Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease that is characterized by inflammatory lesions mainly affecting the optic nerve and spinal cord[1-3] and possibly affecting the brain stem and cerebrum.[2,4,5] Symptoms include visual impairment,[2,6] paralysis, sensory loss, and bladder dysfunction,[1,2] as well as nausea, vomiting, and hiccups from lesions involving the area postrema.[1,2,7] Pain and fatigue are common during and after relapses.[8,9] Disability can occur after one attack and can accumulate with each relapse; unlike in multiple sclerosis, secondary progression is rare.[4,6,7] Treatments that are typically used for multiple sclerosis are not usually beneficial and can be harmful in patients with NMOSD.[2,3,10]

Approximately two thirds or more of patients with NMOSD have IgG antibodies to aquaporin-4 (AQP4-IgG),[4,11] a water-channel protein that is abundant on astrocytic membranes and that is proximate to the blood–brain barrier.[12] Seronegative patients cannot be distinguished clinically from seropositive patients.[3,4,11] In AQP4-IgG–seropositive disease, binding of AQP4-IgG to AQP4 on astrocytic end-feet initiates the activation of the complement cascade, the infiltration of granulocytes into the central nervous system, and antibody-dependent cell-mediated cytotoxicity.[13]

Levels of interleukin-6 are elevated in the cerebrospinal fluid (CSF) of patients with NMOSD, as compared with patients who have multiple sclerosis or noninflammatory neurologic disorders, and interleukin-6 levels in serum and CSF are elevated during NMOSD relapses.[14-16] Interleukin-6 promotes the differentiation of naive T cells into proinflammatory type 17 helper T cells,[17,18] which, along with interleukin-6, promote the differentiation of B cells into AQP4-IgG–producing plasmablasts.[3,18,19]

Immunosuppressant medications are used off-label for the prevention and treatment of acute relapses in patients with NMOSD.[3,20] Satralizumab is a subcutaneously administered humanized monoclonal antibody that binds to both membrane-bound and soluble interleukin-6 receptors and prevents the binding of interleukin-6, thus blocking interleukin-6–signaling pathways that are involved in inflammation.[21,22] As compared with a conventional anti–interleukin-6R antibody, satralizumab was designed to dissociate from the antigen in a pH-dependent manner and to be released into the bloodstream to bind the antigen again, thus prolonging the elimination half-life of the drug in plasma (see the protocol, available with the full text of this article at NEJM.org).[23] We performed a randomized, controlled trial of satralizumab added to immunosuppressant treatment in patients with NMOSD.

METHODS

TRIAL DESIGN

This was a phase 3, international, randomized, double-blind, placebo-controlled, parallel-assignment trial of satralizumab added to baseline immunosuppressant treatment, followed by an open-label extension period. Approval was obtained from the local ethics committee or institutional review board at each trial center. All the patients provided written informed consent. The sponsor, Chugai Pharmaceutical, a member of the Roche Group, designed the trial, provided the trial drug and placebo, paid for professional medical writing, and analyzed the data. The trial was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All the authors vouch for the fidelity of the trial to the protocol as well as for the accuracy and completeness of the reporting of results and adverse events. Confidentiality agreements were in place between the authors and the sponsor.

Patients were randomly assigned in a 1:1 ratio to receive either satralizumab, at a dose of 120 mg, or placebo, administered subcutaneously at weeks 0, 2, and 4 and every 4 weeks thereafter during the double-blind period. Satralizumab was administered to all the patients at the same administration intervals during the open-label extension period (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The double-blind period was planned to end after the occurrence of 26 protocol-defined relapses, on the basis of the sample-size and power calculations described in the Supplementary Appendix. Patients who had a relapse that led to treatment with rescue therapy or who had a protocol-defined relapse as adjudicated by the clinical end-point committee, as well as patients who remained in the trial when the prespecified number of 26 protocol-defined relapses had occurred, were eligible to enter the open-label extension period. Randomization was stratified according to the baseline annualized relapse rate (1 vs. >1) and geographic region (Asia vs. Europe or other).

