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Clinical trial

Eculizumab in Asian patients with anti-aquaporin-IgG-positive neuromyelitis optica spectrum disorder: A subgroup analysis from the randomized phase 3 PREVENT trial and its open-label extension

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ABSTRACT

Background Eculizumab, a terminal complement inhibitor, significantly reduced the risk of relapse compared with placebo in patients with anti-aquaporin-4 immunoglobulin G-positive (AQP4+) neuromyelitis optica spectrum disorder (NMOSD) in the PREVENT trial. We report efficacy and safety analyses in Asian patients in PREVENT and its open-label extension (OLE).

Methods PREVENT was a double-blind, randomized, phase 3 trial. Patients with AQP4+ NMOSD were randomly assigned (2:1) to receive intravenous eculizumab (maintenance dose, 1200 mg/2 weeks) or placebo.

Abbreviations: AE, adverse event; AQP4, aquaporin-4; AQP4+, anti-AQP4 immunoglobulin G-positive; ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; EQ-5D-3L, 5-dimension 3-level EuroQol questionnaire; HR, hazard ratio; IST, immunosuppressive therapy; NMOSD, neuromyelitis optica spectrum disorder; OLE, open-label extension; PREVENT, Prevention of Relapses in Neuromyelitis Optica; PY, patient-year; SAE, serious adverse event; SD, standard deviation.

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Patients who completed PREVENT could receive eculizumab in an OLE. Analyses were performed in a prespecified subgroup of Asian patients.

Results Of 143 patients enrolled, 52 (36.4%) were included in the Asian subgroup (eculizumab, $n = 37$; placebo, $n = 15$); 45 Asian patients received eculizumab in the OLE. Most Asian patients (86.5%) received concomitant immunosuppressive therapy. During PREVENT, one adjudicated relapse occurred in patients receiving eculizumab and six occurred in patients receiving placebo in the Asian subgroup (hazard ratio, 0.05; 95% confidence interval: 0.01–0.35; $p = 0.0002$). An estimated 95.2% of Asian patients remained relapse-free after 144 weeks of eculizumab treatment. Upper respiratory tract infections, headache, and nasopharyngitis were the most common adverse events with eculizumab in the Asian subgroup.

Conclusion Eculizumab reduces the risk of relapse in Asian patients with AQP4+ NMOSD, with a benefit–risk profile similar to the overall PREVENT population. The benefits of eculizumab were maintained during long-term therapy.

Clinical trial registration ClinicalTrials.gov identifiers: NCT01892345 (PREVENT); NCT02003144 (open-label extension).

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory demyelinating disease of the central nervous system, which primarily affects the optic nerves and spinal cord (Wingerchuk et al., 2007). A key feature is the presence of pathogenic auto-antibodies targeting the astrocyte water channel, aquaporin-4 (AQP4), which are detected in 64–88% of patients (Jiao et al., 2013; Waters et al., 2016). The disease is characterized by recurring episodes of optic neuritis and transverse myelitis that lead to cumulative neurologic impairment and disability (Wingerchuk et al., 2007). Early diagnosis and treatment to prevent relapses are essential disease management goals (Kitley et al., 2012).

Race may influence NMOSD pathophysiology (Pandit et al., 2015), with potential implications for treatment. The prevalence of NMOSD varies by race and ethnicity (Flanagan et al., 2016; Hor et al., 2020; Mealy et al., 2012; Viswanathan et al., 2018; Viswanathan and Wah, 2019), and specific genetic alleles in Asian patients, such as human leukocyte antigens DPB1*0501 and DRB1*16:02, may impart greater susceptibility to the disease (Hor et al., 2020; Matsushita et al., 2009; Wang et al., 2011). Race also influences the clinical course and severity of NMOSD (Hor et al., 2020; Kim et al., 2018; Kitley et al., 2012; Sepulveda et al., 2016).

Eculizumab, a humanized monoclonal antibody that inhibits terminal complement activity by blocking the cleavage of complement protein C5 (Thomas et al., 1996), is approved for the treatment of patients with anti-AQP4 immunoglobulin G-positive (AQP4+) NMOSD in the USA, Canada, Europe, Japan, and Australia (Frampton, 2020; Pittock et al., 2019; Soliris Australia Product Information, 2019; SolirisPrescribing Information, 2019). Approval was based on the findings of the international, randomized, phase 3, time-to-event PREVENT trial, in which eculizumab reduced the relative risk of adjudicated relapse by 94.2% compared with placebo in patients with AQP4+ NMOSD (hazard ratio [HR]: 0.058; 95% confidence interval [CI]: 0.017–0.197; $p < 0.0001$) (Pittock et al., 2019; SolirisPrescribing Information, 2019).

We report efficacy and safety analyses for eculizumab in Asian patients with AQP4+ NMOSD from PREVENT (prespecified) and its open-label extension (OLE; *post hoc*).

Methods

2.1. Trial design and patients

PREVENT (Prevention of Relapses in Neuromyelitis Optica) was a randomized, double-blind, placebo-controlled, time-to-event, phase 3 trial conducted in 70 sites in 18 countries. Details of the study methodology have been described previously (Pittock et al., 2019). The trial was designed to continue until 24 patients had an NMOSD relapse, as adjudicated by an independent panel, but was terminated after 23 adjudicated relapses (study power still exceeded 80%). Patients who completed PREVENT were eligible to enroll in an OLE, in which all patients received eculizumab regardless of prior treatment assignment. Both the PREVENT trial and its OLE were conducted in accordance with the Declaration of Helsinki and 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; World Medical Association, 2013). Trial protocols and subsequent amendments were approved by the institutional review board at each participating institution. All patients provided written informed consent before enrollment. Both trials are registered on ClinicalTrials.gov (PREVENT, NCT01892345; OLE, NCT02003144).

