatment in ECU-NMO-302. A historical ARR was computed for each patient based on historical relapses in the 24 months prior to the PREVENT study screening visit. This time period was selected for historical ARR for consistency with the PREVENT study inclusion criteria.

An adjudicated on-trial relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination that persists for more than 24 hours, as confirmed by the treating physician, and that was positively adjudicated by the RAC. The independent RAC confirmed all on-trial relapse events using the clinical criteria described in an RAC. The RAC consisted of three independent medical experts in neurology or neuro-ophthalmology, who were each experienced in the management of patients with NMOSD; this is the same RAC that adjudicated relapses in the PREVENT study. The RAC decides by majority vote whether each relapse meets the predefined objective criteria for an adjudicated on-trial relapse.

Safety

The safety and tolerability of eculizumab was assessed based on AEs, SAEs, and the changes from baseline through study completion in vital signs, laboratory tests, physical examination, electrocardiograms, and the Columbia-Suicide Severity Rating Scale. The investigator was responsible for detecting, assessing, documenting, and reporting all AEs.

Statistical Analysis

Because this is a follow-up open-label study, the investigators did not perform sample size or power calculations. Summaries are presented by treatment group and overall. For continuous variables, summary statistics include mean, SD, median, minimum, and maximum values. Frequencies and percentages were calculated for categorical variables.

The primary analysis (i.e., the change in ARR or the change from historical patient-level ARR to the ECU-NMO-302) was evaluated using the Wilcoxon signed-rank test. Descriptive statistics of the change in the ARR (with 95% CI as measure of dispersion) and the results of the Wilcoxon signed-rank test are presented for the change from historical patient-level ARR overall as well as for the change by treatment group from the PREVENT ARR. A sensitivity analysis of the change in ARR from historical patient-level ARR to adjudicated on-trial ARR is also presented. The number and proportion of patients with on-trial and adjudicated on-trial relapses are summarized, as are the number and proportion of patients experiencing each number of relapses. Time to first on-trial relapse and first adjudicated on-trial relapse are summarized, and figures of the Kaplan-Meier survival estimates are presented.

There were two sets of analysis: the extension FAS, which consisted of all patients who received at least one dose of eculizumab in ECU-NMO-302 (on which the efficacy outcome analyses were performed), and the extension safety set, which consisted of all patients who received at least one dose of eculizumab in ECU-NMO-302. For the latter group, summary tables are presented according to the treatment the patient actually received in both PREVENT and ECU-NMO-302.

At the clinical database cut-off date for the interim analysis (May 31, 2018), [redacted] patients had completed PREVENT because they experienced an on-trial relapse, of which [redacted] patients were enrolled in this study and included in this interim analysis. Subsequent interim analyses will include all enrolled patients, including those patients who did not experience an on-trial relapse in PREVENT.

Patient Disposition

As of the clinical database cut-off date for this analysis, [redacted] patients who had experienced an on-trial relapse during PREVENT had enrolled and were treated in ECU-NMO-302. In the placebo-eculizumab arm, [redacted] patients were included in the FAS and safety set; in the

eculizumab-eculizumab group, [redacted] were included in the FAS and safety sets. Data on patient disposition are shown in Table 16.

Table 16: Patient Disposition (Full Analysis Set): ECU-NMO-302

Status	Placebo/eculizumab (N = [redacted])	Eculizumab/eculizumab (N = [redacted])	Total (N = [redacted])
Treated patients, n (%)	[redacted]	[redacted]	[redacted]
Discontinued, n (%)	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ongoing, n (%)	[redacted]	[redacted]	[redacted]

Source: ECU-NMO-302 study report.[35]

[redacted] Because all patients received the study drug to which they were randomized in the PREVENT study, the FAS and safety set are identical.

[redacted]

Efficacy

In the total population in ECU-NMO-302, there was a reduction of the on-trial ARR (as determined by the treating physician) compared with the historical ARR [redacted] This difference was observed in both the placebo-eculizumab and eculizumab-eculizumab groups, as shown in Table 17. [redacted]

Table 17: Results: On-Trial Annualized Relapse Rate — Full Analysis Set (ECU-NMO-302)

Variable	Statistic	Placebo/eculizumab (N = [redacted])	Eculizumab/eculizumab (N = [redacted])	Total (N = [redacted])
Historical[a] patient ARR[b]	Median (IQR)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
Patient on-trial ARR in ECU-NMO-302	Median (IQR)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median (IQR)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]

Variable	Statistic	Placebo/eculizumab (N =)	Eculizumab/eculizumab (N =)	Total (N =)
Change in ARR between historical ARR and ECU-NMO-320 on trial ARR	95% CI for mean			
	P value[c]			

ARR = annualized relapse rate; CI = confidence interval; IQR = interquartile range; SD = standard deviation.

[a] Based on the 24 months prior to screening in the PREVENT study.

[b] The number of relapses for each patient divided by the number of years in the study period for that patient; summary statistics across all patients are presented.

[c] From Wilcoxon signed-rank test.

Source: ECU-NMO-302 study report.[35]

Table 18).

Table 18: Results: Summary of On-Trial Annualized Relapse Rate — Full Analysis Set (Study ECU-NMO-302)

Statistic	Placebo/eculizumab (N =)	Eculizumab/eculizumab (N =)	Total (N =)
Number of patients with a total on-trial relapse count of the following, n (%)			
0 relapses			
1 relapse			
2 relapses			
3 relapses			
Total number of on-trial relapses			
Total number of patient-years in the study period			
Study-level on-trial ARR[a]			
95% CI[b]			
Estimated proportion of patients relapse-free at the following time points, cumulative probability[c] (95% CI)[d]			
48 weeks			
96 weeks			
144 weeks			

ARR = annualized relapse rate; CI = confidence interval.

[a] Calculated as the total number of on-trial relapses during the study period for all patients divided by the total number of patient-years in the study period.

[b] Wald confidence interval from Poisson regression.

[c] Based on the Kaplan-Meier product limit method.

[d] Based on the complementary log-log transformation.

Source: ECU-NMO-302 study report.[35]

An adjudicated on-trial ARR was computed for a sensitivity analysis based on all adjudicated on-trial relapses for each patient in the extension FAS. When compared to the historical ARR, the adjudicated ARR showed an overall reduction [redacted]) in the total population in ECU-NMO-302 [redacted] Table 19.

Table 19: Results: Adjudicated Annualized Relapse Rate — Full Analysis Set (Study ECU-NMO-302)

Variable	Statistic	Placebo/eculizumab (N = [redacted])	Eculizumab/eculizumab (N = [redacted])	Total (N = [redacted])
Historical[a] patient ARR[b]	Median (IQR)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
Patient adjudicated ARR in ECU-NMO-302	Median (IQR)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
Change in ARR between historical ARR and ECU-NMO-320 adjudicated ARR	Median (IQR)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	95% CI for mean	[redacted]	[redacted]	[redacted]
	P value[c]	[redacted]	[redacted]	[redacted]
Estimated proportion of patients relapse-free at the following time points,				
48 weeks	Cumulative probability[d] (95% CI)[e]	[redacted]	[redacted]	[redacted]
96 weeks		[redacted]	[redacted]	[redacted]
144 weeks		[redacted]	[redacted]	[redacted]

ARR = annualized relapse rate; CI = confidence interval; IQR = interquartile range; SD = standard deviation.

[a] Based on the 24 months prior to screening in the PREVENT study.

[b] The number of relapses for each patient divided by the number of years in the study period for that patient; summary statistics across all patients are presented.

[c] From Wilcoxon signed-rank test.

[d] Based on the Kaplan-Meier product limit method.

[e] Based on the complementary log-log transformation.

Source: ECU-NMO-302 study report.[35]

[redacted]

[redacted] Concomitant supportive IST were used during study ECU-NMO-302 and are presented in Table 20. [redacted]

Table 20: Supportive IST Use During Study (FAS): ECU-NMO-302

Variable	Placebo/eculizumab (N = [redacted])	Eculizumab/eculizumab (N = [redacted])	Total (N = [redacted])
Patients with any IST treatment, n (%)	[redacted]	[redacted]	[redacted]
Azathioprine	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]
Cyclosporine and tacrolimus	[redacted]	[redacted]	[redacted]
Mycophenolate mofetil	[redacted]	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]	[redacted]

FAS = full analysis set; IST = immunosuppressive therapy.

Harms

[redacted]

[redacted] Table 21.

Table 21: Overview of Adverse Events (Full Analysis Set): ECU-NMO-302

Adverse event category	Placebo/eculizumab (N = [redacted]), PY = [redacted]			Eculizumab/eculizumab (N = [redacted]), PY = [redacted]			Total (N = [redacted]), PY = [redacted]		
	Events, n	Rate per 100 PYs	Patients, n (%)	Events, n	Rate per 100 PYs	Patients, n (%)	Events n	Rate per 100 PYs	Patients, n (%)
Events and patients with events	[redacted]								
Deaths			[redacted]			[redacted]			[redacted]
AEs									
Related	[redacted]								[redacted]
Not related	[redacted]		[redacted]						[redacted]
Mild	[redacted]								[redacted]
Moderate	[redacted]		[redacted]						[redacted]
Severe	[redacted]	[redacted]						[redacted]	
AEs leading to withdrawal from study drug	[redacted]								
SAEs	[redacted]								[redacted]
Related	[redacted]					[redacted]			[redacted]
Not related	[redacted]								[redacted]
SAEs leading to withdrawal from study drug	[redacted]								

AE = adverse event; PY = patient-year; SAE = serious adverse event.

Note: Rates are reported per 100 PYs. Treatment-emergent AEs in study ECU-NMO-302 are AEs with a start date on or after the date of the first dose of the study drug in ECU-NMO-302. Related AEs are defined as possibly, probably, or definitely related, and not-related AEs are defined as unrelated or unlikely. Percentages are based on the total number of patients in the extension safety set in the particular treatment group. If a patient had multiple events for a particular relationship or severity category, that patient is counted only once for that relationship or severity.

Source: ECU-NMO-302 study report.[35]

[redacted] Details are presented in Table 22.

Table 22: Adverse Events by Preferred Term (Safety Analysis Set) Reported by More Than Two Patients: ECU-NMO-302

Adverse event category	Placebo/eculizumab (N = [redacted], PY = [redacted])			Eculizumab/eculizumab (N = [redacted], PY = [redacted])			Total (N = [redacted], PY = [redacted])		
	Events, n	Rate per 100 PYs	Patients, n (%)	Events, n	Rate per 100 PYs	Patients, n (%)	Events, n	Rate per 100 PYs	Patients, n (%)
TEAEs and patients with TEAEs	[redacted]								
Nasopharyngitis									
Headache									
Urinary tract infection									
Upper respiratory tract infection									
Back pain									
Constipation									
Contusion									
Fatigue									
Influenza									
Nausea									
Pain in extremity									
Anemia									
Cough									
Diarrhea									
Iron deficiency anemia									
Muscle spasms									
Pyrexia									
Toothache									
Asthma									
Bronchitis									
Cystitis									
Dyspepsia									
Hypoesthesia									
Insomnia									
Leukopenia									
NMOSD[a]									
Oral candidiasis									
Oral herpes									
Oropharyngeal pain									
Paresthesia									
Sinusitis									
Thermal burn									

NMOSD = neuromyelitis optica spectrum disorder; PY = patient-year; TEAE = treatment-emergent AEs

Note: Rates are reported per 100 PYs. Treatment-emergent AEs were adverse events with a start date on or after the first dose date in the study. If a patient had more than one TEAE for a particular preferred term, that patient was counted only once for that preferred term.

[a] NMOSD is typically only reported if it worsens (i.e., if it is a hospitalization diagnosis such as [a serious adverse event]), as occurred for these [redacted] patients.

