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Benefits of eculizumab in AQP4+ neuromyelitis optica spectrum disorder: Subgroup analyses of the randomized controlled phase 3 PREVENT trial

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ABSTRACT

Background: Antibodies to the aquaporin-4 (AQP4) water channel in neuromyelitis optica spectrum disorder (NMOSD) are reported to trigger the complement cascade, which is implicated in astrocyte damage and subsequent neuronal injury. The PREVENT study demonstrated that the terminal complement inhibitor eculizumab reduces adjudicated relapse risk in patients with anti-AQP4 immunoglobulin G-positive (AQP4+) NMOSD. The objective of this analysis was to evaluate the efficacy of eculizumab in reducing relapse risk and its safety in AQP4+ NMOSD across clinically relevant subgroups in PREVENT.

Methods: In the randomized, double-blind, time-to-event, phase 3 PREVENT trial, 143 adults received eculizumab (maintenance dose, 1200 mg/2 weeks) or placebo (2:1), with stable-dose concomitant immunosuppressive therapy (IST) permitted (except rituximab and mitoxantrone). *Post hoc* analyses of relapses and adverse events

Abbreviations: AE, adverse event; AQP4, aquaporin-4; AQP4+, anti-aquaporin-4 immunoglobulin G-positive; ARR, annualized response rate; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IST, immunosuppressive therapy; MG, myasthenia gravis; NE, not estimable; NMOSD, neuromyelitis optica spectrum disorder; PY, patient-year; SAE, serious adverse event; SD, standard deviation.

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were performed for prespecified and *post hoc* subgroups based on concomitant IST and prior rituximab use, demographic and disease characteristics, and autoimmune comorbidity.
Results: The significant reduction in relapse risk observed for eculizumab versus placebo in the overall PREVENT population was consistently maintained across subgroups based on concomitant IST and previous rituximab use, age, sex, region, race, time since clinical onset of NMOSD, historical annualized relapse rate, baseline Expanded Disability Status Scale score, and history of another autoimmune disorder. The serious infection rate was lower with eculizumab than placebo regardless of rituximab use in the previous year, concomitant IST use, or history of another autoimmune disorder.
Conclusion: Across a wide range of clinically relevant AQP4+ NMOSD patient subgroups in PREVENT, eculizumab therapy was consistently effective versus placebo in reducing relapse risk, with no apparent increase in serious infection rate.
Trial registration: NCT01892345 (ClinicalTrials.gov).

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune central nervous system disorder characterized by an unpredictable relapsing course and relapse-dependent cumulative disability (Huda et al., 2019; Mealy et al., 2019; Wingerchuk et al., 1999; Wingerchuk et al., 2007). The underlying immunopathogenic mechanism is autoimmunity against the aquaporin-4 (AQP4) water channel, resulting in complement-mediated astrocytic damage and subsequent neuronal injury (Duan et al., 2018; He et al., 2017; Hinson et al., 2012; Jiao et al., 2013; Saadoun et al., 2010). The safety and efficacy of eculizumab, a humanized monoclonal antibody that blocks the terminal complement system, were demonstrated in the pivotal phase 3 PREVENT trial (Pittock et al., 2019), in which eculizumab was well tolerated and the overall risk of adjudicated relapse was reduced by 94.2% versus placebo in adults with anti-AQP4 immunoglobulin G-positive (AQP4+) NMOSD (Soliris US Prescribing Information, 2019).

Patients with NMOSD often have complex disease and treatment histories (Romeo and Segal, 2019). Factors including a patient's sex, race, and age at disease onset, and interventions such as immunosuppressive therapy (IST), have been found to influence the course of AQP4+ NMOSD (Palace et al., 2019). The objective of the current analysis was to evaluate the impact of clinically relevant factors on relapse-risk reduction with eculizumab, using data from a range of patient subgroups that were either prespecified or defined *post hoc* from PREVENT. The prespecified subgroups were based on patient demographics (age, sex, region, race), randomization strata (defined by disability and IST status since last pre study relapse), and concomitant IST and prior rituximab use. In addition, the *post hoc* defined subgroups were based on disease characteristics (time since clinical onset of NMOSD, baseline disability status, historical annualized relapse rate [ARR]), and the presence of autoimmune comorbidities. Given that the presence of comorbid autoimmune disorders and the use of IST and rituximab are known to impact the immune response, safety outcomes were analyzed *post hoc* in patients in these subgroups. Specifically, these subgroups comprised patients who received rituximab in the year before PREVENT, patients who received eculizumab with concomitant IST, and patients with a history of an autoimmune disorder in addition to a diagnosis of NMOSD.

2. Methods

2.1. Overview of PREVENT trial design

The methodology of the phase 3, randomized, double-blind, placebo-controlled, time-to-event PREVENT trial, including study design, patient eligibility, study treatment, and assessments, has been described in detail previously (Pittock et al., 2019). Briefly, eligible participants were adults with AQP4+ NMOSD with 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 an Expanded Disability Status Scale (EDSS) score of 7.0 or less. Patients who received mitoxantrone or rituximab during the previous 3 months were excluded.

Participants were randomized 2:1 to receive eculizumab or matching placebo administered intravenously between April 2014 and October 2017. Patients were vaccinated against *Neisseria meningitidis* serotypes A, C, W and Y at least 14 days before receiving study treatment, or were vaccinated and received appropriate antibiotic treatment until 14 days after vaccination (Pittock et al., 2019). Patients were also vaccinated against serotype B where available and recommended by local or national guidelines. Patients randomized to eculizumab received 900 mg weekly for the first four doses, followed by a maintenance regimen of 1200 mg every 2 weeks. Eculizumab or placebo administration continued until physician-determined relapse, trial discontinuation, or the end of the trial. The trial was stopped after 23 of the 24 prespecified adjudicated relapses. Treatment with concomitant IST was permitted (except rituximab or mitoxantrone) if the dosing regimen was stable at screening, with dose changes only permitted following physician-determined relapse or safety concerns.

