RESEARCH ARTICLE

Ravulizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder

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Objective: CHAMPION-NMOSD (NCT04201262) is a phase 3, open-label, externally controlled interventional study evaluating the efficacy and safety of the terminal complement inhibitor ravulizumab in adult patients with anti–aquaporin-4 antibody–positive (AQP4+) neuromyelitis optica spectrum disorder (NMOSD). Ravulizumab binds the same complement component 5 epitope as the approved therapeutic eculizumab but has a longer half-life, enabling an extended dosing interval (8 vs 2 weeks).

Methods: The availability of eculizumab precluded the use of a concurrent placebo control in CHAMPION-NMOSD; consequently, the placebo group of the eculizumab phase 3 trial PREVENT (n = 47) was used as an external comparator. Patients received weight-based intravenous ravulizumab on day 1 and maintenance doses on day 15, then once every 8 weeks. The primary endpoint was time to first adjudicated on-trial relapse.

Results: The primary endpoint was met; no patients taking ravulizumab (n = 58) had an adjudicated relapse (during 84.0 patient-years of treatment) versus 20 patients with adjudicated relapses in the placebo group of PREVENT (during 46.9 patient-years; relapse risk reduction = 98.6%, 95% confidence interval = 89.7%–100.0%, $p < 0.0001$). Median (range) study period follow-up time was 73.5 (11.0–117.7) weeks for ravulizumab. Most treatment-emergent adverse events were mild/moderate; no deaths were reported. Two patients taking ravulizumab experienced meningococcal infections. Both recovered with no sequelae; one continued ravulizumab treatment.

Interpretation: Ravulizumab significantly reduced relapse risk in patients with AQP4+ NMOSD, with a safety profile consistent with those of eculizumab and ravulizumab across all approved indications.

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Additional supporting information can be found in the online version of this article.

Introduction

Anti–aquaporin-4 antibody–positive (AQP4+) neuromyelitis optica spectrum disorder (NMOSD) is a rare, severely disabling autoimmune neuroinflammatory disease of the central nervous system, typically causing transverse myelitis and optic neuritis.[1,2] It is characterized by recurrent, unpredictable relapses (also known as attacks) that result in accumulation of irreversible neurologic disability.[3]

The pathogenesis of NMOSD involves activation of the complement cascade via binding of aquaporin-4 autoantibodies to aquaporin-4 water channels on astrocytes. This results in cleavage of the terminal complement component 5 (C5) into C5a, which is a potent proinflammatory anaphylatoxin, and C5b, which is a critical coordinator of membrane attack complex formation. In patients with AQP4+ NMOSD, these active components are responsible for inflammation and astrocyte destruction.[4,5]

The emergence of C5 inhibition as a treatment strategy represented a crucial advancement in the management of this rare disease.[6] Eculizumab is a humanized monoclonal antibody that specifically binds and inhibits C5, preventing its cleavage. In the phase 3 PREVENT clinical trial (NCT01892345), eculizumab administered intravenously once every 2 weeks was associated with a 94.2% reduction in NMOSD relapse risk compared with matching placebo.[4] In the second half of 2019, eculizumab was the first, and remains the only, terminal complement inhibitor to receive approval for the treatment of adults with AQP4+ NMOSD.[7]

Ravulizumab is a recombinant, humanized monoclonal antibody structurally related to eculizumab with equivalent high specificity for the same C5 epitope.[8] Ravulizumab was created by substituting 4 amino acids in the eculizumab frame at the complementary binding region and the neonatal fragment crystallizable (FcRn) region, resulting in efficient recycling and augmented endosomal dissociation of C5. These changes increase the half-life of ravulizumab compared with eculizumab, thereby extending the duration of C5 inhibition[8] and enabling a prolonged dosing interval (intravenously, once every 8 vs 2 weeks).

CHAMPION-NMOSD (NCT04201262) is a pivotal interventional trial designed to minimize placebo exposure in this rare disease population. It aims to assess the efficacy and safety of ravulizumab in patients with AQP4+ NMOSD, using the PREVENT placebo group as an external comparator.

Subjects and Methods

Trial Design and Oversight

CHAMPION-NMOSD (NCT04201262, https://www.clinicaltrials.gov/ct2/show/NCT04201262) is a phase 3, externally placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with AQP4+ NMOSD. Given the potentially devastating consequences of a single NMOSD attack and the availability of eculizumab, use of a concurrent placebo comparator was considered unethical.[9] At the time of study design and initiation, alternative targeted therapies for AQP4+ NMOSD (eg, satralizumab, inebilizumab) were not approved, precluding their use as active comparators in a head-to-head clinical trial. To conduct a noninferiority trial using eculizumab as a comparator for ravulizumab, an estimated 8,600 patients would have been required for a trial with 90% power, 5% type I error, and a 1.25 noninferiority margin, assuming 8% of patients relapse in each arm. However, because NMOSD is a rare disease, recruiting this number of patients in a timely manner was considered not feasible. Results reported for the PREVENT trial led to rapid review and regulatory approval in 2019 for eculizumab in NMOSD; as of 2022, eculizumab has been approved in the EU, UAE, and 13 other countries for the treatment of NMOSD. Given the ethical dilemma and desire to avoid a placebo-controlled trial, as well as the fact that ravulizumab is a very similar molecule to eculizumab, in consultation with health authorities regarding the trial design, the decision was made to use the placebo group of PREVENT as an external comparator. To ensure a valid comparison, key study design elements from PREVENT were maintained in CHAMPION-NMOSD: similar inclusion/exclusion criteria, concomitant medications, adjudication procedures, and endpoints. CHAMPION-NMOSD was powered to detect a treatment effect comparable to that of eculizumab in PREVENT, with a 2-sided alpha of 0.05, relapse-free rates at 12 months of 0.92 and 0.63 in the ravulizumab and placebo groups, respectively, and a dropout rate of 2%-10%.

The study contains 4 periods: screening, primary treatment, long-term extension, and safety follow-up (Fig 1). Per protocol, the end of the primary treatment period could be triggered if 2 patients had an adjudicated on-trial relapse and all patients had completed 26 weeks on study. However, if 2 patients had not had an adjudicated on-trial relapse by the time all patients had completed 50 weeks on study, the end of the primary treatment period was to be triggered at that time. Here, we present results through the end of the primary treatment period for all patients enrolled.

The trial was conducted in accordance with the provisions of the Declaration of Helsinki,[10] the International Conference on Harmonisation guidelines for Good Clinical Practice,[11] and applicable regulatory requirements. The trial was approved by institutional review boards at each participating institution. All patients provided written informed consent before participation. Alexion, AstraZeneca Rare Disease, designed the trial in consultation with the lead author and key regulatory authorities, provided the trial agent, and analyzed the data. Confidentiality agreements were in place between the authors and Alexion, AstraZeneca Rare Disease. All authors confirm the completeness and accuracy of the data presented herein, the reporting of adverse events (AEs) as stipulated in the protocol, and the fidelity of the trial to the protocol. Protocol amendments occurring after the trial started are specified in the supplement.

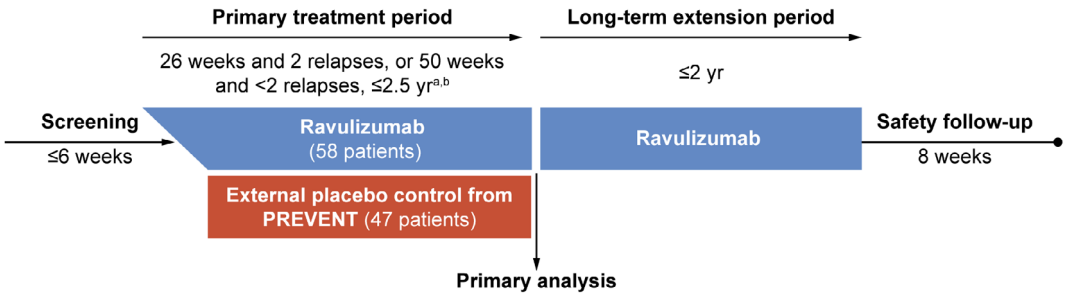

FIGURE 1: CHAMPION-NMOSD trial design. [a]The end of the primary treatment period was to be triggered when 2 patients had an adjudicated on-trial relapse and all patients had completed, or discontinued before, 26 weeks on study. If 2 patients had not had an adjudicated on-trial relapse by the time all patients had completed, or discontinued before, 50 weeks on study, the end of the primary treatment period was to be triggered at that time. [b]No patients had an adjudicated on-trial relapse during the study; the end of the primary treatment period was triggered when all patients had completed, or discontinued before, 50 weeks on study.

