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Long-Term Ravulizumab Efficacy and Safety in AQP4 Antibody–Positive Neuromyelitis Optica Spectrum Disorder

Final CHAMPION-NMOSD Results

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Abstract

Background and Objectives

Ravulizumab, a complement component 5 inhibitor, was approved for the treatment of adults with anti–aquaporin-4 antibody–positive (AQP4-Ab+) neuromyelitis optica spectrum disorder (NMOSD) based on results of the primary treatment period (PTP) of CHAMPION-NMOSD, a phase 3, open-label, external placebo-controlled trial. Here, we report the final efficacy and safety results of CHAMPION-NMOSD (PTP and the long-term extension [LTE]).

Methods

Adult patients with AQP4-Ab+ NMOSD received an IV, weight-based loading dose of ravulizumab on day 1 and a maintenance dose on day 15 and every 8 weeks thereafter. After completion of the PTP (up to 2.5 years), patients could enter the LTE. The primary endpoint was time to first adjudicated on-trial relapse. The placebo group of the eculizumab phase 3 trial PREVENT was used as an external comparator because eculizumab availability at CHAMPION-NMOSD initiation precluded the use of concurrent placebo control.

Results

Of 58 patients enrolled in the trial, 56 entered and 55 completed the LTE. The overall median (range) follow-up was 170.3 (11.0–243.0) weeks, with 100.8 (53–137) weeks during the LTE. No patient receiving ravulizumab had an adjudicated on-trial relapse throughout the PTP (84.0 patient-years) and LTE (105.7 patient-years); relative reduction in risk of relapse vs placebo (n = 47) was 98.9% (95% CI 91.8–100; $p < 0.0001$). Treatment-emergent adverse events (TEAEs) and serious TEAEs were reported in 94.8% and 27.6% of patients, respectively, during the PTP and LTE. Most TEAEs were grade 1 and unrelated to ravulizumab. One patient discontinued ravulizumab because of TEAEs. Two cases of meningococcal infection occurred during the PTP; none occurred in the LTE. One death due to hypertensive heart disease (unrelated to ravulizumab) occurred during the LTE.

Discussion

Long-term ravulizumab treatment (median follow-up, >3 years) continued to show significant relapse risk reduction in patients with AQP4-Ab+ NMOSD, and the safety profile was consistent with the known safety profile for ravulizumab.

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Class of Evidence
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Supplementary Material

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Glossary

AQP4-Ab+ = anti–aquaporin-4 antibody-positive; **ARR** = annualized relapse rate; **EDSS** = Expanded Disability Status Scale; **EQ-5D** = EuroQol 5-dimension; **gMG** = generalized myasthenia gravis; **HAI** = Hauser Ambulation Index; **HR** = hazard ratio; **IST** = immunosuppressive therapy; **LTE** = long-term extension; **NMOSD** = neuromyelitis optica spectrum disorder; **PNH** = paroxysmal nocturnal hemoglobinuria; **PTP** = primary treatment period; **TEAE** = treatment-emergent adverse event; **VAS** = visual analog scale.

Trial Registration Information

ClinicalTrials.gov, NCT04201262; EudraCT: 2019-003352-37. Submitted December 11, 2019. First patient enrolled: December 13, 2019. clinicaltrials.gov/study/NCT04201262.

Classification of Evidence

This study provides Class III evidence that long-term ravulizumab treatment, as compared with placebo, decreases the probability of clinical relapse in patients with AQP4-Ab+ NMOSD.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, chronic, autoimmune disease of the CNS that typically causes transverse myelitis and optic neuritis.[1] It is more common among women and non-White populations, with onset typically during adulthood.[2] Patients experience unpredictable relapses, leading to accumulation of irreversible neurologic disability.[1,3,4] Relapse prevention is therefore critical for reducing disability accumulation in patients.[3] Given the chronic nature of NMOSD, ensuring long-term clinical benefit of a treatment with an acceptable safety profile is of paramount importance.

Anti–aquaporin-4 antibody–positive (AQP4-Ab+) NMOSD is characterized by complement-mediated astrocyte damage, leading to axonal degeneration and neural cell death.[5] Therefore, complement component 5 (C5) inhibition is a key strategy for disease management.[6] Eculizumab, a humanized monoclonal antibody, was the first C5 inhibitor approved for adults with AQP4-Ab+ NMOSD[7] and is approved in multiple countries and regions, including Argentina, Canada, China, the European Union, Japan, and the United States.[8-13] Eculizumab, dosed every 2 weeks, significantly reduced the risk of adjudicated relapses in patients with AQP4-Ab+ NMOSD vs placebo in the phase 3 PREVENT trial (NCT01892345).[14,15]

Another C5 inhibitor, ravulizumab, was approved for AQP4-Ab+ NMOSD in China, the European Union, Japan, Latin America (Argentina, Brazil, and Mexico), and the United States among other regions and countries[11,16-20] based on the results of the external placebo-controlled, phase 3 CHAMPION-NMOSD trial (NCT04201262).[21] Ravulizumab, a recombinant humanized monoclonal antibody, was developed from eculizumab to have an extended half-life, allowing for a longer dosing interval of 8 weeks, potentially reducing patient burden.[22]

CHAMPION-NMOSD was conducted between 2019 and 2024 across 11 countries and comprised 2 core intervention periods: a primary treatment period (PTP)[21] and a long-term extension (LTE). The trial met its primary endpoint demonstrating longer time to first adjudicated on-trial relapse vs placebo from the PREVENT trial at the end of the PTP. No adjudicated on-trial relapse was observed in the ravulizumab group (n = 58) across 84.0 patient-years compared with 20 of 47 patients in the PREVENT placebo group with an adjudicated relapse across 46.9 patient-years of follow-up. Ravulizumab reduced the risk of relapse by 98.6% vs placebo ($p < 0.0001$). The safety profile was consistent with that for eculizumab and ravulizumab in NMOSD and other indications.[21] In this analysis of CHAMPION-NMOSD, we evaluated the long-term efficacy and safety of ravulizumab in patients with AQP4-Ab+ NMOSD and we are reporting the end of study results from the LTE of CHAMPION-NMOSD.