During the double-blind period, patients were permitted to continue baseline treatment with a stable dose of azathioprine (maximum, 3 mg per kilogram of body weight per day), mycophenolate mofetil (maximum, 3000 mg per day), or oral glucocorticoids (maximum, 15 mg of prednisolone equivalent per day) in addition to the trial drug. Adolescents (patients 12 to 17 years of age) were permitted to continue receiving stable doses of azathioprine or mycophenolate mofetil plus oral glucocorticoids in addition to satralizumab or placebo. The use of anti-CD20 agents, including rituximab, was not permitted during the trial and for 6 months before baseline. Increases in the dose or changes in the baseline treatment were not permitted during the double-blind period; dose decrease was permitted for safety reasons. During the extension period, patients received satralizumab with or without baseline treatment; making changes to or discontinuing baseline treatment was permitted.

TRIAL PARTICIPANTS

Eligible patients were adolescents or adults (12 to 74 years of age) who had AQP4-IgG–seropositive or AQP4-IgG–seronegative neuromyelitis optica as defined by published criteria[24] or who had AQP4-IgG–seropositive NMOSD at screening with idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral-segment spinal cord lesions on magnetic resonance imaging) or recurrent or simultaneous optic neuritis in both eyes.[4] The percentage of AQP4-IgG–seronegative patients was limited to approximately 30% of the total population of adults (those 18 to 74 years of age) in the trial.

Patients were required to have had at least two relapses in the 2 years before screening, with at least one relapse occurring in the previous 12 months. To be eligible, patients had to have an Expanded Disability Status Scale (EDSS) score of 0 to 6.5 at screening (on a scale from 0 to 10, with a score of 0 representing no disability and a score of 10 representing death), and the dose of permitted baseline treatments must have remained stable for 8 weeks before baseline. Key exclusion criteria were previous treatment with any agent targeting the interleukin-6 pathway, alemtuzumab, total-body irradiation, or bone marrow transplantation at any time; the use of eculizumab, belimumab, or multiple sclerosis disease–modifying treatment within 6 months before baseline; or the use of anti-CD4 agents, cladribine, or mitoxantrone within 2 years before baseline.

END POINTS

The primary efficacy end point was the first protocol-defined relapse in the double-blind period in a time-to-event analysis. Protocol-defined relapses were new or worsening objective neurologic symptoms with one of the following: an increase of at least 1.0 on the EDSS from a baseline score of more than 0 (or an increase of ≥2.0 from a baseline score of 0); an increase of at least 2.0 on one appropriate symptom-specific functional-system score for the pyramidal system, cerebellar system, brain stem, sensory system, bowel or bladder, or a single eye; an increase of at least 1.0 on more than one symptom-specific functional-system score with a baseline score of at least 1.0; or an increase of at least 1.0 on a symptom-specific functional-system score in a single eye with a baseline score of at least 1.0. Symptoms were required to be attributable to neuromyelitis optica or NMOSD, to persist for more than 24 hours, and to not be attributable to confounding clinical factors such as fever, infection, injury, change in mood, or adverse reactions to medications. Relapses were adjudicated by a clinical end-point committee whose members were unaware of the trial-group assignments. A sensitivity analysis was conducted for the first clinical relapse in the double-blind period in a time-to-event analysis; such events included both protocol-defined and investigator-assessed relapses that did not meet the trial-specified criteria for a protocol-defined relapse.

Key secondary efficacy end points were the change from baseline to week 24 in the visual-analogue scale (VAS) score for pain (on a scale from 0 to 100, with higher scores indicating more pain) and in the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score (on a scale from 0 to 52, with lower scores indicating more fatigue).[25] Additional secondary end points were the score changes from baseline to week 24 on the following assessments: the 36-item Short Form Health Survey (SF-36; eight sections with scores transformed to 0 to 100, with lower scores indicating greater disability); the EuroQol-5 Dimensions (EQ-5D) instrument (scored

on a scale from −0.109 to 1, with higher scores indicating a better health state); the modified Rankin scale (scored from 0 [no symptoms] to 6 [death]); the Zarit Burden Interview (an assessment given to the patient's caregiver [if any] and scored from 0 [no burden] to 88 [severe burden], with higher scores indicating a greater burden on caregivers); the EDSS score; visual acuity (according to the Snellen chart; values are presented as adjusted mean changes in the test distance, divided by letter size, and are expressed as a decimal); and the percentage of patients free from relapse. Safety outcome measures included the incidence and severity of adverse events and serious adverse events. Relapses were not categorized as adverse events.