Adults were eligible for inclusion in the PREVENT trial if they had neuromyelitis optica or NMOSD according to 2006 (Wingerchuk et al., 2006) or 2007 (Wingerchuk et al., 2007) criteria, were seropositive for AQP4-immunoglobulin G, and had an Expanded Disability Status Scale (EDSS) score of 7 or less. Patients were required to have 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 must have occurred in the last 12 months. Stable-dose regimens of immunosuppressive therapies (ISTs) for relapse prevention were permitted, but treatment with mitoxantrone or rituximab during the previous 3 months was not allowed.

2.2. Randomization and blinding

Patients were randomly assigned (2:1 ratio) to receive eculizumab or matching placebo. Randomization was performed centrally using an interactive voice or web response system, and stratified across centers into four strata: EDSS score ≤ 2.0; EDSS score 2.5–7.0 and no previous IST except for corticosteroids alone; EDSS score 2.5–7.0 and continuing the same IST after the last relapse before screening (although doses may have changed); and EDSS score 2.5–7.0 and new IST or discontinuing an existing therapy after the last relapse. Patients, investigational site personnel, sponsor staff, and staff directly associated with the conduct of the trial were blinded to treatment assignments. A blinded induction phase was completed prior to OLE entry to preserve study blinding. During this phase, patients from the PREVENT eculizumab group received eculizumab 1200 mg (weeks 1 and 3) or placebo (weeks 2 and 4), and patients in the PREVENT placebo group received eculizumab 900 mg weekly for the first four doses before receiving the eculizumab maintenance dose of 1200 mg every 2 weeks.

2.3. Treatment

Intravenous eculizumab 900 mg was given weekly for the first four doses, followed by 1200 mg every 2 weeks until relapse, trial discontinuation, or trial end. Stable-dose IST received at screening was continued unchanged during PREVENT, unless relapse or toxicities necessitating dose adjustments occurred; IST could be changed during the OLE at the discretion of the physician. Intravenous immunoglobulin

and plasma exchange were permitted for the acute treatment of relapses only. Before receiving study treatment, all patients were vaccinated against *Neisseria meningitidis* serotypes A, C, W, and Y (vaccination against serotype B was administered as required by country guidelines).

2.4. Assessments and endpoints

Patient demographics, including details of race as reported by the patient, were collected at screening. Neurologic function assessments, including visual acuity and disability, were performed at baseline, at weeks 4, 8, and 12 and every 12 weeks thereafter, and at trial discontinuation or termination. Relapses were identified and managed by the investigator (physician-determined), and subsequently adjudicated by an independent committee composed of two neurologists and one neuro-ophthalmologist (adjudicated relapse). A relapse was defined as new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination that persisted for more than 24 h, with 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 supportive clinical findings. After a relapse had occurred, patients were followed for 6 weeks and then offered entry to the OLE. Safety assessments included the incidence and severity of all adverse events (AEs, defined by the study protocol to include the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during study drug exposure, whether or not causally related to the study drug; NMOSD relapses that met the definition of an AE were included) and serious adverse events (SAEs). Treatment-related AEs were categorized by investigators as possibly, probably, or definitely related to study treatment, and also included any AEs with an unknown relationship.

The primary efficacy endpoint was the time to first adjudicated relapse. Secondary efficacy endpoints included the adjudicated annualized relapse rate (ARR) and changes from baseline in EDSS (Kurtzke, 1983), modified Rankin Scale (van Swieten et al., 1988), Hauser Ambulation Index (Hauser et al., 1983), and 5-dimension 3-level EuroQol questionnaire (EQ-5D-3L) visual analog scale and summary index scores (EuroQol Research Foundation, 2018). Physician-determined relapses requiring hospitalization and details of acute treatments were also recorded.

2.5. Statistical analysis

Analyses were performed in a prespecified Asian race subgroup of the PREVENT trial and its OLE; interim data from the OLE (data cut-off, October 31, 2018) were used. The PREVENT trial was not designed or powered for subgroup analyses. Except for the primary endpoint, data were descriptive only and no formal statistical comparisons were performed.

Efficacy analyses of data from PREVENT were performed in all patients who were randomized to treatment and who had received at least one dose of study drug. Time to first adjudicated relapse was analyzed using an unstratified log-rank test to compare eculizumab versus placebo in the Asian race subgroup. HRs were estimated using a Cox proportional-hazards model, with treatment group as a covariate, and CIs were based on inverting the score test under the Cox model to correspond with the log-rank p values (Lin et al., 2016). The Kaplan–Meier product limit method was used to estimate the proportion of patients who were free from relapse at specific time points. Adjudicated ARRs were calculated by dividing the total number of adjudicated on-trial relapses by the total number of patient-years (PYs) in the study period, and CIs were based on a Poisson regression model with treatment group as a covariate. Analysis of time to first adjudicated relapse was also performed on the combined PREVENT and OLE analysis set, which included all participants who had received at least one dose of eculizumab in either study. Analysis methods for the proportion of patients who were free from relapse at specific time points and ARR were similar to those used in the PREVENT study. For other secondary efficacy endpoints, changes in scores from baseline to the end of the PREVENT study period or the interim analysis data cut-off of the OLE were reported and the differences summarized. AEs were summarized for the safety population, which included all patients who received at least one dose of study drug. Statistical analyses were performed using SAS® software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

3.1. Patient characteristics

From April 2014 to October 2017, a total of 143 patients were randomized and received study treatment (eculizumab, $n = 96$; placebo, $n = 47$), of whom 52 (36.4%) were included in the Asian race subgroup of PREVENT (eculizumab, $n = 37$; placebo, $n = 15$; Fig. 1). The median (range) duration of study treatment in this group was 95.7 (14.1–192.1) weeks in the eculizumab group and 51.9 (14.0–208.1) weeks in the placebo group. Most patients in the PREVENT Asian subgroup were receiving concomitant IST at baseline (eculizumab, 33/37, 89.2%; placebo, 12/15, 80.0%).

