

Subgroup analyses from the phase 3 PREVENT study in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder

P605

Sean J. Pittock;¹ Achim Berthele;² Kazuo Fujihara;³⁻⁵ Ho Jin Kim;⁶ Michael Levy;^{7,8} Jacqueline Palace;⁹ Ichiro Nakashima;^{3,10} Murat Terzi;¹¹ Natalia Totolyan;¹² Shanthi Viswanathan;¹³ Kai-Chen Wang;^{14,15} Amy Pace;¹⁶ Kenji P. Fujita;^{16*} Marcus Yountz;¹⁶ Róisín Armstrong;¹⁶ Dean M. Wingerchuk¹⁷

¹Mayo Clinic, Rochester, MN, USA; ²Klinikum rechts der Isar, Technical University of Munich, Munich, Germany; ³Tohoku University, Sendai, Japan; ⁴Fukushima Medical University, Fukushima City, Japan; ⁵Southern TOHOKU Research Institute for Neuroscience (STRINS), Koriyama, Japan; ⁶Research Institute and Hospital, National Cancer Center, Goyang, South Korea; ⁷Johns Hopkins University, Baltimore, MD, USA; ⁸Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; ⁹John Radcliffe Hospital, Oxford, UK; ¹⁰Tohoku Medical and Pharmaceutical University, Sendai, Japan; ¹¹Ondokuz Mayıs University, Samsun, Turkey; ¹²First Pavlov State Medical University of St Petersburg, St Petersburg, Russia; ¹³Kuala Lumpur Hospital, Kuala Lumpur, Malaysia; ¹⁴Cheng-Hsin General Hospital, Taipei, Taiwan; ¹⁵School of Medicine, National Yang Ming University, Taipei, Taiwan; ¹⁶Alexion Pharmaceuticals, Boston, MA, USA; ¹⁷Mayo Clinic, Scottsdale, AZ, USA

*Formerly of Alexion Pharmaceuticals.

INTRODUCTION AND PURPOSE

- Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing, autoimmune, inflammatory disorder that damages the central nervous system.^{1,2}
- Recurrent attacks of optic neuritis and transverse myelitis are associated with poor recovery and incremental accumulation of neurological disability.^{1,2}
- Prevention of relapses is a primary goal of treatment. A range of immunosuppressive therapies (ISTs), including corticosteroids, azathioprine, mycophenolate mofetil and rituximab, are used to treat patients with NMOSD.³
- At least two-thirds of patients with NMOSD have aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies;^{4,5} these antibodies are reported to trigger the complement cascade, which is implicated in astrocyte destruction and neuronal injury.⁶
- Eculizumab is a humanized monoclonal antibody that inhibits the terminal complement protein C5.⁷
- In the phase 3, randomized, double-blind PREVENT study (NCT01892345) in adults with AQP4-IgG-positive NMOSD,⁸ the risk of adjudicated relapse was reduced by 94% with eculizumab versus placebo.⁹
 - Hazard ratio (HR): 0.058; 95% confidence interval (CI): 0.017–0.197; $p < 0.0001$.⁹
 - The proportions of patients with an adjudicated relapse in the eculizumab and placebo groups were 3.1% (3/96) and 42.6% (20/47), respectively.⁸
- Here, we report *post hoc* efficacy analyses in pre-specified subgroups, including those defined according to concurrent IST used during the trial.

METHODS

- PREVENT trial details have been published previously⁸ but are provided in brief in Panel A.

Panel A. PREVENT trial methodology⁸

- 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 (EDSS) 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 IST continued if stable dose at baseline.
 - Treatment continued until patient experienced a physician-determined relapse, patient discontinued or trial ended.
- Assessments and outcomes.
 - Blinded, independent expert committee adjudicated physician-determined relapses.
 - Primary efficacy endpoint was time to first adjudicated relapse for overall population.

