

Impact of eculizumab on hospitalization rates and relapse treatment in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: findings from the phase 3 PREVENT study

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INTRODUCTION AND PURPOSE

- Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune, inflammatory disorder that damages the central nervous system.^{1,2}
- NMOSD is characterized by recurrent attacks of neurological dysfunction, most commonly optic neuritis and transverse myelitis; relapses resulting in hospitalization are common.^{1,2}
- Eculizumab is a humanized monoclonal antibody that inhibits the terminal complement protein C5.³
- In the phase 3, randomized, double-blind PREVENT study (NCT01892345) in adults with aquaporin-4 immunoglobulin G (AQP4-IgG)-positive NMOSD,⁴ there was a 94% reduction in relapse risk with eculizumab versus placebo.⁵
 - Hazard ratio: 0.058; 95% confidence interval (CI): 0.017–0.197; $p < 0.0001$.⁵
- The aim of the current analysis was to compare rates of hospitalization and the use of acute relapse treatment regimens in the eculizumab and placebo groups in PREVENT, with a view to analysing the impact on healthcare resource utilization.

METHODS

- PREVENT trial details have been published previously⁴ but are provided in brief in **Panel A**.

Panel A. Design, patients, treatment and relapses⁴

- Design.
 - International, phase 3, randomized, double-blind, parallel-group, placebo-controlled, time-to-event trial.
- Patients.
 - Main inclusion criteria: age ≥ 18 years; AQP4-IgG-seropositive status; ≥ 2 relapses in previous 12 months or ≥ 3 in previous 24 months (with ≥ 1 in previous 12 months); Expanded Disability Status Scale score ≤ 7.0 .
 - Main exclusion criteria: rituximab or mitoxantrone treatment in previous 3 months, intravenous immunoglobulin in previous 3 weeks, or prednisone dosages > 20 mg/day (or equivalent for other corticosteroids) at screening.
- Treatment.
 - Vaccinated against *Neisseria meningitidis* before trial treatment.
 - Randomly allocated (2:1) to intravenous eculizumab or matching placebo, with eculizumab administered at 900 mg weekly for first four doses, then 1200 mg every 2 weeks from following week.
 - Permitted immunosuppressive therapy continued if stable dose at baseline.
 - Treatment continued until patient experienced a physician-determined relapse, patient discontinued or trial ended.
- Relapses.
 - Physician-determined relapses adjudicated by a blinded, independent expert committee.

Assessments, outcome measures and statistical analyses

- Hospitalizations were recorded as a component of the adverse event (AE) tracking performed throughout the study.
- Relapse-related treatments were those administered within 30 days of the relapse onset.
- Summary data were calculated for:
 - all AEs requiring hospitalization, comprising relapses (physician-determined and adjudicated) and other AEs
 - relapse-related (physician-determined and adjudicated) use of intravenous methylprednisolone, plasma exchange and high-dose oral corticosteroids.

Table 1. Baseline demographic and clinical characteristics

Characteristic	Eculizumab (n = 96)	Placebo (n = 47)
Female, n (%)	88 (91.7)	42 (89.4)
Mean (SD) age, years		
At first dose of trial medication	43.9 (13.32)	45.0 (13.29)
At initial clinical presentation	35.8 (14.03)	38.5 (14.98)
Diagnosis, n (%)		
Neuromyelitis optica	69 (71.9)	38 (80.9)
NMOSD	27 (28.1)	9 (19.1)
Mean (SD) ARR 24 months before screening	1.94 (0.896)	2.07 (1.037)
Median (range) EDSS score	4.00 (1.0–7.0)	4.00 (1.0–6.5)
Acute treatments for relapses in the 24 months before screening, n (%)		
Corticosteroids ^a	95 (99.0)	44 (93.6)
High-dose oral corticosteroids	50 (52.1)	25 (53.2)
IV methylprednisolone	91 (94.8)	40 (85.1)
Plasma exchange	50 (52.1)	17 (36.2)
IV immunoglobulin	6 (6.3)	3 (6.4)
Other	23 (24.0)	14 (29.8)

Adapted from *New England Journal of Medicine*, Pittock SJ et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. doi: 10.1056/NEJMoa1900866. Copyright © 2019; Massachusetts Medical Society.
^aPatients could be treated with both oral and IV steroids.
ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; IV, intravenous; NMOSD, neuromyelitis optica spectrum disorder; SD, standard deviation.