Relapses were identified and managed by the treating physician, and subsequently adjudicated by an independent committee. The primary efficacy endpoint was the time to first adjudicated relapse. This was changed from the original primary efficacy endpoint of time to first physician-determined relapse by protocol amendment after 88 patients were enrolled. Additional details are included in the methodology of the primary publication (Pittock et al., 2019).

2.2. Subgroup analysis

2.2.1. Prespecified subgroups

Patient subgroups were prespecified in PREVENT for descriptive data summaries according to: concomitant IST use (corticosteroids alone, azathioprine with/without corticosteroids, mycophenolate mofetil with/without corticosteroids, other IST with/without corticosteroids [including cyclophosphamide, cyclosporine, methotrexate, mizoribine, and tacrolimus]; no IST [monotherapy]); any history of rituximab use; patient demographics (based on geographic region [Americas, Asia–Pacific, Europe], age [$<$ 45 years, $\geq$ 45 years], sex, and race); and randomization strata (based on baseline EDSS score and IST status since last pre study relapse [low EDSS score, $\leq$ 2.0; high EDSS score, 2.5–7.0, and treatment-naive; high EDSS score, 2.5–7.0, and continuing same IST since last pre study relapse; high EDSS score, 2.5–7.0, and changes in IST since last pre study relapse]).

2.2.2. Subgroups defined post hoc for the efficacy analysis

Patient subgroups were defined *post hoc* according to disease characteristics at baseline: time since onset of first NMOSD symptoms ($<$ 5 years vs $\geq$ 5 years); baseline EDSS score ($<$ 4.0 vs $\geq$ 4.0), historical ARR in the 24 months before screening ($\leq$ 1.5 vs $>$ 1.5); and history of another autoimmune disorder (yes vs no).

2.2.3. Subgroups defined post hoc for safety analysis

To characterize safety further in the context of treatment history and

comorbidity, three subgroups were defined *post hoc*: patients treated with rituximab in the previous year, because rituximab may have a prolonged effect on B-cell profiles (Nissimov et al., September 13, 2019; Stockholm); patients using concomitant ISTs, to evaluate the impact of chronic immunosuppression on the safety profile of eculizumab; and patients with a history of another autoimmune disorder (Shahmohammadi et al., 2019).

2.2.4. Endpoints

The primary efficacy endpoint of time to first adjudicated relapse was summarized for all prespecified and *post hoc* (efficacy) subgroups. Adverse events (AEs), serious AEs (SAEs), and serious infections over time were summarized for the *post hoc* (safety) subgroups.

2.2.5. Statistical analysis

The sample size for the overall PREVENT study population was based on the percentage of patients who were hypothesized to be relapse-free (80% for eculizumab; 40% for placebo) at 12 months (hazard ratio [HR], 0.24). In PREVENT, with 2:1 randomization for the trial groups, it was calculated that 24 events in 132 patients would provide 90% power 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. The randomization technique has previously been described (Pittock et al., 2019).

All statistical analyses of both prespecified and *post hoc* subgroups were performed *post hoc*, because the PREVENT trial was not designed or powered for subgroup analyses. Time to first adjudicated relapse was analyzed using an unstratified log-rank test. HRs were estimated using a Cox proportional-hazards model, with treatment group as a covariate, and confidence intervals were based on inverting the score test under the Cox model to correspond with the log-rank p values (Lin et al., 2016). Interaction p values were based on a Cox proportional-hazards model with interaction terms. Proportions of patients who were relapse-free at week 48 were estimated using the Kaplan–Meier product-limit method. 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 negatively and those who discontinued the trial regimen early. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

2.3. Standard protocol approvals, registrations, and patient consents

The PREVENT trial (ClinicalTrials.gov number, NCT01892345; EudraCT number, 2013-001150-10) was conducted in accordance with the provisions of the Declaration of Helsinki (World Medical Association, 2013), the International Conference on Harmonisation guidelines for Good Clinical Practice (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2001), and applicable regulatory requirements. The trial was approved by the institutional review board at each participating institution. All patients provided written informed consent before participation.

2.4. Data availability statement

Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, 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 (statistical analysis plan and protocol) 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 at http://alexion.com/research-development (link to data-request form: https://alexion.com/contact-alexion/medical-information).

3. Results

3.1. Patients

In total, 143 patients were treated in PREVENT (eculizumab, n = 96; placebo, n = 47). Patient disposition, and demographic and clinical characteristics of the PREVENT study population were detailed in the primary study report (Pittock et al., 2019). Overall, 90.9% of participants (130/143) were female, and mean age at first receipt of trial treatment was 44.3 years (standard deviation [SD], 13.27). The geographic distribution of patients among Europe, the Americas, and Asia–Pacific was roughly equal (35.7% [51/143], 30.8% [44/143], and 33.6% [48/143], respectively). Most patients were White (49.0% [70/143]) or Asian (36.4% [52/143]), and 11.9% (17/143) were Black/African–American (Table 1). The median time from clinical onset of NMOSD to first dose of study drug was 4.8 years (range, 0.4–44.9 years), and 23.1% of study participants (33/143) had a history of another autoimmune disorder (autoimmune thyroiditis [n = 7], rheumatoid arthritis [n = 7], systemic lupus erythematosus [n = 10], Sjögren's syndrome [n = 7], myasthenia gravis [MG; n = 2], psoriasis [n = 2], autoimmune hemolytic anemia [n = 1], immune thrombocytopenic purpura [n = 1], and lupus hepatitis [n = 1]). The mean (SD) ARR in the 24 months prior to screening was 1.99 (0.943). The median EDSS score at PREVENT baseline was 4.0 (range, 1.0–7.0).

