ORIGINAL ARTICLE

Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder

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ABSTRACT

BACKGROUND

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing, autoimmune, inflammatory disorder that typically affects the optic nerves and spinal cord. At least two thirds of cases are associated with aquaporin-4 antibodies (AQP4-IgG) and complement-mediated damage to the central nervous system. In a previous small, open-label study involving patients with AQP4-IgG–positive disease, eculizumab, a terminal complement inhibitor, was shown to reduce the frequency of relapse.

METHODS

In this randomized, double-blind, time-to-event trial, 143 adults were randomly assigned in a 2:1 ratio to receive either intravenous eculizumab (at a dose of 900 mg weekly for the first four doses starting on day 1, followed by 1200 mg every 2 weeks starting at week 4) or matched placebo. The continued use of stable-dose immunosuppressive therapy was permitted. The primary end point was the first adjudicated relapse. Secondary outcomes included the adjudicated annualized relapse rate, quality-of-life measures, and the score on the Expanded Disability Status Scale (EDSS), which ranges from 0 (no disability) to 10 (death).

RESULTS

The trial was stopped after 23 of the 24 prespecified adjudicated relapses, given the uncertainty in estimating when the final event would occur. The mean (±SD) annualized relapse rate in the 24 months before enrollment was 1.99±0.94; 76% of the patients continued to receive their previous immunosuppressive therapy during the trial. Adjudicated relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in the placebo group (hazard ratio, 0.06; 95% confidence interval [CI], 0.02 to 0.20; P<0.001). The adjudicated annualized relapse rate was 0.02 in the eculizumab group and 0.35 in the placebo group (rate ratio, 0.04; 95% CI, 0.01 to 0.15; P<0.001). The mean change in the EDSS score was −0.18 in the eculizumab group and 0.12 in the placebo group (least-squares mean difference, −0.29; 95% CI, −0.59 to 0.01). Upper respiratory tract infections and headaches were more common in the eculizumab group. There was one death from pulmonary empyema in the eculizumab group.

CONCLUSIONS

Among patients with AQP4-IgG–positive NMOSD, those who received eculizumab had a significantly lower risk of relapse than those who received placebo. There was no significant between-group difference in measures of disability progression. (Funded by Alexion Pharmaceuticals; PREVENT ClinicalTrials.gov number, NCT01892345; EudraCT number, 2013-001150-10.)

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This article was published on May 3, 2019, at NEJM.org.

DOI: 10.1056/NEJMoa1900866

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune, inflammatory disorder of the central nervous system that has a prevalence of 0.5 to 10 persons (predominantly women) per 100,000 population.[1] It is characterized mainly by recurrent optic neuritis and myelitis, and such attacks are frequently associated with poor recovery.[2,3] Immunosuppressive therapies, including rituximab, are used for relapse prevention in NMOSD[4,5] without regulatory approval, but 25 to 60% of patients receiving these medications continue to have recurrent attacks.[5-7]

Aquaporin-4 (AQP4) is a water channel protein expressed mainly by astrocytes in the central nervous system.[8,9] Antibodies of the IgG class against AQP4 are present in 65 to 88% of patients with NMOSD.[10,11] Preclinical data indicate that AQP4-IgG triggers the complement cascade,[12,13] which leads to inflammation and the formation of the membrane attack complex. The membrane attack complex is implicated in astrocyte destruction and neuronal injury but is not seen in experimental models in the presence of a complement inhibitor.[14]

Eculizumab, a humanized monoclonal antibody, inhibits the terminal complement protein C5 and prevents its cleavage into C5a, which is proinflammatory, and C5b, which coordinates the formation of membrane attack complex.[15] In an open-label study involving 14 patients with highly clinically active, AQP4-IgG–positive disease, the use of eculizumab reduced the frequency of relapse.[16] We conducted a phase 3, randomized, double-blind, placebo-controlled, time-to-event trial (PREVENT [Prevention of Relapses in Neuromyelitis Optica]) to evaluate the efficacy and safety of eculizumab in patients with AQP4-IgG–positive NMOSD.

Methods

Trial Design and Oversight

From April 2014 through October 2017, we enrolled patients at 70 sites, primarily hospital clinics, in 18 countries. At baseline (day 1), we randomly assigned patients in a 2:1 ratio to receive either eculizumab or placebo. The patients were stratified across sites according to the score on the Expanded Disability Status Scale (EDSS) on day 1 (≤2.0 or 2.5 to 7.0 on a scale ranging from 0 [no disability] to 10 [death]) and the use of concomitant immunosuppressive therapy (no previous immunosuppressive therapy, except for glucocorticoids alone; continuing the same immunosuppressive therapy after the last relapse before screening, although doses may have changed; or receiving new immunosuppressive therapy or discontinuing an existing therapy after the last relapse). Patients, site staff members, and the representatives of the sponsor (Alexion Pharmaceuticals) were unaware of the trial-group assignments, and trial agents and treatment kits appeared identical. (Details regarding the design of the trial are provided in the protocol and in Fig. S1 in the Supplementary Appendix, both of which are available with the full text of this article at NEJM.org.)