STATISTICAL ANALYSIS

Prespecified efficacy analyses were based on the intention-to-treat population and an event-driven design. The primary analysis was performed after the occurrence of 26 protocol-defined relapse events, as described in the statistical analysis plan (see the protocol). Sample-size and power calculations are described in the Supplementary Appendix. A two-sided log-rank test was used, stratified according to baseline annualized relapse rate and geographic region. Kaplan–Meier analysis was used to estimate the distribution of time to the first protocol-defined relapse. The treatment effect was expressed by hazard ratios and 95% confidence intervals with the use of a Cox proportional-hazards model stratified according to baseline annualized relapse rate and geographic region.

Data from patients who discontinued the trial, who received rescue therapy, who had an increase or change in their baseline treatment, or who were continuing in the trial at the data-cutoff date were treated as censored. To evaluate the influence of early censoring, four post hoc analyses with the use of multiple imputation for patients with censored data, excluding patients who were still continuing in the trial at the data-cutoff date, were conducted, and these are presented with the main analysis of the primary outcome.

Prespecified efficacy end points (the percentages of patients free from relapse, with 95% confidence intervals) at 24-week intervals were used to describe the distribution of time to the first protocol-defined relapse. Changes in the key secondary end points (VAS pain and FACIT-F scores) were analyzed by means of the analysis of covariance method. For the key secondary analyses, our statistical analysis plan imputed missing values with the use of the baseline-observation-carried-forward method. For the secondary end points, the results of post hoc imputation analyses for missing data are given as the main results. For missing data relating to secondary continuous end points except for visual acuity, a mixed-effects model repeated-measures analysis was used to incorporate all the data in the double-blind period.

A serial gatekeeping method was used to control the rate of false positives at an overall significance level of 5% for the primary end point and the two key secondary end points only. These three end points were analyzed in hierarchical order, beginning with the primary end point, followed by the VAS pain end point, and ending with the FACIT-F end point; P values were not to be presented if statistical significance was not met for an end point that was higher in the testing hierarchy. Differences in annualized relapse rates were adjusted by the baseline annualized relapse rate and geographic region with the use of a Poisson regression model. Because there was no plan for adjustment for multiple comparisons for the remaining secondary outcomes, differences between groups are presented as point estimates with confidence intervals that were not adjusted for multiplicity. No clinical inferences can be made from those results. A prespecified subgroup analysis for the time to the first protocol-defined relapse according to the AQP4-IgG serologic status at screening (seropositive or seronegative according to enzyme-linked immunosorbent assay) was performed. The AQP4-IgG serologic status was determined on the basis of the central laboratory test result.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 83 patients were randomly assigned to a trial group — 41 to the satralizumab group and 42 to the placebo group (Fig. 1). Patients were enrolled at 34 sites in 11 countries (Table S1); 5 sites enrolled no patients. The characteristics of the patients at baseline were similar in the