In total, 76.2% of patients (109/143) continued to receive their baseline IST regimen during the trial. Nearly one-third of patients (32.2%; 46/143) had a history of rituximab use at any time except in the 3 months before entering PREVENT, and 24.5% (35/143) had used rituximab within 1 year before entering PREVENT.

3.2. Risk of adjudicated relapse

Patients who received eculizumab experienced a reduced risk of relapse compared with those who received placebo in all subgroups analyzed (both prespecified [Fig. 1A] and those defined *post hoc* [Fig. 1B]); these risk reductions reached significance in all but three subgroups (other IST, Black/African–American, and Americas subgroups). The benefits of eculizumab over placebo were consistent across the baseline characteristics used to define the subgroups, with HRs ranging from 0.000 (no events) to 0.202. There were no significant differences in risk reduction between subgroups for each variable, demonstrated by interaction p values ranging from 0.9994 to 0.1738.

Eculizumab was associated with significant reductions versus placebo in risk of adjudicated relapse in patients concomitantly treated with corticosteroids alone, azathioprine with/without corticosteroids, mycophenolate mofetil with/without corticosteroids, or no IST (monotherapy). A nonsignificant risk reduction was observed in the other IST subgroup, which was limited by small sample size (Fig. 1A). In all prespecified IST subgroups, the proportions of patients who were relapse-free at week 48 were consistently higher with eculizumab than with placebo (Fig. 2) (Pittock et al., 2019). Eculizumab was also associated with significant reductions versus placebo in risk of adjudicated relapse for patients with any history of rituximab treatment or without such a history (Fig. 1A). The proportion of patients who were relapse-free at week 48 was higher with eculizumab (100.0%) than with placebo (62.5%) in this subgroup (Fig. 2D).

Table 1
Prespecified and *post hoc* subgroups by study treatment.

	Eculizumab (n = 96)	Placebo (n = 47)	Overall (N = 143)
Prespecified subgroups			
Baseline IST, n (%)			
Corticosteroids alone	16 (16.7)	11 (23.4)	27 (18.9)
Azathioprine ± corticosteroids	37 (38.5)	13 (27.7)	50 (35.0)
Mycophenolate mofetil ± corticosteroids	17 (17.7)	8 (17.0)	25 (17.5)
Other IST ± corticosteroids	5 (5.2)	2 (4.3)	7 (4.9)
No IST	21 (21.9)	13 (27.7)	34 (23.8)
History of rituximab use[a], n (%)			
Yes	26 (27.1)	20 (42.6)	46 (32.2)
No	70 (72.9)	27 (57.4)	97 (67.8)
Region, n (%)			
Americas	29 (30.2)	15 (31.9)	44 (30.8)
Asia–Pacific	35 (36.5)	13 (27.7)	48 (33.6)
Europe	32 (33.3)	19 (40.4)	51 (35.7)
Age, n (%)			
< 45 years	47 (49.0)	24 (51.1)	71 (49.7)
≥ 45 years	49 (51.0)	23 (48.9)	72 (50.3)
Sex, n (%)			
Female	88 (91.7)	42 (89.4)	130 (90.9)
Male	8 (8.3)	5 (10.6)	13 (9.1)
Race, n (%)			
Asian	37 (38.5)	15 (31.9)	52 (36.4)
Black/African–American	9 (9.4)	8 (17.0)	17 (11.9)
White	46 (47.9)	24 (51.1)	70 (49.0)
Other	4 (4.2)	0 (0.0)	4 (2.8)
Randomization strata			
Low EDSS score (≤ 2.0)	11 (11.5)	5 (10.6)	16 (11.2)
High EDSS score (2.5–7.0) and treatment-naive	12 (12.5)	5 (10.6)	17 (11.9)
High EDSS score (2.5–7.0) and continuing same IST	44 (45.8)	22 (46.8)	66 (46.2)
High EDSS score (2.5–7.0) and changes in IST	29 (30.2)	15 (31.9)	44 (30.8)
Post hoc subgroups			
Time since clinical onset of NMOSD, n (%)			
< 5 years	48 (50.0)	25 (53.2)	73 (51.0)
≥ 5 years	48 (50.0)	22 (46.8)	70 (49.0)
Baseline EDSS score, n (%)			
< 4.0	47 (49.0)	17 (36.2)	64 (44.8)
≥ 4.0	49 (51.0)	30 (63.8)	79 (55.2)
Historical ARR[b], n (%)			
≤ 1.5	46 (47.9)	19 (40.4)	65 (45.5)
> 1.5	50 (52.1)	28 (59.6)	78 (54.5)
History of another autoimmune disorder, n (%)			
Yes	23 (24.0)	10 (21.3)	33 (23.1)
No	73 (76.0)	37 (78.7)	110 (76.9)

ISTs were used concomitantly throughout the trial, except rituximab. Patients previously receiving rituximab could be included in the trial if they had not received treatment in the 3 months before screening. ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; IST, immunosuppressive therapy; NMOSD, neuromyelitis optica spectrum disorder.

[a] Any historical use of rituximab (note that the previous rituximab subgroup in the safety analysis comprised patients who had used rituximab in the year prior to PREVENT's baseline).

[b] ARR in the 24 months before screening.