Inclusion and Exclusion Criteria

Patients aged 18 years or older with a diagnosis of AQP4+ NMOSD according to the 2015 international consensus diagnostic criteria[12] (serum anti–aquaporin-4 antibody status confirmed using a cell-based assay from an accredited laboratory), a history of at least 1 relapse in the 12 months before screening, and an Expanded Disability Status Scale (EDSS) score of ≤7 were eligible to participate.[13] As was the case in PREVENT, patients who were receiving immunosuppressive therapies (ISTs) for relapse prevention were eligible for inclusion if they were receiving stable-dose regimens. Exclusion criteria were previous or current treatment with a complement inhibitor, evidence of active systemic infection, history of *Neisseria meningitidis* infection, and previous participation in PREVENT. Furthermore, to maintain consistency with PREVENT exclusion criteria, patients who received mitoxantrone or rituximab during the 3 months before screening and those who received intravenous immunoglobulin during the 3 weeks before screening were excluded.

Trial Procedures

All patients were vaccinated against meningococcal infections ≥2 weeks before initiating ravulizumab, per local vaccination guidelines.

Patients received a body-weight–based loading dose of ravulizumab (2,400–3,000mg) via intravenous infusion on day 1, followed by a body-weight–based maintenance dose (3,000–3,600mg) on day 15, then once every 8 weeks. To maintain consistency with PREVENT (wherein treatment visits took place once every 2 weeks) and to minimize the risk of nonreporting or delayed reporting of relapse symptoms or AEs, phone call visits were implemented by the study sites every 2 weeks between scheduled dosing visits.

Treating physicians identified on-trial relapses according to the same criteria used in the PREVENT study[4]: new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination that persisted for >24 hours; signs and symptoms attributable to NMOSD; and onset preceded by ≥30 days of clinical stability. If potential relapse symptoms were reported during a scheduled biweekly phone call, patients were asked to have an onsite relapse evaluation visit as soon as possible to determine whether the patient's symptoms met the protocol-defined criteria for a relapse. To evaluate a potential relapse, magnetic resonance imaging (MRI) of the brain, cervical spine, and/or thoracic spine and/or optical coherence tomography were performed at the discretion of the treating physician. MRI images from screening and at the time of a potential relapse event were reviewed by an independent neuroradiologist who provided an interpretation report to the relapse adjudication committee (RAC). Isolated changes in imaging in the absence of related clinical findings were not considered to be indicative of relapse. Treating physicians determined the appropriate relapse treatment as well as any potential changes in ISTs. In contrast to PREVENT, patients in CHAMPION-NMOSD could continue to receive the study drug ravulizumab after a physician-determined relapse. All on-trial relapses were evaluated retrospectively, adhering to the same on-trial relapse criteria used by the treating physician, by an independent 3-member RAC. An adjudicated on-trial relapse refers to a relapse that was positively confirmed by the RAC.

To ensure that relapses were not overlooked by treating physicians and to mitigate any concerns of bias, cases of interest (COIs) were also adjudicated by the RAC. Patients who were seen by a treating physician for a relapse evaluation visit during which the treating physician determined that the patient had not had an on-trial relapse were considered to be COIs. In addition, to ensure ascertainment of all COIs, the study team conducted a protocol-defined periodic clinical database review of sentinel AEs: for example, back pain, hiccups, hemiparesthesia, and pruritis. Sentinel AEs that were associated with changes on the neurologic examination or contemporaneous MRI, or that resulted in hospitalization or treatment with intravenous methylprednisolone were considered to be COIs. All COIs were submitted to the RAC for adjudication.

Safety assessments included monitoring of AEs, clinical laboratory parameters, vital-sign measurements, electrocardiogram parameters, and evaluation for the presence of suicidal ideation or behavior.

Outcomes

The primary efficacy endpoint was time to first adjudicated on-trial relapse and associated relapse risk reduction in the ravulizumab group compared with the PREVENT placebo group.

Secondary endpoints were assessed at a type I error of 0.05 in a prespecified hierarchical order (shown): adjudicated on-trial annualized relapse rate (ARR; first), clinically important change from baseline in Hauser Ambulation Index (HAI)[14] score, changes from baseline in European Quality of Life–5 Dimensions (EQ-5D) index and EQ-5D visual analog scale (VAS),[15] and clinically important worsening from baseline in EDSS score[13] (last). To maintain the type I error for the trial, if one of the endpoints was missed, the p values of the remaining endpoints would be considered nominal. The comparator rate for the ARR of 1 relapse in 4 patient-years (0.25) was chosen to represent a conservative ARR that may be experienced in the population of patients with NMOSD. This comparison was selected, as opposed to a comparison with placebo, because of differences in study design between CHAMPION-NMOSD and PREVENT, which result in differences in follow-up times for patients after a relapse. Published registry data support an ARR of 0.6 in patients with NMOSD receiving commonly used therapies,[16] with another published analysis indicating a range of ARRs from 0.2 to 0.63 in patients receiving various first-line therapies for NMOSD.[17] The ARR endpoint would be considered statistically significant if the adjudicated on-trial ARR was <0.25 with a 2-sided $p \leq 0.05$.

Safety endpoints included incidence of treatment-emergent AEs (TEAEs), treatment-emergent serious AEs (TESAEs), and TEAEs leading to discontinuation of study drug. TEAEs presented herein exclude AEs of NMOSD relapse.

Statistical Analysis

Statistical analyses were performed using SAS version 9.4. A log-rank test was used to analyze between-group differences for the primary endpoint; the analysis included all patients who had received at least 1 dose of study drug. Hazard ratios (HRs) and risk reductions were summarized from a Cox proportional hazards model.

For consistency with PREVENT, changes in HAI, EQ-5D index, EQ-5D VAS, and EDSS scores were assessed from baseline (day of first dose of study drug or placebo) to either the end of the primary treatment period, or, for patients with physician-determined relapse, the week 6 relapse follow-up visit.

Additional statistical information, including statistical tests used for the secondary efficacy endpoints, can be found in the supplement.

Because using an external comparator could introduce confounding, a sensitivity analysis was conducted using propensity scores to balance treatment groups,[18] and a tipping-point analysis (E-value) was used to estimate, in terms of a relative risk, the amount of unmeasured confounding that would have been required to account for the treatment effect.[9,19] The E-value was calculated using the HR from the Cox proportional hazards model for both the estimate and the upper 95% confidence limit. This measure, which expresses the magnitude of the treatment effect in terms of a relative risk of at least 1, represents the amount of confounding that would be required to account for the treatment effect. For example, an E-value of the upper confidence limit 8.45 indicates that only an unmeasured confounder that is associated with an 8.45 times greater risk of adjudicated on-trial relapse and that occurs in 8.45 times more patients in the placebo group than in the study drug group would result in a nonsignificant treatment effect. Propensity scores were estimated from a logistic regression using the following baseline characteristics as covariates: region (Americas, Asia–Pacific, Europe), sex, age at first dose, background use of IST (yes/no), baseline EDSS score, and ARR in the 24 months before screening. Using propensity scores, time to first adjudicated on-trial relapse was evaluated using stabilized inverse probability of treatment weighting (sIPTW) to further balance baseline covariates between treatment groups.[20]

Results

Participant Enrollment and Baseline Characteristics

In total, 58 patients from 36 sites across 11 countries were enrolled in the study and received ravulizumab, between December 13, 2019 (first patient enrolled) and March 15, 2022 (end of primary treatment period; Fig 2). The PREVENT placebo group consisted of 47 patients who were enrolled between April 2014 and October 2017. Two patients who received ravulizumab discontinued treatment before the end of the primary treatment period: one following meningococcal infection, and the other 6 months after the diagnosis of invasive lobular breast carcinoma owing to ongoing cancer treatment. Baseline demographic and clinical characteristics of both treatment groups are given in Tables 1 and 2.