The trial was designed to continue until 24 patients had a relapse of NMOSD, as adjudicated by an independent panel. After a review of blinded data, representatives of the sponsor terminated the trial after 23 patients had had an adjudicated relapse, given the uncertainty in estimating when the final event would occur. The patients who completed the trial could enter an extension trial and receive open-label treatment with eculizumab.

The trial was conducted in accordance with the provisions of the Declaration of Helsinki,[17] the International Conference on Harmonisation guidelines for Good Clinical Practice,[18] and applicable regulatory requirements. The trial was approved by the institutional review board at each participating institution. All the patients provided written informed consent before participation.

Alexion Pharmaceuticals designed the trial in consultation with two academic authors, provided the trial agents, and analyzed the data. The sponsor paid for professional writing assistance. Confidentiality agreements were in place between the authors and Alexion Pharmaceuticals. All the authors vouch for the completeness and accuracy of the data, the reporting of adverse events as stipulated in the protocol, and the fidelity of the trial to the protocol.

Patients

Eligibility criteria included an age of at least 18 years; a diagnosis of neuromyelitis optica or NMOSD, according to 2006[19] or 2007[3] criteria, respectively; AQP4-IgG–seropositive status, as confirmed with the use of a commercially available cell-binding kit assay (Euroimmun) analyzed centrally at Mayo Medical Laboratories; a history of at least two relapses during the previous 12 months

or three relapses during the previous 24 months, at least one of which had occurred within the previous 12 months; and a score of 7 or less on the EDSS.[20] Patients who were receiving immunosuppressive therapies for relapse prevention were eligible for inclusion if they were receiving stable-dose regimens.

Exclusion criteria included treatment with mitoxantrone or rituximab during the previous 3 months, the receipt of intravenous immune globulin during the previous 3 weeks, the receipt of prednisone doses greater than 20 mg per day or the equivalent for other glucocorticoids at screening, and unresolved meningococcal disease or systemic bacterial or other infection considered to be clinically significant or not treated with appropriate antibiotics. (A complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix.)

TRIAL PROCEDURES

Patients were vaccinated against *Neisseria meningitidis* before receiving a trial agent (Fig. S1 in the Supplementary Appendix). Eculizumab or matching placebo was administered intravenously over approximately 35 minutes (range, 25 to 45 minutes). Patients received 900 mg of eculizumab weekly for the first four doses. Starting the following week, patients received a maintenance regimen of 1200 mg every 2 weeks until relapse, trial discontinuation, or the end of the trial. Immunosuppressive therapies that patients were receiving at baseline were changed only if the treating physician determined that a relapse had occurred or had safety concerns; changes to immunosuppressive therapy after relapses were unrestricted. (Details regarding concomitant medications are provided in the Supplementary Appendix.)

Patients were evaluated within 48 hours after a possible relapse and again following intervals of 1 week, 4 weeks, and 6 weeks by the treating physician and by EDSS raters. (The EDSS raters, who were also unaware of trial-group assignments, were not involved in patient care.)

Treating physicians identified relapses according to the following criteria: a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination that persisted for more than 24 hours, signs and symptoms attributable to NMOSD rather than other causes, and onset preceded by at least 30 days of clinical stability. Changes in imaging were not considered to be an indication of relapse without related clinical findings. Treating physicians determined the appropriate relapse therapy.

On July 1, 2016, after the enrollment of 88 patients, the protocol was amended to create an independent relapse adjudication committee consisting of two neurologists and one neuro-ophthalmologist who were unaware of trial-group assignments and who reviewed all physician-determined relapses; adjudications were performed retrospectively and with the same criteria that were used by treating physicians. (Details regarding relapse assessment and adjudication are provided in the Supplementary Appendix and the protocol.)

Neurologic function, including visual acuity, and disability assessments were performed at baseline, at weeks 4, 8, and 12 and every 12 weeks thereafter, and at the time of trial discontinuation or termination. Raters assessed patients using the EDSS. Treating physicians or appropriately trained site staff members assessed visual acuity with the Snellen chart; they also evaluated the patients using the modified Rankin scale,[21] with scores ranging from 0 (no disability) to 6 (death), and the Hauser Ambulation Index,[22] with scores ranging from 0 to 9, with higher scores indicating decreased independent ambulation. Patients completed the European Quality of Life 5-Dimension 3-Level (EQ-5D-3L) questionnaire[23] consisting of a visual analogue scale with scores ranging from 0 to 100 and a summary index score ranging from less than 0 to 1; higher scores on each component represent better health status.

Safety assessments included monitoring for adverse events, evaluation of vital signs, a physical examination, the performance of electrocardiography and clinical laboratory tests, and evaluation for the presence of suicidal ideation or behavior. Additional details regarding safety monitoring, including definitions of adverse events, are provided in the Supplementary Appendix.