Source: ECU-NMO-302 study report.[35]

[redacted]

[redacted]

During the study, there were no clinically meaningful changes from baseline in any hematology, chemistry, urinalysis, or electrocardiogram parameters, as well as no significant changes in any vital sign measurement, body weight, or Columbia-Suicide Severity Rating Scale score.

Critical Appraisal

This is an open-label, long-term extension study. Similar to other before-after observational designs, the study limitations stem from the observational evaluation of the data, where time-varying confounding due to external predictors not controlled by the randomization process may have emerged during the study; for example, the risk of relapse and its severity may not be the same over time, which could modify relapse rates.

There seems to be at least a moderate risk of selection bias due to the inclusion of a relatively small number of participants from the original randomized trial up until the cut-off date of the interim analysis, although blinding was preserved from PREVENT during the first (blinded) phase of this study, which could mitigate bias. There is low risk of misclassification bias or bias due to deviations from the intended interventions. All patients so far have been under adequate follow-up and surveillance, and there seems to be proper avoidance of missing data from these participants.

Other limitations were noticed when comparing data from this open-label study with data from PREVENT. For instance, from PREVENT it was noticed that the frequency of relapses was about 10% higher for the physician-rated relapses than for the adjudicated-rated relapses. These differences might imply difficulties in external validity, although it still is uncertain from this observational study.

The sample size until the interim analysis of this extension study could be considered small for addressing efficacy outcomes; however, NMOSD is a rare disease and given that one of the main objectives of this extension study is the evaluation of safety outcomes, small sample sizes can still provide information regarding the detection of large effects. Until the cut-off date for this interim analysis, treatment with eculizumab was well tolerated in the [redacted] patients with NMOSD, and the safety results were consistent with the safety profile of eculizumab in the PREVENT study.

Although the population of this extension study is overall similar to the population from PREVENT, which might be considered representative of the population with NMOSD with AQP4 antibodies present, it is difficult to draw any conclusions on the maintenance of effect in these patients.

Observational Evidence (Pittock [2013])[12]

This study was an open-label trial conducted between October 2009 and November 2010 and aimed to investigate the use and safety of eculizumab in patients with NMOSD.[12]

Methods

This was a non-randomized, single-arm pilot study, in which investigators recruited patients aged at least 18 years who had a diagnosis of NMOSD, were AQP4-IgG-seropositive, and had at least two attacks in the previous six months or three in the previous 12 months. Attacks were treated with 1 g IV methylprednisolone daily for five days or, when not tolerated, with IVIG for five days.

Interventions

Two weeks after a screening visit (when a meningococcal vaccine was administered), patients began treatment with 600 mg intravenous eculizumab weekly for four weeks, 900 mg in the fifth week, and then 900 mg every two weeks for 48 weeks.

Outcomes

Primary end points included efficacy (measured by number of attacks [new worsening of neurological function lasting for more than 24 hours and not attributable to an identifiable cause]) and safety. Secondary end points were disability (measured by EDSS), ambulation (using the HAI), and visual acuity (using the visual component of the OSIS, based on the visual FSS of the EDSS). At follow-up visits (after six weeks and three, six, nine, and 12 months of treatment, and three and 12 months after discontinuation), a complete neurological examination was undertaken and an AE questionnaire completed.

Statistical Analysis

Only descriptive statistics were provided.

Patient Disposition

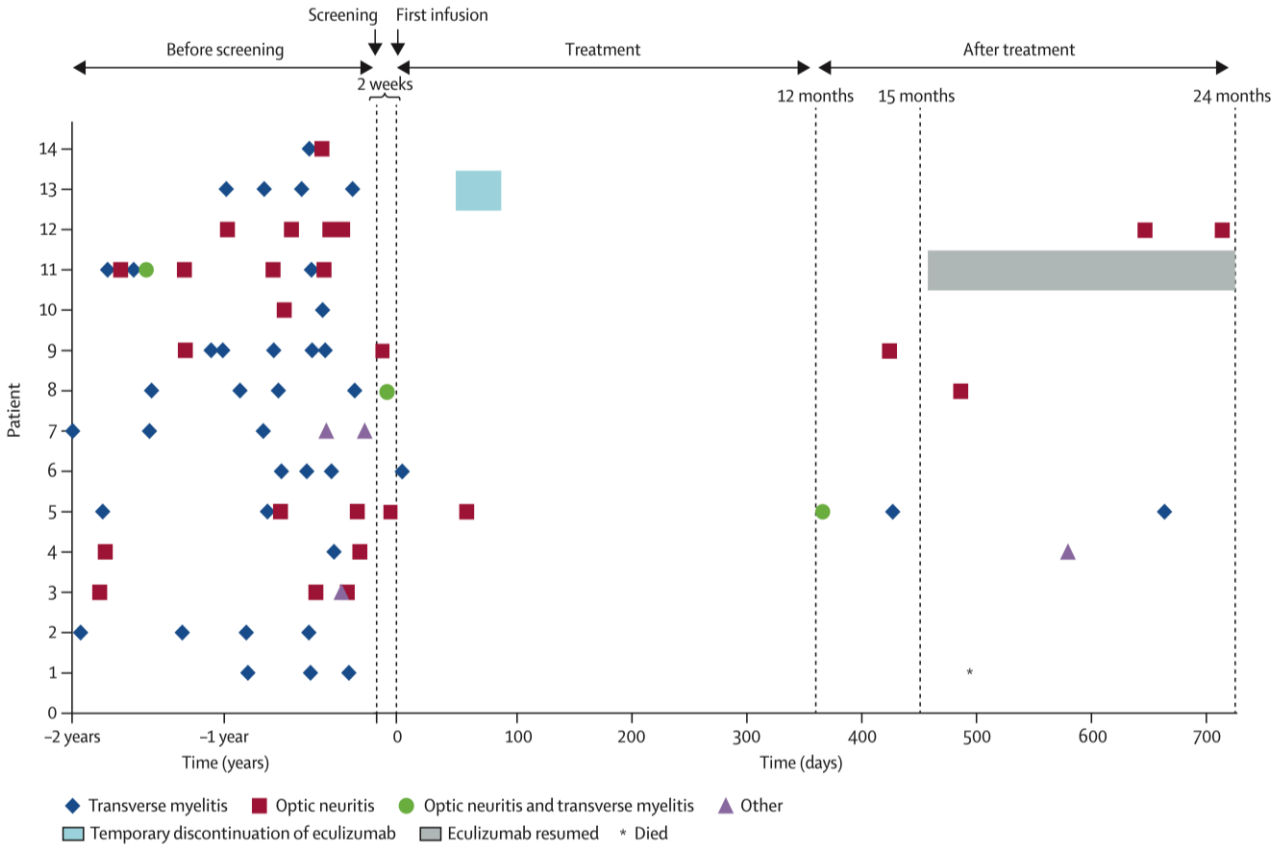
The study included 14 patients, all of whom were women. Overall, previous treatment was judged to have failed (≥ 1 attack when receiving treatment) in six patients, despite a trial of more than 90 days with at least one immunosuppressant drug. All patients were followed up with until completement of treatment. All 14 patients began alternative immunotherapy at the 12-month visit. Complete 12-month follow-up after eculizumab withdrawal was available for 12 patients (patient 1 died after a myocardial infarction; patient 11 restarted eculizumab outside the protocol and had no attacks during follow-up).

Efficacy

Of the 14 patients enrolled, after 12 months of eculizumab treatment, 12 patients were relapse-free and two had had possible attacks. The median number of attacks per year fell from three before treatment (range: two to four) to zero (range: zero to one) during treatment. No patient had worsened disability by any outcome measure. The median score on the EDSS improved from 4.3 (range: 1.0 to 8.0) before treatment to 3.5 (range: 0 to 8.0) during treatment (P = 0.0078). Two patients improved by two points and three improved by one point on the HAI; no change was recorded for the other patients. Visual acuity had improved in at least one eye by one point in four patients, and by two points in one patient;

no change was recorded for the other patients. Eight attacks in five patients were reported within 12 months of eculizumab withdrawal. These patients are presented in Figure 5.

Figure 5: Attack Frequency With Eculizumab Treatment in an Open-Label Single-Arm Study



Reprinted from Lancet Neurol, Vol 12(6), Pittock et al., Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study, Pages No. 554-562, Copyright (2013), with permission from Elsevier.[12]

Harms

Headache was the most frequent AE (nine of 14 patients), followed by dizziness, diarrhea, and nausea (six patients each). One patient had meningococcal sepsis and sterile meningitis about two months after the first eculizumab infusion but resumed treatment after full recovery. No other drug-related SAEs occurred.

Critical Appraisal

Due to the nature of the study design (a single-arm, open-label pilot study, before-after treatment) this study provides very low certainty (due to high risk of bias) in its internal and external validity. The treatment effect size observed on reduction in attacks and disability in patients when receiving eculizumab is notable but considered to support the rationale for further investigation in well-designed randomized trials. Furthermore, the differences in doses in this study compared to PREVENT and product monographs of the study drug are noticeable.

Conclusions

One small (N = 14) open-label pilot study assessed the effect and tolerability of eculizumab in a sample of patients and evaluated its feasibility in future trials. Due to the nature of the study design, it was considered as having high risk of bias. In this study, eculizumab was well tolerated, reduced attack frequency, and improved neurological disability measures in 12 out of 14 patients with NMOSD.

Indirect Evidence

Introduction

Given the lack of head-to-head studies for eculizumab, this review was conducted to summarize and appraise the indirect evidence comparing eculizumab to other drugs used in the treatment of NMOSD.

CADTH conducted an independent literature search to identify relevant ITCs that included the patients, interventions, and outcomes as identified in the CDR Clinical Review protocol (Table 4). No ITCs met the criteria for inclusion.

One ITC[15] of therapeutics for NMOSD excluding eculizumab was identified in the literature and is summarized in brief for the purpose of providing supplemental evidence that may be useful in understanding the context of treatments for NMOSD. This ITC did not restrict studies to AQP4 antibody-positive patients.

Description of Indirect Comparison (Huang et al.)[15]

The ITC included all comparative studies that compared at least two interventions for the prevention of relapse in patients with NMOSD. The interventions assessed were immunosuppressive agents, including azathioprine, mycophenolate mofetil, cyclophosphamide, and monoclonal antibodies, such as rituximab, eculizumab, and tocilizumab. Dosing information was not specified in the study selection criteria.

Methods of ITC (Huang et al.)[15]

The objective of the ITC was to compare and rank immunotherapies (including azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, eculizumab, and tocilizumab) in terms of effectiveness and tolerability in preventing NMOSD.

Studies included in the ITC were identified via systematic literature search. The authors searched MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and ClinicalTrials.gov databases up to November 21, 2018. Two reviewers independently performed the search, extracted the data, and evaluated risk of bias using the Cochrane risk of bias tool and the Newcastle–Ottawa Scale. A third reviewer examined all the data.

The primary outcome of the ITC was the ARR. Secondary outcomes included the EDSS score, and HRs for counts of AEs. The ITC was performed using a Bayesian Markov chain Monte Carlo model. Standardized mean differences and 95% CIs were reported for continuous variables. Hazard ratios were used for count variables, with 95% CIs using a random effects Poisson model. Convergence was assessed using a burn-in phase of 60,000 iterations after 20,000 iterations of the annealing algorithm.

Results of ITC (Huang et al.)[15]

The systematic review identified 310 studies; overall, six studies were included in the ITC An overview of study and patient characteristics included in the ITC is provided in Table 23.

For the ITC, comparisons were made for the following treatments: cyclosporine A, azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab. Risk of bias was not high in any of the included studies. The level of evidence was grade 2 for the RCT and grade 3 for the observational studies.

