

# Impact of eculizumab on reported quality of life in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: findings from the PREVENT study

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## INTRODUCTION AND PURPOSE

- Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disorder that is characterized by the accumulation of significant disability as a consequence of NMOSD attacks,<sup>1,2</sup> and is associated with a negative impact on health-related quality of life (QoL).<sup>3,4</sup>
- Eculizumab is a humanized monoclonal antibody that inhibits the terminal complement protein C5.<sup>5</sup>
- In the phase 3, randomized, double-blind PREVENT study (NCT01892345) in adults with aquaporin-4 immunoglobulin G (AQP4-IgG)-positive NMOSD,<sup>6</sup> there was a 94% reduction in relapse risk with eculizumab versus placebo.<sup>7</sup>
  - Hazard ratio: 0.058, 95% confidence interval (CI): 0.017–0.197;  $p < 0.0001$ .<sup>7</sup>
- Secondary outcome measures included changes from baseline in QoL measured using the European Quality of Life 5-Dimension 3-Level questionnaire (EQ-5D-3L).<sup>6</sup> Mean (standard deviation) changes were numerically higher (improved QoL) with eculizumab than with placebo for:
  - visual analogue scale scores (5.4 [18.53] and 0.6 [16.39] respectively; nominal  $p$  value: 0.0309)
  - index scores (0.05 [0.179] and –0.04 [0.212], respectively; nominal  $p$  value: 0.0077).
- Here, we examine further aspects of QoL in the PREVENT study population using individual dimensions from the EQ-5D-3L index score and data from the 36-item Short-Form Health Survey (SF-36), a patient-reported questionnaire designed to assess generic QoL in healthy and ill adults.

## METHODS

- PREVENT trial details have been published previously<sup>6</sup> but are provided in brief in **Panel A**.

### Panel A. Design, patients and treatment<sup>6</sup>

- Design.
  - International, phase 3, randomized, double-blind, parallel-group, placebo-controlled, time-to-event trial.
- Patients.
  - Main inclusion criteria: age  $\geq 18$  years; AQP4-IgG-seropositive status;  $\geq 2$  relapses in previous 12 months or  $\geq 3$  in previous 24 months (with  $\geq 1$  in previous 12 months); Expanded Disability Status Scale (EDSS) score  $\leq 7.0$ .
  - 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.

### QoL and safety assessments

- Patients completed the EQ-5D-3L and SF-36 at baseline, weeks 4, 8 and 12, and every 12 weeks thereafter.
- The EQ-5D-3L index score is derived from the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- The SF-36 consists of 36 items organized into eight scales (physical functioning, social functioning, role limitations due to physical health, bodily pain, general health perceptions, mental health, role limitations due to emotional problems, and vitality) and reported health transition.
  - There are two summary measures: one of physical health (the physical component score [PCS]) and one of mental health (the mental component score [MCS]). The PCS and MCS for the general population in the USA are each 50.<sup>8</sup>
- QoL outcomes reported here comprise:
  - the association between baseline SF-36 scores and patient disability (as assessed using the EDSS; *post hoc* analyses)
  - changes from baseline in EQ-5D-3L dimension scores (*post hoc* analyses) and in SF-36 scores (pre-specified tertiary endpoint)

**Table 1. Baseline demographic and clinical characteristics (A) and baseline SF-36 scores (B)**

Characteristic	Eculizumab (n = 96)	Placebo (n = 47)
Female, n (%)	88 (91.7)	42 (89.4)
Mean (SD) age, years	43.9 (13.32)	45.0 (13.29)
At first dose of trial medication	35.8 (14.03)	38.5 (14.98)
At initial clinical presentation		
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)

**B.**

SF-36 scores	Eculizumab (n = 96)	Placebo (n = 47)
PCS	38.6 (9.83)	36.9 (10.85)
MCS	47.0 (12.55)	44.0 (11.40)
Physical functioning	39.1 (11.15)	37.6 (11.00)
Social functioning	42.5 (11.60)	39.3 (11.67)
Role limitations physical	37.6 (11.33)	35.1 (11.13)
Bodily pain	43.3 (10.95)	39.8 (10.76)
General medical health	40.2 (8.28)	40.4 (10.41)
Mental health	46.0 (11.51)	44.5 (11.53)
Role limitations emotional	43.3 (13.54)	40.0 (13.99)
Vitality	46.1 (9.44)	41.9 (10.65)

Table 1A is 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.  
Data in Table 1B are mean (SD).  
ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; MCS, mental component score; NMOSD, neuromyelitis optica spectrum disorder; PCS, physical component score; SD, standard deviation; SF-36, 36-item Short-Form Health Survey.

- clinically meaningful changes in SF-36 PCS and MCS for eculizumab and placebo (an increase of 5 points or more was considered to be a clinically meaningful improvement and a reduction of 5 points or more a clinically meaningful deterioration; *post hoc* analyses)<sup>9</sup>
- clinically meaningful deteriorations in PCS and MCS in patients with adjudicated relapses compared with those without adjudicated relapses (analyses limited to the placebo group because only three adjudicated relapses occurred in the eculizumab group; *post hoc* analyses).
- Safety assessments included monitoring for adverse events (AEs).