END POINTS

The primary efficacy end point in this time-to-event trial was the first adjudicated relapse. The original primary efficacy end point was the first physician-determined relapse, which was changed to a sensitivity analysis by protocol amendment after 88 patients had been enrolled. There were

six hierarchically ordered secondary efficacy end points: the adjudicated annualized relapse rate and changes from baseline in scores on the EDSS, modified Rankin scale, Hauser Ambulation Index, EQ-5D-3L visual analogue scale, and EQ-5D-3L summary index. In the original statistical analysis plan, the EDSS score was evaluated first in the hierarchy before the annualized relapse rate. After a reassessment of the relative clinical importance of the trial end points but before the trial data were unblinded, the sponsor changed the hierarchy in the final version of the statistical analysis plan. Adverse-event data were calculated with and without physician-determined relapses of NMOSD that met the definition of a serious adverse event. Investigators assessed the relationship between adverse events and trial regimen and recorded the relationship using predefined categories (not related and unlikely, possibly, probably, or definitely related).

STATISTICAL ANALYSIS

The sample size for this trial was based on the percentage of patients who we estimated would be relapse-free (80% for eculizumab; 40% for placebo) at 12 months (hazard ratio, 0.24). With 2:1 randomization for the trial groups, we calculated that 24 events in a population of 132 patients would provide a power of 90% to determine the prespecified between-group difference on the basis of a two-sided log-rank test at a 5% level of significance, assuming a 10% dropout rate.

We used a stratified log-rank test to analyze between-group differences for the primary end point in the modified intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of a trial agent. (In our trial, the modified intention-to-treat population was the same as the intention-to-treat population because all the patients who had undergone randomization also received at least one dose of a trial agent.) We used a stratified Cox proportional-hazards model with the trial group as a covariate to estimate the hazard ratio for the primary end point. Data for patients who did not have an adjudicated relapse were censored at the end of the trial period, including those who had a physician-determined relapse that was adjudicated as not being a relapse and those who discontinued the trial regimen early. Sensitivity analyses for the primary end point are described in the statistical analysis plan and the Supplementary Appendix.

To analyze the adjudicated annualized relapse rate, we performed a Poisson regression analysis with the trial group, historical annualized relapse rate, and randomization strata as covariates. For the between-group differences in the remaining secondary efficacy end points, we used a stratified, randomization-based nonparametric analysis of covariance that was adjusted for the baseline score on each scale. We calculated differences in least-squares means and 95% confidence intervals using analyses of covariance after adjustment for the baseline score on each scale and randomization strata. Missing data were replaced by the last-observation-carried-forward method, as described in the statistical analysis plan and the statistical information section in the Supplementary Appendix.

To control for the overall type-I error at 0.05 for multiple hypothesis tests,[24] we used a fixed-sequence hierarchical testing procedure, with the primary end point followed by the six secondary efficacy end points in the order described earlier. Point estimates and 95% confidence intervals are provided for the first outcome with a P value greater than 0.05 and then for all subsequent outcomes in the hierarchy. No inferences can be drawn from results after the failure of statistical significance in the hierarchy.

RESULTS

PATIENTS

A total of 96 patients received eculizumab and 47 received placebo (Fig. 1). Overall, 91% of the patients were women. At baseline, the mean (±SD) annualized relapse rate during the previous 24 months was 1.99±0.94, and the median scores on the EDSS, modified Rankin scale, and Hauser Ambulation Index indicated moderate-to-severe disability (Table 1, and Table S1 in the Supplementary Appendix). Of the 143 patients, 46 (32%) had received rituximab previously but not within the 3 months before screening. A total of 34 patients (24%) did not receive any concomitant immunosuppressive therapy during the trial. The baseline characteristics of the patients were well balanced between the two groups.

A higher percentage of patients receiving eculizumab (17%) than placebo (6%) discontinued their participation in the trial; the corresponding rates of discontinuation were 9.3 and 5.6 per 100 patient-years, respectively (Fig. 1, and Table S2 in the Supplementary Appendix).