Significant adjudicated relapse-risk reductions with eculizumab versus placebo were observed in patients from Europe and Asia–Pacific, and a nonsignificant relapse-risk reduction was observed for patients from the Americas. Eculizumab was associated with significant reductions versus placebo in risk of adjudicated relapse for patients younger than 45 years of age and those of 45 years of age and older, for women and men, and for White and Asian patients. A nonsignificant risk reduction was observed in the Black/African–American subgroup, which was limited by small sample size. No relapses were observed in patients of other races (Fig. 1A). In addition, eculizumab was associated with significant reductions versus placebo in risk of adjudicated relapse in all four randomization strata: subgroups defined by low EDSS score (≤ 2.0), high EDSS score (2.5–7.0) and treatment-naive, high EDSS score (2.5–7.0) and continuing the same IST, and high EDSS score (2.5–7.0) and changes in IST (Fig. 1A).

Finally, there were significant adjudicated relapse-risk reductions with eculizumab versus placebo regardless of time since clinical onset of NMOSD (< 5 years or ≥ 5 years before PREVENT), baseline EDSS score (< 4.0 or ≥ 4.0), historical ARR (≤ 1.5 or > 1.5), and history of another autoimmune disorder (with or without such a history; Fig. 1B).

3.3. Safety

3.3.1. Rates of SAEs related to trial agent and all serious infections during PREVENT

In all *post hoc* safety subgroups, both the rates of SAEs considered possibly, probably, or definitely related to trial agent and the rates of serious infections were lower in the eculizumab arm than in the placebo arm. In patients who had used rituximab in the previous year, the rate of trial-agent-related SAEs was 6.7 versus 13.2 events/100 patient-years (PY), and the rate of serious infections was 10.1 versus 13.2 events/100 PY. Only two patients in this subgroup experienced a serious infection with eculizumab, both within the first 6 months of eculizumab treatment.

Among patients who used concomitant ISTs during PREVENT, the trial-agent-related SAE rate was 7.8 versus 24.8 events/100 PY, and the