Methods

Trial Design

CHAMPION-NMOSD, a global, open-label, phase 3 trial, evaluated the efficacy and safety of ravulizumab in adult patients with AQP4-Ab+ NMOSD. The trial used the placebo group of PREVENT as a comparator because it was considered unethical to randomize patients to placebo when eculizumab was available for AQP4-Ab+ NMOSD at the time of CHAMPION-NMOSD initiation. The full-trial design and PTP procedures were published previously.[21] Briefly, CHAMPION-NMOSD consisted of 4 periods: screening, PTP, LTE, and safety follow-up. Baseline was defined as the day of first study drug dose. As reported previously,[21] no adjudicated on-trial relapse was observed during the PTP; therefore, according to the protocol, the PTP end was triggered when all patients receiving ravulizumab had completed ≥50 weeks of treatment or discontinued before that time. Patients who completed 50 weeks remained in the PTP until all patients completed 50 weeks on trial.

Subsequently, patients were offered the opportunity to enroll in the LTE.

Standard Protocol Approvals, Registrations, and Patient Consents

The trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and applicable regulatory requirements. The trial was approved by institutional review boards at each participating site, and all patients provided written informed consent before participation. The trial is registered with ClinicalTrials.gov (NCT04201262) and EudraCT (2019-003352-37). The study protocol and statistical analysis plan are available in eSAP 1 and eSAP 2, respectively.

Inclusion and Exclusion Criteria

Eligibility criteria, described previously,[21] included patients aged 18 years or older with AQP4-Ab+ NMOSD (diagnosed per the 2015 international consensus diagnostic criteria[23]) who had ≥1 relapse in the 12 months before screening and an Expanded Disability Status Scale (EDSS) score ≤7.0. Patients receiving immunosuppressive therapy (IST) for relapse prevention must have been on a stable dose regimen. Vaccination against *Neisseria meningitidis* in the 3 years before initiating ravulizumab per local vaccination guidelines was required. For patients initiating ravulizumab <2 weeks after immunization, appropriate prophylactic antibiotics were required until 2 weeks after vaccination. Mitoxantrone or rituximab during the 3 months before screening, IV immunoglobulin during the 3 weeks before screening, and a history of *N. meningitidis* infection or other systemic infections were exclusionary.

Trial Procedure

All patients received a weight-based IV loading dose (2,400–3,000 mg) of ravulizumab on day 1 and a maintenance dose (3,000–3,600 mg) on day 15 and once every 8 weeks thereafter.

Treating physicians identified on-trial relapses by new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination that persisted for >24 hours and onset preceded by ≥ 30 days of clinical stability. In addition, the signs and symptoms had to be attributable to NMOSD. MRI was conducted at the treating physician's discretion to evaluate a potential relapse. Isolated changes on MRI or other imaging examinations with no related clinical findings were not considered an on-trial relapse. Treating physicians were responsible for determining the appropriate treatment and any potential changes in ISTs. All on-trial relapses were evaluated retrospectively by an independent 3-member relapse adjudication committee using the same criteria as the treating physicians. Confirmed relapses are reported here as adjudicated on-trial relapses.

Endpoints and Assessments

The primary endpoint was time to first adjudicated on-trial relapse and associated relapse risk reduction. Key secondary endpoints included adjudicated on-trial annualized relapse rate (ARR), clinically important change from PTP baseline in Hauser Ambulation Index (HAI) score (range: 0–9; higher scores indicating decreased independent ambulation),[24] changes from baseline in EuroQol 5-dimension (EQ-5D) questionnaire index (range: 0–1; higher scores indicating higher health utility) and EQ-5D visual analog scale (VAS; range: 0–100; higher scores indicating higher perceived quality of health),[25] and clinically important worsening from baseline in EDSS score (range: 0 [no disability]–10 [death]).[26] Clinically important changes in HAI score included clinical worsening (defined as ≥2-point increase from a baseline score of 0 or ≥ 1-point increase from a baseline score of ≥1) and clinical improvement (defined as ≥1-point decrease from a baseline score of ≥2); a stable HAI score was defined as ≤1-point increase from a baseline score of 0, ≤1-point decrease from a baseline score of 1, or a baseline score of ≥2 and no additional change. Clinically important worsening in EDSS score was defined as ≥2.0-point increase from a baseline score of 0.0, ≥1.0-point increase from a baseline score of 1.0–5.0, or ≥0.5-point increase from a baseline score of >5.0; patients who did not meet the definition of worsening were evaluated as "no worsening (improvement or no change)."

Post hoc analyses were conducted to evaluate confirmed and sustained clinically important worsening on EDSS, clinical improvements in EDSS scores from baseline to the study's end or stable scores, and confirmed and sustained disability improvements on EDSS. Confirmed clinically important worsening on EDSS was defined as the clinically important worsening that was maintained for ≥5 months before the study's end. The clinically important worsening was considered sustained if no stable or improved values relative to baseline were observed following the first confirmed clinically important worsening. A clinical improvement in EDSS score was defined as ≥1-point decrease at the end of the study from a baseline EDSS score of 2.0–5.5 or ≥0.5-point decrease from a baseline score of >5.5. Patients with a baseline score of <2.0 did not meet the definition of clinical improvement and were categorized as stable unless they exhibited clinical worsening. Confirmed disability improvement in EDSS score was defined as clinical improvement maintained across ≥5 months. Sustained disability improvement on EDSS was defined as no stable or worse value since the first improvement.