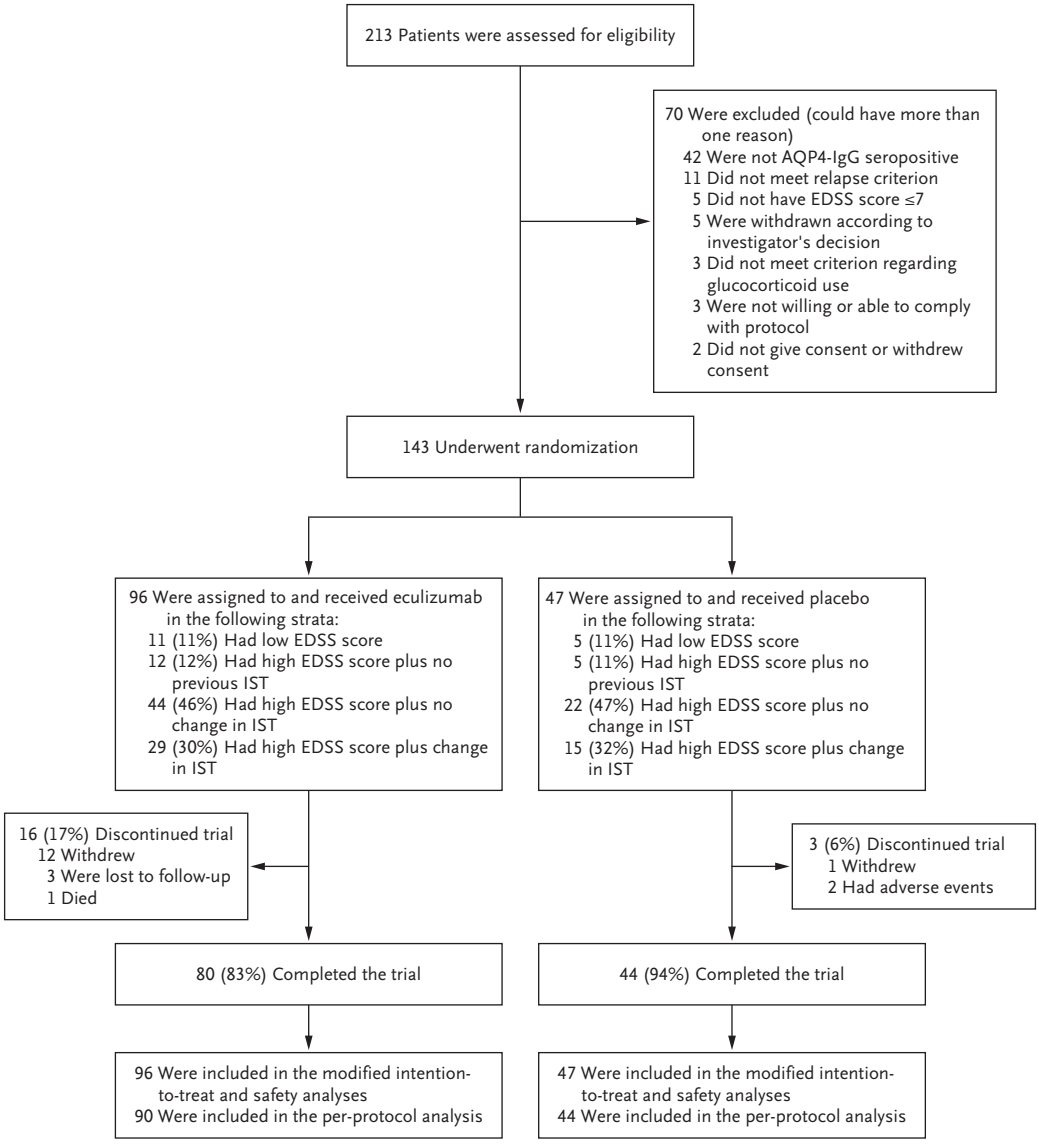


Figure 1. Enrollment, Randomization, and Follow-up.

Definitions of the analysis populations are provided in the Methods section (modified intention-to-treat population) and the Supplementary Appendix (safety and per-protocol populations, including the reasons for exclusion from the per-protocol population). Randomization was stratified according to patients' scores on the Expanded Disability Status Scale (EDSS) (≤2.0 or 2.5–7.0) and their status with respect to previous immunosuppressive therapy (IST) (no previous therapy, unchanged therapy, or changed therapy). IST was considered to have been unchanged if no therapy had been started or discontinued after the last relapse before screening, although doses may have changed; patients who had previously received only glucocorticoid therapy were considered to have received no previous IST. Patients were considered to have completed the trial if the treating physician determined that they had had a relapse or if the trial had ended because 23 positively adjudicated relapses had occurred in 23 patients. AQP4-IgG denotes aquaporin-4 IgG.

EFFICACY

The primary end point of adjudicated relapse occurred in 3 of 96 patients (3%) in the eculizumab group and in 20 of 47 (43%) in the placebo group (hazard ratio, 0.06; 95% confidence interval [CI], 0.02 to 0.20; P<0.001) (Table 2 and Fig. 2A). The median time until the first adjudicated relapse was not reached in the eculizumab group and was