Table 23: Characteristics of Included Studies

	Kageyama (2013)		Chen (2016)		Xu (2016)			Zhang (2017)		Nikoo (2017)		Yang (2018)		
Study design	Retrospective study		Prospective study		Prospective study			Retrospective study		RCT		Prospective study		
Level of evidence	3		3		3			3		2		3		
Interventions	CyA	AZA	MMF	AZA	MMF	AZA	CTX	RTX	AZA	RTX	AZA	MMF	AZA	RTX
Sample size	9	9	105	105	38	119	41	31	34	33	35	30	22	20
Follow-up, months	32.0	40.0	16.8	36.0	15.2	16.3	13.6	27.5	31.3	12.0	12.0	28.5	26.0	29.0
AQP4+, n (%)	9 (100)	9 (100)	89 (84.8)	91 (86.7)	33 (86.8)	110 (92.4)	37 (90.2)	25 (80.7)	28 (82.4)	13 (39.4)	20 (57.1)	13 (43.3)	8 (36.4)	10 (50.0)
Age, years	45.0	55.0	44.0	41.6	31.6	39.7	40.2	42.4	42.2	35.3	32.4	NR	NR	NR
Disease duration, months	72.0	96.0	22.8	32.4	14.3	23.0	23.3	48.6	49.0	74.8	73.4	9.5	9.0	11.0
Regimen	150 mg/day p.o.	100 mg/day p.o.	20 mg/kg/day p.o.	2 mg/kg/day p.o.	1,500 mg/day p.o.	100 mg/day p.o.	400 mg/week IV	100 mg/week IV	2 mg/kg/day p.o.	1,000 mg/2 weeks IV	2–3 mg/kg/day p.o.	1,000 mg/day p.o.	2 mg/kg/day p.o.	100 mg/week IV
Outcome measures	ARR; EDSS		ARR; EDSS; adverse events		ARR; EDSS; adverse events			ARR; EDSS; adverse events		ARR; EDSS; adverse events		ARR; EDSS; adverse events		

AQP4+ = aquaporin-4 positive; ARR = annualized relapse rate; AZA = azathioprine; CTX = cyclophosphamide; CyA = cyclosporine A; EDSS = Expanded Disability Status Scale; MMF = mycophenolate mofetil; NR = not reported; p.o. = orally; RCT = randomized controlled trial; RTX = rituximab.

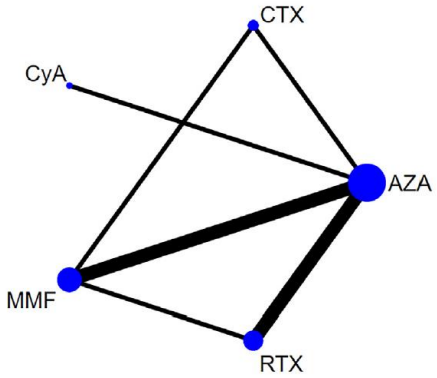
Source: Huang et al. (2019).[15]

Annualized Relapse Rate

For the analysis related to ARR, six studies contributed data. The network of evidence for ARR is presented in Figure 6. According to the authors, no evidence of heterogeneity was found in an integral inconsistency test for the primary outcome (P = 0.29).

Treatment with rituximab was more efficacious than treatment with azathioprine, with a standardized mean difference of –0.86 (95% CI, –1.60 to –0.11).

Figure 6: Evidence Network for Annualized Relapse Rate



AZA = azathioprine; CTX = cyclophosphamide; CyA = cyclosporine A; MMF = mycophenolate mofetil; RTX = rituximab.

Source: Huang et al., 2019[15]

Table 24: ITC Estimate for ARR

	Standardized mean difference (95% CI)			
	Rituximab	**Cyclosporine A**	**Mycophenolate mofetil**	**Azathioprine**
Cyclosporine A	–0.18 (–1.97 to 1.63)	NA	NA	NA
Mycophenolate mofetil	–0.70 (–1.62 to 0.26)	–0.53 (–2.05 to 0.99)	NA	NA
Azathioprine	–0.86 (–1.60 to –0.11)[a]	–0.69 (–2.39 to 1.01)	–0.15 (–0.89 to 0.57)	NA
Cyclophosphamide	–0.98 (–2.31 to 0.40)	–0.79 (–2.71 to 1.12)	–0.27 (–1.45 to 0.91)	–0.12 (–1.29 to 1.08)

Note: Values greater than zero favour the intervention in the column. Interventions are ordered in accordance with efficacy ranking.

[a] Statistically significant results.

ARR = annualized relapse rate; CI = confidence interval; ITC = indirect treatment comparison; NA = not applicable.

Source: Huang et al. (2019).[15]

EDSS Score

For the analysis related to lowering of the EDSS score, six studies contributed data. There was significant inconsistency, according to an integral inconsistency test (P = 0.00). Results from the ITC showed no statistically significant improvement associated with any one treatment compared to another.

Table 25: ITC Estimate for EDSS Score

	Standardized mean difference (95% CI)			
	Rituximab	Cyclosporine A	Mycophenolate mofetil	Azathioprine
Cyclosporine A	–0.35 (–2.18 to 1.47)	NA	NA	NA
Mycophenolate mofetil	–0.50 (–1.50 to 0.57)	–0.14 (–1.94 to 1.69)	NA	NA
Azathioprine	–0.55 (–1.37 to 0.29)	–0.20 (–1.83 to 1.44)	–0.06 (–0.88 to 0.75)	NA
Cyclophosphamide	–1.32 (–2.83 to 0.19)	–0.96 (–3.08 to 1.12)	–0.82 (–2.18 to 0.49)	–0.77 (–2.11 to 0.54)

Note: Values < 0 favour the intervention in the column. Interventions are ordered in accordance with efficacy ranking.

CI = confidence interval; EDSS = Expanded Disability Status Scale; ITC = indirect treatment comparison; NA = not applicable.

Source: Huang et al. (2019).[15]

Adverse Events

For the analysis related to AEs, the number of studies that contributed data was not provided. Heterogeneity was not reported. Results from the ITC showed no statistically significant improvement in harms associated with any one treatment compared to another.

Table 26: ITC Estimate for AEs

	Hazard ratio (95% CI)		
	Mycophenolate mofetil	Rituximab	Azathioprine
Rituximab	1.31 (0.15 to 9.67)	NA	NA
Azathioprine	4.47 (0.94 to 20.33)	3.48 (0.71 to 18.71)	NA
Cyclophosphamide	7.82 (0.74 to 98.49)	6.09 (0.42 to 110.50)	1.73 (0.18 to 20.85)

Note: Values greater than 1 favour the intervention in the column. Interventions are ordered in accordance with safety ranking.

AE = adverse event; CI = confidence interval; ITC = indirect treatment comparison; NA = not applicable.

Source: Huang et al. (2019).[15]

Critical Appraisal of ITC (Huang et al.) [15]

The methods used to conduct the systematic review generally appear to be appropriate. The review included a search of multiple databases completed by two independent reviewers, who were also responsible for data extraction and bias assessment. Risk of bias was assessed using the Cochrane risk of bias tool and the Newcastle–Ottawa Scale. A search of reference lists of relevant publications and grey literature were not performed. The authors provided detailed summary tables of relevant data from the included trials, which facilitated assessment of the similarity between studies.

The treatments included were generally relevant to this CDR; however, dosages were not specified and no studies of eculizumab with an active comparator were identified in the literature. The absence of dose information increased the potential for heterogeneity and may contribute to external validity issues. The included studies were mainly observational; one RCT was included. The ITC did not have inclusion criteria based on AQP4 status, which may have contributed to heterogeneity. Not all immunosuppressants assessed in the ITC were used as monotherapies; therefore, the actual effectiveness of the drug may differ from what was reported in the ITC. Some data from the individual studies had to be estimated by the authors of the ITC as those data were not listed individually. These aspects of the ITC highlight internal validity concerns.

Summary

One ITC[15] of therapeutics for NMOSD excluding eculizumab was identified in the literature. Findings from this ITC determined that rituximab was superior to azathioprine for the reduction of ARR. No significant findings were reported for reduction in EDSS score or occurrence of AEs. However, strong conclusions about the relative effectiveness and safety of the drugs used for NMOSD cannot be made given the major internal and external validity issues identified in the ITC.

Discussion

Summary of Available Evidence

One phase III time-to-event RCT was included in this CDR report. PREVENT (N = 143) was a multi-centre, double-blind, placebo-controlled RCT in patients 18 years of age and older with a diagnosis of NMO or NMOSD. The primary objective of PREVENT was to assess the efficacy of eculizumab treatment, as compared with placebo, in relapsing NMOSD patients based on time to first relapse and relapse risk reduction. PREVENT also aimed to characterize the overall safety and tolerability of eculizumab compared with placebo in relapsing NMOSD patients. The duration of PREVENT was designed to last until 24 patients experienced an on-trial adjudicated relapse. Patients were randomized 2:1 to receive eculizumab (900 mg weekly for the first four doses starting on day 1, followed by 1,200 mg every two weeks starting at week 4) or placebo. Subgroup analysis was performed for time to first adjudicated relapse by IST medication used at baseline.

The key limitations of PREVENT were the disproportionately higher percentage of patients who discontinued treatment prematurely in the eculizumab group compared with the placebo group, the likely underestimation of the ARR in both treatment groups related to censoring of patients after the primary outcome event (relapses after the first relapse), limited efficacy assessments based on clinically relevant subgroups, and inability to interpret findings related to functional status and HRQoL because the hierarchical statistical analysis failed at a higher order comparison.

The long-term extension study of PREVENT assessed the safety and efficacy of eculizumab for up to 5.5 years (as of the last interim analysis) in [redacted] patients who had previously experienced an on-trial relapse (assessed by the treating physician) in PREVENT. Annualized relapse rate, EDSS score, mRS score, HAI score, EQ-5D score, visual KFS score, and harms were assessed. Other evidence considered in brief included a small (N = 14) open-label pilot study that assessed the effect and tolerability of eculizumab (using an alternative dose) and an ITC of therapeutics for NMOSD excluding eculizumab.

A description and analysis of AQP4-IgG detection tests for patients with NMOSD is provided in Appendix 5.

Interpretation of Results

Efficacy

Eculizumab statistically and clinically significantly improved the time to first adjudicated on-trial relapse (primary end point) and adjudicated on-trial ARR (secondary end point) compared to treatment with placebo, regardless of concurrent IST use. The statistically and clinically significant findings for the relapse outcomes were consistent with the findings of relapse as assessed by the treating physician, although when relapses were assessed by treating physicians, there was a 10% to 15% increase in the number of relapses observed compared to when the RAC assessed relapses. The protocol for PREVENT originally based the primary and secondary relapse-related outcomes on assessment by the treating physician, but a protocol change made midway through the trial changed the method of relapse assessment to be based on adjudication by an independent committee. It is likely that use of adjudication was more objective and strengthened the robustness of the results, as the committee was independent, blinded, and composed of an appropriate mix of

specialists for NMOSD (two neurologists and one neuro-ophthalmologist). CADTH heard from a panel of specialists with expertise in the management of NMOSD that preventing relapses is a key clinical outcome because of the potentially deleterious impact of relapses on patient function and quality of life. Use of an adjudicated primary outcome reduces inter-site variability in assessments and over-reporting bias that may have influenced attending physician–determined relapses, as the need for immediate treatment of relapses could impact the classification of an event as a relapse. This would explain the increase observed in relapses when assessed by attending physicians in PREVENT. While it is expected that adjudication increased the validity of relapse determination, it deviates from how relapse is assessed in clinic and is thus less generalizable. According to the clinical experts consulted for this review, regardless of the method of assessment (adjudicated or physician determined), the efficacy end points related to relapse were important in determining a clinically meaningful response to treatment in patients with NMOSD. The consistency in findings based on both methods of assessment highlight the robustness of the time to first relapse efficacy findings for eculizumab. The long-term extension study included patients who were treated with eculizumab for up to 5.5 years. While the efficacy results indicated that treatment with eculizumab may reduce ARR compared to historical ARR, numerous limitations pertaining to the study design prevent strong conclusions from being made.