Study Duration

Because no patient had an adjudicated on-trial relapse during the study, the end of the primary treatment period was triggered when all patients in the ravulizumab group had completed a minimum of 50 weeks of treatment or discontinued before that time point. Patients who completed 50 weeks on study remained in the primary treatment period until all patients completed 50 weeks on study. Therefore, the overall treatment duration for each patient varied depending on when they enrolled in the study. The median (range) study period follow-ups for the ravulizumab and PREVENT placebo groups were 73.5 (11.0–117.7) and 36.0 (1.9–117.7) weeks, respectively.[4] In order to align with the maximum duration of the ravulizumab arm, the duration of placebo for this analysis was stopped at 117.7 weeks, which limited follow-up for 5 patients in the placebo arm who did not experience relapses following 117.7 weeks.

Efficacy

The primary endpoint (time to first adjudicated on-trial relapse) was met. No patient had an adjudicated on-trial relapse in the ravulizumab group over the course of 84.0 patient-years, compared with 20 patients who had an adjudicated relapse in the PREVENT placebo group over the course of 46.9 patient-years. The HR of the primary

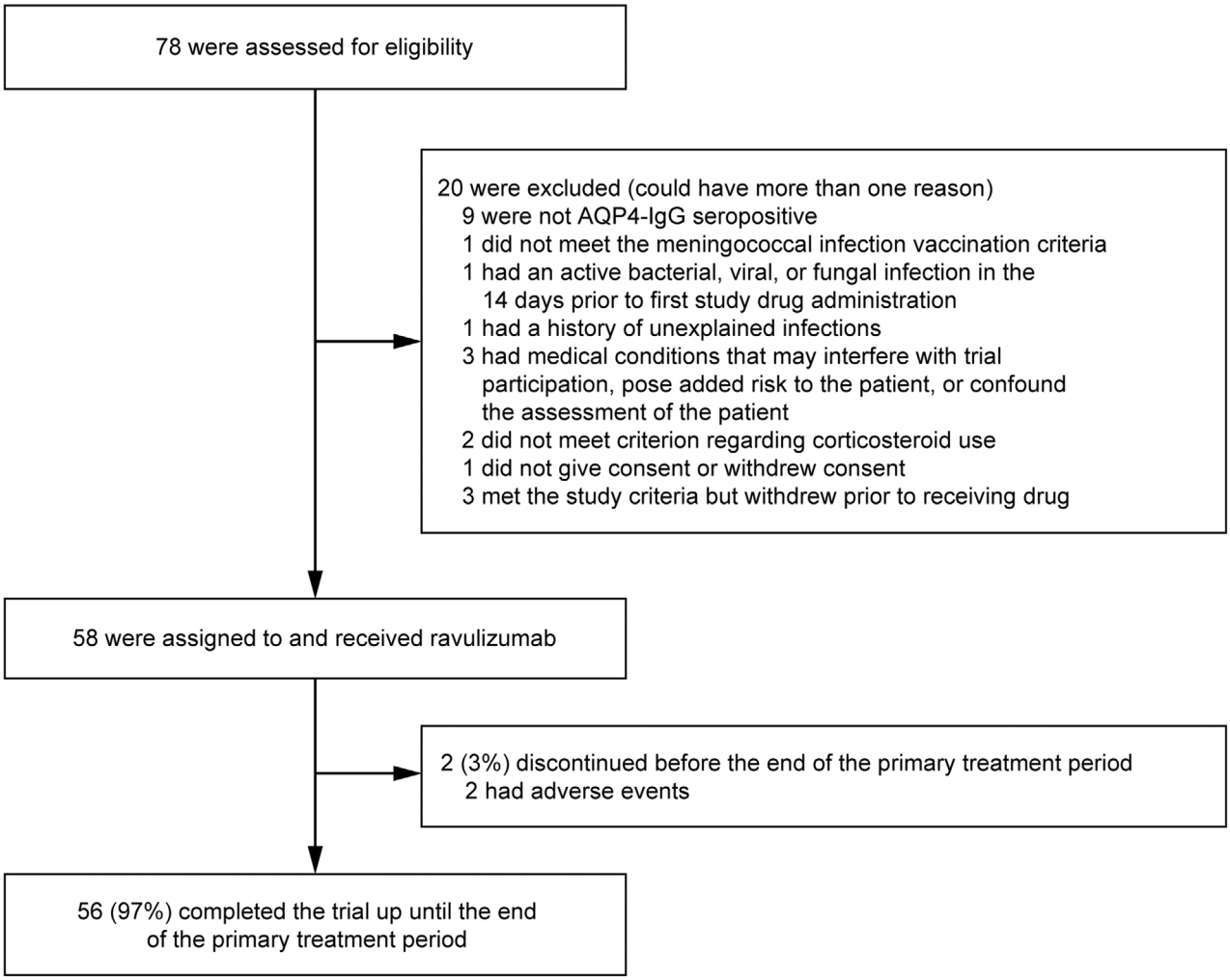

FIGURE 2: Enrollment and follow-up of patients in the single-arm CHAMPION-NMOSD study. AQP4-IgG = aquaporin-4 immunoglobulin G.

endpoint for ravulizumab compared with placebo was 0.014 (95% confidence interval [CI] = 0.000–0.103), representing a 98.6% reduction in the risk of relapse (log-rank $p < 0.0001$; Fig 3A). Physician-determined relapses occurred in 2 patients in the ravulizumab group, neither of whom were adjudicated positively (Table 3). In contrast, 29 patients in the PREVENT placebo group had physician-determined relapses, of which 20 were adjudicated positively. In a exploratory analysis of physician-determined relapses, the HR of the primary endpoint for ravulizumab compared with placebo was 0.039 (95% CI = 0.009–0.164), representing a 96.1% (95% CI = 83.6–99.1) reduction in the risk of relapse (log-rank $p < 0.0001$). The proportion of patients who were free from physician-determined relapses at week 48 in the ravulizumab arm was 0.965, compared with 0.506 in the placebo arm.

Overall, two of the secondary endpoints were met, ARR and HAI. The secondary endpoint of reduction in ARR with ravulizumab versus the prespecified ARR of 0.25 (1 adjudicated relapse in 4 patient-years) was met ($p < 0.0001$; Table 4). Furthermore, the proportion of patients experiencing clinically important worsening in HAI score was significantly lower with ravulizumab (2/58 patients, 3.4%) than with placebo (11/47 patients, 23.4%, odds of worsening with ravulizumab compared with PREVENT placebo group: 0.155, $p = 0.0228$; see Table 4). Neither of the 2 patients with worsening in HAI score had physician-determined relapses. Overall, the mean (standard deviation) change from baseline in HAI score for patients treated with ravulizumab was −0.1 (0.63) and, for those in the PREVENT placebo group, was 0.5 (1.61).