From January 2015 onwards, 119 participants from PREVENT were enrolled in the OLE and received eculizumab. These included 45 Asian participants (eculizumab, $n = 32$; placebo, $n = 13$). A combined total of 137 participants in PREVENT and/or OLE, including 50 Asian participants, received eculizumab and are referred to hereafter as the 'combined set'. Most patients (92.0%) were female, and the mean age was 43.4 (standard deviation [SD], 12.8) years at first receipt of trial treatment. The median (range) duration of treatment with eculizumab in the combined set was 98.6 (1.0–212.0) weeks, and the mean ARR during the previous 24 months was 2.06 (SD, 1.01).

Patient demographics and clinical characteristics at baseline are presented in Table 1 for both the PREVENT Asian subgroup and the combined set.

3.2. Efficacy

3.2.1. Relapse risk

During PREVENT, one adjudicated relapse occurred in 37 Asian patients treated with eculizumab and six adjudicated relapses occurred in 15 patients treated with placebo (Table 2); relapses were attributed to optic neuritis in the eculizumab group ($n = 1$), and to transverse myelitis ($n = 5$) and area postrema syndrome ($n = 1$) in the placebo group. Treatment with eculizumab significantly reduced the risk of adjudicated relapse (primary study endpoint) by 95.0% compared with placebo (HR, 0.05; 95% CI: 0.01–0.35; $p = 0.0002$; Fig. 2**A**). After 48 weeks of treatment in PREVENT, an estimated 97.3% (95% CI: 82.3–99.6) of Asian patients in the eculizumab group and 72.2% (95% CI: 41.7–88.6) of Asian patients in the placebo group were relapse-free. During the OLE, one further adjudicated relapse occurred after a median (range) follow-up of 98.1 (2.3–213.3) weeks (in a patient randomized to eculizumab in PREVENT), giving a total of two adjudicated relapses in the Asian combined set. An estimated 95.2% (95% CI: 81.7–98.8%) of patients remained relapse-free after 144 weeks of treatment with eculizumab in the Asian combined set (Fig. 2**B**), compared with 93.9% (95% CI: 87.5–97.1%) of the overall PREVENT/OLE combined set. Details of all relapses in the Asian subgroup are provided in **Table A.1**. In the PREVENT Asian subgroup, the adjudicated ARR (secondary study endpoint) during PREVENT was 0.02 (95% CI: 0.00–0.11) in patients treated with eculizumab and 0.29 (95% CI: 0.13–0.65) in those receiving placebo (Table 2). The adjudicated ARR with eculizumab treatment in the combined set was 0.02 (95% CI: 0.01–0.08; Table 2).