### Statistical analyses

- The association between baseline SF-36 score and baseline patient disability was analysed using an analysis of covariance with baseline EDSS group (low: baseline EDSS score  $< 4.0$ ; high: baseline EDSS score  $\geq 4.0$ ) as covariate.
- Changes from baseline to study end for the EQ-5D-3L dimension and SF-36 scores were analysed using a randomization-based, non-parametric analysis of covariance adjusted for baseline scores and stratified by randomization strata.
- A proportional odds model analysis was conducted for analyses of clinically meaningful changes in PCS and MCS by treatment group, and a logistic regression model was used to analyse the association between having adjudicated relapses and clinically meaningful deterioration in PCS or MCS in the placebo group. Each model was adjusted for baseline SF-36 scores and baseline EDSS scores.

## RESULTS

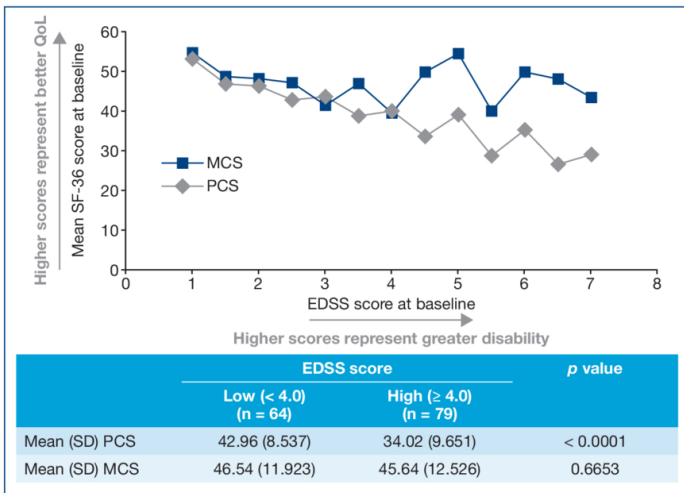
### Patients

- In total, 143 patients received trial treatment (eculizumab, n = 96; placebo, n = 47) and baseline characteristics were balanced between treatment groups (Table 1A).<sup>6</sup>

### Baseline SF-36 scores

- Baseline SF-36 scores were similar between treatment groups, and the average PCS was substantially lower than the average for the general population of the USA (50) (Table 1B).<sup>8</sup>
- At baseline, patients with EDSS scores of at least 4 (greater disability) had significantly worse PCS scores than patients with lower EDSS scores (Figure 1). Corresponding differences for the MCS were not significant.

**Figure 1. Relationship between baseline SF-36 scores and baseline EDSS scores**

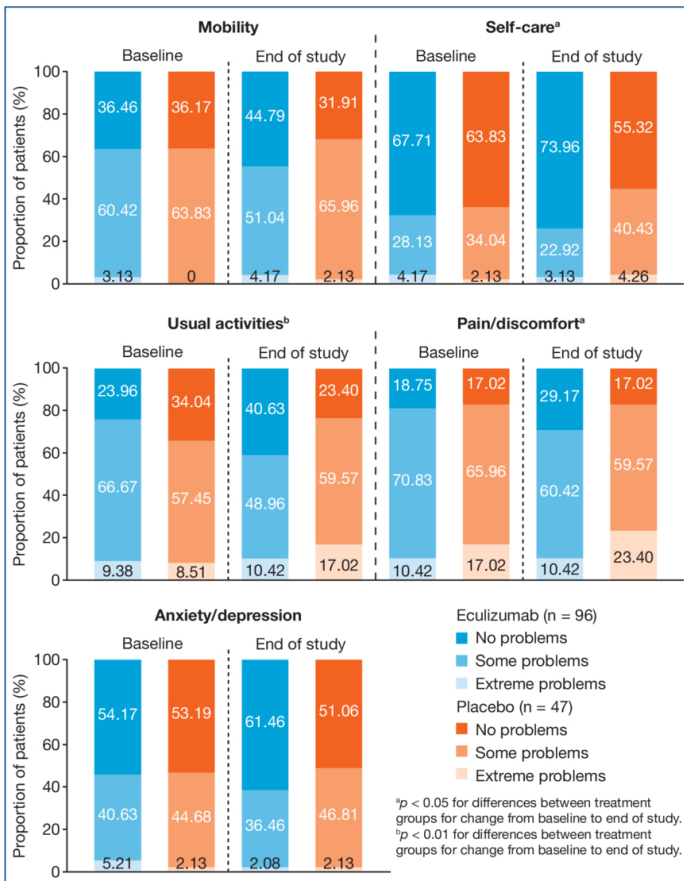


Data are pooled for eculizumab and placebo groups. SF-36 scores range between 0 and 100, with higher scores representing better health. EDSS scores range from 0 to 10, with higher scores representing greater disability. EDSS, Expanded Disability Status Scale; MCS, mental component score; PCS, physical component score; QoL, quality of life; SD, standard deviation; SF-36, 36-item Short-Form Health Survey.