Subgroup analyses based on IST use (baseline corticosteroids, baseline azathioprine, baseline mycophenolate mofetil, other ISTs, no IST use, and prior rituximab) were descriptive in nature but found no substantial differences between groups. These analyses were limited by small sample sizes. The subgroup analysis that was performed provides some limited insight into the effect of eculizumab on specific groups of patients. Data based on patients not receiving concomitant IST versus patients receiving concomitant IST were only available from a post hoc analysis in the 2019 Pittock[11] publication. These data indicate that the treatment effect of eculizumab within the subgroups is consistent with the overall treated population and that the effect may be more pronounced in patients who had not been treated with IST. However, the interpretation of these results is limited due to the small sample size and descriptive nature of the results. Strong conclusions regarding the efficacy of eculizumab in patients based on whether or not they received concomitant IST cannot be made. No subgroup analyses were available for patients who had failed treatment with other therapeutics. There was an absence of subgroup analysis based on mobility-related impairment versus vision-related impairment. PREVENT had no subgroup analysis based on the baseline severity of disease. However, the study did have exploratory data on the severity of the relapse, which indicated greater severity of relapses in the placebo arm than in the eculizumab arm. The assessments of these subgroups would have provided valuable insight that could have helped guide policy decisions and implementation of eculizumab within the Canadian health care system.

The proportion of patients that discontinued PREVENT was greater in the eculizumab arm (16.7%) compared with the placebo arm (6.4%). The most common reason for discontinuation was attributed to “withdrawal by patient,” but the specific reason for withdrawal was not specified for most patients. A sensitivity analysis of the primary end point, imputing all discontinuations in the eculizumab treatment group as adjudicated on-trial relapse events, showed an attenuated finding (HR = 0.297; 95% CI = 0.154 to 0.572; P = 0.0001) corresponding to a risk reduction of 70.3%, which remained clinically relevant. This finding supports the robustness of conclusions of treatment effectiveness in the eculizumab arm, regardless of discontinuations.

Adjudicated on-trial ARR was the first secondary end point assessed in the hierarchy. While ARR is a common end point in studies of NMOSD, the utility of this end point is unclear as, by design, patients in PREVENT who experienced a relapse would subsequently complete the trial; thus, the ARR would not have necessarily captured all relapses occurring after the first. The effectiveness of eculizumab on subsequent relapses is unknown.

Although the secondary end points evaluated in PREVENT were considered clinically relevant, the interpretation of these is made difficult by the design of the study and breaking of the statistical analysis hierarchy. Reduction in disability caused by NMOSD was identified as an important outcome based on feedback from a patient group consulted for this review. The EDSS was used to assess disability in PREVENT; however, the difference in change from baseline between eculizumab and placebo was not statistically significant, and the method of handling missing data was limited to the LOCF method. This finding prevented the statistical and clinical interpretation of other secondary outcomes pre-specified in the statical testing hierarchy related to disability, HRQoL, and symptoms. Input provided by patients with NMOSD and their caregivers indicated that the increasing disability associated with NMOSD impacts all areas of a person's life, including employment, independence, isolation, cognitive function, and mobility. The results of the trial (and the absence of evaluation of outcomes related to the ability to work) prevent any conclusions being made about the efficacy of eculizumab in affecting these outcomes, which are important to patients.

PREVENT was a placebo-controlled trial. Although there are currently no treatments indicated for NMOSD by Health Canada, patients are typically treated in clinic with other drugs such as azathioprine, mycophenolate mofetil, and rituximab. In PREVENT, patients were excluded from the trial if they had used rituximab, mitoxantrone, or IVIG within three months of screening. The use of a placebo control group may impact the external validity of the study results.

The comparative efficacy of eculizumab to other treatments for NMOSD (e.g., rituximab) could not be explored based on the use of a placebo comparator in PREVENT. Although one ITC for NMOSD treatments was identified in the literature, it did not include eculizumab as a comparator.

PREVENT was a multi-site study that included patients from North and South America, Europe, Australia, and Asia. No patients were recruited from Canada. PREVENT was based on patients who tested AQP4 antibody seropositive. It is estimated that approximately 10% to 30% of patients with NMO or NMOSD are AQP4 antibody seronegative.[1,2,4,5] The inclusion criteria of PREVENT created a study population that was likely to experience a relapse based on their historical relapses (at least two relapses in last 12 months or three relapses in the last 24 months, with at least one relapse in the 12 months prior to screening). The historical history of relapse activity is not specified in the indicated population for eculizumab. Therefore, it is expected that the number of relapses observed in the trial was greater than would be expected in the clinical setting, although the impact on the relative difference in relapse is unknown. Despite issues related to the study design and the study population, the findings from PREVENT are expected to be generalizable to the Canadian clinical population.

Harms

Adverse events were reported by most patients. In PREVENT, 91.7% of patients in the eculizumab arm and 95.7% of patients in the placebo arm experienced an AE. The most

common AE was upper respiratory infection, which affected more patients in the eculizumab arm (29.2%) than in the placebo arm (12.8%). The differential impact of upper respiratory infection was determined to be a reasonable effect, likely due to the mechanism of action of eculizumab based on feedback from the clinical experts consulted for the review. SAEs occurred more often in patients treated with placebo; however, the difference in SAEs was largely eliminated when the SAE for worsening of NMOSD was excluded. The on-trial death of one patient treated with eculizumab was attributed to infectious pleural effusion and was considered by the investigator to be "probably related to the study drug." This patient had other factors that investigators believed to have contributed to the death (including the patient's history of pulmonary disease). Overall, treatment with eculizumab was well tolerated, and safety results were consistent with the safety profile of eculizumab for indications in which it is already approved. However, the sample size was small, with only 96 patients in the eculizumab arm.

The comparative safety of eculizumab to other treatments for NMOSD (e.g., rituximab) could not be assessed based on the use of a placebo comparator in PREVENT and the absence of relevant ITCs.

The long-term extension study assessed safety associated with the continued use of eculizumab in patients who had previously experienced an on-trial relapse in PREVENT. In terms of AEs, treatment with eculizumab for the [redacted] patients was well tolerated, and safety results were consistent with the safety profile of eculizumab observed in PREVENT.

Conclusions

Eculizumab statistically and clinically significantly improves the time to first adjudicated on-trial relapse (primary end point) and adjudicated on-trial ARR (secondary end point) compared to treatment with placebo, regardless of concurrent IST use. Eculizumab may also reduce the severity of relapses that occur, but this analysis was only exploratory in the study. Eculizumab did not demonstrate a statistically significant benefit in terms of disability status (change in EDSS) versus placebo. The lack of a statistically significant difference for the change from baseline on the EDSS precluded drawing conclusions on the effects of eculizumab on subsequent end points in the hierarchical testing sequence, such as functional status and HRQoL. Adverse events for upper respiratory infection occurred more frequently for patients treated with eculizumab compared with placebo; no other important safety signals were observed in the main study.

The efficacy or safety results of the long-term extension study are difficult to interpret based on the interim analysis available for patients treated with eculizumab.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 24, 2020
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(Soliris* or eculizumab* or solirus or H5G11* or H5G1 1* or 5G11* or 5G1 1* or A3ULP0F556).ti,ab,kf,ot,hw,rn,nm.
2	Neuromyelitis Optica/
3	(neuromyelitis optica* or NMSOD or devic* or myelooptic neuropathy* or neuropticomyelitis* or opticospinal MS or optic neuromyelitis or opticomyelitis or optic neuroencephalomyelopath* or neuro-optic myelitis or ophthalmoneuromyelitis or myeloopticoneuropath* or myeloptico neuropath* or Myelopticoneuropath* or (NMO and spectrum*)).ti,ab,kf.
4	2 or 3
5	1 and 4
6	5 use medall
7	*eculizumab/
8	(Soliris* or eculizumab* or H5G11* or H5G1 1* or 5G11* or 5G1 1*).ti,ab,kw,dq.
9	7 or 8
10	myelooptic neuropathy/
11	(neuromyelitis optica* or NMSOD or devic* or myelooptic neuropathy* or neuropticomyelitis* or opticospinal MS or optic neuromyelitis or opticomyelitis or optic neuroencephalomyelopath* or neuro-optic myelitis or ophthalmoneuromyelitis or myeloopticoneuropath* or myeloptico neuropath* or Myelopticoneuropath* or (NMO and spectrum*)).ti,ab,kw,dq.
12	10 or 11
13	9 and 12
14	13 use oemezd
15	14 not (conference review or conference abstract).pt.
16	6 or 15
17	remove duplicates from 16

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: (Soliris* OR eculizumab* OR h5G1.1) AND (neuromyelitis optica* OR NMSOD or devic* OR myelooptic neuropathy* OR neuropticomyelitis* OR opticospinal MS OR optic neuromyelitis OR opticomyelitis OR optic neuroencephalomyelopath* OR neuro-optic myelitis OR ophthalmoneuromyelitis OR myeloopticoneuropath* OR myeloptico neuropath* OR Myelopticoneuropath*)	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Search dates:	March 17–19, 2020
Keywords:	Soliris* OR eculizumab* OR h5G1.1
Limits:	None
Updated:	Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics

Appendix 2: Excluded Studies

Table 27: Excluded Studies

Reference	Reason for exclusion
Pittock SJ, Lennon VA, McKeon A, et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. *Lancet Neurol*. 2013;12(6):554-562.[12]	Intervention, different dose Study design, open label

Appendix 3: Detailed Outcome Data

Table 28: Major Protocol Deviations in PREVENT

	PREVENT	
	Eculizumab	Placebo
Any major deviation, n (%)	37 (38.5)	20 (42.6)
Informed consent	13 (13.5)	9 (19.1)
Randomization	9 (9.4)	6 (12.8)
Visit schedule	7 (7.3)	8 (17.0)
Study procedures/tests	11 (11.5)	3 (6.4)
Safety reporting	7 (7.3)	4 (8.5)
Investigational product	9 (9.4)	1 (2.1)
Concomitant medication	5 (5.2)	1 (2.1)
Source document	5 (5.2)	1 (2.1)
Eligibility and entry criteria	2 (2.1)	1 (2.1)

Source: Clinical Study Report for PREVENT.[10]

Table 29: Adjudicated On-Trial Relapses by Treatment Group and IST Subgroups

	PREVENT							
	Time to first adjudicated on-trial relapse[a]						Adjudicated on-trial relapse rate	
		Number of patients contributing to the analysis	Patients with a relapse, n (%)	Estimated proportion of patients relapse-free at 48 weeks	P value	Total number of adjudicated on-trial relapses	Total number of patient-years in study period	Relapse rate
Baseline corticosteroids	Eculizumab N = 16	16	0	1.0	0.0133	0	26.42	0
	Placebo N = 11	11	4 (36.4)	0.636		4	18.24	0.22
Baseline azathioprine	Eculizumab N = 37	37	2 (5.4)	0.945	0.0013	2	61.37	0.03
	Placebo N = 13	13	5 (38.5)	0.692		5	8.52	0.59
Baseline mycophenolate mofetil	Eculizumab N = 17	17	1 (5.9)	1.0	0.0446	1	30.88	0.03
	Placebo N = 8	8	3 (37.5)	0.714		3	11.05	0.27
Other ISTs	Eculizumab N = 5	5	0	1.0	0.1573	0	8.80	0
	Placebo N = 2	2	1 (50.0)	0.5		1	1.81	0.55
No IST use	Eculizumab N = 21	21	0	1.0	< 0.001	0	43.85	0
	Placebo N = 13	13	7 (53.8)	0.606		8	12.79	0.63