3.2.2. Disability outcomes

In the Asian subgroup, all disability outcome measures were

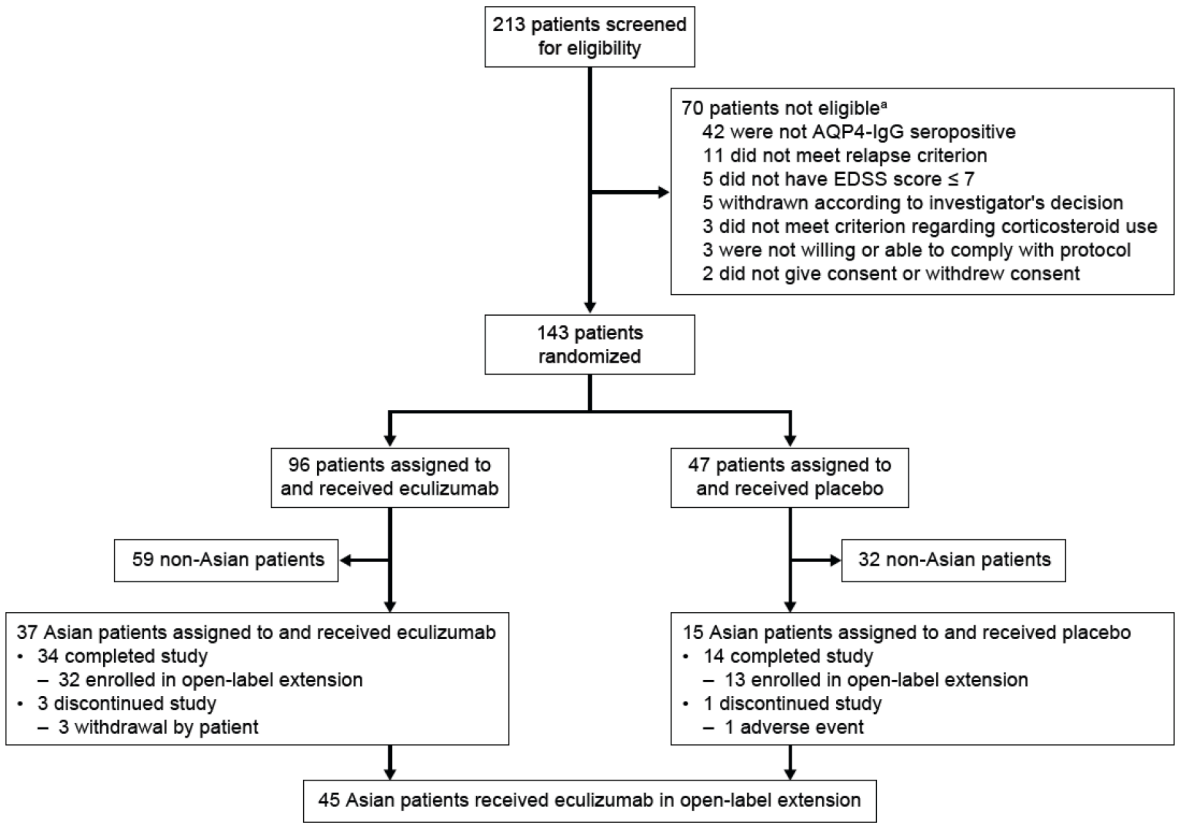

Fig. 1. Study profile.
AQP4-IgG, aquaporin-4 immunoglobulin G; EDSS, Expanded Disability Status Scale.
[a] Patients could be excluded for more than one reason.

numerically improved with eculizumab from baseline in PREVENT, and these improvements were maintained with eculizumab treatment in the OLE (Table 2). Improvements were greater with eculizumab than placebo during PREVENT for all disability outcomes; except for the EQ-5D-3L visual analog scale, which showed similar improvements in both treatment groups. By the end of PREVENT, worsening of EDSS (defined as an increase of ≥ 2, ≥ 1, or ≥ 0.5 from a baseline score of 0, 1–5, or ≥ 5.5, respectively) occurred in four patients (10.8%) in the eculizumab group and three patients (20.0%) in the placebo group. By the end of PREVENT, worsening of the Hauser Ambulation Index (defined as an increase of ≥ 2 or ≥ 1 from a baseline of 0 or ≥ 1, respectively) occurred in three patients (8.1%) in the eculizumab group and two patients (13.3%) in the placebo group.

3.2.3. *Relapses requiring hospitalization*

During PREVENT, three Asian patients (8.1%) in the eculizumab group and six (40.0%) in the placebo group had physician-determined relapses requiring hospitalization. The annualized rate of relapse-related hospitalizations was lower in patients treated with eculizumab (0.04; 95% CI: 0.01–0.14) than in patients treated with placebo (0.29; 95% CI: 0.13–0.65; **Table A.2**). Acute treatments for relapses in the Asian subgroup included intravenous methylprednisolone (eculizumab, 10.8% vs placebo, 40.0%), high-dose oral steroids (5.4% vs 13.3%), and plasma exchange (2.7% vs 20.0%).

3.2.4. *Changes in concomitant IST use during the OLE*

During the OLE, 12 of 45 Asian patients (26.7%) had dose reductions in concomitant supportive IST. No patients started IST, had dose increases, or changed their existing IST during the OLE.

3.3. *Safety*

In the Asian subgroup, the rate of AEs was 837 events/100 PY in the eculizumab group and 842 events/100 PY in the placebo group during PREVENT, and 773 events/100 PY in the combined set (Table 3). Rates of AEs categorized as treatment-related by investigators were 229, 111, and 209 events/100 PY in the eculizumab group, placebo group, and combined set, respectively. Most AEs were mild or moderate in severity. Common AEs occurring more frequently in the eculizumab group than in the placebo group among Asian patients during PREVENT were headache (99 vs 19 events/100 PY), upper respiratory tract infections (53 vs 14 events/100 PY), dyspepsia (42 vs 14 events/100 PY), nasopharyngitis (31 vs 19 events/100 PY), dizziness (13 vs 5 events/100 PY), hordeolum (10 vs 0 events/100 PY) and contusion (i.e. local bruising; 9 vs 5 events/100 PY). After a median (range) study duration of 101.4 (9.1–213.3) weeks, the most commonly reported AEs with eculizumab in the combined set were headache (78 events/100 PY), upper respiratory tract infections (39 events/100 PY), and nasopharyngitis (33 events/100 PY).

The rate of SAEs among Asian patients was 29 events/100 PY in the eculizumab group and 82 events/100 PY in the placebo group in PREVENT, and 28 events/100 PY in the combined set; these rates included NMOSD relapses, which occurred at higher rates in the placebo group (29 events/100 PY) than in the eculizumab group (6 events/100 PY). Rates of SAEs categorized as treatment-related by investigators were 9, 19, and 8 events/100 PY, respectively. Treatment-related SAEs in the PREVENT eculizumab group were pneumonia ($n = 1$), renal abscess ($n = 1$), sepsis ($n = 1$), bronchitis ($n = 1$), cellulitis ($n = 1$), and atrial fibrillation ($n = 1$), and in the PREVENT placebo group were pancytopenia ($n = 1$), abdominal pain ($n = 1$), herpes zoster ($n = 1$), and viral upper respiratory infection ($n = 1$). Treatment-related SAEs during the

Table 1
Baseline patient demographics and clinical characteristics in the Asian subgroup.