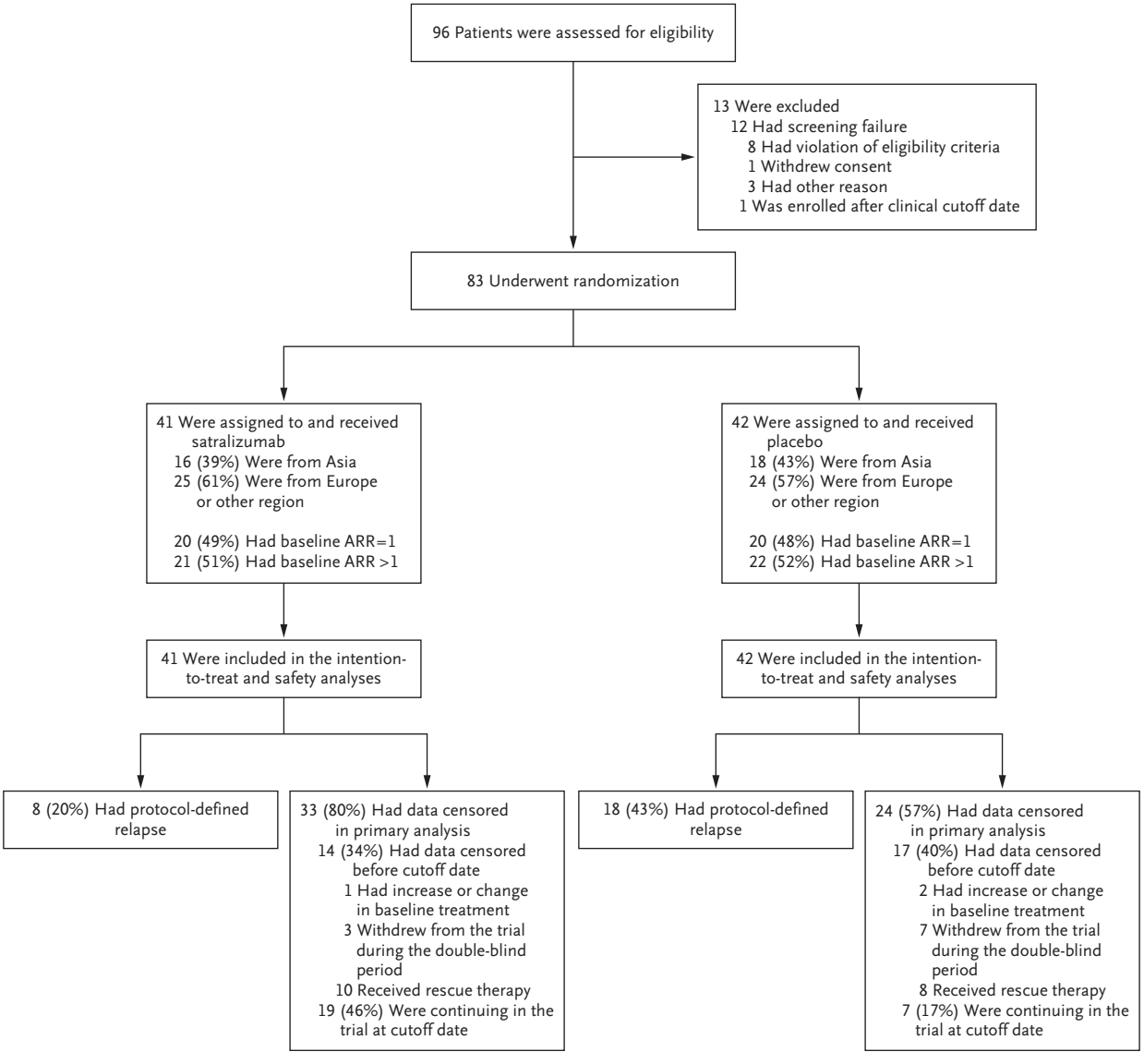

Figure 1. Randomization and Follow-up of the Trial Participants.

The data-cutoff date was June 6, 2018. Protocol-defined relapse was adjudicated by the clinical end-point committee. ARR denotes annualized relapse rate.

two groups (Table 1 and Table S2). The median treatment duration during the double-blind period was 107.4 weeks (range, 2 to 224) in the satralizumab group and 32.5 weeks (range, 0 to 180) in the placebo group. Patients in the placebo group had a shorter time to relapse and a higher incidence of withdrawal from the trial than did those in the satralizumab group. The median treatment duration among all the patients receiving satralizumab in the double-blind and extension periods was 143.1 weeks (range, 15 to 224).

EFFICACY

A total of 8 of 41 patients (20%) receiving satralizumab had a protocol-defined relapse, as com-

pared with 18 of 42 patients (43%) receiving placebo (hazard ratio, 0.38; 95% confidence interval [CI], 0.16 to 0.88; adjusted P=0.02) (Fig. 2A). Analyses with the use of multiple imputations for censored data for the primary end point, which excluded patients who were still continuing in the trial at the data-cutoff date, resulted in hazard ratios ranging from 0.34 to 0.44, with log-rank P values of 0.01 to 0.04 (Table 2). The percentage of patients who were free from relapse at 48 weeks was 89% in the satralizumab group and 66% in the placebo group; at 96 weeks, these values were 78% and 59%, respectively (Table S3).

The first key secondary end point of the adjusted mean between-group difference in the change in the VAS pain score from baseline to week 24 was not significant (between-group difference, 4.08; 95% CI, −8.44 to 16.61; P=0.52) (Table 2). Subsequent end points in the hierarchy are therefore presented as point estimates and confidence intervals only, and no inferences can be made from the results. The second key secondary end point of the between-group difference in the mean change in the FACIT-F score from baseline to week 24 was −3.10 (95% CI, −8.38 to 2.18) (Table 2). (Scores through week 120 are shown in Figs. S2 and S3; additional details are provided in Table S4.)