Assessments, outcome measures and statistical analyses

- Pre-specified subgroup summaries for time to first adjudicated relapse were based on IST use (five subgroups for concomitant IST use; two subgroups according to whether or not rituximab was previously used), geographic region, age, sex, race and randomization stratum.
 - Time to first adjudicated relapse was analysed *post hoc* using an unstratified log-rank test. HRs were estimated using a Cox proportional hazards model, with treatment group as covariate, and Wald CIs.
 - Interaction p values were based on a Cox proportional hazards model, with interaction term.
- Safety assessments included monitoring for adverse events (AEs).

RESULTS

Patients

- In the overall population, 143 patients received trial treatment (eculizumab, $n = 96$; placebo, $n = 47$).
- The mean (standard deviation) annualized relapse rate in the 24 months before screening was 1.99 (0.943), and the median EDSS score (4.00) indicated moderate-to-severe disability.
- In total, 76.2% of patients continued to receive their previous IST during the trial, and 32.2% had received rituximab previously.
 - Of the 34 patients who received no ISTs during the study, 10 were treatment-naïve and 24 had previously received ISTs.
- Baseline demographics were generally similar across the pre-specified IST subgroups (Table 1).

Time to first adjudicated relapse

- Time to first adjudicated relapse was increased with eculizumab compared with placebo in all subgroups analysed (Figure 1).
 - Significant treatment effects were observed in all subgroups for IST use, region, age, sex and race, except for the smallest subgroups in which the differences were similar to the others but did not reach nominal significance owing to small sizes (patients using other ISTs, $n = 7$; Black/African American patients, $n = 17$, among whom none of the nine patients receiving eculizumab experienced a relapse), and in patients from the Americas owing to the performance of the placebo arm.
 - In patients who had received rituximab more than 3 months before the study, the adjudicated relapse risk reduction was 90.7% with eculizumab compared with placebo ($p = 0.0055$).

- The proportion of patients who were relapse-free at week 48 was consistently higher with eculizumab than with placebo in all pre-specified IST subgroups (Figure 2).

Safety

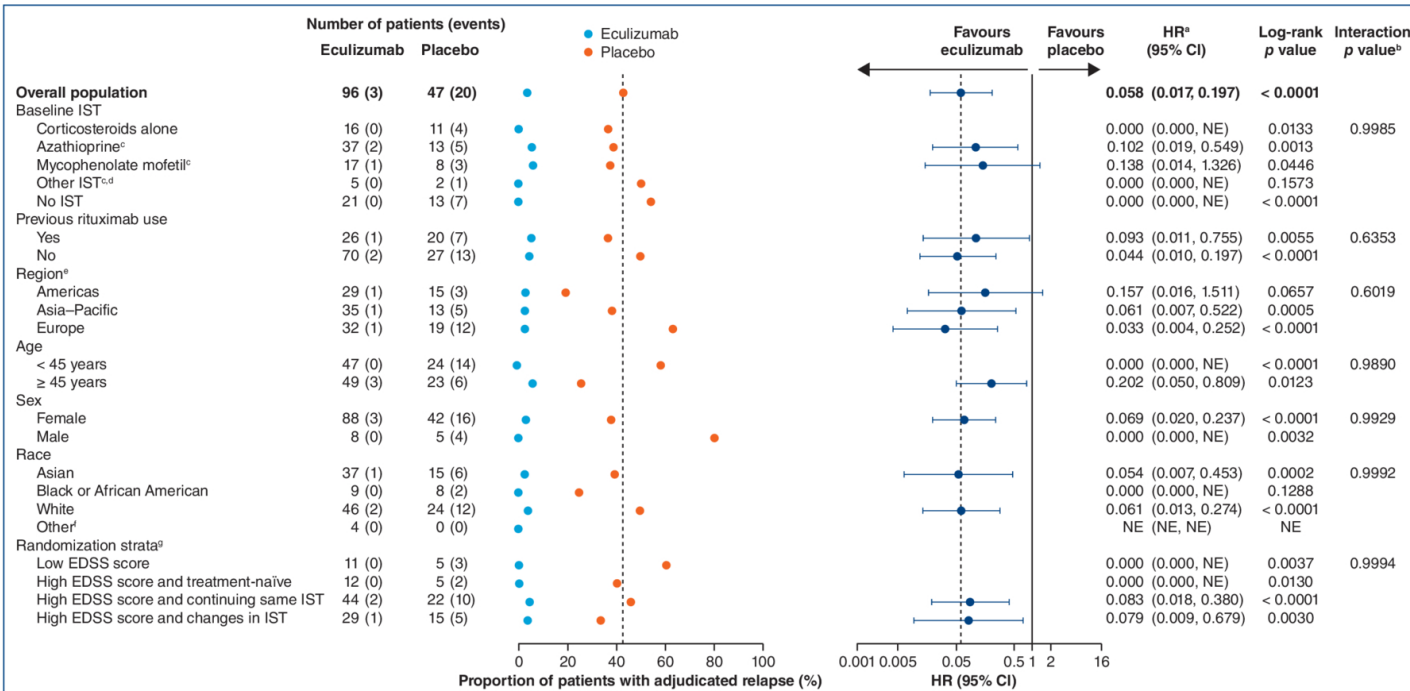
- Safety data for the overall population have been reported previously⁸ and are described in brief below.
- Overall rates of AEs per 100 patient-years were 749.3 and 1160.9 in the eculizumab and placebo groups, respectively (including NMOSD relapses that met the definition of a serious AE; Table 2). The rates of headache and upper respiratory tract infection were higher in patients receiving eculizumab than in those receiving placebo. There was one fatal AE of pulmonary empyema in a patient receiving eculizumab and azathioprine.
- There were no cases of meningococcal infection.
- No new safety signals were observed in subgroups defined by IST use (Table 2).
- Longer-term safety data for eculizumab will be provided in oral presentation number 142 (Thursday 12 September).