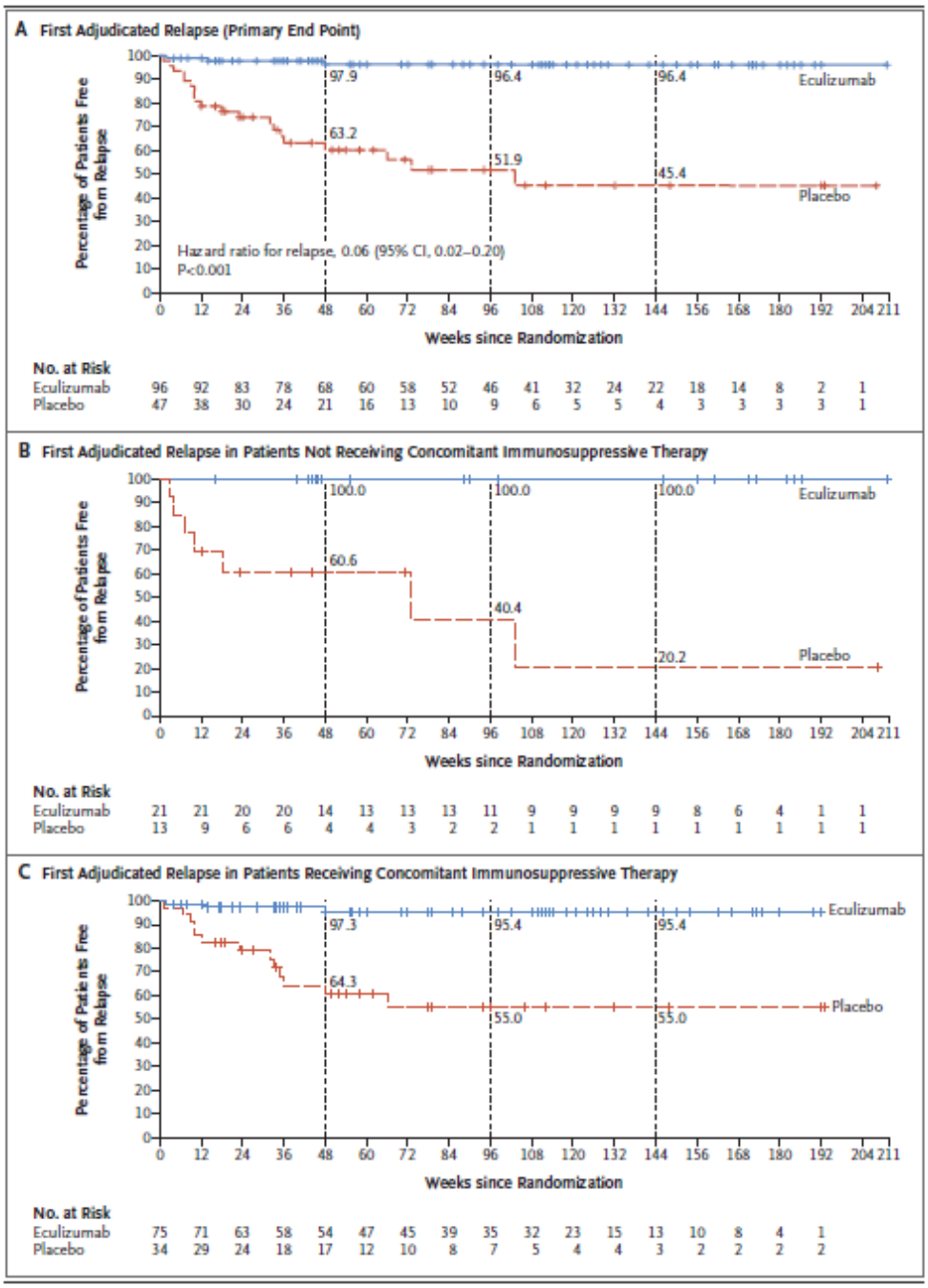
	PREVENT							
	Time to first adjudicated on-trial relapse[a]						Adjudicated on-trial relapse rate	
		Number of patients contributing to the analysis	Patients with a relapse, n (%)	Estimated proportion of patients relapse-free at 48 weeks	P value	Total number of adjudicated on-trial relapses	Total number of patient-years in study period	Relapse rate
Prior rituximab	Eculizumab N = 26	26	1 (3.8)	1.0	0.0055	1	17.09	0.03
	Placebo N = 20	20	7 (35.0)	0.625		7	37.77	0.41

IST = immunosuppressive therapy.

[a] P value from unstratified log-rank test; full analysis set.

Source: Clinical Study Report for PREVENT.[10]

Figure 7: Post Hoc Analysis: Time to First Adjudicated Relapse by Concomitant IST Status



IST = immunosuppressive therapy.

Source: The New England Journal of Medicine, Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder, 381(7):614-625. Copyright © (2019) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[11]

Table 30: Relapse-Related Efficacy Outcomes (as Determined by the Treating Physician)

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Time to first on-trial relapse[a,b]		
Number of patients contributing to the analysis	96	47
Patients with a relapse, n (%)	14 (14.6)	29 (61.7)
Follow-up time, weeks, median (min, max)	89.43 (1.29, 211.14)	36.00 (0.57, 208.57)
Estimated proportion of patients relapse-free at:		
48 weeks, cumulative probability (95% CI)	0.893 (0.811 to 0.941)	0.506 (0.355 to 0.638)
96 weeks, cumulative probability (95% CI)	0.846 (0.746 to 0.909)	0.358 (0.213 to 0.505)
114 weeks, cumulative probability (95% CI)	0.825 (0.717 to 0.895)	0.313 (0.169 to 0.469)
Percent reduction	82.0	
Hazard ratio (95% CI)	0.180 (0.095 to 0.343)	
P value	< 0.0001	
On-trial annualized relapse rate[b,c]		
Number of patients with a total relapse count of:		
0 relapses, n (%)	82 (85.4)	18 (38.3)
1 relapse, n (%)	14 (14.6)	27 (57.4)
2 relapses, n (%)	0	2 (4.3)
Total number of relapses	14	31
Total number of patient-years in study period	171.32	52.41
Adjusted annualized relapse rate (95% CI)	0.066 (0.036 to 0.120)	0.446 (0.272 to 0.732)
Rate ratio (95% CI)	0.147 (0.078 to 0.278)	
P value	< 0.0001	

CI = confidence interval.

[a] Log-rank test including strata for the randomization stratification variable; based on a stratified Cox proportional hazards model; full analysis set. Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period. Stratified analyses are based on four randomization strata for Expanded Disability Status Scale (EDSS) and immunosuppressive therapy (IST): (1) low EDSS at randomization (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naive at randomization; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.

[b] P value has not been adjusted for multiple testing.

[c] Based on a Poisson regression adjusted for randomization strata and historical annualized relapse rate in the 24 months prior to screening.

Table 31: Other Efficacy Outcomes by Subset

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Visual KFS in patients with abnormal baseline visual function[a,b]		
Number of patients contributing to the analysis	82	32
Baseline, mean (SD)	3.7 (1.83)	3.9 (1.70)
End of study visual KFS score, mean (SD)	2.8 (1.52)	3.3 (1.80)
Change from baseline, mean (SD)	–1.0 (1.02)	–0.60 (0.87)
P value	0.0002	

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
HAI in patients with abnormal baseline ambulatory function[b,c]		
Number of patients contributing to the analysis	83	44
Baseline, mean (SD)	2.7 (2.10)	2.3 (1.32)
End of study HAI score, mean (SD)	2.3 (2.32)	2.8 (2.13)
Change from baseline, mean (SD)	–0.5 (1.11)	0.5 (1.65)
P value	0.0002	

KFS = Kurtzke Functional System; HAI = Hauser Ambulation Index; SD = standard deviation.

[a] P value from randomization-based nonparametric analysis of covariance (ANCOVA) adjusted for baseline score and four randomization strata for Expanded Disability Status Scale (EDSS) and immunosuppressive therapy (IST): (1) low EDSS at randomization (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naive at randomization; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization; full analysis set with abnormal baseline visual function (baseline visual KFS = 1 to 6); full analysis set.

[b] P value has not been adjusted for multiple testing.

[c] P value from randomization-based nonparametric ANCOVA adjusted for baseline score and four randomization strata for EDSS and IST: (1) low EDSS at randomization (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naive at randomization; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization; full analysis set with abnormal baseline ambulatory function (baseline HAI value = 1 to 9); full analysis set.

Source: Clinical Study Report for PREVENT.[10]

Table 32: Sensitivity Analysis Using ANCOVA

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Disability progression		
Expanded Disability Status Scale[a]		
Number of patients contributing to the analysis	96	47
Change from baseline, LS mean (SEM)	–0.26 (0.096)	0.03 (0.133)
Difference in the LS mean (95% CI)	–0.29 (–0.59 to 0.01)	
P value	0.0603	
Modified Rankin Scale[b]		
Change from baseline, LS mean (SEM)	–0.32 (0.084)	0.00 (0.115)
Difference in the LS mean (95% CI)	–0.32 (–0.57 to –0.06)	
P value	0.0154	
Health-related quality of life		
EQ-5D-3L VAS[b]		
Change from baseline, LS mean (SEM)	7.76 (1.892)	1.33 (2.573)
Difference in the LS mean (95% CI)	6.43 (0.63 to 12.23)	
P value	0.0302	
EQ-5D-3L index score[b]		
Change from baseline, LS mean (SEM)	0.06 (0.021)	–0.03 (0.029)
Difference in the LS mean (95% CI)	0.09 (0.02 to 0.15)	
P value	0.0075	
SF-36 physical component[b]		
Change from baseline, LS mean (SEM)	3.96 (0.969)	0.76 (1.305)

	PREVENT	
	Eculizumab N = 96	Placebo N = 47
Difference in the LS mean (95% CI)	3.20 (0.27 to 6.13)	
P value	0.0325	
SF-36 mental component[b]		
Change from baseline, LS mean (SEM)	2.46 (1.113)	1.24 (1.514)
Difference in the LS mean (95% CI)	1.23 (–2.18 to 4.63)	
P value	0.4779	
Symptoms		
Visual Kurtzke Functional System[b]		
Change from baseline, LS mean (SEM)	–0.75 (0.101)	–0.47 (0.141)
Difference in the LS mean (95% CI)	–0.27 (–0.58 to 0.04)	
P value	0.0879	
Hauser Ambulation Index Score[b]		
Change from baseline, LS mean (SEM)	–0.50 (0.147)	0.37 (0.201)
Difference in the LS mean (95% CI)	–0.87 (–1.32 to –0.42)	
P value	0.0002	

ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; LS = least square; SEM = standard error of the mean; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

[a] P value from ANCOVA adjusted for baseline score and randomization immunosuppressive therapy strata.

[b] P value from ANCOVA adjusted for baseline score and four randomization strata.

Source: Clinical Study Report for PREVENT.[10]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- relapse
- EDSS
- mRS
- HAI
- EQ-5D
- SF-36
- visual acuity assessed with the visual KFS
- OSIS.

Table 33: Outcome Measures Included in Each Study

Outcome measure	PREVENT trial
Relapse	Primary
EDSS	Secondary
mRS	Secondary
HAI	Secondary
EQ-5D	Secondary
SF-36	Secondary
Visual acuity (assessed with the visual Kurtzke Functional System)	Secondary
OSIS	Tertiary

EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions; HAI = Hauser Ambulation Index; mRS = modified Rankin Scale; OSIS = Optic-Spinal Impairment Scale; SF-36 = Short Form (36) Health Survey.

Findings

The validity, reliability, responsiveness, and MID of each outcome measure were summarized and evaluated. Interpretation of the reliability and validity metrics was based on the following criteria:

- Inter-rater reliability, kappa statistics (level of agreement):[36]
  - < 0 = poor agreement
  - 0.00 to 0.21 = slight agreement
  - 0.21 to 0.40 = fair agreement
  - 0.41 to 0.60 = moderate agreement
  - 0.61 to 0.8 = substantial
  - 0.81 to 1.00 = almost perfect agreement.