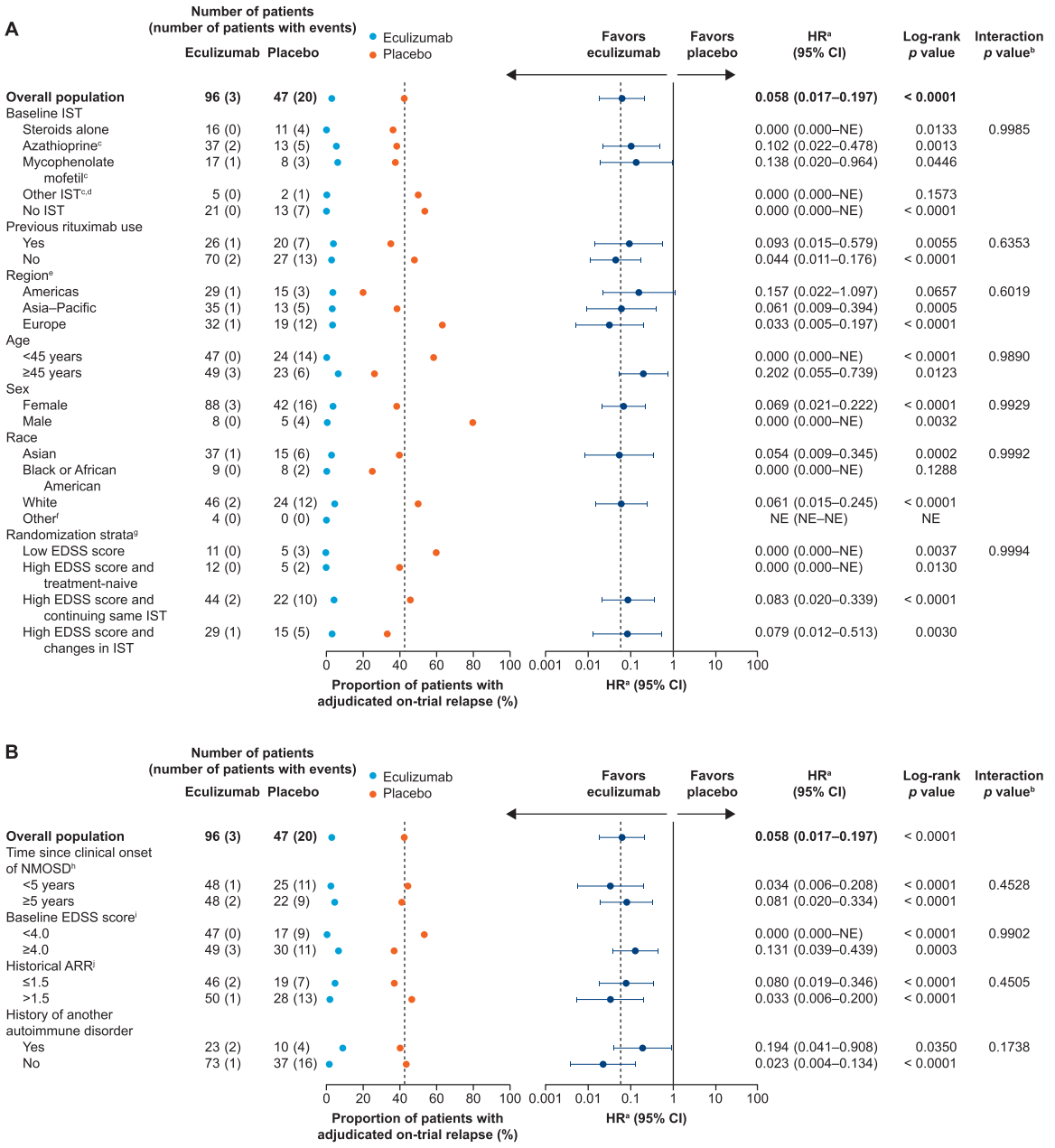

Fig. 1. Risk of adjudicated relapse according to (A) prespecified subgroups and (B) clinically relevant subgroups.
HRs are undefined in subgroups with no relapses in at least one treatment arm, for which they are 0.000, or for subgroups with no relapses in either treatment arm, for which they are not estimable. Dotted vertical lines show the proportion of patients receiving placebo in the overall population who experienced a relapse (left) and the HR for the overall population (right). The statistical test for interaction assesses whether the treatment effect varies by the different levels of the subgroup variable. ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IST, immunosuppressive therapy; NE, not estimable; NMOSD, neuromyelitis optica spectrum disorder.

[a] For subgroups, based on a Cox proportional-hazards model with treatment covariate, and with CIs based on inverting the score test to correspond with the log-rank *p* values.

[b] Based on a Cox proportional-hazards model with interaction term.

[c] With or without corticosteroids.

[d] Other ISTs include cyclophosphamide, cyclosporine, methotrexate, mizoribine, and tacrolimus.

[e] Americas: Argentina and the USA; Asia–Pacific: Australia, Hong Kong, Japan, Korea, Malaysia, Taiwan, and Thailand; Europe: Croatia, Czech Republic, Denmark, Germany, Italy, Russia, Spain, Turkey, and the UK.

[f] 'Other' race includes American–Indian or Alaskan Native, unknown, and other.

[g] Low and high EDSS scores are $\leq$ 2.0, and $\geq$ 2.5 to $\leq$ 7.0, respectively; continued/changed ISTs are since previous relapse.

[h] Time since clinical onset of NMOSD to first study dose date.

[i] Observed baseline EDSS.

[j] Historical ARR in the 24 months prior to screening.