Table 1. Baseline demographic and clinical characteristics according to pre-specified IST subgroups

		Female, n (%)	Mean (SD) age, years, at:		Diagnosis, n (%)		Mean (SD) ARR*	Median (range) EDSS score
			first dose of trial medication	initial clinical presentation	NMO	NMOSD		
Overall population	Eculizumab (n = 96)	88 (91.7)	43.9 (13.32)	35.8 (14.03)	69 (71.9)	27 (28.1)	1.94 (0.896)	4.00 (1.0–7.0)
	Placebo (n = 47)	42 (89.4)	45.0 (13.29)	38.5 (14.98)	38 (80.9)	9 (19.1)	2.07 (1.037)	4.00 (1.0–6.5)
No IST	Eculizumab (n = 21)	20 (95.2)	41.7 (13.47)	30.4 (11.92)	19 (90.5)	2 (9.5)	1.8 (0.67)	4.00 (1.5–7.0)
	Placebo (n = 13)	12 (92.3)	37.5 (9.22)	31.5 (10.29)	11 (84.6)	2 (15.4)	1.9 (0.82)	4.00 (1.5–6.0)
Corticosteroids only	Eculizumab (n = 16)	15 (93.8)	45.2 (12.03)	41.6 (11.03)	9 (56.3)	7 (43.8)	2.3 (1.35)	3.00 (1.5–7.0)
	Placebo (n = 11)	8 (72.7)	44.9 (14.98)	40.5 (17.13)	8 (72.7)	3 (27.3)	2.3 (1.00)	5.50 (2.0–6.5)
Azathioprine \pm corticosteroids	Eculizumab (n = 37)	34 (91.9)	43.4 (13.66)	34.7 (14.17)	27 (73.0)	10 (27.0)	1.9 (0.80)	3.50 (1.0–7.0)
	Placebo (n = 13)	12 (92.3)	46.2 (9.11)	38.5 (11.84)	10 (76.9)	3 (23.1)	1.9 (0.72)	4.00 (1.5–6.5)
Mycophenolate mofetil \pm corticosteroids	Eculizumab (n = 17)	14 (82.4)	46.8 (14.40)	39.3 (16.98)	10 (58.8)	7 (41.2)	2.1 (0.81)	4.50 (2.0–6.5)
	Placebo (n = 8)	8 (100.0)	52.4 (18.21)	46.6 (19.80)	7 (87.5)	1 (12.5)	2.5 (1.73)	4.25 (1.0–6.5)
Other ISTs \pm corticosteroids	Eculizumab (n = 5)	5 (100.0)	43.4 (13.46)	34.8 (14.04)	4 (80.0)	1 (20.0)	1.5 (0.72)	4.00 (3.5–6.5)
	Placebo (n = 2)	2 (100.0)	57.5 (6.36)	39.5 (21.92)	2 (100.0)	0 (0.0)	1.4 (0.68)	4.25 (3.5–6.0)
Previous rituximab	Eculizumab (n = 26)	22 (84.6)	45.0 (12.78)	37.2 (14.94)	17 (65.4)	9 (34.6)	2.0 (0.56)	4.25 (1.5–7.0)
	Placebo (n = 20)	18 (90.0)	43.0 (14.93)	35.9 (15.06)	16 (80.0)	4 (20.0)	1.8 (0.70)	4.00 (1.0–6.5)