The majority of patients treated with ravulizumab (52/58 patients, 89.7%; see Table 4) experienced no clinical worsening of EDSS scores (odds of worsening with ravulizumab compared with PREVENT placebo group: 0.332, $p = 0.0588$). The median (range) change from

TABLE 1. Demographic and Clinical Characteristics of the Patients at Baseline

Characteristic	Ravulizumab (n = 58)	PREVENT Placebo Group (n = 47)	SMD
Female, *n* (%)	52 (89.7)	42 (89.4)	0.01
Mean age (±SD), years			
At first receipt of trial agent	47.4 ± 13.8	45.0 ± 13.3	0.18
At initial clinical presentation	42.3 ± 15.2	38.5 ± 15.0	0.25
Age group, *n* (%)			
<45 years	25 (43.1)	24 (51.1)	−0.16
≥45 years	33 (56.9)	23 (48.9)	0.16
Region			
Americas	21 (36.2)	15 (31.9)	0.09
Europe	17 (29.3)	19 (40.4)	−0.23
Asia-Pacific	20 (34.5)	13 (27.7)	0.15
Race, *n* (%)			
Asian	21 (36.2)	15 (31.9)	0.09
Black or African American	6 (10.3)	8 (17.0)	−0.20
White	29 (50.0)	24 (51.1)	−0.02
Other or unknown	2 (3.4)	0 (0.0)	NA
Mean BMI (±SD), kg/m^2	26.68 ± 6.50	25.65 ± 5.24	0.18
Mean ARR during previous 24 months (±SD)	1.87 ± 1.59	2.07 ± 1.04	−0.15
Time since last relapse, months			
Mean (±SD)	6.6 (3.1)	4.7 (2.8)	0.64
Median (range)	6.8 (1.4−13.2)	3.8 (1.0−12.4)	
Type of relapse during previous 24 months, *n* (%)			
Optic neuritis	25 (43.1)	22 (46.8)	–0.07
Transverse myelitis	34 (58.6)	42 (89.4)	–0.75
Brain stem symptoms or area postrema	15 (25.9)	15 (31.9)	–0.13
Cerebral symptoms	6 (10.3)	5 (10.6)	–0.01
EDSS score[a]			
Mean (±SD)	3.30 ± 1.58	4.26 ± 1.51	−0.62
Median (range)	3.25 (0.0 to 7.0)	4.00 (1.0 to 6.5)	
EQ-5D index score[b]			
Mean (±SD)	0.77 ± 0.22	0.68 ± 0.20	0.41
Median (range)	0.82 (0.04 to 1.00)	0.71 (0.27 to 1.00)	
EQ-5D VAS score[c]			
Mean (±SD)	73.6 ± 14.8	59.1 ± 20.4	0.81
Median (range)	77.5 (30 to 97)	60 (0 to 95)	
HAI score[d]			
Mean (±SD)	1.2 ± 1.42	2.1 ± 1.40	−0.70
Median (range)	1 (0 to 7)	2 (0 to 6)	

Percentages reported are subject to rounding and may not sum to 100. The SMD represents the number of standard deviations that the mean differences are from zero.

[a]EDSS scores ranged from 0 (no disability) to 10 (death).[13]

[b]EQ-5D index scores range from 0 (with 0 being the value of a health state equivalent to dead) to 1 (the value of full health), with higher scores indicating higher health utility.[15]

[c]EQ-5D VAS scores range from 0 (the worst imaginable health) to 100 (the best imaginable health), with higher scores indicating higher perceived quality of health.[15]

[d]HAI scores range from 0 to 9, with higher scores indicating decreased independent ambulation.[14]

ARR = annualized relapse rate; BMI = body mass index; EDSS = Expanded Disability Status Scale; HAI = Hauser Ambulation Index; NA = not available; SD = standard deviation; SMD = standardized mean difference; VAS = visual analog scale.

baseline in EDSS score for patients treated with ravulizumab was 0.0 (−3.0 to +1.0) and for those in the PREVENT placebo group, was 0.0 (−2.0 to +2.5). Six patients (10.3%) in the ravulizumab group experienced a clinically important worsening in EDSS score, with a median increase of 1 point (minimum = 1.0, maximum = 1.0) from baseline (see Table 4), none of whom had a physician-determined on-trial relapse or concomitant worsening in HAI score (Fig 4). In contrast, in the PREVENT placebo group, 11 patients (23.4%) experienced a clinically important worsening in EDSS score, with a median increase of 1.5 points (minimum = 0.5, maximum = 2.5) from baseline. Nine of these 11 patients had a contemporaneous physician-determined on-trial relapse; 6 of these 9 relapses were adjudicated positively. The changes from baseline in EQ-5D index score were not statistically significantly different between the ravulizumab and PREVENT placebo groups; therefore, no further inferences could be made on the remaining secondary endpoints, including EDSS (see Table 4).

In a prespecified subgroup analysis, patients receiving ravulizumab monotherapy (n = 30, 44.0 patient-years) had a 97.9% reduction in relative risk of relapse compared with patients in PREVENT receiving placebo in the absence of concomitant IST(s) (n = 13, 11.1 patient-years, HR = 0.021, 95% CI = 0.000–0.176, log-rank $p < 0.0001$; see Fig 3B). In a prespecified exploratory analysis of patients who received rituximab in the year before screening, there was a 93.7% reduction in relative risk of relapse in patients receiving ravulizumab (n = 20) compared with patients in PREVENT receiving placebo (n = 17, HR = 0.063, 95% CI = 0.000–0.562, log-rank $p = 0.0078$; see Fig 3C). In patients who did not receive rituximab in the year before screening, there was a 98.1% reduction in relapse risk in patients receiving ravulizumab (n = 38) compared with placebo (n = 30, HR = 0.019, 95% CI = 0.000–0.142, log-rank $p < 0.0001$). The interaction p value for patients who received rituximab in the year before screening compared with those who did not was 0.6774, indicating no difference in the treatment effect among patients who received rituximab in the prior year and those who did not.

Sensitivity Analysis

After weighting, the standardized mean difference for all covariates included in the propensity score calculation was between −0.25 and 0.25, indicating that the objective of balancing baseline characteristics between treatment groups was achieved. Using the sIPTW approach, the estimated HR for adjudicated on-trial relapses in the ravulizumab group versus the PREVENT placebo group was 0.014 (95% CI = 0.000–0.101; see Fig 3D), a relapse risk reduction of 98.6% (95% CI = 89.9–100.0%, $p < 0.0001$) and E-value for upper 95% confidence limit of 8.45. The E-value defines the magnitude of an unmeasured confounder required to account for the treatment effect; in this case, the E-value of the upper confidence limit indicates that only an unmeasured confounder associated with an 8.45 times greater risk of adjudicated on-trial relapse and that occurs in 8.45 times more patients in the placebo group would result in a nonsignificant treatment effect.

Safety

Overall, 328 TEAEs and 8 treatment-emergent serious adverse events (TESAEs) were reported in the ravulizumab group (Table 5). Of those, 38 TEAEs and 3 TESAEs were categorized as being related to ravulizumab by investigators (see Table 5). The most common TEAEs (in >10% of patients) were COVID-19 (24.1% of patients), headache (24.1%), back pain (12.1%), arthralgia (10.3%), and urinary tract infection (10.3%). The most common TEAEs (in >10% of patients) for the PREVENT placebo group (excluding NMOSD relapses) were nausea (25.5%), headache (21.3%), urinary tract infection (19.1%), pain in extremity (21.3%), nasopharyngitis (17.0%), vomiting (17.0%), back pain (12.8%), cough (12.8%), diarrhea (12.8%), dizziness (12.8%), fatigue (10.6%), and upper respiratory tract infection (12.8%). In the ravulizumab group, no clinically significant post-baseline trends were observed over time in electrocardiogram results or laboratory parameters.

Two patients developed meningococcal infections during treatment with ravulizumab, despite having received vaccination against *Neisseria meningitidis* serotypes A, C, W, Y, and B. Patient 1 (5th decade) was taking ravulizumab monotherapy and developed infection with serotype W135, 21 days after the first ravulizumab dose. Patient 2 (2nd decade) was taking ravulizumab with concomitant mycophenolate mofetil and prednisolone and developed infection with serotype B, 483 days after the first ravulizumab dose. Of note, Patient 2 had been exposed to rituximab 13 months before initiating ravulizumab treatment; 2 weeks before the occurrence of the meningococcal infection, their CD19 B-cell count remained reduced (0.04×10^9/l; normal reference range, 0.11 to 0.70×10^9/l). Both patients were treated rapidly with antibiotics and intensive care, and both recovered fully with no sequelae. Patient 1 withdrew from the study after recovering, whereas Patient 2 chose to continue receiving ravulizumab in the study.