### Changes in EQ-5D-3L and SF-36 scores

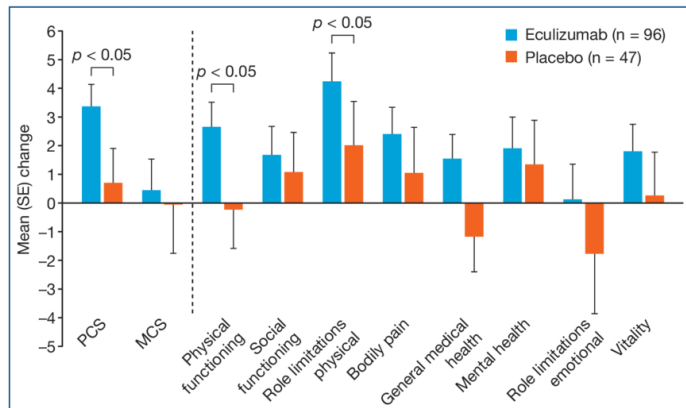
- Changes in the proportions of patients reporting problems in EQ-5D-3L dimensions favoured eculizumab over placebo (Figure 2). Differences were significant between groups for self-care, usual activities and pain/discomfort.

**Figure 2. EQ-5D-3L dimension scores at baseline and study end**



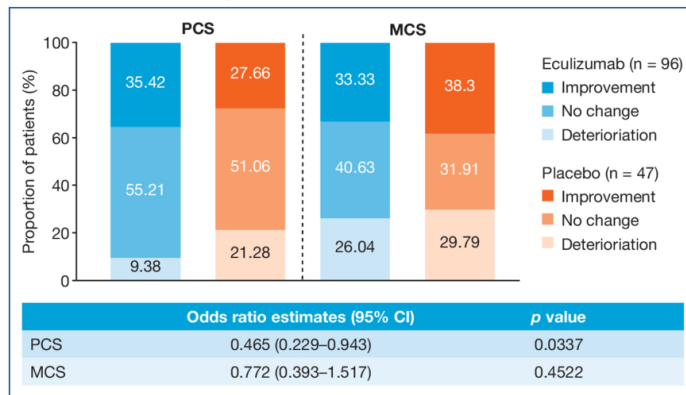
EQ-5D-3L, European Quality of Life 5-Dimension 3-Level questionnaire.

**Figure 3. Change from baseline to study end in SF-36 scores**



Scores range between 0 and 100, with higher scores representing better health. Domain scores contribute in different proportions to PCS and MCS.  
MCS, mental component score; PCS, physical component score; SE, standard error; SF-36, 36-item Short-Form Health Survey.

**Figure 4. Categorical analysis of clinically meaningful changes in SF-36 scores between baseline and study end**



CI, confidence interval; MCS, mental component score; PCS, physical component score; SF-36, 36-item Short-Form Health Survey.

- Improvements between baseline and study end were significantly greater with eculizumab than placebo for PCS and for two domains of the SF-36 (physical functioning and role limitations due to physical health) (Figure 3).
- Based on analyses of clinically meaningful changes in SF-36 scores, eculizumab, compared with placebo, significantly decreased the probability of PCS deterioration and increased the probability of PCS improvement (Figure 4).
  - Probabilities of MCS deterioration and improvement were not affected by treatment.
- In the placebo group, patients with adjudicated relapses were significantly more likely to have a clinically meaningful deterioration in PCS than those without adjudicated relapses (odds ratio: 0.151; 95% CI: 0.026–0.871;  $p = 0.0345$ ).
  - There was no significant difference in the corresponding analysis for MCS deterioration (odds ratio: 0.763; 95% CI: 0.174–3.352;  $p = 0.7202$ ).

### Safety

- Safety data have been reported previously,<sup>6</sup> and are described in brief below.
  - Overall rates of AEs per 100 patient-years were 749.3 for eculizumab and 1160.9 for placebo (including NMOSD relapses meeting the definition of a serious AE). Headache and upper respiratory tract infection were more common in the eculizumab group than in the placebo group. There was one fatal AE of pulmonary empyema in the eculizumab group.
  - No cases of meningococcal infection were reported.
- Longer-term safety data for eculizumab will be provided in oral presentation number 142 (Thursday 12 September).

## CONCLUSIONS

- Patients with AQP4-IgG-positive NMOSD experience diminished QoL, which is correlated with severity of disability as measured by the EDSS.
- Eculizumab, compared with placebo, significantly improved PCS, as well as physical functioning and role limitations due to physical health scores on the SF-36. Eculizumab also significantly decreased the probability of PCS worsening and increased the probability of PCS improvement. Changes favouring eculizumab were also apparent for EQ-5D-3L dimensions.
- Further data regarding the impact of eculizumab on disability measures in NMOSD will be provided in poster number P1343 (Friday 13 September).

### References

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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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