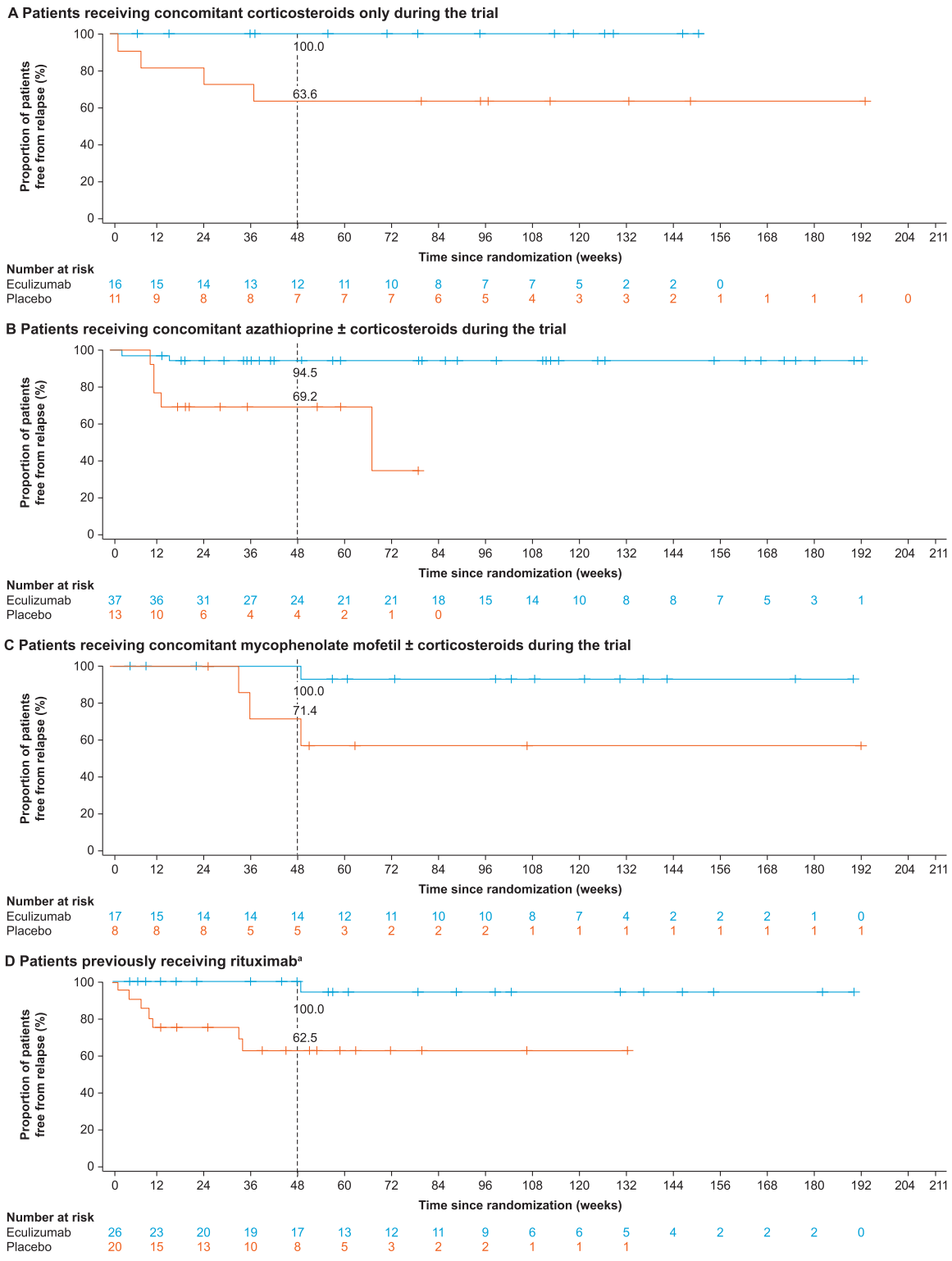

Fig. 2. Time to first adjudicated relapse according to IST use.
Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period, including those who had a physician-determined relapse that was adjudicated negatively and those who discontinued the trial regimen early. The tick marks indicate censoring of data. Proportions of patients who were relapse-free at week 48 were estimated using the Kaplan–Meier product-limit method. Analysis of time to first adjudicated relapse is not shown for seven patients, who received other ISTs during the study, owing to the small sample size. IST, immunosuppressive therapy.
[a] Patients previously receiving rituximab could be included in the trial if they had not received rituximab in the 3 months before screening.

Table 2
Summary of AEs and SAEs for *post hoc* (safety) subgroups.

		Rate of AEs per 100 PY; patients with AEs, n (%)		Rate of SAEs per 100 PY[a,b]; patients with SAEs, n (%)	
		Any	Related to trial agent[c]	Any	Related to trial agent[c]
Overall population	Eculizumab (n = 96; 172.8 PY)	749.3; 88 (91.7)	211.8; 49 (51.0)	30.7; 30 (31.3)	7.5; 9 (9.4)
	Placebo (n = 47; 53.1 PY)	1160.9; 45 (95.7)	163.7; 27 (57.4)	88.4; 26 (55.3)	24.5; 9 (19.1)
Rituximab use within previous year					
Yes	Eculizumab (n = 18; 29.8 PY)[d]	1025.8; 18 (100.0)	496.1; 11 (61.1)	46.9; 7 (38.9)	6.7; 2 (11.1)
	Placebo (n = 17; 15.2 PY)	1029.1; 17 (100.0)	138.5; 9 (52.9)	66.0; 8 (47.1)	13.2; 2 (11.8)
No	Eculizumab (n = 78; 143.0 PY)	691.7; 70 (89.7)	152.5; 38 (48.7)	27.3; 23 (29.5)	7.7; 7 (9.0)
	Placebo (n = 30; 38.0 PY)	1213.6; 28 (93.3)	173.7; 18 (60.0)	97.4; 18 (60.0)	29.0; 7 (23.3)
Concomitant IST use					
Yes	Eculizumab (n = 75; 128.5 PY)	776.9; 69 (92.0)	217.2; 38 (50.7)	33.5; 25 (33.3)	7.8; 8 (10.7)
	Placebo (n = 34; 40.2 PY)	1167.8; 32 (94.1)	159.0; 18 (52.9)	79.5; 18 (52.9)	24.8; 6 (17.6)
No	Eculizumab (n = 21; 44.4 PY)	669.5; 19 (90.5)	196.1; 11 (52.4)	22.5; 5 (23.8)	6.8; 1 (4.8)
	Placebo (n = 13; 12.9 PY)	1139.5; 13 (100.0)	178.3; 9 (69.2)	116.3; 8 (61.5)	23.3; 3 (23.1)
History of another autoimmune disorder					
Yes	Eculizumab (n = 23; 44.0 PY)	781.8; 22 (95.7)	175.0; 11 (47.8)	36.4; 11 (47.8)	6.8; 3 (13.0)
	Placebo (n = 10; 11.1 PY)	882.3; 10 (100.0)	207.1; 7 (70.0)	63.0; 6 (60.0)	9.0; 1 (10.0)
No	Eculizumab (n = 73; 128.8 PY)	738.2; 66 (90.4)	224.3; 38 (52.1)	28.7; 19 (26.0)	7.8; 6 (8.2)
	Placebo (n = 37; 42.0 PY)	1234.5; 35 (94.6)	152.2; 20 (54.1)	95.1; 20 (54.1)	28.5; 8 (21.6)

AEs include NMOSD relapses.
AE, adverse event; IST, immunosuppressive therapy; NMOSD, neuromyelitis optica spectrum disorder; PY, patient-year; SAE, serious adverse event.
[a] One patient receiving eculizumab and concomitant IST (azathioprine) died during the trial.
[b] The only serious AEs experienced by more than one patient in either group were pneumonia (experienced by three patients receiving eculizumab and one receiving placebo), and cellulitis, sepsis, and urinary tract infection (each experienced by two patients receiving eculizumab and none receiving placebo).
[c] Related AEs are those considered to be possibly, probably, or definitely related to the trial agent.
[d] One patient in the eculizumab arm of the prior rituximab subgroup experienced trial-agent-related AEs of feeling cold and a burning sensation after most infusions.

serious infection rate was 11.7 versus 17.4 events/100 PY for eculizumab versus placebo. The prevalence of serious infections in patients receiving eculizumab and concomitant ISTs was consistently low throughout PREVENT. Finally, the rates of trial-agent-related SAEs and serious infections in patients with a history of another autoimmune disorder was 6.8 versus 9.0 events/100 PY (Tables 2 and 3).