- Internal consistency (Cronbach alpha) and test-retest reliability: ≥ 0.7 is considered acceptable[37]
- Validity, between-scale comparison (correlation coefficient, r):[38]
  - ≤ 0.3 = weak
  - 0.3 to ≤ 0.5 = moderate
  - > 0.5 = strong.

Table 34: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Relapse	There were two methods to evaluate relapses: (1) determined by the attending physician and (2) adjudicated via a committee of experts. Generic, clinically assessed outcome measure, 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 more than 24 hours as confirmed by the treating physician. The signs and symptoms must be attributed to NMO (i.e., not caused by 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 is not considered an on-trial relapse. The relapse must be preceded by at least 30 days of clinical stability. All potential relapses must have been evaluated by both the treating physician and the EDSS rater. The treating physician made the decision as to whether the clinical signs, symptoms, and neurological change (objective findings on exam) met the protocol definition of an on-trial relapse.	Not applicable in the context of measurement scales, although internal validity is reinforced by the concept of blinding of the outcome assessors.	Not identified.
EDSS	Ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. The Kurtzke functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other) and ambulation are rated in the context of a standard	Validity has been established, and the EDSS is usually used as the gold standard for evaluating new scales.[39] Reliability has low to moderate values, with inter-rater kappa values between 0.32 and 0.76 for EDSS and between 0.23 and 0.58 for the individual functional systems. For scores below 3.5, reliability is regarded as good.[39]	No MID specific to NMOSD was found. Indirect estimates can be obtained from patients with MS, where one study found that a change of 1.5 points as a single score was considered enough

Outcome measure	Type	Conclusions about measurement properties	MID
	neurological examination, and then these ratings (KFS scores) are used in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score.		deterioration from the patient perspective.[28] This was in agreement with a second study, which defined a 1.5-point increase from baseline 0 as important; from a baseline of 1 to 5.5, a 1-point increase was considered important, and from a baseline score ≥ 6, a 0.5-point increase was considered important.[29]
mRS	The mRS is a generic, commonly used, clinician-reported scale for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. The scale ranges from 0 (no disability) to 6 (death).	No studies on NMOSD or MS patients evaluating validity or reliability were identified. The instrument is reliable and has been well validated in patients suffering disability from stroke,[30] implying, however, an issue with its construct validity when applied to patients with NMOSD.	None identified for patients with NMOSD or MS.
OSIS	The OSIS is a generic instrument that assesses visual acuity and motor, sensory, and urinary sphincter functions.	No studies on validity or reliability for this scale were found for patients with either NMOSD or MS.	None identified.
HAI	To evaluate gait and assess the time and effort used by the patient to walk 8 m. The scale ranges from 0 to 9, with 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst (restricted to wheelchair; unable to transfer self independently).	No studies on NMOSD assessing validity or reliability were identified. Inter-rater reliability seems adequate (ICC = 0.96) as does the test-retest reliability (ICC = 0.91).[40,41] Criterion and construct validity are reported as excellent when correlated with other instruments assessing gait and ambulation.[41-43]	None identified for patients with NMOSD or MS.
EQ-5D	Generic preference-based HRQoL instrument, consisting of a VAS and a composite index score of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	One systematic review[31] assessing the EQ-5D (9 studies) in patients with MS: • Content validity. The EQ-5D included certain domains such as walking (mobility) and mood (anxiety/depression) that patients considered important to their quality of life; other critical domains such as fatigue and cognition are not included in EQ-5D. • Convergent validity of impairment (gait, speed, severity) was moderate (pooled correlation estimate = 0.35; 95% CI, 0.25 to 0.45). For activity limitations, the pooled correlation was 0.51 (95% CI, 0.45 to 0.57). When EQ-5D was compared against measures evaluating	None identified for patients with NMOSD. A MID was reported for fatigue in only 1 study (in patients with MS),[44] although this dimension is not included in the EQ-5D.

Outcome measure	Type	Conclusions about measurement properties	MID
		HRQoL, the correlation value was 0.56 (95% CI, 0.54 to 0.59). • Discriminative validity was evaluated in 3 studies. The mobility item lacked discriminative ability. The EQ-5D was able to differentiate between all EDSS levels, except between EDSS levels 3 and 4. • Test-retest reliability: The intra-class correlation coefficient for test-retest reliability of the EQ-5D was 0.81 (acceptable).	
SF-36	Generic self-reported questionnaire consisting of eight domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The SF-36 also yields 2 summary measures of physical health (PCS) and mental health (MCS) derived from scale aggregates. Higher global scores are associated with better quality of life.	No studies on patients with NMOSD were found. The instrument has been validated in patients with MS and neurological disabilities. One systematic review[32] with 7 studies and 3,142 patients showed proper reliability (Cronbach alpha 0.70 for all subscales) and validity (with correlations ranging from 0.5 to 0.81) for all domains. Two studies showed good to excellent internal consistency for the total instrument and for all subscales (within PCS and MCS), with the exception of social function. Correlations between SF-36 subscales and impairment measures were weak. Inter-rater reliability between patients with disabilities and their caretakers was moderate.	No MID studies were found for patients with NMOSD. Indirect evidence from patients with MS was obtained. Only the physical functioning, physical role, social functioning, and PCS from the SF-36 were included in 1 study.[33] MID ranges for the SF-36 domains were as follows: 4 to 9 points for physical functioning, 6 to 8 for physical role, and 6 to 7 for social functioning; for the PCS score, the MID was consistently 6.
Visual acuity (assessed with the visual KFS)	The EDSS (described above) quantifies disability in 8 functional systems and allows an FSS to be assigned in each of these. This review focused on the visual functional system, which is part of the EDSS.	In terms of reliability, there was a fair agreement in visual KFS found in 1 study with a Cohen kappa value of 0.39.[34] No values or assessments on validity directly related to the visual KFS were found, making it difficult to ascertain the convergent and discriminant validity of this specific functional system.	No MID can be calculated for visual acuity within the FSS or EDSS, and no further information could be obtained.

EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions; FSS = functional system score; HAI = Hauser Ambulation Index; HRQoL = health-related quality of life; ICC = intraclass correlation coefficient; KFS = Kurtzke Functional System; MCS = mental component score; MID = minimal important difference; mRS = modified Rankin Scale; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; OSIS = Optic-Spinal Impairment Scale; PCS = physical component score; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

Expanded Disability Status Scale

The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. The Kurtzke functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other) and ambulation are rated in the context of a standard neurological examination, and then these ratings (KFS scores) are used in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score.

EDSS steps 1.0 to 4.5 refer to people who are fully ambulatory. A patient's disability can be limited to a single functional system reflected, for example, in an EDSS score of 4.0 (e.g., bilateral vision loss, severe ataxia, paresis in at least two limbs, or marked reduction in sensation in at least one limb), or involve different functional systems that may or may not be reflected in the EDSS score. For example, following a relapse of NMOSD, a range of changes in EDSS scores are possible from 0 for an area postrema relapse (symptoms not captured by EDSS) to a higher score that reflects impairment of ambulation. EDSS steps 5.0 to 9.5 are defined by impairment to ambulation.

The EDSS is a method of quantifying disability in MS, and it replaced the previous disability status scales used in MS. The EDSS quantifies disability in eight functional systems and allows neurologists to assign an FSS in each of these. The functional systems are:

- pyramidal
- cerebellar
- brainstem
- sensory
- bowel and bladder
- visual
- cerebral
- other.

Table 35: Kurtzke Expanded Disability Status Scale

0.0	Normal neurological examination.
1.0	No disability, minimal signs in 1 FS.
1.5	No disability, minimal signs in more than 1 FS.
2.0	Minimal disability in 1 FS.
2.5	Mild disability in 1 FS or minimal disability in 2 FSs.
3.0	Moderate disability in 1 FS, or mild disability in 3 or 4 FSs. Fully ambulatory.
3.5	Fully ambulatory but with moderate disability in 1 FS and more than minimal disability in several others.
4.0	Fully ambulatory without aid; self-sufficient; up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 m.
4.5	Fully ambulatory without aid; up and about much of the day; able to work a full day; may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 m.
5.0	Ambulatory without aid or rest for about 200 m; disability severe enough to impair full daily activities (work a full day without special provisions).
5.5	Ambulatory without aid or rest for about 100 m; disability severe enough to preclude full daily activities.
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 m with or without resting.
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 m without resting.
7.0	Unable to walk beyond approximately 5 m even with aid; essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day.
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair.
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms.

8.5	Essentially restricted to bed much of day; has some effective use of arms; retains some self-care functions.
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow.
10.0	Death due to MS.

FS = functional system; MS = multiple sclerosis.

Measurement Properties

CADTH found one systematic review with 54 studies addressing the validity and reliability of the EDSS.[39] Validity has been established, and the EDSS is usually used as the gold standard for evaluating new scales. However, there have been some criticisms related to its reliability.

Reliability has been assessed as being low to moderate, with inter-rater kappa values between 0.32 and 0.76 for EDSS and between 0.23 and 0.58 for the individual functional systems. For scores below 3.5, reliability is regarded as good.

The review found that the EDSS is sensitive to change in disease progression.

Minimal Important Difference

No MID specific for NMOSD was found. Indirect estimates can be obtained from patients with MS, and one study found that a change of 1.5 points as a single score was considered enough deterioration from the patient perspective.[28] This was in agreement with a second study, which defined a 1.5-point increase from baseline 0 as important; from a baseline of 1 to 5.5, a one-point increase was considered important, and from a baseline score greater than or equal to 6, a 0.5-point increase was considered important.[29]

Limitations

Some critiques exist related to low reliability values and flaws that limit the usefulness of the EDSS, particularly a lack of precision regarding the definition of the degree of the deficit in some functional categories of the scale and the subjective examination in the overall definition of the scale.[45]

Modified Rankin Scale

The mRS is a generic, commonly used clinician-reported scale for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. The scale ranges from 0 (no disability) to 6 (death).

The scale runs from 0 to 6, running from perfect health without symptoms to death:

0 = No symptoms.

1 = No significant disability. Able to carry out all usual activities, despite some symptoms.

2 = Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3 = Moderate disability. Requires some help, but able to walk unassisted.

4 = Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5 = Severe disability. Requires constant nursing care and attention; bedridden; incontinent.

6 = Dead.

Measurement Properties

No studies on patients with NMOSD or MS evaluating validity or reliability were identified. The mRS is reliable and has been well validated in patients suffering disability due to a stroke,[30] implying, however, an issue with its construct validity when applied to patients with NMOSD.

Minimal Important Difference

None identified for patients with NMOSD or MS.

Limitations

The inter-judge reproducibility seems better if the assessment is tied with a semi-structured conversation. The convergence validity in patients with stroke has been assessed by comparing it to the scales for disability in the Barthel index. Given that there is no direct assessment of this tool in patients with NMOSD, the validation of the instrument might suffer in construct and convergence validity.

Optic-Spinal Impairment Scale

This scale is a generic physician-reported instrument that was used in the PREVENT study to assess the severity of an individual relapse, specifically for optic neuritis and transverse myelitis relapses based on the OSIS visual acuity domain. The instrument consists of the following domains:

Visual acuity

0 = normal

1 = scotoma but visual acuity (corrected) better than 20/30

2 = visual acuity 20/30 to 20/59

3 = visual acuity 20/60 to 20/100

4 = visual acuity 20/101 to 20/200

5 = visual acuity 20/201 to 20/800

6 = count fingers only

7 = light perception only

8 = no light perception.