TABLE 2. Treatment Received at Baseline

Characteristic	Ravulizumab ($n = 58$)	PREVENT Placebo Group ($n = 47$)	SMD
Supportive IST used at any time before the trial, *n* (%)	50 (86.2)	45 (95.7)	−0.34
Azathioprine	13 (22.4)	26 (55.3)	−0.72
Ciclosporin and tacrolimus	1 (1.7)	3 (6.4)	−0.24
Corticosteroids	29 (50.0)	30 (63.8)	−0.28
Cyclophosphamide	0 (0.0)	5 (10.6)	NA
Intravenous immunoglobulin	1 (1.7)	2 (4.3)	−0.15
Methotrexate	0 (0.0)	5 (10.6)	NA
Mitoxantrone	1 (1.7)	3 (6.4)	−0.24
Mizoribine	0 (0.0)	2 (4.3)	NA
Mycophenolate mofetil	7 (12.1)	15 (31.9)	−0.49
Satralizumab	1 (1.7)	0 (0.0)	NA
IST at baseline, *n* (%)	28 (48.3)	34 (72.3)	−0.51
None	30 (51.7)	13 (27.7)	0.51
Glucocorticoids alone	12 (20.7)	11 (23.4)	–
Azathioprine with or without glucocorticoids	7 (12.1)	13 (27.7)	–
Mycophenolate mofetil with or without glucocorticoids	6 (10.3)	8 (17.0)	–
Other drug with or without glucocorticoids[a]	3 (5.2)	2 (4.3)	–
Previous rituximab treatment[b], *n* (%)	21 (36.2)	20 (42.6)	−0.13
Time since last rituximab dose, months			
Mean (±SD)	7.2 (3.9)	12.9 (11.4)	−0.67
Median (range)	6.5 (3.8−21.9)	9.6 (4.8−48.1)	

Percentages reported are subject to rounding and may not sum to 100. The SMD represents the number of standard deviations that the mean differences are from zero.

[a]Other drugs included methotrexate, cyclosporine, cyclophosphamide, and tacrolimus.

[b]Patients who received rituximab during the 3 months before screening were excluded from the trial. This exclusion criterion was chosen to maintain consistency with PREVENT, and because the mechanism of action of rituximab is incompatible with that of ravulizumab. More specifically, rituximab selectively depletes B cells, mainly through complement-dependent cytotoxicity, and B-cell lysis is inhibited by 90% in the presence of eculizumab.[22]

IST = immunosuppressive therapy; SD = standard deviation; SMD = standardized mean difference.

Discussion

In this phase 3, external placebo-controlled, open-label, multicenter clinical trial, treatment with ravulizumab every 8 weeks significantly reduced relapse risk in patients with AQP4+ NMOSD compared with the PREVENT placebo group, adding further evidence supporting the use of C5 inhibitors as a treatment for this rare disease.

The relapse risk reduction of 98.6% observed with ravulizumab in CHAMPION-NMOSD is consistent with that observed with eculizumab in PREVENT and its long-term extension.[4,21] Furthermore, ravulizumab was associated with a significant reduction in HAI score worsening compared with PREVENT placebo, demonstrating a reduction in the accumulation of mobility-associated disability. Although clinically important worsening in EDSS score was observed in 6 patients treated with ravulizumab, it should be noted that these changes were not confirmatory of disability progression. Specifically, observed changes in EDSS scores were not accompanied by either a concomitant worsening in HAI scores or a positively

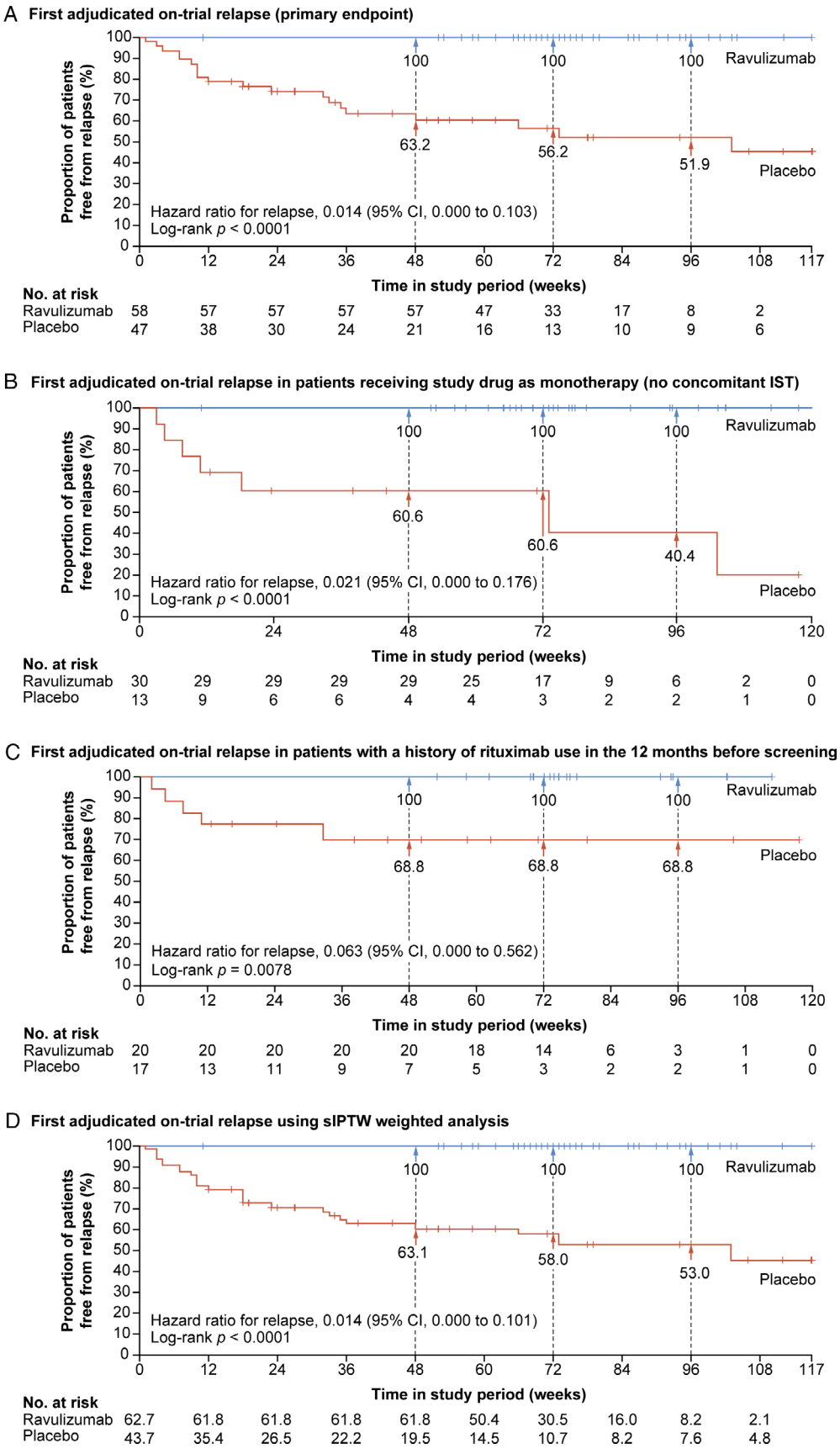

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TABLE 3. Summary of Physician-Identified On-Trial Relapses in the Ravulizumab Group

Age at First Dose of Study Drug, yr	Historical ARR[a]	IST Subgroup at Baseline	EDSS Score at Baseline	Day of Event Onset/Total Study Period Follow-up Time, Days	Type of On-Trial Relapse (Severity[b])	Hospitalized for Event	RAC Adjudication of Relapse	Reasons for Negative Adjudication
34	2.25	No IST usage	5.5	177/790, ongoing	Optic neuritis bilateral (minor)	Not hospitalized	Negative	Insufficient evidence of objective clinical findings of relapse event. MRI findings most consistent with prior inflammation, not an acute episode.
68	3.26	Steroids alone	6.0	109/533, ongoing	Transverse myelitis partial (minor)	Not hospitalized	Negative	Insufficient evidence of objective clinical findings of relapse event. MRI does not show new pathology.

[a]Historical ARR in the 24 months prior to screening.
[b]Relapse severity is derived from Opticospinal Impairment Score.
Abbreviation: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IST = immunosuppressive therapy; MRI = magnetic resonance imaging; RAC = relapse adjudication committee.

adjudicated on-trial relapse. It is also important to note that the EDSS scoring system was not developed for use in NMOSD and the scores are dependent upon the judgment of the observing physician.[13] Given this, scoring on this scale likely involved a degree of subjectivity, particularly for the range of values observed in this study, for which the scale may be considered an insensitive measure of disability. EDSS scores in these 6 patients fluctuated, and, in 1 patient, decreased by the end of the primary treatment period after an earlier rise. Together with the finding that none of the 6 patients with clinically important worsening in EDSS score experienced concomitant clinically important worsening in HAI score, these observations suggest that a fluctuation in EDSS score when viewed in isolation from other clinical information was not associated with, or indicative of, a relapse.