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Eculizumab (N=96)	Placebo (N=47)	All Patients (N=143)
Female sex — no. (%)	88 (92)	42 (89)	130 (91)
Age — yr			
At first receipt of trial agent	43.9±13.32	45.0±13.29	44.3±13.27
At initial clinical presentation	35.8±14.03	38.5±14.98	36.6±14.35
Diagnosis — no. (%)			
Neuromyelitis optica	69 (72)	38 (81)	107 (75)
NMOSD	27 (28)	9 (19)	36 (25)
Longitudinally extensive transverse myelitis	14 (15)	5 (11)	19 (13)
Optic neuritis	8 (8)	2 (4)	10 (7)
Optic neuritis or longitudinally extensive transverse myelitis coexisting with systemic autoimmune disease	3 (3)	1 (2)	4 (3)
Optic neuritis or transverse myelitis associated with brain lesions	1 (1)	1 (2)	2 (1)
Other	1 (1)	0	1 (1)
Annualized relapse rate during previous 24 mo	1.94±0.90	2.07±1.04	1.99±0.94
Type of relapse during previous 24 mo — no. (%)†			
Optic neuritis	58 (60)	22 (47)	80 (56)
Transverse myelitis	74 (77)	42 (89)	116 (81)
Brain-stem symptoms‡	18 (19)	15 (32)	33 (23)
Cerebral symptoms	10 (10)	5 (11)	15 (10)
Median score on EDSS (range)§	4.00 (1.0–7.0)	4.00 (1.0–6.5)	4.00 (1.0–7.0)
Immunosuppressive therapy at baseline — no. (%)			
None	21 (22)	13 (28)	34 (24)
Glucocorticoids alone	16 (17)	11 (23)	27 (19)
Azathioprine with or without glucocorticoids	37 (39)	13 (28)	50 (35)
Mycophenolate mofetil with or without glucocorticoids	17 (18)	8 (17)	25 (17)
Other drug with or without glucocorticoids¶	5 (5)	2 (4)	7 (5)
Previous rituximab treatment — no. (%)‖	26 (27)	20 (43)	46 (32)

* Plus–minus values are means ±SD. Additional data are provided in Table S1 in the Supplementary Appendix. NMOSD denotes neuromyelitis optica spectrum disorder.
† In addition, other symptoms were reported for 23 patients (24%) receiving eculizumab and 10 (21%) receiving placebo. This category was used when an investigator was unable to determine a definitive relapse type; symptoms included weakness, gait imbalance or ataxia, neuropathic pain, burning, paresthesia, limb tingling, limb numbness, blurring of vision, neurogenic bladder symptoms, headache, and spasms.
‡ Symptoms of area postrema syndrome (intractable nausea, vomiting, or hiccups) were reported in 8 patients (8%) receiving eculizumab and 7 (15%) receiving placebo.
§ Scores on the Expanded Disability Status Scale (EDSS) range from 0 (no disability) to 10 (death).[20]
¶ Other drugs include cyclosporine, cyclophosphamide, methotrexate, mizoribine, and tacrolimus.
‖ Patients who had received rituximab could be included in the trial if they had not taken the drug in the 3 months before screening.

reached at 103 weeks in the placebo group. Most relapses were of myelitis (Table S3 in the Supplementary Appendix).

The results of the time-to-event sensitivity analyses were consistent with those in the primary analysis (Fig. S2 in the Supplementary Appendix). In the sensitivity analysis of the first physician-determined (nonadjudicated) relapse (the original primary end point), relapses occurred in 14 patients (15%) in the eculizumab group and 29 (62%)

Table 2. Efficacy End Points.*

End Point	Eculizumab (N=96)	Placebo (N=47)	Hazard or Rate Ratio or Difference (95% CI)†	P Value
Primary end point				
First adjudicated relapse — no. (%)	3 (3)	20 (43)	0.06 (0.02 to 0.20)	<0.001
Secondary end points				
Adjudicated annualized relapse rate (95% CI)	0.02 (0.01 to 0.05)	0.35 (0.20 to 0.62)	0.04 (0.01 to 0.15)	<0.001
Mean change from baseline				
Score on EDSS‡	−0.18±0.81	0.12±0.95	−0.29 (−0.59 to 0.01)	NA
Score on modified Rankin scale§	−0.24±0.72	0.09±0.75	−0.32 (−0.57 to −0.06)	NA
Score on Hauser Ambulation Index¶	−0.39±1.08	0.51±1.61	−0.87 (−1.32 to −0.42)	NA
Score on EQ-5D-3L visual analogue scale‖	5.42±18.53	0.57±16.39	6.43 (0.63 to 12.23)	NA
Score on EQ-5D-3L index‖	0.05±0.18	−0.04±0.21	0.09 (0.02 to 0.15)	NA

* Plus–minus values are means ±SD. Analyses are based on data from the modified intention-to-treat population for all end points. Hypothesis testing comparing eculizumab with placebo was performed with the use of a fixed-sequence hierarchical testing procedure that included the primary end point and the six secondary efficacy end points in the order shown in the table and described in the Statistical Analysis section. No inferences can be drawn from the results after the failure of statistical significance in the hierarchy, as indicated by not applicable (NA).

† The hazard ratio (for the primary end point), rate ratio (for the annualized relapse rate), and the difference in the least-squares mean value (for the remaining end points) is for the eculizumab group as compared with the placebo group.

‡ Scores on the Expanded Disability Status Scale (EDSS) range from 0 (no disability) to 10 (death).

§ Scores on the modified Rankin scale range from 0 (no disability) to 6 (death).

¶ Scores on the Hauser Ambulation Index range from 0 to 9, with higher scores indicating decreased independent ambulation.