Safety outcomes are reported only for patients receiving ravulizumab and included treatment-emergent adverse events (TEAEs), serious TEAEs, and adverse events (AEs) leading to treatment discontinuation. TEAEs were coded using the *Medical Dictionary for Regulatory Activities*, version 27.1. Safety data for the PREVENT placebo group have been reported previously.[14]

Statistical Analyses

Efficacy and safety endpoints were assessed in all patients receiving ≥1 dose of ravulizumab. Statistical analyses were performed using Statistical Analysis Software version 9.4 (SAS®, SAS Institute, Cary, NC) or higher. The time to first adjudicated on-trial relapse was evaluated using a log-rank test to assess differences between ravulizumab and PREVENT placebo. Hazard ratio (HR) and risk reduction were summarized from a Cox proportional hazards model. Because no relapses occurred in the ravulizumab treatment arm, Firth adjustment with profile likelihood confidence limits[27] was used to estimate the HR and risk reduction. Hypothesis testing was 2-sided and performed at the 0.05 level of significance. Kaplan-Meier estimates of the proportion of patients with no adjudicated on-trial relapse were assessed across time points, with 95% CIs based on the complementary log-log transformation. Follow-up duration for the PREVENT placebo arm was truncated in the PTP analysis to align with duration of the ravulizumab arm available at that time.[21] This was not necessary in the current analysis as the maximum ravulizumab treatment duration exceeded that of PREVENT placebo because per PREVENT trial termination criteria, the trial was concluded after 23 of the 24 prespecified adjudicated relapses occurred, and patient follow-up was limited to 6 weeks after a relapse.[14]

HAI, EDSS, EQ-5D index, and EQ-5D VAS scores were assessed as the change from PTP baseline to the end of the study period (the last available visit for patients in the trial). For the HAI score, the number and proportion of patients in each clinically important change category (clinical improvement, stable HAI, and clinical worsening) were calculated along with Clopper-Pearson 95% CIs. Similarly, for EDSS, the number and proportion of patients with clinically important worsening (yes/no) were calculated along with Clopper-Pearson 95% CIs. Mean changes from baseline in EQ-5D index and EQ-5D VAS scores are presented with 95% CIs.

Data Availability

Alexion, AstraZeneca Rare Disease, will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods such as data deidentification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy.[28]

Results

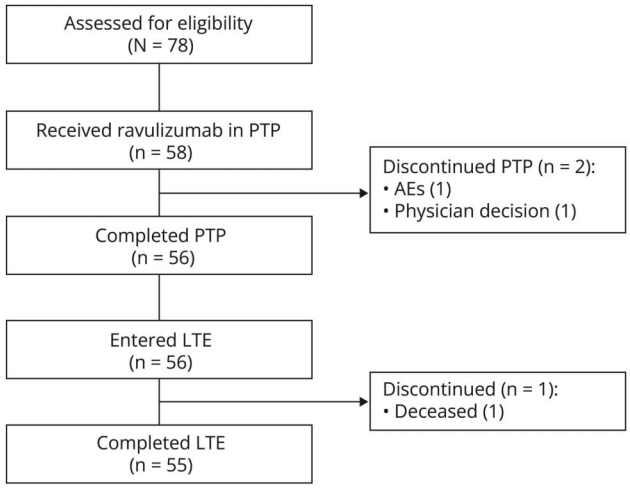
Patient Enrollment and Baseline Characteristics

Of 58 patients receiving ravulizumab in CHAMPION-NMOSD, 56 completed the PTP and entered the LTE (Figure 1). Two patients discontinued treatment during the PTP: 1 due to meningococcal infection and 1 due to physician decision after a diagnosis of invasive breast cancer.[21] Overall, 55 patients (94.8%) completed treatment in the LTE; 1 death due to hypertensive heart disease occurred during the LTE.

Demographics and baseline clinical characteristics of patients in CHAMPION-NMOSD and those in the placebo group from the PREVENT trial have been reported previously[21] and were generally similar between groups. The mean (SD) age of patients at diagnosis was 44.2 (14.5) years and 41.1 (14.4) years in the ravulizumab and placebo groups, respectively. Patients started treatment at the mean (SD) age of 47.4 (13.8) years in the ravulizumab group and 45.0 (13.3) years in the placebo group. Most patients were women (ravulizumab, 52/58 [89.7%]; placebo, 42/47 [89.4%]).

During the 24 months before screening, the median (first quartile [Q1], third quartile [Q3]) ARR was 1.44 (0.96, 2.08; mean [SD]: 1.87 [1.59]) in the ravulizumab group and 1.92 (1.44, 2.40; mean [SD]: 2.07 [1.04]) in the PREVENT placebo group. The mean (SD) time since last relapse was 6.6 (3.1) months and 4.7 (2.8) months, respectively. The baseline mean (SD) HAI scores were 1.2 (1.4) in the ravulizumab group and 2.1 (1.4) in the placebo group. Mean (SD) EDSS scores were 3.3 (1.6; median [Q1, Q3]: 3.3 [2.0, 4.0]) and 4.3 (1.5; median [Q1, Q3]: 4.0 [3.5, 5.5]), respectively. The baseline mean (SD) EQ-5D index and VAS scores were 0.77 (0.22) and 73.6 (14.8), respectively, in the ravulizumab group and 0.68 (0.20) and 59.1 (20.4) in the placebo group.