With a dosing interval of 8 weeks, ravulizumab offers the potential to reduce the treatment burden for patients and to decrease health care resource utilization. Additionally, more than half the patients in the present study received ravulizumab as monotherapy. These patients experienced a statistically significant reduction in relapse risk compared with those receiving placebo without concomitant IST in PREVENT, highlighting the potential use of ravulizumab as a relapse-preventative monotherapy for NMOSD, thereby sparing patients the potential side effects associated with IST use.

As in PREVENT, rituximab was not permitted as concomitant IST in CHAMPION-NMOSD because of the potential impact on the efficacy of meningococcal vaccination and the incompatibility between the mechanism of action of rituximab (selective depletion of B cells, mainly through complement-dependent cytotoxicity) and terminal complement inhibition.[22] Published studies evaluating the impact of terminal complement inhibitors, such as ravulizumab and eculizumab, on the activity of rituximab (which is dependent on complement) have demonstrated a reduction in B-cell lysis.[22–25] Additionally, as in PREVENT, patients in CHAMPION-NMOSD who received rituximab during the 3 months before screening were excluded from the trial. Although the efficacy of ravulizumab may have been influenced by previous exposure to rituximab (>3 months before screening) due to long-lasting B-cell depletion, we believe that it is highly unlikely to have impacted the outcome of the trial. This is

FIGURE 3: Kaplan–Meier estimates of time to first adjudicated relapse during the trial. Shown are Kaplan–Meier estimates (A) for all patients who received at least 1 dose of trial agent, (B) for patients taking the trial agent as monotherapy (no concomitant immunosuppressive therapy [IST]), (C) for patients who were recorded as having received rituximab in the 12 months before the study screening period, and (D) using stabilized inverse probability of treatment weighting (sIPTW)-weighted analysis. Because there were no relapses in the ravulizumab arm, Firth penalized likelihood was used to estimate the hazard ratio and the relapse risk reduction, and profile likelihood was used to estimate the 95% confidence interval (CI).

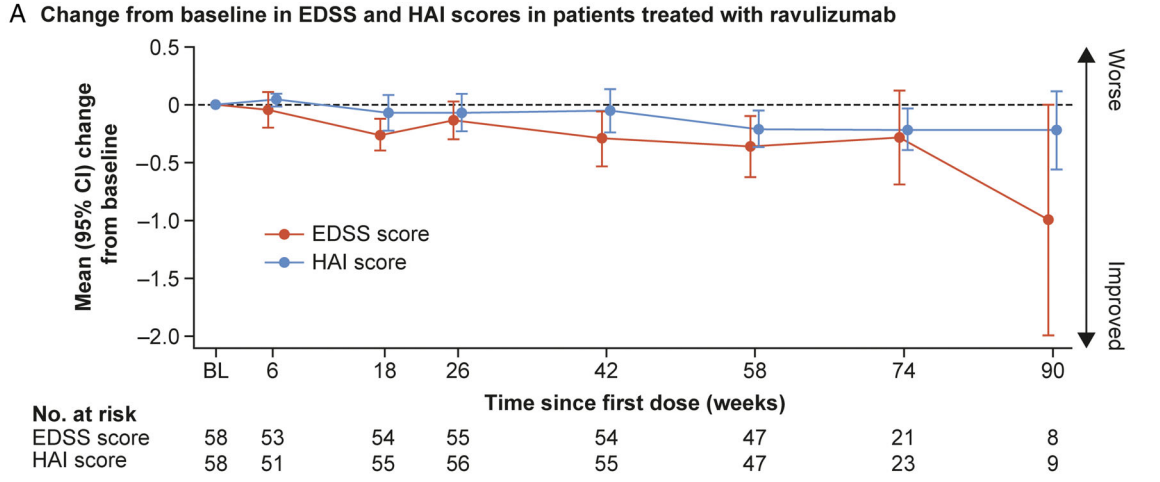
TABLE 4. Secondary Efficacy Endpoints

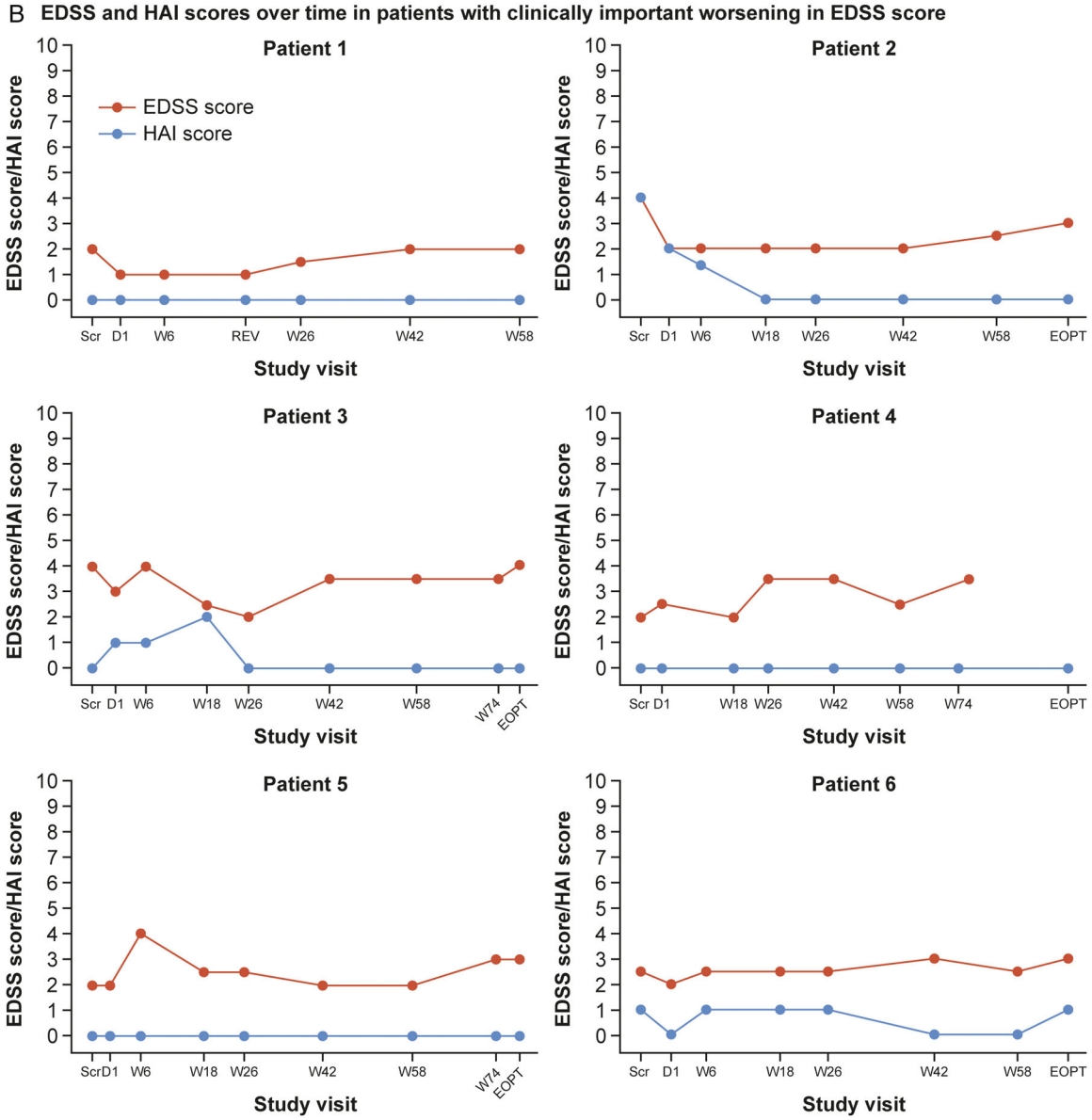
Endpoint	Test	Statistic	Ravulizumab, n = 58	PREVENT Placebo Group, n = 47	*p*
Adjudicated on-trial ARR	ARR_{Rav},[a] Poisson regression[b]	Adjusted ARR (95% upper CL)	0.000 (0.044)	N/A	<0.0001[a]
Change from baseline in HAI score[c]	Treatment group comparison, logistic regression	No clinically important worsening, n (%)[d]	56 (96.6)	36 (76.6)	0.0228
		Clinically important worsening, n (%)[d]	2 (3.4)	11 (23.4)	
Change from baseline in EQ-5D index score[e]	Treatment group comparison, ANCOVA of the ranked change	Mean ± SD	0.005 ± 0.1522	−0.043 ± 0.2115	0.0567
		Median	0.000	0.000	
		Range	−0.33 to 0.50	−0.67 to 0.41	
Change from baseline in EQ-5D VAS score[f]	Treatment group comparison, ANCOVA of the ranked change	Mean ± SD	2.6 ± 14.1	0.6 ± 16.4	N/A[g]
		Median	0.5	0.0	
		Range	−45 to 40	−28 to 40	
Change from baseline in EDSS score[h]	Treatment group comparison, logistic regression	No clinically important worsening, n (%)[i]	52 (89.7)	36 (76.6)	N/A[g]
		Clinically important worsening, n (%)[i]	6 (10.3)	11 (23.4)	