- Rates were defined as the total number of events in the study period divided by the total number of patient-years in the study period.
- CI and p values are from a Poisson regression with treatment group covariate.
- Baseline and safety summaries reported were pre-specified, as were resource utilization summaries and analyses of physician-determined relapses.

RESULTS

Patients and key study outcomes

- All 143 patients who underwent randomization also received blinded trial treatment (eculizumab, $n = 96$; placebo, $n = 47$).⁴
- Baseline characteristics were balanced between treatment groups (**Table 1**).⁴
- Median (range) duration of trial treatment was 89.43 (3.1–211.1) and 41.29 (6.1–208.1) weeks in the eculizumab and placebo groups, respectively.
- Longer-term safety data for eculizumab will be provided in oral presentation number 142 (Thursday 12 September).

Hospitalizations

- In total, 28 patients (29.2%) receiving eculizumab experienced at least one AE requiring hospitalization, compared with 25 (53.2%) receiving placebo; the numbers of events were 45 and 41, respectively.
- The most common events requiring hospitalization were physician-determined relapses; infections were the most common non-relapse AEs requiring hospitalization (**Table 2**).
- The annualized rates of hospitalization resulting from physician-determined relapses were significantly reduced in patients who received eculizumab compared with those receiving placebo (0.04 vs 0.31, respectively; $p < 0.0001$; **Figure 1A**).
 - Differences were also significant for adjudicated relapses and for hospitalizations resulting from AEs other than relapses (**Figure 1A**).

Relapse-related medication use

- The proportions of patients with relapses who required acute treatment with oral/intravenous corticosteroids or plasma exchange are shown in **Table 3**.
- The annualized rates of treatment use related to physician-determined relapses were significantly lower in the eculizumab group than in the placebo group for intravenous corticosteroids and plasma exchange (0.07 vs 0.42 and 0.02 vs 0.19, respectively;⁵ $p \leq 0.0001$; **Figure 1B**).
 - Rates were also significantly lower for the treatment of adjudicated relapses with high-dose oral corticosteroids, intravenous corticosteroids and plasma exchange in the eculizumab group versus the placebo group (**Figure 1B**).

Table 2. AEs requiring hospitalization

AE	Eculizumab (n = 96)		Placebo (n = 47)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)
NMOSD relapse				
Physician-determined ^a	6	6 (6.3)	16	15 (31.9)
Adjudicated ^{b,c}	2	2 (2.1)	14	14 (29.8)
Other AE				
Pneumonia	3	3 (3.1)	0	0 (0.0)
Cellulitis	2	2 (2.1)	0	0 (0.0)
Sepsis	2	2 (2.1)	0	0 (0.0)
Urinary tract infection	2	2 (2.1)	0	0 (0.0)
Visual impairment	2	1 (1.0)	0	0 (0.0)
Bronchitis	1	1 (1.0)	1	1 (2.1)
Cholecystitis acute	1	1 (1.0)	1	1 (2.1)
NMOSD ^d	0	0 (0.0)	2	2 (4.3)
Orthostatic hypotension	0	0 (0.0)	2	1 (2.1)

Table shows AEs that occurred more than once in the total study population.

Please scan the QR code to download the full version of Table 2.