	PREVENT Eculizumab (*n* = 37)	Placebo (*n* = 15)	OLE Eculizumab (*n* = 45)	Combined set[a] Eculizumab (*n* = 50)
Sex, *n* (%)				
Female	35 (94.6)	13 (86.7)	43 (95.6)	46 (92.0)
Male	2 (5.4)	2 (13.3)	2 (4.4)	4 (8.0)
Mean (± SD) age, years				
At first study dose	42.3 (± 12.7)	45.9 (± 12.7)	44.0 (± 12.9)	43.4 (± 12.8)
At initial clinical presentation	35.2 (± 12.8)	39.0 (± 14.7)	35.6 (± 13.3)	36.4 (± 13.5)
Diagnosis, *n* (%)				
Neuromyelitis optica	26 (70.3)	11 (73.3)	32 (71.1)	35 (70.0)
NMOSD	11 (29.7)	4 (26.7)	13 (28.9)	15 (30.0)
Longitudinally extensive transverse myelitis	6 (16.2)	0 (0)	5 (11.1)	6 (12.0)
Optic neuritis	3 (8.1)	2 (13.3)	5 (11.1)	5 (10.0)
Optic neuritis or longitudinally extensive transverse myelitis coexisting with systemic autoimmune disease	0 (0)	1 (6.7)	1 (2.2)	1 (2.0)
Optic neuritis or transverse myelitis associated with brain lesions	1 (2.7)	1 (6.7)	1 (2.2)	2 (4.0)
Other	1 (2.7)	0 (0)	1 (2.2)	1 (2.0)
Mean (± SD) annualized relapse rate during previous 24 months	1.90 (± 0.80)	2.33 (± 1.37)	2.05 (± 1.05)	2.06 (± 1.01)
Median (range) score				
EDSS[b]	3.5 (1.0–7.0)	4.0 (2.0–6.5)	4.0 (0.0–7.0)	4.0 (0.0–7.0)
Modified Rankin Scale[c]	2.0 (0–4)	2.0 (0–4)	2.0 (0–4)	2.0 (0–4)
Hauser Ambulation Index[d]	1.0 (0–8)	2.0 (0–5)	1.0 (0–8)	2.0 (0–8)
EQ-5D-3L[e]				
Visual analog scale	70 (10–90)	50 (0–90)	73 (5–98)	68 (5–98)
Index	0.78 (0.16–1.00)	0.71 (0.31–1.00)	0.78(0.08–1.00)	0.78 (0.08–1.00)
Immunosuppressive therapy at baseline,[f] *n* (%)				
No	4 (10.8)	3 (20.0)	11 (24.4)	9 (18.0)
Yes	33 (89.2)	12 (80.0)	34 (75.6)	41 (82.0)
Previous rituximab treatment, *n* (%)	3 (8.1)	2 (13.3)	4 (8.9)	4 (8.0)

EDSS, Expanded Disability Status Scale; EQ-5D-3L, 5-dimension 3-level EuroQol questionnaire; NA, not available; NMOSD, neuromyelitis optica spectrum disorder; OLE, open-label extension; SD, standard deviation.
Note: Age at first dose and EDSS are relative to the first dose of study drug in the given study, and relative to the first dose of eculizumab in either study for the combined set.
[a] All patients who received eculizumab in PREVENT and/or the OLE.
[b] Scores on the EDSS range from 0 (no disability) to 10 (death).
[c] Scores on the modified Rankin Scale range from 0 (no disability) to 6 (death).
[d] Scores on the Hauser Ambulation Index range from 0 to 9, with higher scores indicating decreased independent ambulation.
[e] Scores on the EQ-5D-3L visual analog scale range from 0 to 100, and summary index scores range from < 0 to 1. Higher scores indicate better health status.
[f] Baseline in the OLE was defined as the last available assessment prior to the first dose of eculizumab in the OLE.

Table 2
Efficacy in the Asian subgroup.

Endpoint	PREVENT Eculizumab (*n* = 37)	Placebo (*n* = 15)	Hazard or rate ratio (95% CI)[a]	*p* value	Combined set[b] Eculizumab (*n* = 50)
First adjudicated relapse, number of events	1	6	0.05 (0.01–0.35)	0.0002	2
Adjudicated annualized relapse rate (95% CI)	0.02 (0.00–0.11)	0.29 (0.13–0.65)	0.04 (0.01–0.42)	–	0.02 (0.01–0.08)
Mean (± SD) change from baseline[c]					(*n* = 49)
EDSS score[d]	–0.22 (± 0.85)	–0.10 (± 1.04)	–	–	–0.21 (0.87)
Modified Rankin Scale score[e]	–0.3 (± 0.5)	0.1 (± 0.4)	–	–	–0.3 (0.5)
Hauser Ambulation Index score[f]	–0.3 (± 0.9)	0.3 (± 1.1)	–	–	–0.3 (1.0)
EQ-5D-3L[g]					
Visual analog scale score	9.6 (± 19.5)	9.5 (± 17.3)	–	–	6.0 (18.3)
Index score	0.07 (± 0.18)	0.00 (± 0.22)	–	–	0.06 (0.18)

CI, confidence interval; EDSS, Expanded Disability Status Scale; EQ-5D-3L, 5-dimension 3-level EuroQol questionnaire; OLE, open-label extension; SD, standard deviation.
[a] Hazard ratio (primary endpoint) and rate ratio (annualized relapse rate) for eculizumab versus placebo.
[b] All patients who received eculizumab in PREVENT and/or the OLE.
[c] Baseline for the combined set is defined as the last available assessment prior to the first dose of eculizumab for patients randomized to the eculizumab group in PREVENT, or the OLE baseline for patients randomized to the placebo group in PREVENT.
[d] Scores on the EDSS range from 0 (no disability) to 10 (death).
[e] Scores on the modified Rankin Scale range from 0 (no disability) to 6 (death).
[f] Scores on the Hauser Ambulation Index range from 0 to 9, with higher scores indicating decreased independent ambulation.
[g] Scores on the EQ-5D-3L visual analog scale range from 0 to 100, and summary index scores range from < 0 to 1. Higher scores indicate better health status.