[a]The ARR_{Rav} was tested against a null hypothesis of 0.25. The comparator rate of 0.25 was chosen to represent a conservative ARR that may be experienced in the neuromyelitis optica spectrum disorder patient population.
[b]Per the statistical analysis plan, no relapses would be statistically significant. Because the Poisson regression would not run with 0 relapses, the *p* value and upper CL are from an ad hoc exact test.
[c]HAI scores range from 0 to 9, with higher scores indicating decreased independent ambulation.[14]
[d]Clinically important worsening in HAI score was evaluated as a change from baseline (first day of treatment) to either the end of the primary treatment period, or, for patients with a physician-determined relapse, the week 6 follow-up visit. Clinically important worsening was conditional on the baseline value and was defined as a baseline HAI score of 0 with a subsequent increase of ≥2 points or a baseline HAI score > 0 with a subsequent increase of ≥1 point. The analysis was performed using logistic regression, adjusting for baseline HAI.
[e]EQ-5D index scores range from 0 (with 0 being the value of a health state equivalent to dead) to 1 (the value of full health), with higher scores indicating higher health utility.[15] The analysis was performed using ranked analysis of covariance, adjusting for the baseline value.
[f]EQ-5D VAS scores range from 0 (the worst imaginable health) to 100 (the best imaginable health), with higher scores indicating higher perceived quality of health.[15] The analysis was performed using analysis of covariance of the ranks of the change from baseline, adjusting for the ranks of the baseline values.
[g]Because statistical significance for clinically important change from baseline in EQ-5D score was not met, *p* values for subsequent lower ranking secondary efficacy endpoints are not presented.
[h]EDSS scores ranged from 0 (no disability) to 10 (death).[13]
[i]Clinically important worsening in EDSS score was evaluated as a change from baseline (first day of treatment) to either the end of the primary treatment period or, for patients with a physician-determined relapse, the week 6 follow-up visit. Clinically important worsening was conditional on the baseline value and was defined as a baseline EDSS score of 0 with a subsequent increase of ≥2 points, a baseline EDSS score between 1 and 5 with a subsequent increase of ≥1 point, or a baseline EDSS score > 5 with a subsequent increase of ≥0.5 points. The analysis was performed using logistic regression, adjusting for baseline EDSS.
Abbreviation: ANCOVA = analysis of covariance; ARR = annualized relapse rate; ARR_{Rav} = annualized relapse rate of ravulizumab; CL = confidence limit; EDSS = Expanded Disability Status Scale; EQ-5D = European Quality of Life–5 Dimensions; HAI = Hauser Ambulation Index; N/A = not applicable; SD = standard deviation; VAS = visual analog scale.

based on published observations from PREVENT showing that the efficacy of eculizumab in preventing relapses was unaffected by previous treatment with rituximab.[26,27] Furthermore, the relapse risk reduction observed with ravulizumab compared with placebo remained statistically significant for patients who received rituximab in the year before screening, suggesting that previous rituximab use did not confound assessment of the effectiveness of ravulizumab. The generation of evidence supporting the use of targeted complement inhibition within 3 to 12 months after receiving rituximab is important to inform real-world instances of switching treatments.

The overall safety profile of ravulizumab observed in CHAMPION-NMOSD was consistent with that of





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eculizumab established over time across multiple indications,[4,21,28,29] and with that of ravulizumab in other indications (eg, generalized myasthenia gravis, paroxysmal nocturnal hemoglobinuria, and atypical hemolytic uremic syndrome).[30–32] By inhibiting the terminal complement system, ravulizumab increases the risk of meningococcal infection[33]; all patients were vaccinated before initiating ravulizumab to mitigate this risk. However, 2 cases of meningococcal infection were observed in vaccinated patients treated with ravulizumab in the present study; prompt recognition and treatment of the infection resulted in both patients recovering without sequelae, highlighting the importance of following established risk mitigation measures regarding meningococcal infections in patients receiving terminal complement inhibitors. Meningococcal infection is actively monitored in the postmarketing environment. As of October 1, 2021, the cumulative postmarketing reporting rate for meningococcal infections with eculizumab across all indications is approximately 0.25 per 100 patient-years (181 cases per 70,679 patient-years) and has remained stable over time. In addition, as of December 31, 2021, the cumulative postmarketing reporting rate for meningococcal infections with ravulizumab across indications is approximately 0.05 cases per 100 patient-years (3 cases per 5,734 patient-years).

Strengths and Limitations

The use of placebo in clinical trials is a well-recognized ethical challenge in rare diseases.[34] Single-arm trials with external comparators have been used to evaluate experimental drugs in rare and severe diseases, including pivotal trials that resulted in regulatory approvals.[35] Because of the NMOSD treatment landscape at the time of study design, an external placebo comparator was used to maximize the use of previous control cohort data and to minimize unnecessary risk of severe relapse. A limitation of this study is that the treating physicians, RAC, and patients were all unblinded. Multiple strategies were employed to mitigate potential bias arising from the unblinded nature of the trial in these parties. Treating physicians were provided with the same criteria on when to report suspected relapses as in PREVENT, and the RAC reviewed all suspected relapses using the same relapse criteria and the same available clinical evidence as in PREVENT. To mitigate potential bias in patients, and to replicate the cadence of patient and study site staff interactions in PREVENT, biweekly phone visits were implemented in this trial to ensure that patients had equivalent opportunities to report AEs and potential relapse symptoms. If potential relapse symptoms were identified during these phone visits, an in-person relapse evaluation visit would have been scheduled as soon as possible. To minimize potential bias further, the database was systematically reviewed per protocol to identify potential missed relapses and other COIs, and both physician-identified on-trial relapses and COIs were adjudicated by the independent RAC. It is our hope that the innovations in trial design undertaken in CHAMPION-NMOSD will further the advancement of research in rare diseases, especially in situations when the availability of an approved treatment ethically precludes the use of placebo control, and/or limited patient populations prevent the recruitment of sufficient patients to power a noninferiority trial against existing approved treatments.