Figure 1 Patient Enrollment and Follow-Up During CHAMPION-NMOSD (PTP and LTE)



Of 58 patients enrolled in CHAMPION-NMOSD, 56 completed the PTP and entered the LTE. Among patients who entered the LTE, 55 completed their treatment. Overall, 3 patients discontinued treatment and there was 1 death during the trial. AE = adverse event; LTE = long-term extension; PTP = primary treatment period.

At PTP baseline, 27 patients (46.6%) in the ravulizumab group and 34 (72.3%) in the placebo group were taking concomitant ISTs. Corticosteroids alone were the most common IST among patients receiving ravulizumab (11 patients [19.0%]), and azathioprine with or without corticosteroids was the most common IST in the PREVENT placebo group (13 [27.7%]). Nine patients (15.5%) receiving ravulizumab and 12 (25.5%) receiving placebo were taking corticosteroids in addition to another IST. Prior rituximab treatment was reported in 21 patients (36.2%) in the ravulizumab group, with a mean (SD) treatment gap of 7.2 (3.9) months since the last rituximab dose. In the PREVENT placebo group, 20 patients (42.6%) had previously received rituximab, with a mean (SD) gap of 12.9 (11.4) months since the last dose.

Efficacy

None of the 58 patients receiving ravulizumab in CHAMPION-NMOSD had an adjudicated on-trial relapse during the entire trial duration (median follow-up, 170.3 [range, 11.0–243.0] weeks; 189.7 patient-years) compared with 20 patients who had an adjudicated on-trial relapse in the PREVENT placebo group (median follow-up, 36.0 [range, 1.9–208.6] weeks; 52.4 patient-years). The HR (95% CI) for adjudicated on-trial relapse was 0.011 (0.000, 0.082) for ravulizumab vs placebo, representing a 98.9% (95% CI 91.8–100) reduction in the risk of relapse (log-rank $p < 0.0001$) with ravulizumab treatment (Figure 2). Overall, 3 patients receiving ravulizumab had a physician-identified on-trial relapse: 2 patients during the PTP[21] and 1 during the LTE. All 3 events were negatively adjudicated because of insufficient evidence to support objective findings of a relapse event. In addition, MRI findings did not show the relevant pathology. The adjudicated ARR with ravulizumab treatment was 0 (95% upper confidence limit, 0.019, $p < 0.0001$) (Table 1).

At the end of the trial, 55 of 58 patients (94.8%) receiving ravulizumab were stable or had clinically important improvements in HAI scores from the PTP baseline, while 3 patients (5.2%) had clinical worsening (Table 1). One of these patients had a physician-identified relapse (eFigure 1A) at approximately week 14, which did not coincide with HAI worsening, first reported at week 26. The mean change in HAI scores with ravulizumab was consistent throughout the trial, with no notable change (Figure 3A). The mean (SD) change in HAI score from baseline to the end of the trial was −0.2 (0.74).

At the trial's end, of 58 patients receiving ravulizumab, 53 (91.4%) showed no clinically important worsening and 5 (8.6%) showed clinically important worsening on EDSS from baseline (Table 1). One of these 5 patients had a physician-identified relapse (eFigure 1A); however, it did not coincide with EDSS worsening. Per the post hoc analyses, 1 patient (1.7%) had a confirmed clinically important worsening on EDSS, which was sustained for 18.4 months from the first worsening to the trial's end. Clinical improvements in EDSS scores from baseline to trial's end were observed in 16 patients (27.6%; 95% CI 16.7%–40.9%) and scores remained stable in 37 (63.8%; 95% CI 50.1%–76.0%). Confirmed disability improvement from baseline EDSS scores was observed in 12 of 50 patients (24.0%) with baseline score ≥2.0; sustained improvements were observed in 9 of 50 patients (18.0%). The mean (SD) time from the first improvement to trial's end was 35.3 (8.5; median [Q1, Q3]: 35.0 [30.7, 42.4]) months.

The overall mean change in EDSS score decreased from baseline across the PTP and LTE (Figure 3B), with a mean (SD; 95% CI) change of −0.40 (1.0; −0.66, −0.14) from baseline to the trial's end; the median (Q1, Q3) change from baseline was 0 (−1.0, 0). Among patients who experienced clinically important worsening in EDSS scores at the study end, clinically important worsening in HAI scores rarely accompanied clinically important worsening in EDSS scores (eFigure 1).

No substantial change was observed in EQ-5D index and EQ-5D VAS scores through the trial (Table 1). In exploratory analyses, no meaningful change from baseline in visual acuity was observed in the ravulizumab group at the trial's end. No worsening in color vision or confrontational visual fields was reported with ravulizumab; these parameters were not evaluated for the placebo group because they were not measured in PREVENT.