ISTs were used concomitantly throughout the trial, except rituximab. Patients previously receiving rituximab could be included in the trial if they had not received rituximab in the 3 months before screening. *During the 24 months before screening. ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; IST, immunosuppressive therapy; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; SD, standard deviation.

Figure 1. Time to first adjudicated relapse according to pre-specified subgroups



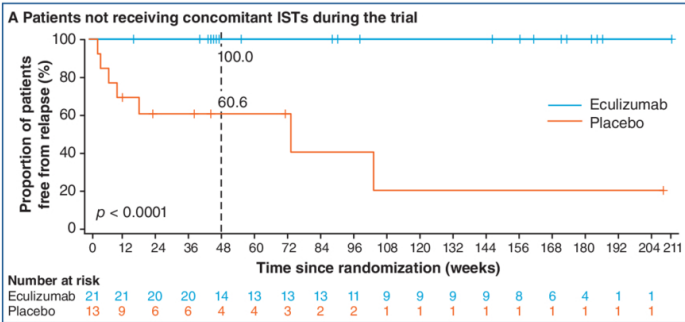
HRs are undefined in subgroups with no relapses in at least one treatment arm. Dotted vertical lines show proportion of patients receiving placebo in the overall population who experienced a relapse (left) and the HR for the overall population (right). The statistical test for interaction assesses whether the treatment effect varies by the different levels of the subgroup variable. *Based on a Cox proportional hazards model, with treatment covariate, and Wald CIs. *Based on a Cox proportional hazards model, with interaction term. *With or without corticosteroids. *Other ISTs include cyclophosphamide, cyclosporine, methotrexate, mizoribine and tacrolimus. *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. *Other races include American Indian or Alaskan Native, unknown and other. *Low and high EDSS scores are ≤ 2.0 , and ≥ 2.5 to ≤ 7.0 , respectively; continued/changed ISTs are since previous relapse. CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IST, immunosuppressive therapy; NE, not estimable.

Table 2. Adverse event summary according to pre-specified IST subgroups in the PREVENT trial