OLE were infective tenosynovitis ($n = 1$) and NMOSD ($n = 1$). No patients discontinued eculizumab because of SAEs, and no deaths were reported in Asian patients.

No meningococcal infections were reported in Asian patients during PREVENT and the OLE (until interim analysis cut-off date). Rates of other serious infections were similar in Asian patients receiving eculizumab or placebo (12 vs 10 events/100 PY; **Table A.3**), and in the Asian and overall combined sets (9 vs 11 events/100 PY). There was no evidence of increasing incidences of treatment-related AEs or infections over 24 months with eculizumab (**Table A.4**).

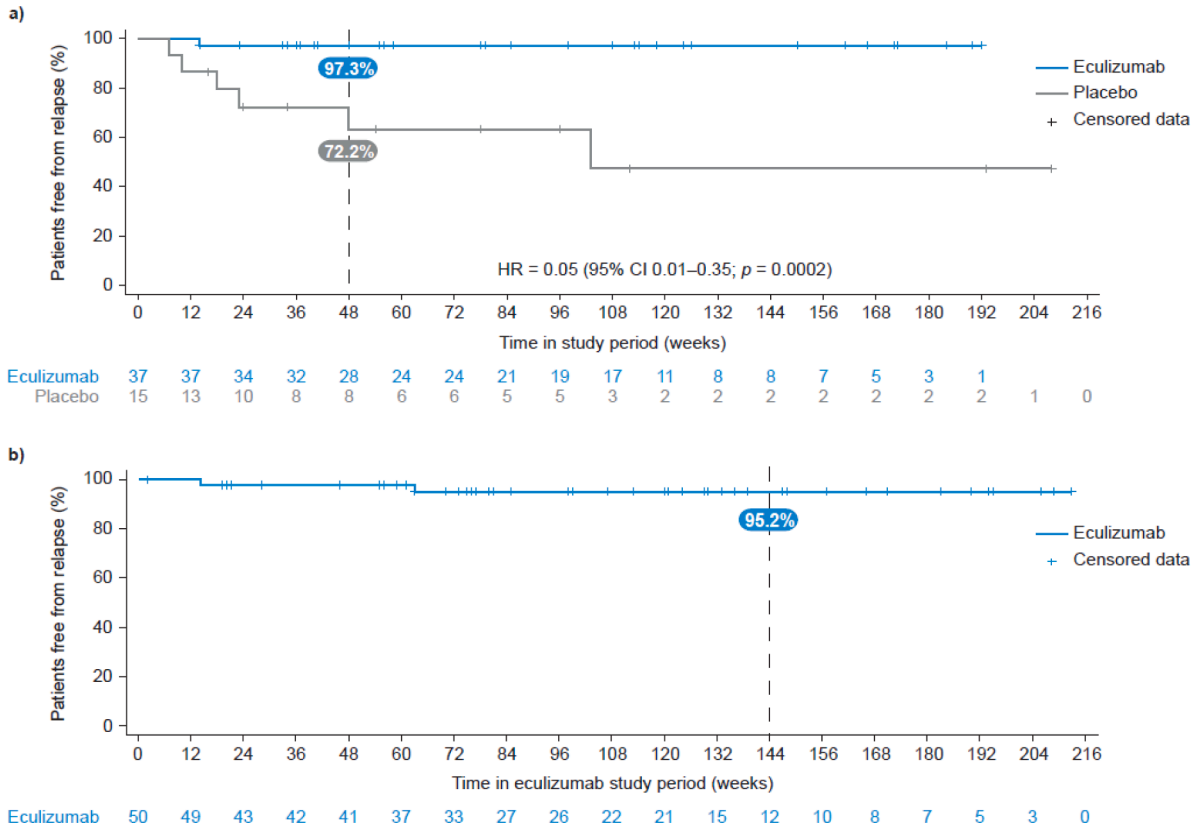

Fig. 2. Time to first adjudicated relapse in the Asian subgroup in a) the PREVENT core study, and b) in the PREVENT and OLE studies of long-term eculizumab treatment (combined set[a]).
CI, confidence interval; HR, hazard ratio; OLE, open-label extension.
[a] All patients who received eculizumab in PREVENT and/or its OLE.
Note: Tick marks indicate censored patients. For Fig. 2A, patients who did not experience an adjudicated relapse were censored at the end of the study period. For Fig. 2B, patients who did not experience an adjudicated relapse were censored at the end of the PREVENT study period if the patients did not enroll in the OLE, or at the OLE interim cut-off date if the patients enrolled in the OLE. Proportions of patients who were free from relapse were estimated using the Kaplan–Meier product limit method. Cut-off date for OLE: October 31, 2018. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Discussion

In this prespecified subgroup analysis of the PREVENT trial, Asian patients with AQP4+ NMOSD who were treated with eculizumab had a significantly lower risk of relapse than Asian patients who received placebo (HR, 0.05; 95% CI: 0.01–0.35). As in the overall PREVENT study population, a high proportion of Asian patients (86.5%) received concomitant IST at enrollment (this proportion was similar in the eculizumab [89.2%] and placebo [80.0%] groups), with the remainder receiving eculizumab as a monotherapy. The effect size of eculizumab on the primary study endpoint among Asian patients was consistent with that observed in the overall PREVENT study population (HR, 0.058; 95% CI: 0.017–0.197; $p < 0.0001$) (Pittock et al., 2019; SolirisPrescribing Information, 2019). *Post hoc* analyses of interim data from the OLE showed that the effect of eculizumab in Asian patients was maintained, with a total of two adjudicated relapses reported across both PREVENT and the OLE after a median follow-up of 98.1 weeks. Similar proportions of patients in the Asian and overall combined sets were relapse-free at 144 weeks of eculizumab treatment (95% and 94%, respectively). Analyses of disability measures supported eculizumab's long-term efficacy, with improvements sustained with eculizumab treatment during the OLE.