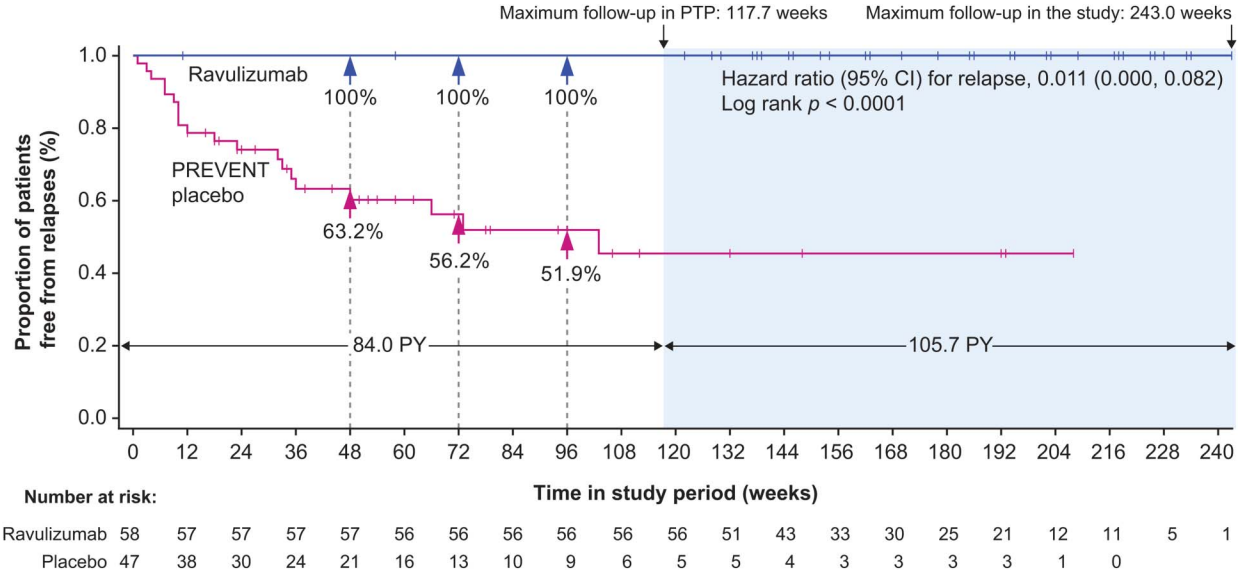
Changes in IST Use

In CHAMPION-NMOSD, changes to concomitant ISTs were not permitted until after week 106, unless the patient experienced a relapse or an AE. Two patients discontinued concomitant ISTs before week 106 for reasons other than safety and were noted as protocol deviations; 8 patients changed their ISTs (3 decreased dose and 5 discontinued) because of safety concerns. Nineteen patients received concomitant ISTs for more than 106 weeks; of these, 9 (47.4%) either decreased dose (n = 7) or discontinued (n = 2) their ISTs. Overall, 17 of 27 patients (63.0%) taking concomitant ISTs at baseline either reduced dose or discontinued ≥1 IST at any time during the trial (eFigure 2). No patient increased their current IST(s) doses or started a new IST for relapse prevention during the trial.

Safety

Overall, 605 TEAEs were reported in 55 of 58 patients (94.8%), with a rate of 318.8 TEAEs per 100 patient-years in the ravulizumab group. Of 605 TEAEs, 60 (9.9%) in 27 of 58 patients (46.6%) were considered treatment-related by the investigator (Table 2). Most TEAEs (423 events [69.9%] in 50/58 patients [86.2%]) were grade 1. The most common TEAEs (in ≥15% of patients) were COVID-19, headache, urinary tract infection, and upper respiratory tract infection (Table 2). One patient withdrew from the trial during PTP because of 2 nonserious TEAEs of bronchitis and *Stenotrophomonas* infection and 1 serious TEAE of meningococcal

Figure 2 Kaplan-Meier Estimates of Time to First Adjudicated Relapse in Patients Receiving Ravulizumab in CHAMPION-NMOSD (PTP and LTE) vs Those in the Placebo Arm of the PREVENT Trial



No patients receiving ravulizumab had an adjudicated on-trial relapse during the entire trial duration (median follow-up, 170.3 [range, 11.0–243.0] weeks) compared with 20 patients with adjudicated on-trial relapse in the PREVENT placebo group (median follow-up, 36.0 [range, 1.9–208.6] weeks). Tick marks indicate censoring of data. Data for patients who did not have an adjudicated on-trial relapse were censored at the end of the study period. LTE = long-term extension; PTP = primary treatment period; PY = patient-years.

encephalitis. Of the 22 serious TEAEs (3.6%) reported in 16 of 58 patients (27.6%), 4 events (0.7%) in 4 of 58 patients (6.9%) were considered to be treatment-related. The 4 treatment-related serious TEAEs were cellulitis, pneumonia, meningococcal encephalitis, and meningococcal sepsis. As previously published, meningococcal infections occurred during the PTP in 2 patients receiving ravulizumab who had been vaccinated against meningococcal infection (details in eAppendix).[21] Both patients were treated with antibiotics and intensive care and recovered without sequelae[21]; 1 of these remained in the trial and continued to receive ravulizumab into the LTE. No meningococcal infections occurred during the LTE. No deaths occurred during the PTP.[21] One patient died during the LTE; the patient had a history of hypertension, and the death due to hypertensive heart disease was assessed as unrelated to ravulizumab.

Classification of Evidence

This study provides Class III evidence that long-term ravulizumab treatment, as compared with placebo, decreases the probability of clinical relapse in patients with AQP4-Ab+ NMOSD.

Discussion

In a published analysis of the PTP in the pivotal phase 3 CHAMPION-NMOSD trial, patients with AQP4-Ab+ NMOSD who were treated with ravulizumab experienced no adjudicated on-trial relapse over the course of 84 patient-years.[21] Results from the current analysis of the CHAMPION-NMOSD LTE build on the PTP findings and demonstrate the long-term efficacy of ravulizumab for AQP4-Ab+ NMOSD. Here, we show that after an additional 105.7 patient-years of follow-up through the end of the LTE (overall, median 170.3 weeks and 189.7 patient-years), no patient receiving ravulizumab experienced an adjudicated relapse. In addition, the significant effect of ravulizumab vs placebo on the time to first adjudicated on-trial relapse and relapse risk reduction observed during the PTP (HR [95% CI], 0.014 [0.000–0.103])[21] was maintained with additional follow-up time during the LTE (0.011 [0.000, 0.082]).