The annualized relapse rate during the double-blind period was 0.11 (95% CI, 0.05 to 0.21) in the satralizumab group and 0.32 (95% CI, 0.19 to 0.51) in the placebo group (between-group difference, 0.34; 95% CI, 0.15 to 0.77). The open-label extension period was not included in the calculation for the annualized relapse rate. The analysis of the effect of subgroups on the estimate of protocol-defined relapse in the double-blind period is shown in Figure S4.

In the AQP4-IgG–seropositive subgroup (which included patients with neuromyelitis optica or NMOSD), 3 of 27 patients (11%) receiving satralizumab had a protocol-defined relapse, as compared with 12 of 28 patients (43%) receiving placebo (hazard ratio, 0.21; 95% CI, 0.06 to 0.75) (Fig. 2B). In the AQP4-IgG–seronegative subgroup (patients with neuromyelitis optica only), 5 of 14 patients (36%) receiving satralizumab had a protocol-defined relapse, as compared with 6 of 14 patients (43%) receiving placebo (hazard ratio, 0.66; 95% CI, 0.20 to 2.24) (Fig. 2C). The results of analyses of other secondary end points are shown in Table 2. The sensitivity analysis of time to any relapse, including both protocol-defined and non–protocol-defined relapses, was consistent with the analysis of protocol-defined relapse (Fig. S5).

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Satralizumab (N=41)	Placebo (N=42)
Age — yr		
Mean	40.8±16.1	43.4±12.0
Range	13–73	14–65
Female sex — no. (%)	37 (90)	40 (95)
Age at clinical presentation — yr	35.4±16.9	38.8±12.0
Geographic region — no. (%)		
Asia	16 (39)	18 (43)
Europe or other†	25 (61)	24 (57)
Diagnosis — no. (%)‡		
Neuromyelitis optica	33 (80)	28 (67)
Neuromyelitis optica spectrum disorder	8 (20)	14 (33)
AQP4-IgG–seropositive status — no. (%)	27 (66)	28 (67)
Annualized relapse rate in previous 2 yr	1.5±0.5	1.4±0.5
EDSS score§	3.83±1.57	3.63±1.32
VAS pain score¶	27.6±28.2	34.6±26.1
FACIT-F score‖	34.7±10.5	33.9±11.3
Treatment at baseline — no. (%)		
Oral glucocorticoids	17 (41)	20 (48)
Azathioprine	16 (39)	13 (31)
Mycophenolate mofetil	4 (10)	8 (19)
Azathioprine plus glucocorticoids	3 (7)	0
Mycophenolate mofetil plus oral glucocorticoids	1 (2)	1 (2)

* Plus–minus values are means ±SD. There were no significant differences between groups. There were no missing values for any baseline demographic data. Percentages may not total 100 because of rounding.
† Other geographic region refers to the United States.
‡ Patients either had neuromyelitis optica according to published criteria[24] (seropositive or seronegative for antibodies against aquaporin-4 [AQP4-IgG]) or had neuromyelitis optica spectrum disorder (AQP4-IgG–seropositive status only) according to published criteria[4] with idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral-segment spinal cord lesions on magnetic resonance imaging) or recurrent or simultaneous optic neuritis in both eyes.
§ Scores on the Expanded Disability Status Scale (EDSS) range from 0 (normal neurologic examination) to 10 (death).
¶ Scores on the visual-analogue scale (VAS) for the assessment of pain range from 0 to 100, with higher scores indicating more pain.
‖ Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) range from 0 to 52, with lower scores indicating more fatigue.