Although CHAMPION-NMOSD was designed to be as similar as possible to PREVENT, between-group differences in baseline characteristics were possible. This potential was minimized by elements of the trial design, and the ultimate impact of these differences on the trial results was assessed using propensity score–weighted analyses (sIPTW) and was found to be negligible given the consistent results between the primary analysis and the sIPTW-weighted analysis. Additionally, to preserve scientific validity, consistency with PREVENT was maintained whenever possible. There were differences in 2 inclusion criteria that relate to underlying NMOSD characteristics. First, the diagnostic criteria used to identify NMOSD in CHAMPION-NMOSD were the updated 2015 International Panel for NMO Diagnosis criteria,[12] whereas the 2006[36] and 2007[2] criteria were used to identify neuromyelitis optica and NMOSD, respectively, in PREVENT. Because all participants in PREVENT were seropositive for anti–aquaporin-4 antibodies, they would all have met the 2015 criteria. Second, PREVENT required eligible patients to have at least 2 relapses in the 12 months before screening or at least 3 relapses in the 24 months before screening, with at least 1 occurring in the 12 months before screening. However, data published after PREVENT was designed showed a modest reduction of 4 to

FIGURE 4: Expanded Disability Status Scale (EDSS) and Hauser Ambulation Index (HAI) scores during the primary treatment period in patients receiving ravulizumab. Shown are EDSS and HAI scores (A) for all patients who received at least 1 dose of ravulizumab and (B) for the 6 patients who experienced clinically significant worsening in EDSS score during the primary treatment period. EDSS scores ranged from 0 (no disability) to 10 (death). HAI scores range from 0 to 9, with higher scores indicating decreased independent ambulation. Baseline (BL) is defined as the first day of ravulizumab treatment. CI = confidence interval; D = day; EOPT = end of primary treatment period; REV = relapse evaluation visit; Scr = screening; W = week.

TABLE 5. Summary of TEAEs in the Ravulizumab Group, Excluding NMOSD Relapses

Adverse Event Category	Ravulizumab, n = 58	
	Events, n	Patients, n (%)
Any TEAE	328	53 (91.4)
Any TEAE related to trial agent, as determined by investigator[a]	38	26 (44.8)
Any TEAE according to severity[b]		
Severe[c]	13	9 (15.5)
Moderate	71	29 (50.0)
Mild	244	48 (82.8)
TEAE leading to discontinuation of agent	3	1 (1.7)
TEAE reported in >10% of patients		
COVID-19	14	14 (24.1)
Headache	24	14 (24.1)
Back pain	8	7 (12.1)
Arthralgia	6	6 (10.3)
Urinary tract infection	7	6 (10.3)
Any TESAE	8	8 (13.8)
Related to trial agent, as determined by investigator	3	3 (5.2)
Death	0	—
Meningococcal infections	2	2 (3.4)
TESAE related to trial agent, as determined by investigator[a]		
Pneumonia	1	1 (1.7)
Meningococcal sepsis	1	1 (1.7)
Meningococcal encephalitis	1	1 (1.7)

Note: TEAEs are adverse events with a start date on or after the date of the first dose of study drug. Percentages reported are subject to rounding and may not sum to 100.

[a]TEAEs and TESAEs were categorized as being related or unrelated to ravulizumab by treating physicians.

[b]TEAEs reported as grade 1 were mapped to mild, grade 2 to moderate, and grades 3–5 to severe.

[c]Severe TEAEs were those that interrupted a patient's usual daily activities and may have required systemic drug therapy or other treatment; severe events are usually incapacitating.

Abbreviation: NMOSD = neuromyelitis optica spectrum disorder; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

8% in the risk of future relapses between patients who had 1 versus 2 relapses in the previous 24 months[37]; these data informed the inclusion criteria for CHAMPION-NMOSD. Furthermore, a recent review of clinical trials in NMOSD with relapse inclusion criteria that were less restrictive than those used in PREVENT showed a similar time to first relapse in the placebo arm and similar historical ARR.[38] Despite heterogeneity of inclusion criteria, a meta-analysis of relapse prevention in controlled trials of monoclonal antibodies or ISTs consistently showed a greater proportion of relapse-free patients at 24 months compared with placebo.[39] In addition, based on the placebo relapse-free survival rates reported in Pittock's review,[38] 21 to 25 relapses would have been expected in the first 46 weeks of CHAMPION-NMOSD. Based on this evidence, this change in inclusion criteria was not expected to have substantially affected the potential for relapse in patients enrolled in CHAMPION-NMOSD compared with those in PREVENT. Results from the weighted propensity score analysis to balance baseline covariates were in line with the primary results, suggesting that differences in baseline characteristics included in the weighted analysis did not confound the overall treatment effect. The E-value observed in the tipping-point analysis, a measure that reframes the magnitude of the treatment effect, suggests that considerable unmeasured confounding would be needed to account for the observed relapse risk reduction with ravulizumab.

In conclusion, in patients with AQP4+ NMOSD, ravulizumab significantly reduced relapse risk compared with placebo, with no patients in the ravulizumab group experiencing an adjudicated on-trial relapse over a median duration of 73.5 weeks. Current risk mitigation strategies, including vaccination, education, and ongoing vigilance, are effective in managing the increased risk of meningococcal infection conferred by C5 inhibition. Building on existing experience with eculizumab in this setting, ravulizumab represents a potential new therapy for adults with AQP4+ NMOSD that combines strong efficacy, a well-established safety profile, and an 8-week dosing interval.

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Author Contributions

S.J.P., M.Y., K.A., and Y.M. contributed toward the concept and study design. M.Y. and K.A. contributed toward

acquisition and statistical analysis of the data. All authors contributed toward drafting the text and/or preparing the figures.

Potential Conflicts of Interest

S.J.P. has received personal compensation for serving on scientific advisory boards for F. Hoffmann-La Roche (which manufactures satralizumab, an approved targeted therapy for NMOSD) and his institution has received grants; his institution has received grants, personal fees, nonfinancial support, research support, and compensation for serving as a consultant for Alexion, AstraZeneca Rare Disease (which holds the patent rights to ravulizumab [used in this study] and eculizumab [used in the PREVENT study]). He holds Patent # 9,891,219B2, Application # 12–573,942, Methods for Treating Neuromyelitis Optica (NMO) by Administration of Eculizumab to an Individual That Is Aquaporin-4 (AQP4)-IgG Autoantibody Positive, which has been issued and for which he has received royalties. He also reports grants, personal fees, nonfinancial support, and other support from MedImmune (which produces inebilizumab, an approved anti-CD19 antibody used in NMOSD). He has received a grant from Novelmed. M.B. has received institutional support for research or speaking from Alexion, AstraZeneca Rare Disease. J.L.B. has received personal fees from Alexion, AstraZeneca Rare Disease and F. Hoffmann-La Roche; and grants from Alexion, AstraZeneca Rare Disease. A.B. reports compensation for clinical trials received by his institution from Alexion, AstraZeneca Rare Disease, Biogen (which produces rituximab, an approved B-cell–depleting immunosuppressive therapy used in NMOSD), and F. Hoffmann-La Roche; and personal fees and nonfinancial support from Alexion, AstraZeneca Rare Disease, Biogen, and F. Hoffmann-La Roche. M.L. reports research support from Alexion, AstraZeneca Rare Disease; and serves as a consultant for Alexion, AstraZeneca Rare Disease. I.N. has received honoraria for serving on the scientific advisory board and for serving as a speaker for Alexion, AstraZeneca Rare Disease. C.O.-G. has received honoraria for speaking and serving on advisory boards from Biogen. J.P. has received grants and support for scientific meetings and honoraria for advisory work from Alexion, AstraZeneca Rare Disease, MedImmune, and F. Hoffmann-La Roche. She also holds shares in AstraZeneca (of which Alexion, AstraZeneca Rare Disease is a part). F.P. has received honoraria and research support from Alexion, AstraZeneca Rare Disease; has received research grant support from Biogen and F. Hoffmann-La Roche; has received honoraria for lectures, presentations, and speakers bureaus and support for attending meetings from Alexion, AstraZeneca Rare Disease, Biogen, and F. Hoffmann-La Roche; and has served as an advisory board member for F. Hoffmann-La Roche. C.P. has served as a speaker and consultant and has received advisor fees, research support, and travel grants from Alexion, AstraZeneca Rare Disease, Biogen, and F. Hoffmann-La Roche. K.A. and Y.M. are employees of Alexion, AstraZeneca Rare Disease and hold stock options. M.Y. was an employee of Alexion, AstraZeneca Rare Disease at the time this research was undertaken. H.J.K. has received consultancy/speaker fees from Alexion, AstraZeneca Rare Disease, Biogen, and F. Hoffmann-La Roche.

Data Availability Statement

Data underlying the findings described in this article may be obtained in accordance with the Alexion, AstraZeneca Rare Disease data-sharing policy, which is described at https://alexion.com/our-research/research-and-development.

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