The safety profile of eculizumab in Asian patients was similar to that observed in the overall PREVENT study population (Pittock et al., 2019), and in other approved indications (paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and generalized myasthenia gravis (Brodsky et al., 2008; Hillmen et al., 2006; Howard et al., 2017; SolirisPrescribing Information, 2019). The most common AEs with eculizumab were upper respiratory tract infection, headache, and nasopharyngitis, although both upper respiratory tract infection (53 vs 31 events/100 PY) and headache (99 vs 55 events/100 PY) occurred at higher rates among Asian patients than in the overall study population (Pittock et al., 2019). We are unaware of factors that might explain these differences between populations. *Post hoc* analysis has demonstrated that the rates of trial agent-related AEs during PREVENT were similar in patients who received eculizumab with and without concomitant ISTs (217.2 AEs/100 PY and 196.1 AEs/100 PY, respectively) (Palace et al., 2021).

There was no evidence of an increased rate of serious infections with eculizumab in the Asian subgroup compared with the overall study population, and no cases of meningococcal infection were reported. In the Asian region, all major meningococcal serogroups (A, B, C, W, and Y) are present, albeit with wide variability in their distribution (Borrow et al., 2016; Vyse et al., 2011). All patients receiving eculizumab should be immunized with a meningococcal vaccine at least 2 weeks before initiating treatment to address the potential risk of meningococcal disease associated with eculizumab therapy, and it is important that physicians comply with national vaccine recommendations to ensure adequate coverage (Pittock et al., 2020). Patients should also be monitored carefully for early signs of infection after starting treatment, because vaccination reduces, but does not eliminate, the risk of meningococcal infections.

Table 3
Adverse events[a,b] in the Asian subgroup.

	PREVENT						Combined set[c]		
	Eculizumab ($n = 37$; PY = 68.4)			Placebo ($n = 15$; PY = 20.8)			Eculizumab ($n = 50$; PY = 101.7)		
	Events, *n*	Rate per 100 PY	Patients, *n* (%)	Events, *n*	Rate per 100 PY	Patients, *n* (%)	Events, *n*	Rate per 100 PY	Patients, *n* (%)
Any AE	573	837	34 (91.9)	175	842	15 (100.0)	786	773	45 (90.0)
Treatment-related AEs	157	229	20 (54.1)	23	111	8 (53.3)	213	209	28 (56.0)
AE according to severity									
Mild	504	736	34 (91.9)	123	592	12 (80.0)	681	669	43 (86.0)
Moderate	60	88	23 (62.2)	48	231	11 (73.3)	88	87	30 (60.0)
Severe	9	13	6 (16.2)	4	19	4 (26.7)	17	17	13 (26.0)
Any SAE	20	29	13 (35.1)	17	82	12 (80.0)	28	28	20 (40.0)
Treatment-related SAEs	6	9	4 (10.8)	4	19	4 (26.7)	8	8	6 (12.0)
SAEs leading to discontinuation	0	0	0 (0.0)	1	5	1 (6.7)	0	0	0 (0.0)
AEs reported in ≥ 15% of patients in either group or the combined set									
Upper respiratory tract infection	36	53	15 (40.5)	3	14	2 (13.3)	40	39	16 (32.0)
Headache	68	99	12 (32.4)	4	19	3 (20.0)	79	78	14 (28.0)
Nasopharyngitis	21	31	8 (21.6)	4	19	3 (20.0)	34	33	11 (22.0)
Diarrhea	10	15	7 (18.9)	3	14	3 (20.0)	11	11	7 (14.0)
Neuromyelitis optica spectrum disorder	4	6	4 (10.8)	6	29	6 (40.0)	7	7	6 (12.0)
Nausea	16	23	7 (18.9)	6	29	2 (13.3)	16	16	7 (14.0)
Dizziness	9	13	7 (18.9)	1	5	1 (6.7)	9	9	7 (14.0)
Conjunctivitis	5	7	4 (10.8)	7	34	3 (20.0)	5	5	4 (8.0)
Contusion	6	9	6 (16.2)	1	5	1 (6.7)	12	12	10 (20.0)
Dyspepsia	29	42	4 (10.8)	3	14	3 (20.0)	31	31	4 (8.0)
Hordeolum	7	10	6 (16.2)	0	0	0 (0.0)	7	7	6 (12.0)
Vomiting	2	3	2 (5.4)	6	29	4 (26.7)	2	2	2 (4.0)
Depression	0	0	0 (0.0)	4	19	3 (20.0)	1	1	1 (2.0)
Constipation	4	6	4 (10.8)	1	5	1 (6.7)	8	8	8 (16.0)

AE, adverse event; OLE, open-label extension; PY, patient-year; SAE, serious adverse event.

[a] AEs are those with a start date on or after the date of the first dose of study drug; treatment-related AEs/SAEs are defined as possibly, probably or definitely related to treatment, and include any AE/SAE with an unknown relationship to treatment. Percentages are based on the total number of patients in the safety set. If a patient had multiple events for a particular relationship or severity category, the patient was counted only once for that relationship or severity.

[b] In the safety analysis of PREVENT and its OLE, the development of an undesirable medical condition or the deterioration of a pre-existing medical condition was considered an AE. Neuromyelitis optica spectrum disorder relapses that met the definition of an AE were therefore included.