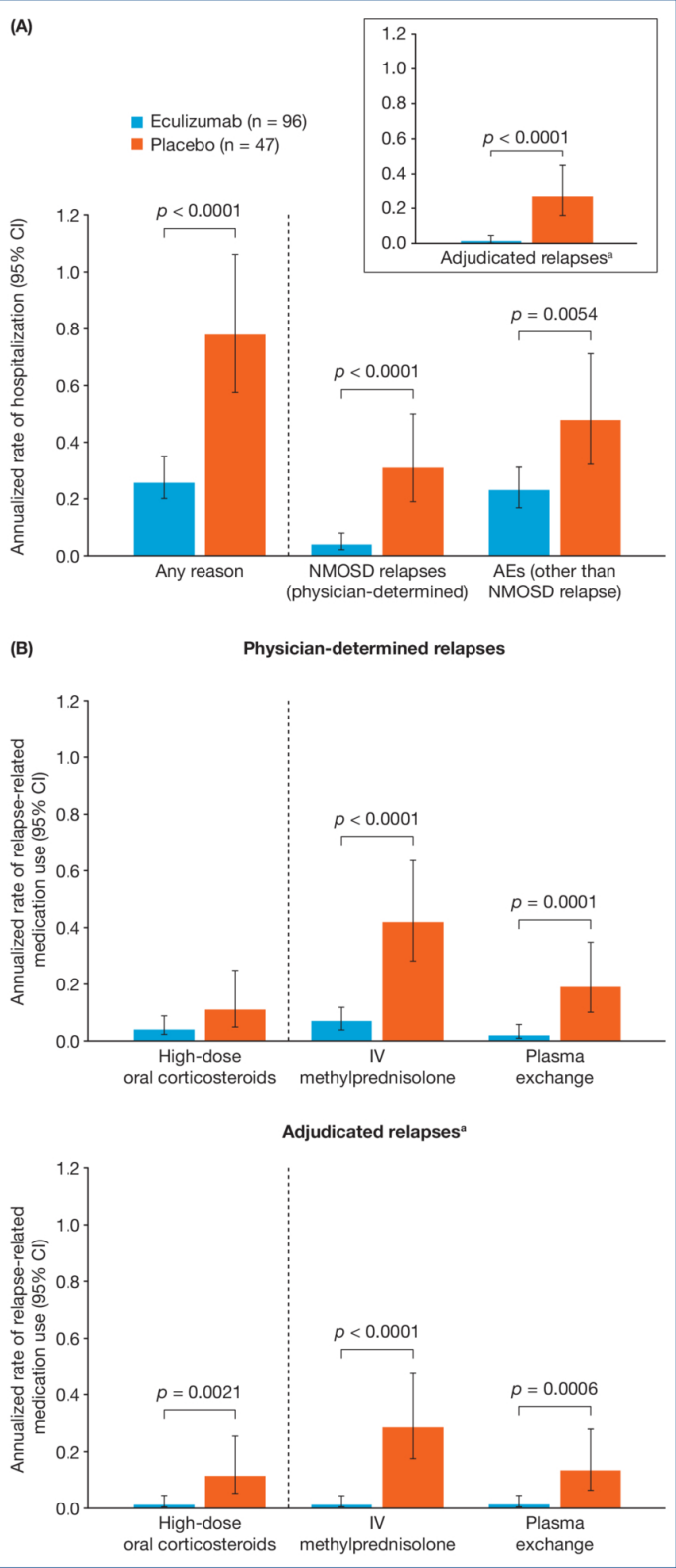
^aTypes of physician-determined relapses as follows: eculizumab, TM (4), ON (2); placebo, TM (11), ON (3), ON/TM (1), BS (1). ^bTypes of adjudicated relapses as follows: eculizumab, TM (1), ON (1); placebo, TM (11), ON (2), BS (1). ^cAdjudicated relapses are a subset of physician-determined relapses, adjudicated by a blinded, independent expert committee. ^dSuspected relapse, but physician determined that it did not meet the definition of an on-trial relapse. AE, adverse event; BS, brain stem; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; TM, transverse myelitis.

Table 3. NMOSD relapses requiring acute treatment

	Eculizumab (n = 96)		Placebo (n = 47)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Physician-determined relapses				
High-dose oral corticosteroids	7	7 (7.3)	6	6 (12.8)
IV methylprednisolone	12	12 (12.5)	22	22 (46.8)
Plasma exchange	4	4 (4.2)	10	9 (19.1)
Adjudicated relapses				
High-dose oral corticosteroids	2	2 (2.1)	6	6 (12.8)
IV methylprednisolone	2	2 (2.1)	15	15 (31.9)
Plasma exchange	2	2 (2.1)	7	7 (14.9)

Adjudicated relapses are a subset of physician-determined relapses, adjudicated by a blinded, independent expert committee.
IV, intravenous; NMOSD, neuromyelitis optica spectrum disorder.

Figure 1. Healthcare resource utilization in PREVENT: annualized rates of (A) hospitalization and (B) relapse-related medication use



None of the patients received acute treatment with IV immunoglobulin.
Annualized rates were defined as the total number of AEs requiring hospitalization/relapses requiring treatment divided by the total number of patient-years in the study period.
^aAdjudicated relapses are a subset of physician-determined relapses, adjudicated by a blinded, independent expert committee.
AE, adverse event; CI, confidence interval; IV, intravenous; NMOSD, neuromyelitis optica spectrum disorder.

CONCLUSIONS

- Compared with placebo, eculizumab was associated with reduced annualized rates of hospitalization and reduced acute relapse-related use of intravenous corticosteroids or plasma exchange in the PREVENT trial.
- These data indicate potential for a favourable effect on healthcare resource utilization with eculizumab in the real-world setting.

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Disclosures

RA, AP and MY – employees of and hold stock in Alexion; KPF – formerly an employee of Alexion and holds stock in Alexion.
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