Motor function

0 = normal

1 = abnormal signs (hyperreflexia, Babinski sign) without weakness

2 = mild weakness (Medical Research Council grade 5– or 4+) in affected limb(s)

3 = moderate weakness (grade 3 or 4) in one or two Upper Motor Neuron muscles in affected limb(s)

4 = moderate weakness (grade 3 or 4) in three Upper Motor Neuron muscles in affected limb(s)

5 = severe weakness (grade 2) in one or more muscles in affected limb(s)

6 = some plegia (grade 0 or 1) muscles in one or more limbs

7 = plegia (grade 0 or 1) of all muscles in one or more limbs.

Sensory function

0 = normal

1 = mild decrease in vibration

2 = mild decrease in pinprick/temperature/proprioception or moderate decrease in vibration

3 = moderate decrease in touch/pin/proprioception or essentially lost vibration sense

4 = loss of all sensory modalities

5 = unknown.

Sphincter function

0 = normal

1 = mild urinary urgency or hesitancy; constipation

2 = moderate urinary urgency, hesitancy, or retention of bladder or bowel; infrequent urinary incontinence (less than once a week)

3 = frequent incontinence or retention requiring intermittent bladder catheterization or aggressive (manual) bowel assistance

4 = indwelling urinary catheter or absence of sphincter control

5 = unknown.

Measurement Properties

No studies on NMOSD or MS patients evaluating validity or reliability were identified.

Minimal Important Difference

None identified for patients with NMOSD or MS.

Limitations

The OSIS has been used in several studies, including PREVENT and ECU-NMO-302; however, no formal assessments of validity and reliability were identified in the literature.

Hauser Ambulatory Index

The HAI evaluates gait and is used to assess the time and effort used by the patient to walk 8 m (28 ft). The scale ranges from 0 to 9, with 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst (restricted to wheelchair; unable to transfer self independently).

0 = Asymptomatic; fully active

1 = Walks normally, but reports fatigue that interferes with athletic or other demanding activities

2 = Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 8 m (25 ft) in 10 seconds or less

3 = Walks independently; able to walk 8 m (25 ft) in 20 seconds or less

4 = Requires unilateral support (cane or single crutch) to walk; walks 8 m (25 ft) in 20 seconds or less

5 = Requires bilateral support (canes, crutches, or walker) and walks 8 m (25 ft) in 20 seconds or less, or requires unilateral support but needs more than 20 seconds to walk 8 m (25 ft)

6 = Requires bilateral support and more than 20 seconds to walk 8 m (25 ft); may use wheelchair* on occasion

7 = Walking limited to several steps with bilateral support; unable to walk 8 m (25 ft); may use wheelchair* for most activities

8 = Restricted to wheelchair; able to transfer self independently

9 = Restricted to wheelchair; unable to transfer self independently.

Note: The use of a wheelchair may be determined by lifestyle and motivation. It is expected that patients in grade 7 will use a wheelchair more frequently than those in grades 5 or 6. Assignment of a grade in the range of 5 to 7, however, is determined by the patient's ability to walk a given distance and not by the extent to which the patient uses a wheelchair.

Measurement Properties

No studies on NMOSD assessing validity or reliability were identified. Inter-rater reliability seems adequate (intraclass correlation coefficient [ICC] = 0.96) as well as the test-retest reliability (ICC = 0.91).[40,41] Criterion and construct validity are reported as excellent when correlated with other instruments assessing gait and ambulation.[41-43]

Minimal Important Difference

None identified for patients with NMOSD or MS.

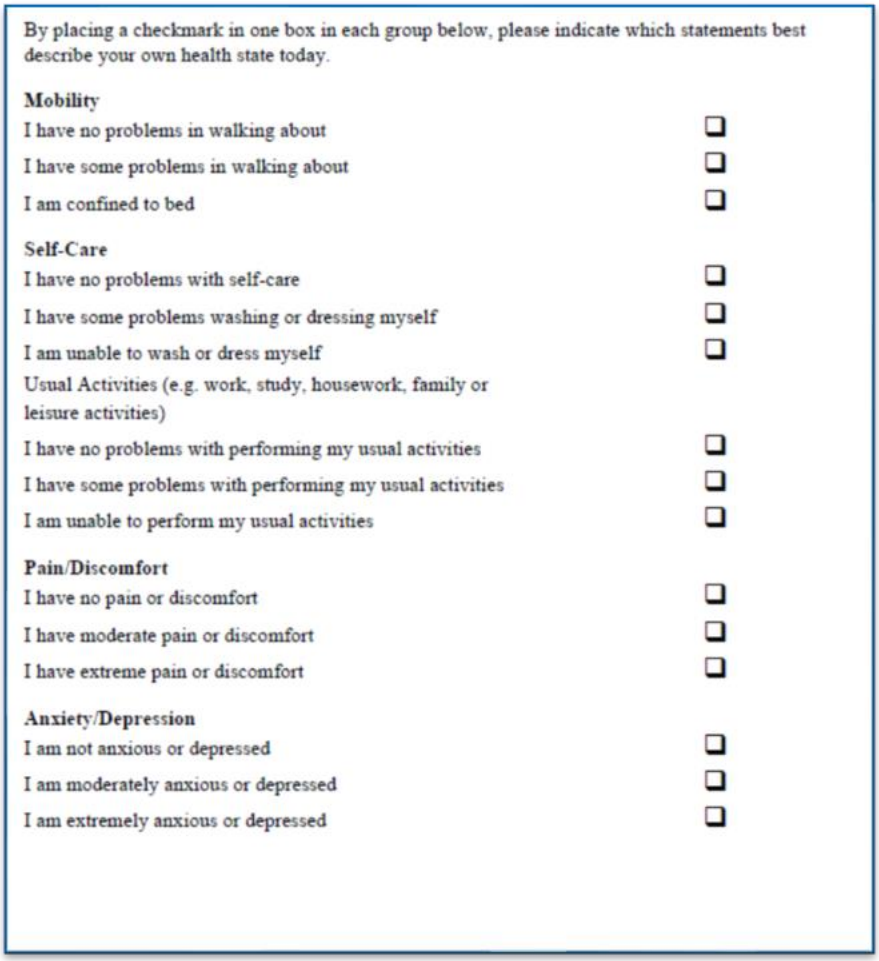
Limitations

Given that there is no direct assessment of this tool in patients with NMOSD, the validation of the instrument might suffer in construct, discriminative, and convergence validity.

EuroQol 5-Dimensions Questionnaire

The EQ-5D is a generic, standardized, patient self-administered instrument that provides a simple, descriptive profile and a single index value for health status. The EQ-5D comprises five dimensions of health: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension consists of three levels (some, moderate, extreme problems), generating a total of 243 theoretically possible health states. The response period is the day of assessment only. Assessments were also made using the EQ VAS, which captures the self-rating of current health status using a visual "thermometer," with the end points of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. The EQ-5D instrument is depicted in Figure 8 below:

Figure 8: EuroQol 5-Dimensions Questionnaire



By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

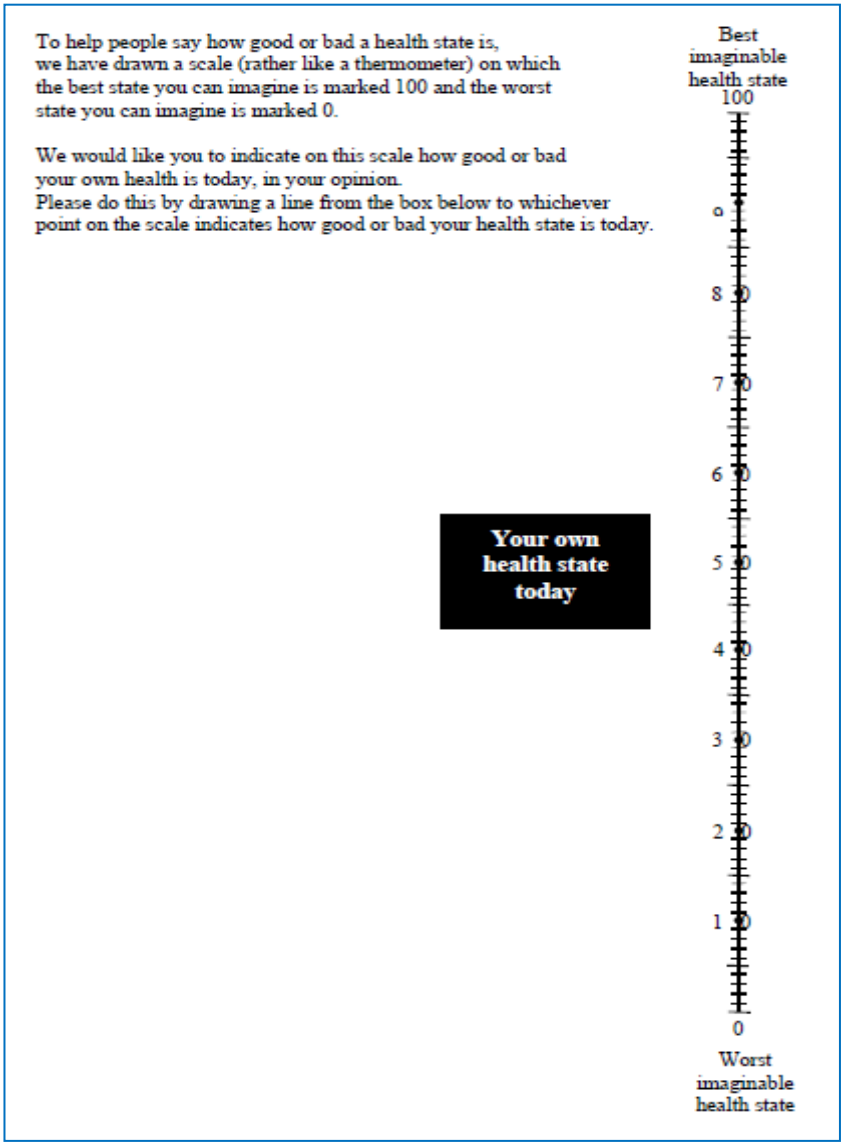
I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

Source: Clinical Study Report for PREVENT.[10]

Figure 9: EuroQol Visual Analogue Scale



Source: Clinical Study Report for PREVENT.[10]

Measurement Properties

No studies on NMOSD were found. However, one systematic review[31] assessing the EQ-5D (nine studies) in patients with MS was available. In terms of the content validity of the EQ-5D, the instrument included domains such as walking (mobility) and mood (anxiety or depression) that patients considered important to their quality of life; other critical domains such as fatigue and cognition are not included in the EQ-5D.

The convergent validity of impairment (gait, speed, severity) was moderate (pooled correlation estimate = 0.35; 95% CI, 0.25 to 0.45). For activity limitations, the pooled

correlation was 0.51 (95% CI, 0.45 to 0.57). When the EQ-5D was compared against measures evaluating health-related quality of life, the correlation value was 0.56 (95% CI, 0.54 to 0.59). Discriminative validity was evaluated in three studies. The mobility item lacked discriminative ability. The EQ-5D was able to differentiate between all EDSS levels except between levels 3 and 4.

In terms of reliability, the test-retest intra-class correlation coefficient of the EQ-5D was found to be acceptable, with a value of 0.81.

Minimal Important Difference

None identified for patients with NMOSD. An MID was reported for fatigue in only one study (in patients with MS), although this dimension is not included in the EQ-5D.[44]

Limitations

Some issues were identified with content validity for patients with MS and, in consequence, with NMOSD.

Short Form (36) Health Survey

The SF-36 is a generic health assessment questionnaire that is used to study the impact of chronic disease on HRQoL. The multi-item questionnaire contains eight dimensions: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The SF-36 also provides two component summaries: the PCS and the MCS, which are created by aggregating the eight domains according to a scoring algorithm.

Measurement Properties

No studies on patients with NMOSD were found. The instrument has been validated in patients with MS and neurological disabilities. One health technology assessment/systematic review[32] with seven studies included and 3,142 patients showed proper reliability (Cronbach alpha 0.70 for all subscales) and validity (with correlations ranging from 0.5 to 0.81). Two studies showed good to excellent internal consistency for the total instrument and for all subscales, with the exception of social function. Correlations between SF-36 subscales and impairment measures were weak. Inter-rater reliability between patients with disabilities and their caretakers was moderate.