Patients with NMOSD who experience relapses and have severe disease have worse outcomes, use more health care resources, and incur higher costs than patients without relapses.[29,30] In most cases, recovery after a relapse is incomplete and worsens with increasing number of relapses,[31] highlighting the importance of relapse prevention. Given the crucial role of effective and well-tolerated treatments in relapse prevention,[3] the end of CHAMPION-NMOSD study results demonstrates that ravulizumab has the potential to not only lower disease burden for patients but also reduce treatment burden through its extended 8-week dosing period, ultimately lowering health care resource utilization and the overall relapse-associated cost, as well as generally improving patients' quality of life. Patients with AQP4-Ab+ NMOSD have a high risk of relapse, with 55% of patients experiencing relapse within a year of initial attack.[32] A retrospective analysis of claims data collected between 2012 and 2019 showed that almost 50% of patients experienced ≥1 relapse during a median follow-up of 2 years.[29] Thus, the absence of an adjudicated on-trial relapse with ravulizumab during the median

Table 1 Secondary Efficacy Endpoints During the PTP and the LTE

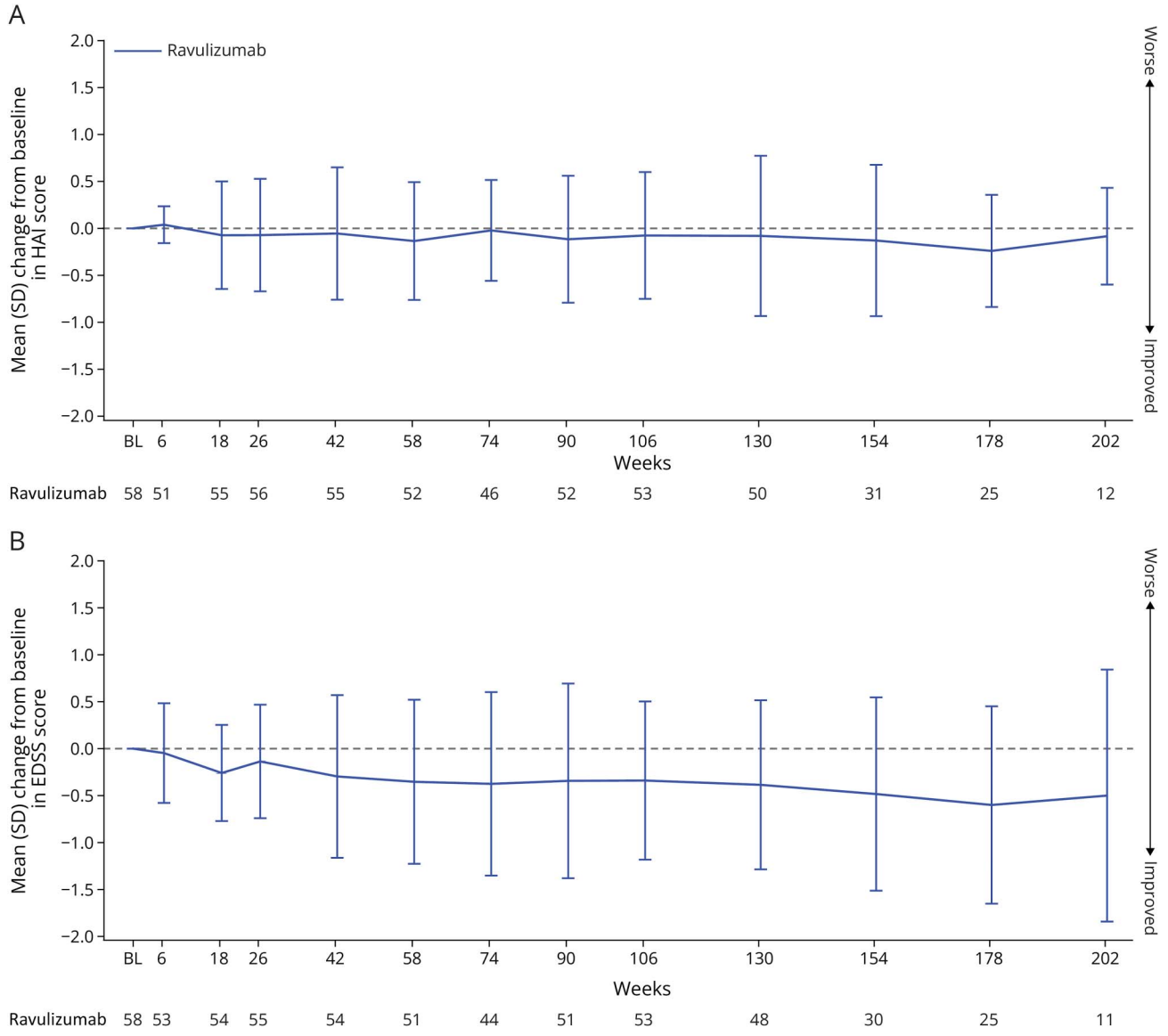
Endpoint	Ravulizumab N = 58
Adjudicated on-trial ARR, adjusted ARR[a] (95% CI); *p*	0 (NA, 0.019); <0.0001
Change from baseline in HAI score,[b] n (%) [95% CI][c]	
Stable	47 (81.0) [68.6 to 90.1]
Clinical improvement	8 (13.8) [6.1 to 25.4]
Clinical worsening	3 (5.2) [1.1 to 14.4]
Change from baseline in EDSS score,[d] n (%) [95% CI][c]	
No clinically important worsening[e]	53 (91.4) [81.0 to 97.1]
Clinically important worsening	5 (8.6) [2.9 to 19.0]
Change from baseline in EQ-5D index[f]	
Mean (95% CI)	0.01 (−0.04 to 0.06)
Median (range)	0 (−0.57 to 0.64)
Change from baseline in EQ-5D VAS[g]	
Mean (95% CI)	1.1 (−3.6 to 5.8)
Median (range)	0.5 (−73 to 40)