[c] All patients who received eculizumab in PREVENT and/or the OLE.

Epidemiologic studies in patients with AQP4+ NMOSD suggest that race influences the clinical course and severity of NMOSD (Kim et al., 2018; Kitley et al., 2012), with lower frequencies of relapses reported in Asian patients than in patients of other races (Kitley et al., 2012; Palace et al., 2019). This is consistent with our analyses, in which the relapse-free rate was slightly higher in the Asian placebo group than in the overall PREVENT placebo group (72% vs 63% at 48 weeks) (Pittock et al., 2019); although this may also have been attributable to small patient numbers. Our analyses provide reassurance that the benefits of eculizumab in the overall PREVENT study population and the Asian subgroup are similar, and that eculizumab is therefore an effective treatment option for Asian patients. One discrete genetic mutation of relevance to the response to eculizumab therapy is a missense heterozygous mutation in C5 (c.2654G→A) that was identified in Japanese patients with paroxysmal nocturnal hemoglobinuria (Nishimura et al., 2014). This mutation prevents C5 binding and inhibition by eculizumab, and is associated with a poor treatment response in patients who carry this mutation (Nishimura et al., 2014). The overall prevalence of this C5 variant in patients with NMOSD is unknown, but low rates of occurrence have been reported in healthy Japanese (3.5%) and Chinese (0.8%) populations (Nishimura et al., 2014). Genetic testing for this mutation was not performed in PREVENT; however, complete and sustained inhibition of C5 was observed in the PREVENT population (target free C5 levels attained in 99% of patients) (Berthele et al., 2020), which is the expected pharmacodynamic effect of eculizumab. We suggest that it is therefore unlikely that this variant was present in the study population.

There has been considerable progress made over the past 5 years in understanding the pathogenesis of NMOSD and identifying novel treatments. In PREVENT, eculizumab significantly reduced the occurrence of adjudicated relapses compared with placebo in patients with AQP4+ NMOSD (3% vs 43%; HR, 0.058; 95% CI: 0.017–0.197; $p < 0.0001$) (Pittock et al., 2019; SolirisPrescribing Information, 2019). In a *post hoc* analysis of PREVENT data, eculizumab has been shown to consistently reduce the occurrence of adjudicated relapses versus placebo when used with concomitant ISTs (4% vs 38%) or as a monotherapy (0% vs 54%) (Pittock et al., 2019). Since the PREVENT trial was completed, pivotal studies of two other disease-modifying agents, i.e. satralizumab and inebilizumab, have been reported. Satralizumab, a humanized monoclonal antibody targeting the interleukin-6 receptor, reduced the rate of adjudicated relapses in patients with AQP4+ NMOSD either as a monotherapy (22% vs 57% with placebo; HR, 0.26; 95% CI: 0.11–0.63; SAkuraStar) (Traboulsee et al., 2020) or when added to stable IST (11% vs 43% with placebo; HR, 0.21; 95% CI: 0.06–0.75; SAkuraSky) (Yamamura et al., 2019). Inebilizumab, an anti-CD19, B cell-depleting antibody, also reduced the risk of adjudicated attacks in patients with AQP4+ NMOSD when used as monotherapy in a phase 2/3 trial (11% vs 42% with placebo; HR, 0.23; 95% CI: 0.12–0.42; $p < 0.0001$; N-MOmentum) (Cree et al., 2019). Each of these trials included Asian patients: SAkuraStar, 15% (Traboulsee et al., 2020); N-MOmentum, 20% (Cree et al., 2019); SAkuraSky, 41% (Yamamura et al., 2019). Subgroup analyses of Asian patients from SAkuraSky ($n = 34$; HR, 0.15) (Yamamura et al., 2019) and from N-MOmentum ($n = 47$; HR, 0.20) (Cree et al., 2019) suggest that the treatment effects of both satralizumab and inebilizumab are consistent in Asian cohorts compared with the overall study populations from each trial. The development of these novel agents provides effective treatment options for individuals with NMOSD. Cost, however, may be a potential barrier to accessing them, particularly for patients living in resource-poor environments (Pardo et al., 2019).

The main limitations of this analysis are that the PREVENT trial was not powered for subgroup assessments, and that the Asian cohort was small. In the Asian subgroup, small differences were observed between

the eculizumab and placebo groups in historical ARR (1.90 and 2.33, respectively) and baseline median EDSS score (3.5 and 4.0, respectively; Table 1). These differences may, however, simply result from the small number of Asian patients. Although the treatment effect in the Asian subgroup was consistent with that observed in the overall PREVENT study population, in which baseline disease characteristics were well balanced (Pittock et al., 2019), it is not possible to confirm whether these small differences affect the observed efficacy of eculizumab in the Asian population. Also, although PREVENT included centers in Japan, Republic of Korea, Hong Kong, Malaysia, Taiwan, and Thailand, the relevance of our findings to other countries within the Asian region, for example India, Vietnam, Laos, Myanmar, and Indonesia, is unknown.

Our analyses demonstrate that the benefits observed with eculizumab in PREVENT and its OLE are also applicable to Asian patients. The safety profile of eculizumab in Asian patients was consistent with that in the overall PREVENT study population, suggesting that eculizumab has a favorable benefit–risk profile in patients of Asian race and should be considered as an effective long-term treatment option in Asian patients with AQP4+ NMOSD.

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/our-research/research-and-development (link to data-request form: https://alexion.com/contact-alexion/medical-information).

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Previous presentations

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Declaration of Competing Interest

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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.2021.102849.

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