Minimal Important Difference

The PCS and MCS and eight dimensions are each measured on a scale of 0 to 100, which are t scores (mean of 50 and SD of 10) that have been standardized to the US general population. Thus, a score of 50 on any scale would be at the average or norm of the general US population, and a score 10 points lower (i.e., 40) would be one SD below the norm. An increase in score indicates improvement in health status on any scale. In general use, a change of two points in the SF-36 PCS and three points in the SF-36 MCS indicates a clinically meaningful improvement, as determined by the patient.

Limitations

Summary scores of SF-36 in the MS patient population should be reported and interpreted with caution. This is the result of the inability to explain variability in the social functioning and SF-36 component scores. In addition, the SF-36 has been reported to overestimate the mental health of patients with MS on the mental health summary scale.

Given that there is no direct assessment in patients with NMOSD, convergence and discriminative validity might be an issue, although that is uncertain, given the absence of studies in patients with this clinical condition.

Visual Acuity Assessed With the Visual KFS

The EDSS (described above) quantifies disability in eight functional systems and allows an FSS to be assigned in each of these. This review focuses on the visual functional system, which is part the EDSS.

Measurement Properties

In terms of reliability, there was fair agreement in visual KFS found in one study with a kappa Cohen value of 0.39.[34] However, no values or assessment on validity directly related to the visual KFS were found, making it difficult to ascertain the convergent and discriminant validity of this specific functional system.

Minimal Important Difference

No MID can be calculated for visual acuity within the FSS, and no further information could be obtained.

Limitations

Given that there is no direct assessment in patients with NMOSD, the convergent and discriminant validity of the instrument is uncertain.

Appendix 5: Description and Analysis of the Aquaporin-4 Antibody Detection Tests in Patients With NMOSD

Background and Aim

A diagnosis of NMOSD for patients who test positive for AQP4-IgG involves one core clinical characteristic (i.e., optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical MRI lesions, or symptomatic cerebral syndrome with NMOSD-typical brain lesions) and the exclusion of alternative diagnoses. A diagnosis of NMOSD for patients who test negative for AQP4-IgG (or have an unknown AQP4-IgG status) requires more stringent clinical and MRI criteria. The International Consensus Diagnostic Criteria for NMOSD are considered the gold standard for evaluating diagnostic tests.[1]

The aim of this section is to describe and critically appraise the body of evidence evaluating the AQP4 antibody detection tests in patients with NMOSD.

Methods

Added to the core systematic literature search performed for this CADTH review, the information specialist team performed a focused search using the same entry terms and search strategy for the topic of NMOSD, with the addition of a search filter for diagnostic studies to detect AQP4 antibodies. Then, the review team screened for titles and abstracts, aiming to include up-to-date systematic reviews addressing this topic (ideally of no more than five years since publication). If no systematic review was found, the team would include and describe individual studies on the same topic. If an outdated systematic review was found, the CADTH team would update the body of evidence from the systematic review. Any systematic review found would be assessed for quality using the ROBIS tool.[46] If no systematic reviews were found, the team would narratively portray the diagnostic values of the tests found from the individual studies, but no meta-analysis was planned. CADTH included any type of antibody-detecting technique used to detect the presence of AQP4 antibodies.

Findings

The CADTH search strategy yielded 42 titles, of which one systematic review was considered of good quality and included.[47] This systematic review was published in 2015, thus CADTH aimed to include and describe further single studies published after the date of the last search strategy date of the systematic review. By doing this, CADTH found and included two studies.[48,49]

Systematic Review

The systematic review was considered to be well designed, with appropriate eligibility criteria and a search strategy without language limitations, and using six different databases. Screening, extraction of data, and risk of bias assessment (using the QUADAS-2 tool) was deemed adequate. Authors used a random-effects model to show a meta-analysis of diagnostic values for the different tests, including pooled sensitivity, specificity, and a plot of the summary of the receiver operating characteristic curve when possible.

The authors of the systematic review found a total of 71 articles, of which only 30 met their inclusion criteria for analysis of having low risk of bias. Overall, the risk of bias in the included studies was moderate due to non-blinding assessments with the reference standard by the interpreters.

Three main subgroups could be constructed: the cell-based assay technique group (with 653 NMO patients and 2,224 controls from 21 studies), the tissue-based assay group (15 studies, including 555 NMO patients and 3,223 controls), and the enzyme-linked immunosorbent assay (ELISA) group (with five studies, including 138 NMO patients and 723 controls). Overall, the cell-based assay group of tests show the best sensitivity and specificity for the detection of NMO, as shown in Table 36.

Table 36: Pooled Diagnostic Test Values

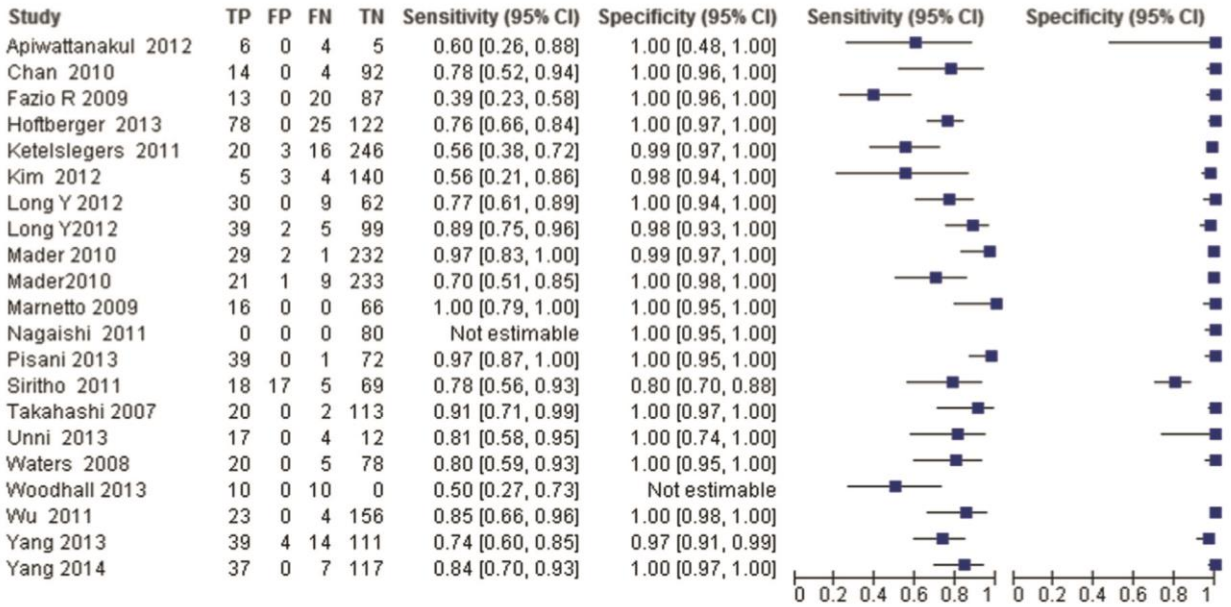
Index test	Studies (patients)	Sensitivity (95% CI)	Specificity (95% CI)
Cell-based assay	21 (2,877)	0.76 (0.67 to 0.82)	0.99 (0.97 to 0.99)
Tissue-based assay	15 (3,778)	0.59 (0.50 to 0.67)	0.98 (0.97 to 0.99)
ELISA	5 (861)	0.65 (0.53 to 0.75)	0.97 (0.96 to 0.99)

CI = confidence interval; ELISA = enzyme-linked immunosorbent assay.

Source: Ruiz-Gaviria et al. (2015).[47]

These values are also presented for the cell-based assay group of tests in Figure 10 and Figure 11.

Figure 10: Forest Plot of the Pooled Sensitivity and Specificity of the Cell-Based Assay Tests for the Diagnosis of NMOSD



CI = confidence interval; FN = false negatives; FP = false positives; NMOSD = neuromyelitis optica spectrum disorder; TN = true negatives; TP = true positives.

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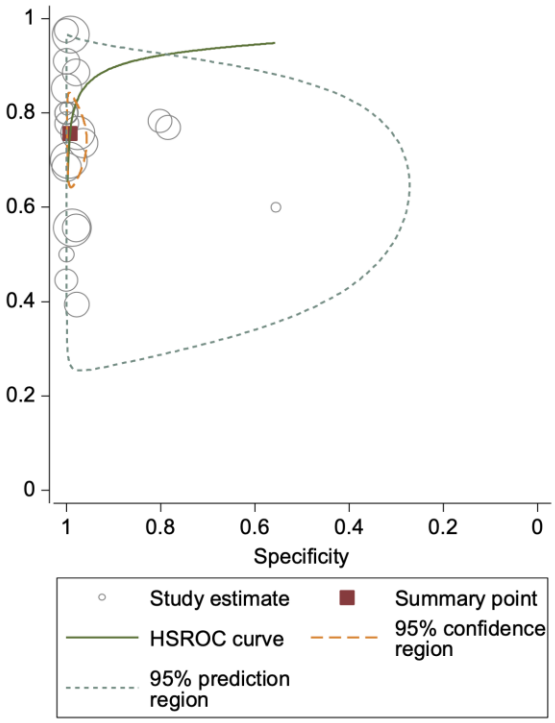
Figure 11: Summary of the Pooled Sensitivity and Specificity as a Receiver Operating Characteristics Plot



HSROC = hierarchical summary receiver operating characteristic.

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The systematic review has some limitations, such as how authors do not describe the reference test or gold standard used for the individual studies (although they describe it as "inappropriate" for most of the studies); furthermore, the review does not address details such as the risk of bias from individual studies or issues about heterogeneity, publication bias, or imprecision of effect estimates. Also, data on prevalence and other diagnostic values of interest (e.g., positive or negative predictive values or diagnostic odds ratios) are not presented.

Other Studies

Two other studies assessing diagnostic tests for detecting AQP4 antibodies and/or diagnosing NMOSD were included.[48,49] The first study[49] is small cohort of 25 patients, eight of whom were AQP4 antibody positive and the rest were seronegative. The study authors evaluate a novel nano-immunosensor to detect antibodies in a group of patients known to have NMOSD and compare them to those without the diagnosis of NMOSD (five with MS, four without MS) and against eight seronegative patients with NMOSD. In this study, the test had a specificity of 100% (95% CI, 63.0 to 100) with a sensitivity of 81.2% (95% CI, 56.5 to 99.0) and an area under the receiver operating characteristic curve of 0.82.

The second study evaluates a new ELISA technique, the ELISA-RSR assay, which is based on the human recombinant AQP4 M23 isoform. This study includes 64 patients with NMOSD and 27 controls (17 with MS and 10 without MS), using the Wingerchuk's criteria as reference standard. With a cut-off value of 2.1 or higher, the test had a sensitivity of 83.3% (95% CI, 62.6 to 95.2) and specificity of 100% (95% CI, 87.1 to 100), with an area under the receiver operating characteristic curve of 0.89 (95% CI, 0.77 to 0.96).

Both studies are considered at high risk of bias due to the lack of a proper blinded evaluation of the reference test (gold standard) and at high risk of imprecision due to small sample sizes, although this was mostly related to the inherent design of the studies, as both are exploratory in nature.

Conclusion

The CADTH team found one systematic review and two small studies evaluating tests for the detection of AQP4 antibodies in patients with NMOSD. Both bodies of evidence have limitations due to risk of bias (unblinded assessment of reference tests) and imprecision of results. However, they present consistent results in terms of a moderate sensitivity (of around 75%) and high specificity (100%). These results have to be used in context with the clinical presentation, as a negative test will not always indicate that the patient is without the disease.

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