‖ Scores on the European Quality of Life 5-Dimension 3-Level (EQ-5D-3L) visual analogue scale range from 0 to 100. Summary index scores on this scale range from <0 to 1. Higher scores on each component indicate better health status.

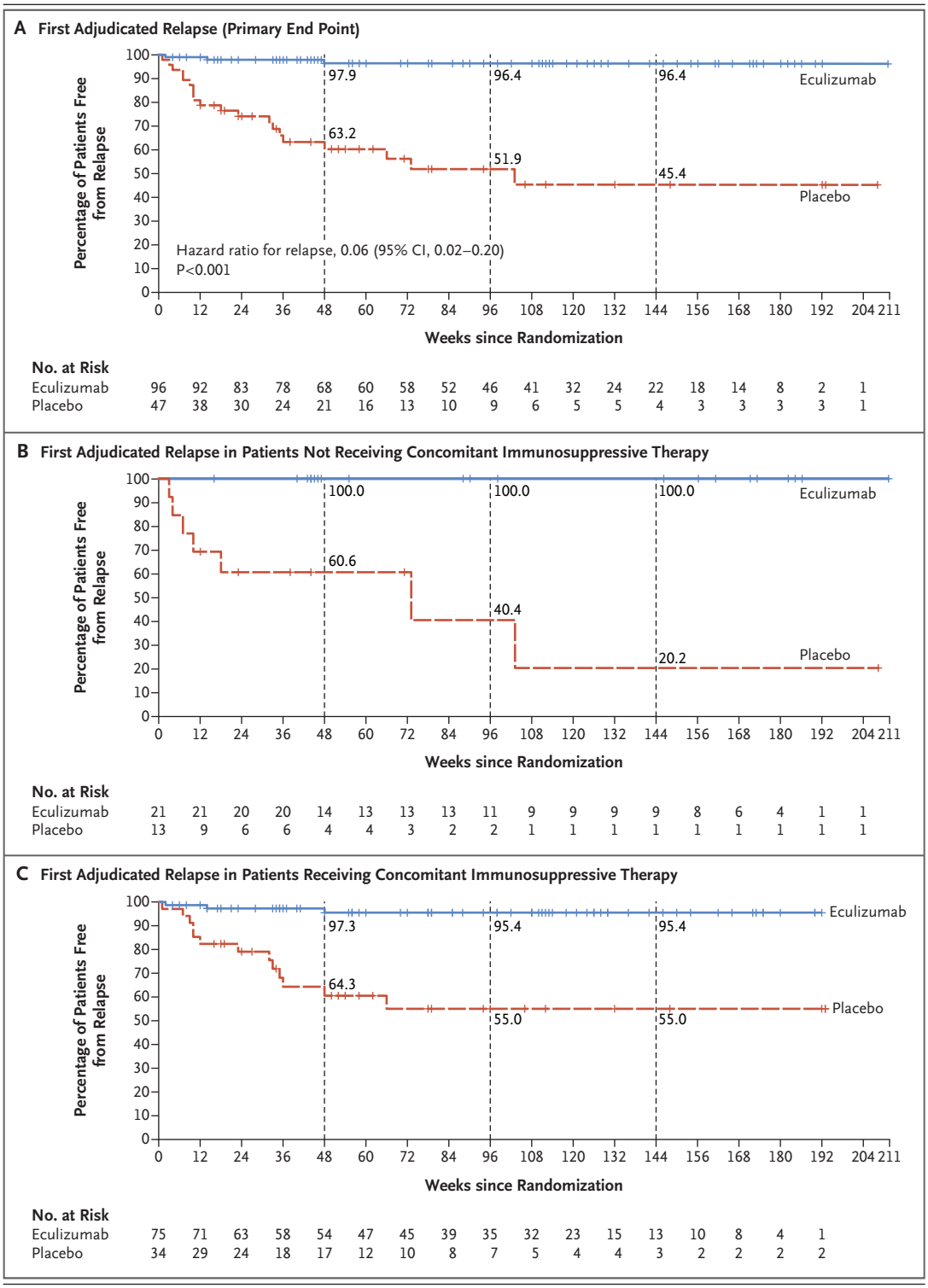
in the placebo group (hazard ratio, 0.18; 95% CI, 0.10 to 0.34; P<0.001) (Fig. S3 in the Supplementary Appendix). Of 45 physician-determined relapses overall, 24 (53%) were adjudicated as relapses. Disagreements in determinations between treating physicians and the adjudication committee were most frequently because the committee considered that there had been insufficient objective change in the neurologic examination (in 18 of 21 relapses adjudicated as not being a relapse) (Table S4 in the Supplementary Appendix).

In the prespecified subgroup analysis involving patients who were not receiving concomitant immunosuppressive therapy, adjudicated relapses occurred in none of the 21 patients in the eculizumab group and in 7 of the 13 patients (54%) in the placebo group. In a post hoc analysis, the corresponding numbers for patients receiving concomitant immunosuppressive therapy were 3 of 75 patients (4%) and 13 of 34 patients (38%), respectively. The time course of relapses in each subgroup suggested a treatment effect consistent with that in the overall population (Fig. 2B and 2C).