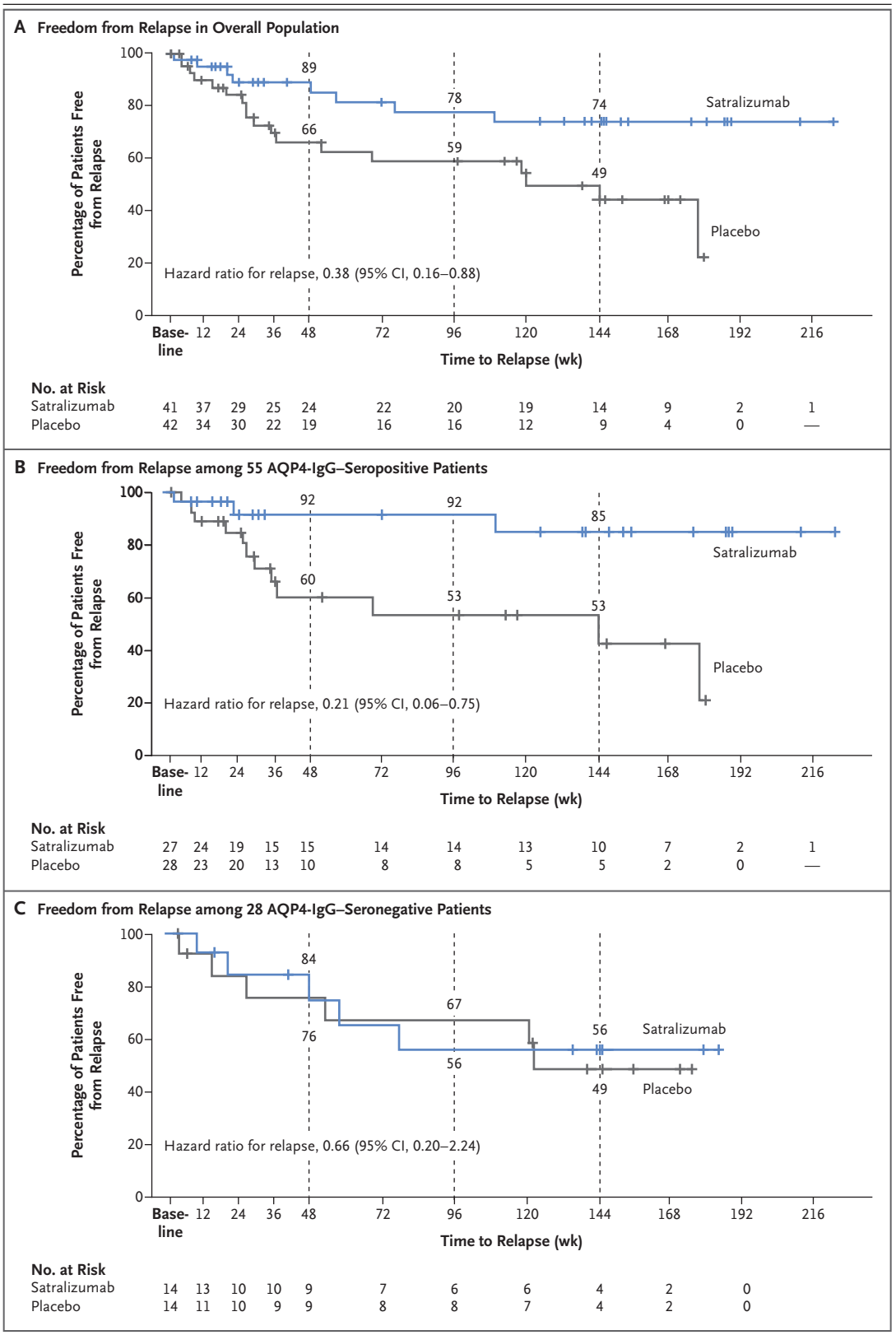

Figure 2 (facing page). Time to First Protocol-Defined Relapse during the Double-Blind Period in the Overall Patient Cohort, the AQP4-IgG–Seropositive Subgroup, and the AQP4-IgG–Seronegative Subgroup.

The analyses were based on the intention-to-treat population. Numbers at the dashed lines indicate the percentages of patients in each group who were free from relapse at 48, 96, and 144 weeks. Protocol-defined relapse was adjudicated by the independent clinical end-point committee. Tick marks indicate censored data. AQP4-IgG denotes IgG antibodies against aquaporin-4.

SAFETY

The length of time of exposure to trial agents in the double-blind period differed between groups owing to the shorter time to relapse and higher number of withdrawals in the placebo group than in the satralizumab group. The mean (±SD) period of treatment in the double-blind period was 94.1±72.6 weeks in the satralizumab group and 66.0±61.4 weeks in the placebo group; this comprised all the patients who underwent randomization and received at least one dose of satralizumab or placebo.