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol5-dimension questionnaire; HAI = Hauser Ambulation Index; LTE = long-term extension; NA = not applicable; NMOSD = neuromyelitis optica spectrum disorder; PTP = primary treatment period; VAS = visual analog scale.
[a] The ARR 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 patients with NMOSD. If the *p* value and upper confidence limit are derived from an exact test.
[b] The change was assessed from PTP baseline to the end of the study period, which was the last available visit for patients in the trial. Clinical worsening was defined as an increase of ≥2 points if the HAI baseline score was 0 or an increase of ≥1 point if the baseline score was >0. Clinical improvement was defined as a decrease of ≥1 point if the baseline score was ≥2. Stable was defined as ≤ 1-point increase if the baseline score was 0, ≤ 1-point decrease if the baseline score was 1, or no change if the baseline score was ≥2. HAI scores range from 0 to 9, with higher scores indicating decreased independent ambulation.[24]
[c] 95% CIs were exact confidence intervals using Clopper-Pearson methodology.
[d] The change was assessed from PTP baseline to the end of the study period, which was the last available visit for patients in the trial.
[e] Clinically important worsening was defined as an increase in EDSS score relative to baseline as follows: increase of ≥2.0 points if the baseline score was 0.0, ≥1.0 point if the baseline score was 1.0–5.0, or ≥0.5 if the baseline score was >5.0. EDSS scores ranged from 0 (no disability) to 10 (death).[26]
[f] The change was assessed from PTP baseline to the end of the study period, which was the last available visit for patients in the trial. EQ-5D index scores ranged 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.[25]
[g] The change was assessed from PTP baseline to the end of the study period, which was the last available visit for patients in the trial. EQ-5D VAS scores ranged from 0 (the worst imaginable health) to 100 (the best imaginable health), with higher scores indicating higher perceived quality of health.[25]

3-year follow-up in CHAMPION-NMOSD is a substantial benefit for patients with AQP4-Ab+ NMOSD. Similar long-term relapse reduction has not been reported in trials of other approved AQP4-Ab+ NMOSD treatments.[14,33,34] Although there are no head-to-head randomized controlled trials evaluating the relative efficacy of treatments, a network meta-analysis of clinical trial data for 4 U.S. Food and Drug Administration-approved AQP4-Ab+ NMOSD treatments (ravulizumab, eculizumab, inebilizumab, and satralizumab) conducted in 2023 showed that ravulizumab is likely to be more effective in preventing relapse compared with inebilizumab and satralizumab; results were similar for ravulizumab vs eculizumab.[35] The network meta-analysis did not include the long-term efficacy data; therefore, long-term efficacy could not be compared. However, given the absence of relapses during a median follow-up of 3 years in CHAMPION-NMOSD, as well as published long-term results for the other treatments,[14,33,34] it is possible that ravulizumab may also be more effective in long-term relapse prevention vs other approved treatments.

The overall safety profile of ravulizumab in CHAMPION-NMOSD was generally consistent with that in the PTP[21] and the known safety profile in other indications, including generalized myasthenia gravis (gMG), paroxysmal nocturnal hemoglobinuria (PNH), and atypical hemolytic uremic syndrome (aHUS).[36-38] Because of its mechanism of action that involves inhibition of the terminal complement system, ravulizumab can increase the risk of meningococcal infection.[16] In CHAMPION-NMOSD, 2 cases of meningococcal infections were reported during the PTP (84 patient-years).[21] One of these patients had previously received rituximab. This treatment was discontinued 13 months before ravulizumab initiation; however, according to a recently published case study, the B-cell depletion persisted.[39] The patient was also taking concomitant mycophenolate mofetil, which was stopped because of persistent lymphopenia and the COVID-19 pandemic 2 weeks before hospitalization for meningococcal sepsis. Overall, these conditions, in conjunction with delayed meningococcal B vaccination (reported in the eAppendix), may have contributed to the incidence of ravulizumab-related

Figure 3 Change From Baseline in the HAI Scores (A) and EDSS Scores (B) During CHAMPION-NMOSD (PTP and LTE) in Patients Receiving Ravulizumab



The mean change in HAI scores with ravulizumab was consistent throughout the trial, with no notable change. The overall mean change in EDSS score decreased from baseline across the PTP and LTE. BL = baseline; EDSS = Expanded Disability Status Scale; HAI = Hauser Ambulation Index; LTE = long-term extension; PTP = primary treatment period.

meningococcal sepsis.[39] This patient recovered completely after antimicrobial therapy and elected to continue ravulizumab treatment. No new cases of meningococcal infections were reported during the LTE (105.7 patient-years). These results are consistent with real-world findings showing that, after 4 years of use, *N. meningitidis* infection rates and associated mortality have remained low (~0.00–0.07 and ~0.00–0.004 per 100 patient-years, respectively) in ravulizumab-treated patients with PNH, aHUS, gMG, or NMOSD (all approved indications).[40] Therefore, along with appropriate risk mitigation strategies,[39,40] ravulizumab treatment presents a positive risk-benefit profile and may be an effective long-term treatment option for patients with AQP4-Ab+ NMOSD.