Eculizumab was associated with a lower adjudicated annualized relapse rate after adjustment (the first secondary end point) than placebo, with rates of 0.02 and 0.35, respectively (P<0.001) (Table 2). No inferences can be made for the remaining secondary end points because the difference between groups for the next end point in the hierarchy, the change in the EDSS score, was not significant (Table 2). (Additional data for disability and quality-of-life outcomes are provided in Figs. S4 and S5 in the Supplementary Appendix.)

SAFETY

The rate of adverse events was 745 per 100 patient-years in the eculizumab group and 1127 per 100 patient-years in the placebo group (Table 3). Higher rates of upper respiratory tract infection and headache were reported in the eculizumab group than in the placebo group, with 31 and 19 events of upper respiratory tract infection per 100 patient-years and 55 and 38 headache events per 100 patient-years, respectively. The rate of adverse events that were categorized as being related to a trial



regimen by investigators was 212 and 164 per 100 patient-years, respectively.

The rate of serious adverse events was 27 and 55 per 100 patient-years in the eculizumab group and the placebo group, respectively, with the exclusion of relapses (Table 3). One patient in the eculizumab group who was receiving concomitant azathioprine died from pulmonary empyema af-

Figure 2 (facing page). First Relapse of Neuromyelitis Optica Spectrum Disorder (NMOSD) during the Trial.
Shown are Kaplan–Meier plots of relapse-free survival among patients who were receiving eculizumab or placebo for NMOSD in the analysis of the primary end point (Panel A), in the prespecified subgroup of patients who were not receiving concomitant immunosuppressive therapy (Panel B), and in the post hoc subgroup of patients who were receiving concomitant immunosuppressive therapy (Panel C). Data are from the modified intention-to-treat population. The tick marks indicate censoring of data. Data for patients who did not have an adjudicated relapse were censored at the end of the trial period, including those who had a physician-determined relapse that was adjudicated as not being a relapse and those who discontinued the trial regimen early. Concomitant immunosuppressive therapies are listed in Table 1.

ter 108 weeks in the trial. The associated cultures yielded *Streptococcus intermedius* and *Peptostreptococcus micros*. Two patients discontinued placebo because of adverse events (pneumonia in one patient and prerenal failure and pancytopenia in the other). Serious adverse events that were categorized by investigators as being related to a trial regimen are described in Table S6 in the Supplementary Appendix.

No cases of meningococcal infection were reported during the trial. The rates of other serious infections were 8 and 15 events per 100 patient-years in the eculizumab group and placebo group, respectively.

DISCUSSION

Among patients with AQP4-IgG–positive NMOSD, those who received eculizumab had a significantly lower risk of relapse than those who received placebo. Approximately three quarters of the patients were receiving concomitant immunosuppressive therapy during the trial.

Immunosuppressive therapies are currently used to prevent NMOSD relapses.[4,5] In an open-label, randomized trial involving 86 patients who had NMOSD with or without AQP4-IgG antibodies, those who received the monoclonal antibody rituximab had a significantly greater reduction from baseline in the annualized relapse rate at 12 months than those who received azathioprine,[25] although neither drug is currently approved for this use. In our trial, rituximab was not permitted as concomitant immunosuppressive therapy because of incompatibility between its mechanism of action and that of the terminal complement inhibitor eculizumab. Specifically, rituximab selectively depletes B cells, mainly through complement-dependent cytotoxicity, and B-cell lysis is inhibited by 90% in the presence of eculizumab.[26] Approximately one third of the patients in our trial had previously received rituximab but not within 3 months before enrolling in the trial.

By blocking the terminal complement system, eculizumab increases the risk of meningococcal and encapsulated bacterial infection.[27,28] In our trial, all the patients received meningococcal vaccination, and no cases of meningococcal infection were reported. The microorganisms that were implicated in our trial patient who died from pulmonary empyema (i.e., *S. intermedius* and *P. micros*) are not associated with complement deficiency. A greater proportion of patients in the eculizumab group than the placebo group withdrew from the trial, even allowing for differences in on-trial time, but only two patients (both of whom were receiving placebo) discontinued owing to adverse events.

This trial has several limitations. First, only patients with AQP4-IgG antibodies were included, so the findings cannot be extrapolated to patients without AQP4-IgG antibodies, a potentially heterogeneous group that may also include those with antibodies against myelin oligodendrocyte glycoprotein.[29] Second, because the trial design precluded follow-up beyond 6 weeks after a single relapse and because the confidence interval for the between-group difference in the change from baseline in the EDSS score included zero in hierarchical testing (implying there was no benefit of the drug on disability progression during the short period of the trial), no formal inferences could be made about other disability and quality-of-life outcomes overall. Third, the trial was terminated after 23 of 24 prespecified adjudicated relapses but retained at least 80% power to detect a between-group difference for the primary end point based on original assumptions for the sample-size calculations. Fourth, on the basis of the same criteria, treating physicians identified more relapses than the adjudication committee. However, the discordance was mostly due to the interpretation of the objective change in the neurologic examination, which we assessed as reflecting concern among treating physicians