In the double-blind period, 37 patients (90%) in the satralizumab group and 40 (95%) in the placebo group had at least one adverse event (Table 3). Overall, the numbers of events per 100 patient-years, including serious adverse events, infections, and serious infections (defined according to *Medical Dictionary for Regulatory Activities*, version 16.1, criteria), were similar among patients treated with satralizumab and those who received placebo (Table S6). There were no deaths and no anaphylactic reactions in either group during the double-blind period or over a mean of 126 weeks of satralizumab therapy. Injection-related reactions were more frequent in the satralizumab group than in the placebo group, and no patient discontinued the trial drug owing to injection-related reactions (Table 3). The safety profile was generally similar among adolescents and adults.

A total of 3 patients (7%) in the satralizumab group and 10 (24%) in the placebo group discontinued the trial agent during the double-blind period. In the satralizumab group, the 3 patients (7%) discontinued owing to adverse events in the double-blind period, as compared with 5 patients (12%) in the placebo group. Among the 65 patients who were evaluated in the combined double-blind and open-label extension periods, 6 patients (9%) receiving satralizumab discontinued the trial owing to adverse events.

DISCUSSION

Preclinical and clinical data have shown an association between interleukin-6 and the pathophysiology of NMOSD.[13,14] In this phase 3 trial, the monoclonal antibody satralizumab, targeting membrane-bound and soluble interleukin-6 receptors, added to stable baseline immunosuppressant treatment, led to a longer time to relapse than placebo. This finding supports a role of interleukin-6–mediated effects in the pathophysiology of NMOSD. Satralizumab had a greater effect than placebo on the primary end point of the relapse rate, but there was no significant difference in effect between the trial groups in the key secondary end points of pain and fatigue.

Subgroup analysis suggests that satralizumab led to a lower risk of relapse than placebo among patients who were AQP4-IgG–seropositive; however, there is insufficient evidence to indicate a lower risk in the AQP4-IgG–seronegative subgroup, because the confidence-interval estimate for this subgroup includes the null value of one. The drug may be ineffective in the latter group, or the discrepancy between seropositive patients and seronegative patients may be explained by the few seronegative patients who were included as a result of the trial design.

The percentages of patients who had adverse events or serious adverse events associated with satralizumab were similar to those in the placebo group. However, there were more injection-site reactions and injection-related reactions in the satralizumab group than in the placebo group.

There were limitations of this trial. These included the small group sizes and the lack of an active comparator. The trial could not determine whether there was a difference between the trial groups at a given week.

Among adolescent and adult patients with NMOSD, satralizumab added to baseline immunosuppressant treatment led to a lower risk of relapse than placebo, particularly among AQP4-IgG–seropositive patients. Longer and larger trials are necessary to determine the efficacy, durability, and safety of satralizumab and to

Table 2. Trial End Points.*

End Point	Satralizumab (N=41)	Placebo (N=42)	Hazard Ratio or Difference (95% CI)	P Value
Primary end point				
Primary analysis: protocol-defined relapse — no. (%)†	8 (20)	18 (43)	0.38 (0.16 to 0.88)	0.02
Sensitivity analyses†‡				
Model 1			0.34 (0.14 to 0.78)	0.01
Model 2			0.37 (0.16 to 0.86)	0.03
Model 3			0.44 (0.20 to 0.95)	0.04
Model 4			0.35 (0.15 to 0.81)	0.02
Key secondary end points§				
Change in VAS pain score at 24 wk	0.35±4.52	−3.73±4.12	4.08 (−8.44 to 16.61)	0.52
Change in FACIT-F score at 24 wk	0.02±2.00	3.12±1.79	−3.10 (−8.38 to 2.18)	
Other end points				
Annualized relapse rate (95% CI)	0.11 (0.05 to 0.21)	0.32 (0.19 to 0.51)	0.34 (0.15 to 0.77)¶	
Change in SF-36 score at 24 wk‖**				
No. of patients	29	28		
Change in physical component summary score	1.10	2.46		
Change in mental component summary score	−0.03	2.28		
Change in EQ-5D score at 24 wk‖††				
No. of patients	28	29		
Score change	−0.002	0.04		
Change in modified Rankin scale score at 24 wk‖‡‡				
No. of patients	29	29		
Score change	−0.03	−0.05		
Change in Zarit Burden Interview score at 24 wk‖§§				
No. of patients	7	9		
Score change	−6.97	−7.06		
Change in EDSS score at 24 wk‖				
No. of patients	29	29		
Score change	−0.10	−0.21		
Change in visual acuity according to Snellen chart at 24 wk¶¶				
No. of patients	29	30		
Change in right eye	0.04	−0.06		
Change in left eye	0.06	−0.01		

* Plus–minus scores are means ±SE. The percentages of patients who were free from relapse are shown in Table S3. Hazard ratios are shown for the primary analysis and the sensitivity analyses. Differences are shown for changes in the VAS and FACIT-F scores and for the annualized relapse rate.