3.3.2. Rates of AEs related to trial agent during PREVENT

Among patients who had used rituximab in the year before PREVENT, the proportions who experienced trial-agent-related AEs during PREVENT were similar with eculizumab (61.1%) and placebo (52.9%). The higher rate with eculizumab (496.1 AEs/100 PY) than with placebo (138.5 AEs/100 PY) in this subgroup was largely driven by recurrent infusion-associated AEs of feeling cold and a burning sensation reported by one eculizumab-treated patient. Among those with or without concomitant IST use during PREVENT, the proportions of patients experiencing trial-agent-related AEs were similar with eculizumab (50.7% and 52.4%, respectively) and placebo (52.9% and 69.2%, respectively); the rates of trial-agent-related AEs were also similar with eculizumab (217.2 AEs/100 PY and 196.1 AEs/100 PY, respectively) and placebo (159.0 AEs/100 PY and 178.3 AEs/100 PY, respectively). In patients with a history of another autoimmune disease, the rates of trial-agent-related AEs and the proportions of patients experiencing them were slightly lower with eculizumab than with placebo (47.8% vs 70.0% and 175.0 AEs/100 PY vs 207.1 AEs/100 PY, respectively; Table 2).

3.3.3. Encapsulated bacterial infections and deaths

No cases of meningococcal infection were reported during PREVENT. Additionally, there were no reports of encapsulated bacterial infections, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, in patients treated with eculizumab. There was one fatal AE of pulmonary empyema in the eculizumab group (Pittock et al., 2019). This patient was receiving concomitant azathioprine, had not used rituximab during the previous year, and had no history of another autoimmune disorder.

4. Discussion

The size and distribution of the PREVENT study population, as well as the scale of the treatment effect of eculizumab recorded during the study, facilitated the *post hoc* analysis of the efficacy and safety of eculizumab according to factors of interest in clinical practice, including those previously identified to influence disease course (Palace et al., 2019), such as patient and disease characteristics, and concomitant/previous IST use. This analysis demonstrated that the clinical benefits of eculizumab are not limited to certain sections of the population of patients with NMOSD, but may be experienced by a wide range of patients with different demographic characteristics (including age, sex, region, and race), IST status (both concomitant IST use and previous rituximab use), autoimmune comorbidities, disease durations, relapse frequencies, and disability status; thus, it included patients at any stage of disease progression and those who may be predicted to have a high risk of relapse and consequent disability.

Table 3
Summary of serious infections over time for *post hoc* (safety) subgroups.

		Serious infections/infestations								
		Rate per 100 PY during PREVENT; patients with events, n (%)	Patients with event, n/N (%)							
			0–6 months	> 6–12 months	> 12–18 months	> 18–24 months	> 24–30 months	> 30–36 months	> 36–42 months	> 42 months
Overall population	Eculizumab (n = 96; 172.8 PY)	9.3; 11/96 (11.5))	4/96 (4.2)	2/83 (2.4)	1/68 (1.5)	1/55 (1.8)	2/41 (4.9)	0/25 (0.0)	1/17 (5.9)	0/6 (0.0)
	Placebo (n = 47; 53.1 PY)	15.1; 6/47 (12.8)	4/47 (8.5)	2/31 (6.5)	0/20 (0.0)	1/12 (8.3)	0/8 (0.0)	0/5 (0.0)	0/3 (0.0)	0/3 (0.0)
Rituximab use within previous year										
Yes	Eculizumab (n =18; 29.8 PY)	10.1; 2/18 (11.1)	2/18 (11.1)	0/15 (0.0)	0/14 (0.0)	0/11 (0.0)	0/5 (0.0)	0/4 (0.0)	0/1 (0.0)	0/0
	Placebo (n = 17; 15.2 PY)	13.2; 2/17 (11.8)	2/17 (11.8)	0/10 (0.0)	0/7 (0.0)	0/3 (0.0)	0/2 (0.0)	0/1 (0.0)	0/0	0/0
No	Eculizumab (n = 78; 143.0 PY)	9.1; 9/78 (11.5)	2/78 (2.6)	2/68 (2.9)	1/54 (1.9)	1/44 (2.3)	2/36 (5.6)	0/21 (0.0)	1/16 (6.3)	0/6 (0.0)
	Placebo (n = 30; 38.0 PY)	15.8; 4/30 (13.3)	2/30 (6.7)	2/21 (9.5)	0/13 (0.0)	1/9 (11.1)	0/6 (0.0)	0/4 (0.0)	0/3 (0.0)	0/3 (0.0)
Concomitant IST use										
Yes	Eculizumab (n = 75; 128.5 PY)	11.7; 10/75 (13.3)	4/75 (5.3)	2/63 (3.2)	1/53 (1.9)	1/42 (2.4)	2/32 (6.3)	0/16 (0.0)	0/10 (0.0)	0/3 (0.0)
	Placebo (n = 34; 40.2 PY)	17.4; 5/34 (14.7)	3/34 (8.8)	2/25 (8.0)	0/16 (0.0)	1/9 (11.1)	0/6 (0.0)	0/4 (0.0)	0/2 (0.0)	0/2 (0.0)
No	Eculizumab (n = 21; 44.4 PY)	2.3; 1/21 (4.8)	0/21 (0.0)	0/20 (0.0)	0/15 (0.0)	0/13 (0.0)	0/9 (0.0)	0/9 (0.0)	1/7 (14.3)	0/3 (0.0)
	Placebo (n = 13; 12.9 PY)	7.8; 1/13 (7.7)	1/13 (7.7)	0/6 (0.0)	0/4 (0.0)	0/3 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
History of another autoimmune disorder										
Yes	Eculizumab (n = 23; 44.0 PY)	6.8; 3/23 (13.0)	2/23 (8.7)	0/19 (0.0)	0/19 (0.0)	1/16 (6.3)	0/11 (0.0)	0/5 (0.0)	0/3 (0.0)	0/2 (0.0)
	Placebo (n = 10; 11.1 PY)	9.0; 1/10 (10.0)	1/10 (10.0)	0/6 (0.0)	0/4 (0.0)	0/2 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
No	Eculizumab (n = 73; 128.8 PY)	10.1; 8/73 (11.0)	2/73 (2.7)	2/64 (3.1)	1/49 (2.0)	0/39 (0.0)	2/30 (6.7)	0/20 (0.0)	1/14 (7.1)	0/4 (0.0)
	Placebo (n = 37; 42.0 PY)	16.7; 5/37 (13.5)	3/37 (8.1)	2/25 (8.0)	0/16 (0.0)	1/10 (10.0)	2/30 (6.7)	0/20 (0.0)	1/14 (7.1)	0/4 (0.0)

IST, immunosuppressive therapy; PY, patient-year.