Table 3. Adverse Events.*

Adverse Event	Eculizumab (N=96)			Placebo (N=47)		
	no. of events	*events/ 100 patient-yr*	*no. of patients (%)*	*no. of events*	*events/ 100 patient-yr*	*no. of patients (%)*
Any adverse event	1288	745	88 (92)	599	1127	43 (91)
Any adverse event related to trial agent, as determined by investigator†	366	212	49 (51)	87	164	27 (57)
Any adverse event according to severity						
Severe‡	27	16	15 (16)	15	28	7 (15)
Moderate	186	108	59 (61)	143	269	25 (53)
Mild	1072	620	86 (90)	441	830	41 (87)
Unknown severity	3	2	3 (3)	0	0	0
Any serious adverse event§	46	27	25 (26)	29	55	13 (28)
Death¶	1	1	1 (1)	0	0	0
Related to trial agent, as determined by investigator‖	13	8	9 (9)	13	24	9 (19)
Adverse event leading to discontinuation of agent	0	0	0	3	6	2 (4)
Adverse event reported in ≥15% of patients in either group**						
Upper respiratory tract infection	54	31	28 (29)	10	19	6 (13)
Headache	95	55	22 (23)	20	38	11 (23)
Nasopharyngitis	50	29	20 (21)	15	28	9 (19)
Nausea	30	17	16 (17)	19	36	12 (26)
Diarrhea	23	13	15 (16)	19	36	7 (15)
Urinary tract infection	45	26	13 (14)	13	24	10 (21)
Limb pain	13	8	11 (11)	11	21	10 (21)
Vomiting	10	6	10 (10)	10	19	8 (17)

* Since patients were assigned in a 2:1 ratio to receive eculizumab or placebo, and patients in the eculizumab group spent more time in the trial than those in the placebo group, adverse events were evaluated during 173 patient-years in the eculizumab group and 53 patient-years in the placebo group. Definitions of adverse events (including serious adverse events) are provided in the Supplementary Appendix. Data are from the safety population and exclude events of neuromyelitis optica spectrum disorder (NMOSD) that were relapses meeting the definition of a serious adverse event. Data that are provided in Table S5 in the Supplementary Appendix include events of NMOSD. Adverse events were coded according to the preferred terms in the *Medical Dictionary for Regulatory Activities,* version 21.0.

† Related adverse events are those categorized by investigators as possibly, probably, or definitely related to a trial agent or as of unknown relationship. Of the adverse events that were considered by investigators to be treatment-related, the most common in the eculizumab group was nausea (in 7 patients [7%]), followed by headache and upper respiratory tract infection (in 6 patients [6%] in each case); the corresponding numbers in the placebo group were 3 (6%), 2 (4%), and 1 (2%).

‡ Severe adverse events 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. The severe adverse events that were reported by more than 1 patient receiving eculizumab were pneumonia, back pain, and limb pain (with each event in 2 patients).

§ The serious adverse events that were reported by more than 1 patient in either group were pneumonia (in 3 patients receiving eculizumab and 1 patient receiving placebo), and cellulitis, sepsis, and urinary tract infection (each in 2 patients receiving eculizumab and none receiving placebo).

¶ The patient died from infectious pleural effusion (reported as pulmonary empyema), which the investigator categorized as probably related to the trial agent. The associated cultures yielded *Streptococcus intermedius* and *Peptostreptococcus micros*, and the patient had an extensive history of pulmonary disease (including bronchiolitis obliterans requiring tracheostomy, pneumonia, asthma, and obstructive sleep apnea) and was an active smoker.

‖ A detailed listing of events is provided in Table S6 in the Supplementary Appendix.

** The 15% cutoff value was applied before the data were rounded.

that relapses should not be overlooked. Despite the discordance, a significantly lower risk of relapse with eculizumab than with placebo was apparent in the sensitivity analysis of physician-determined relapses. Fifth, although the trial was undertaken with a placebo comparator, the use of concomitant immunosuppressive therapy, except rituximab, was permitted.

In conclusion, eculizumab was associated with a lower risk of relapse than placebo among patients with AQP4-IgG–positive NMOSD. Since there was no significant between-group difference in measures of disability progression, the long-term effect of eculizumab in patients with NMOSD warrants further study.

Supported by Alexion Pharmaceuticals.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who participated in this trial and their families; the members of the relapse adjudication committee: Brian Weinshenker, M.D. (chair), Benjamin Greenberg, M.D., and Robert Sergott, M.D.; Izlem Izbudak, M.D., for neuroradiology consultation; Alexion Pharmaceuticals employees Fanny O'Brien, Ph.D., for her contribution to the trial design, and Larisa Miller, Pharm. D., for consultation and insight during the development of the manuscript; and Oxford PharmaGenesis, for medical-writing support.

APPENDIX

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