† The analysis was performed with the use of a Cox proportional-hazards model for the hazard ratio and a two-sided log-rank test for P value stratified according to baseline annualized relapse rate and geographic region.

‡ In Model 1, multiple imputation with a Kaplan–Meier model was applied on the basis of Hsu and Taylor[26] with 100 times iteration; in Model 2, multiple imputation with a Cox proportional-hazards model was applied on the basis of Jackson et al.[27] with 100 times iteration; in Model 3, multiple imputation with a Kaplan–Meier model was applied on the basis of Lipkovich et al.[28] with 100 times iteration; and in Model 4, multiple imputation with a Cox proportional-hazards model was applied on the basis of Lipkovich et al.[28] with 100 times iteration.

§ Values are adjusted means based on analysis of covariance with random hot-deck multiple imputation with 100 times iteration. Treatment group was included as a fixed effect, with baseline measurements and stratification factors as covariates.

¶ The difference was adjusted for the baseline annualized relapse rate and geographic region with the use of a Poisson regression model.

‖ Values are adjusted means from mixed-effect model repeated-measures analysis. Trial group, protocol-specified visit, and treatment-by-visit interaction were included as fixed effects, the baseline measurements and stratification factors were included as covariates, and visit was included as a repeated measure. An unstructured covariance matrix was used.

** The 36-item Short Form Health Survey (SF-36) consists of eight sections, and each score is transformed onto a scale ranging from 0 to 100. Lower scores indicate greater disability. The physical component summary comprises the domains of physical functioning, role-physical, bodily pain, and general health; the mental component summary comprises the domains of vitality, social functioning, role-emotional, and mental health (Table S5).

†† Scores on the EuroQol–5 Dimensions (EQ-5D) instrument range from −0.109 to 1, with higher scores indicating a better health state.

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

§§ Scores on the Zarit Burden Interview, which was given to caregivers (if any), range from 0 (no burden) to 88 (severe burden), with higher scores indicating greater burden on caregivers.

¶¶ Scores on the Snellen chart were converted to logMAR (logarithm of the minimal angle of resolution) values, which are presented as adjusted mean changes in the test distance, divided by letter size, and are expressed as a decimal score. Values are mean changes. Positive numbers indicate improvements in vision.

Table 3. Summary of Adverse Events in the Double-Blind Period (Safety Population).*

Event	Satralizumab (N = 41)		Placebo (N = 42)	
	Patients	Events (95% CI)	Patients	Events (95% CI)
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*
Adverse event	37 (90)	485.2 (437.7–536.5)	40 (95)	514.3 (458.2–575.2)
Serious adverse event	7 (17)	11.5 (5.2–21.8)	9 (21)	20.2 (10.4–35.2)
Death	0	0	0	0
Infection	28 (68)	132.5 (108.2–160.5)	26 (62)	149.6 (120.1–184.1)
Serious infection	2 (5)	2.6 (0.3–9.2)	3 (7)	5.0 (1.0–14.7)
Injection-related reaction	5 (12)	21.7 (12.6–34.7)	2 (5)	3.4 (0.4–12.1)
Anaphylactic reaction†	0	0	0	0
Neoplasm‡	3 (7)	3.8 (0.8–11.2)	3 (7)	5.0 (1.0–14.7)

* The safety population included patients who received at least one dose of satralizumab or placebo.
† Anaphylactic reaction was defined as anaphylaxis (with narrow searches) in the standardized queries of the *Medical Dictionary for Regulatory Activities*, version 16.1.
‡ Benign neoplasm of thyroid gland, colon adenoma, and uterine leiomyoma occurred in one patient each in the satralizumab group. Breast cancer, hepatic cancer, and lipoma occurred in one patient each in the placebo group.

investigate its effect in comparison with other treatments for NMOSD.

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

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

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APPENDIX

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