In CHAMPION-NMOSD, 46.6% of patients were taking concomitant IST, including glucocorticoids, at baseline; by the study's end, 63% of these patients were able to either reduce their dose or discontinue ≥1 IST. Although not approved for NMOSD, ISTs are widely used for relapse prevention with mixed results.[41-44] Results from CHAMPION-NMOSD show that ravulizumab treatment may potentially reduce concomitant IST use, thereby reducing the risk of AEs associated with these treatments. Because of the incompatibility between the mechanism of action of rituximab

Table 2 Summary of TEAEs in Patients Treated With Ravulizumab During the PTP and the LTE

	Ravulizumab N = 58	
Adverse event category	**Events, n**	**Patients, n (%)**
Any TEAE	605	55 (94.8)
Any treatment-related TEAE[a]	60	27 (46.6)
TEAE severity		
Grade 1	423	50 (86.2)
Grade 2	161	41 (70.7)
Grade 3	14	11 (19.0)
Grade 4	6	5 (8.6)
TEAEs leading to discontinuation of study drug	3	1 (1.7)
Any serious TEAE	22	16 (27.6)
Any treatment-related serious TEAE[a]	4	4 (6.9)
Death[b]	1	1 (1.7)
TEAE reported in ≥10% of patients		
COVID-19	31	28 (48.3)
Headache	31	19 (32.8)
Urinary tract infection	21	10 (17.2)
Upper respiratory tract infection	17	9 (15.5)
Back pain	11	8 (13.8)
Diarrhea	9	8 (13.8)
Arthralgia	8	8 (13.8)
Nasopharyngitis	9	6 (10.3)
Pyrexia	7	6 (10.3)
Treatment-related serious TEAEs		
Cellulitis	1	1 (1.7)
Meningococcal encephalitis	1	1 (1.7)
Meningococcal sepsis	1	1 (1.7)
Pneumonia	1	1 (1.7)

Abbreviations: LTE = long-term extension; NMOSD = neuromyelitis optica spectrum disorder; PTP = primary treatment period; TEAE = treatment-emergent adverse event.
[a] The investigator determined whether TEAEs were related to study treatment based on their clinical judgment.
[b] Death was due to grade 5 hypertensive heart disease.

(selective depletion of B cells, mainly through complement-dependent cytotoxicity)[45] and ravulizumab (terminal complement inhibition), concomitant use of rituximab was not permitted in CHAMPION-NMOSD and patients who received rituximab during the 3 months before screening were excluded from participation. In addition, previously published results of a subgroup analysis of CHAMPION-NMOSD PTP in patients who received rituximab during the year before screening showed a significant relapse risk reduction with ravulizumab vs placebo, suggesting that prior rituximab use did not affect ravulizumab efficacy.[21] These data can potentially inform real-world treatment decision-making processes, specifically regarding switching from rituximab treatment.

In addition to experiencing no relapses during the median 3 years of follow-up, most patients demonstrated stable scores or improvements in disability measures (HAI and EDSS) throughout the trial; the mean change from baseline in EDSS scores showed improvement over the course of treatment in the overall population. Although 3 patients had worsening in

HAI scores and 5 had worsening on EDSS at the end of the study, only 1 patient had worsening on both scales. Although this patient was reported to have a physician-identified relapse, the event was negatively adjudicated and the worsening in EDSS and HAI scores did not coincide with the event and varied over time. It is important to note that the EDSS scoring system was initially developed for use in patients with multiple sclerosis[26] and therefore may not be appropriate for measuring disability in patients with NMOSD. The scores are also dependent on the observing physician's judgment, resulting in variability from one assessment to another. Studies have shown that progression independent of relapse activity is rare in NMOSD[46,47] and several nonneurologic factors, such as age-related deconditioning, may affect EDSS scores[46]; therefore, worsening in HAI and EDSS scores in some patients in absence of relapses may not be indicative of progression.

The limitations of this study include the lack of a concomitant comparator. Although placebo-controlled trials are the gold standard for evaluation of new treatments, they present an ethical challenge in the case of rare diseases, especially when an approved treatment exists. The use of an open-label study design for CHAMPION-NMOSD with the external placebo comparator from PREVENT sought to address these concerns, while using multiple strategies, reported previously,[21] to mitigate potential bias emerging from the unblinded nature of the trial. Although CHAMPION-NMOSD was designed to be as similar to PREVENT as possible, inclusion criteria for CHAMPION-NMOSD differed in some instances. However, as discussed in the previous publication of the PTP results,[21] these differences are not likely to have affected the CHAMPION-NMOSD trial outcomes. The demographics and baseline characteristics of patients enrolled in CHAMPION-NMOSD are consistent with those observed in the general patient population with AQP4-Ab+ NMOSD; however, between-group differences in baseline characteristics were possible and could have affected the outcomes. This limitation was minimized by elements of the trial design and further addressed during analysis of the PTP using stabilized inverse probability of treatment weighting (sIPTW).[21] Consistency between results of the primary and sIPTW analyses suggests that differences in baseline characteristics did not confound the overall treatment effect.[21] Furthermore, the treatment effect for ravulizumab vs placebo is too large for a confounder to account for the effect.

In this end of study analysis of the pivotal phase 3 CHAMPION-NMOSD trial, ravulizumab treatment significantly reduced the risk of relapse vs placebo in patients with AQP4-Ab+ NMOSD, with no adjudicated on-trial relapse over a median 170.3 weeks of follow-up. The safety profile of ravulizumab during the LTE was consistent with that seen during the PTP, and no new safety concerns were identified. Thus, CHAMPION-NMOSD LTE results expand on the findings from the PTP to demonstrate the long-term benefits of ravulizumab, including significant relapse reduction and a well-established safety profile of a C5 inhibitor with an 8-week dosing interval, in patients with AQP4-Ab+ NMOSD.

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Author Contributions

S.J. Pittock: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M.H. Barnett: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J.L. Bennett: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. A. Berthele: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J. de Sèze: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Levy: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. I. Nakashima: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. C. Oreja-Guevara: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data J. Palace: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. F. Paul: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. C. Pozzilli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. R. Pathak: drafting/revision of the manuscript for content, including medical writing for content. K. Allen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. B. Parks: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. H.J. Kim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data.

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