In the Americas subgroup, relapse-risk reduction did not reach nominal significance, owing to the performance of the placebo arm (fewer relapses were recorded in placebo-treated patients in this subgroup than in placebo-treated patients from the other regions). The numbers of patients in each treatment arm were approximately balanced across regions, and one adjudicated relapse was reported in eculizumab-treated patients in each region. Differences between adjudicated relapse risks in the placebo arms of the regional subgroups may be random differences, or they may reflect variations in standards of care that could largely account for any apparent between-subgroup variations in the relative efficacy of eculizumab, or they may result from PREVENT not being powered for subgroup analyses.

ISTs have been demonstrated to decrease the likelihood of NMOSD relapses, but may not adequately suppress the disease in many patients (Palace et al., 2019; Poupart et al., 2020). In this analysis, eculizumab consistently reduced relapse risk in patients who were concomitantly using corticosteroids, azathioprine, or mycophenolate mofetil, as well as in those using no concomitant ISTs. Although not approved for the treatment of NMOSD, rituximab is frequently used in clinical practice (Nikoo et al., 2017), based on clinician experience and the results of mostly small, uncontrolled, or retrospective studies that suggest it to be one of the more effective agents (Bedi et al., 2011; Chamberlain et al., 2019; Cree et al., 2005; Damato et al., 2016; Jacob et al., 2008; Nikoo et al., 2017; Pellkofer et al., 2011; Poupart et al., 2020). In a recent randomized, placebo-controlled trial of 38 patients with AQP4+ NMOSD, relapse risk was reduced with rituximab versus placebo (Tahara et al., 2020). Owing to the potential pharmacological interaction between the complement-dependent cytotoxicity of rituximab and the complement-mediated mechanism of action of eculizumab, patients who received rituximab within the 3 months preceding screening were excluded from PREVENT. It is notable, however, that there was a favorable reduction in relapse risk with eculizumab versus placebo in the approximately one-third of PREVENT participants who had a prior history of rituximab treatment and continuing relapses.

Relapse risk was reduced with eculizumab versus placebo in patients with a history of another autoimmune disorder, including MG. Because individuals with MG have been shown to experience rapid and sustained clinical improvements with eculizumab (Howard et al., 2017; Muppidi et al., 2019), this therapy may theoretically provide dual benefits to patients with comorbid NMOSD and MG, although no data on its effect

on other autoimmune conditions were collected during PREVENT.

The rates of trial-agent-related SAEs and serious infections were lower with eculizumab than placebo in all subgroups analyzed for safety, including patients using concomitant ISTs and those who had used rituximab in the previous year. The incidences of trial-agent-related AEs were similar with eculizumab and placebo in all subgroups analyzed for safety. These findings therefore prompt no risk/benefit concerns about initiating eculizumab therapy in individuals using concomitant ISTs, those who have previously used rituximab (despite the potential enduring effect of rituximab on B-cell profiles after treatment cessation) (Nissimov et al., September 13, 2019; Stockholm), or in patients with a history of another autoimmune disorder. Additionally, all PREVENT participants received meningococcal vaccination (against serotypes A, C, W and Y; some were also vaccinated against serotype B), and no cases of meningococcal infection were reported during the study (Pittock et al., 2019). Furthermore, the reported incidence of meningococcal infection with long-term eculizumab therapy is low: one case (in the open-label pilot study) has been reported in clinical trials of eculizumab in NMOSD to date (Pittock et al., 2019; Pittock et al., 2013), and one case was reported during the REGAIN trial of eculizumab in generalized MG and its open-label extension (Howard et al., 2017; Muppidi et al., 2019). Moreover, the rate of meningococcal infection was low and decreased over time in patients with paroxysmal nocturnal hemoglobinuria or atypical hemolytic uremic syndrome and over 28 000 PY of eculizumab exposure (Socie et al., 2019). Data on responses to other vaccinations were not collected during PREVENT.

A clear limitation of the analysis reported here is the small size of some of the patient subgroups. Furthermore, owing to the occurrence of only three adjudicated relapses in eculizumab-treated patients across the whole study population, it is not surprising that no adjudicated relapses were recorded in some subgroups. PREVENT was not powered for subgroup analyses or statistical tests for interaction. Results from *post hoc* analyses should be viewed as providing preliminary information on relationships that could be subject to more rigorous future examination. Finally, subgroup analyses were performed without adjustment for multiplicity, so caution should be taken in the interpretation of the results. Nonetheless, the consistency of the findings with the overall PREVENT population are encouraging and could serve as a basis for more extensive study.

5. Conclusions

In conclusion, the effectiveness of eculizumab in reducing relapse risk is consistent across a wide range of patients with active AQP4+ NMOSD, regardless of sex, age, race, region, concomitant IST use, past rituximab use, disease duration, relapse history, disability status, and autoimmune comorbidities. These data should prove reassuring to physicians considering initiating eculizumab treatment for their patients with AQP4+ NMOSD, including those with continuing relapses despite IST, whatever their demographic characteristics, disease history, and treatment status.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.102641.

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