		AEs, rate per 100 PY; n (%)						Serious AEs, ^{a,b} rate per 100 PY; n (%)		
		Any	Related to trial agent	Severe	Moderate	Mild	Unknown severity	Any	Related to trial agent	Serious infections
Overall population	Eculizumab (n = 96; 172.8 PY)	749.3; 88 (91.7)	211.8; 49 (51.0)	16.8; 17 (17.7)	110.5; 60 (62.5)	620.3; 86 (89.6)	1.7; 3 (3.1)	30.7; 30 (31.3)	7.5; 9 (9.4)	9.3; 11 (11.5)
	Placebo (n = 47; 53.1 PY)	1160.9; 45 (95.7)	163.7; 27 (57.4)	41.4; 12 (25.5)	287.9; 30 (63.8)	831.7; 41 (87.2)	0.0; 0 (0.0)	88.4; 26 (55.3)	24.5; 9 (19.1)	15.1; 6 (12.8)
No IST	Eculizumab (n = 21; 44.4 PY)	669.5; 19 (90.5)	196.1; 11 (52.4)	13.5; 3 (14.3)	130.8; 13 (61.9)	523.0; 19 (90.5)	2.3; 1 (4.8)	22.5; 5 (23.8)	6.8; 1 (4.8)	2.3; 1 (4.8)
	Placebo (n = 13; 12.9 PY)	1139.5; 13 (100.0)	178.3; 9 (69.2)	23.3; 2 (15.4)	348.8; 7 (53.8)	767.4; 12 (92.3)	0.0; 0 (0.0)	116.3; 8 (61.5)	23.3; 3 (23.1)	7.8; 1 (7.7)
Corticosteroids only	Eculizumab (n = 16; 26.6 PY)	503.3; 15 (93.8)	120.2; 7 (43.8)	7.5; 2 (12.5)	97.7; 8 (50.0)	398.2; 14 (87.5)	0.0; 0 (0.0)	26.3; 5 (31.3)	7.5; 1 (6.3)	11.3; 2 (12.5)
	Placebo (n = 11; 18.2 PY)	553.8; 11 (100.0)	76.8; 7 (63.6)	16.5; 3 (27.3)	87.7; 7 (63.6)	449.6; 9 (81.8)	0.0; 0 (0.0)	60.3; 6 (54.5)	11.0; 2 (18.2)	11.0; 2 (18.2)
Azathioprine \pm corticosteroids ^c	Eculizumab (n = 37; 62.1 PY)	796.9; 33 (89.2)	231.8; 19 (51.4)	17.7; 5 (13.5)	85.3; 23 (62.2)	692.3; 32 (86.5)	1.6; 1 (2.7)	29.0; 10 (27.0)	6.4; 3 (8.1)	11.3; 4 (10.8)
	Placebo (n = 13; 9.0 PY)	1067.4; 11 (84.6)	211.3; 6 (46.2)	11.2; 3 (23.1)	189.0; 7 (53.8)	767.2; 10 (76.9)	0.0; 0 (0.0)	122.3; 5 (38.5)	66.7; 2 (15.4)	44.5; 2 (15.4)
Mycophenolate mofetil \pm corticosteroids	Eculizumab (n = 17; 30.9 PY)	992.9; 16 (94.1)	313.7; 9 (52.9)	32.3; 7 (41.2)	145.5; 12 (70.6)	815.0; 16 (94.1)	0.0; 0 (0.0)	42.0; 6 (35.3)	9.7; 3 (17.6)	12.9; 3 (17.6)
	Placebo (n = 8; 11.1 PY)	1992.1; 8 (100.0)	225.4; 3 (37.5)	36.1; 2 (25.0)	504.8; 7 (87.5)	1451.3; 8 (100.0)	0.0; 0 (0.0)	72.1; 5 (62.5)	9.0; 1 (12.5)	9.0; 1 (12.5)
Other ISTs \pm corticosteroids ^c	Eculizumab (n = 5; 8.8 PY)	704.2; 5 (100.0)	68.1; 3 (60.0)	0.0; 0 (0.0)	102.2; 4 (80.0)	590.6; 5 (100.0)	11.4; 1 (20.0)	56.8; 4 (80.0)	11.4; 1 (20.0)	11.4; 1 (20.0)
	Placebo (n = 2; 1.9 PY)	2705.6; 2 (100.0)	312.2; 2 (100.0)	104.1; 2 (100.0)	988.6; 2 (100.0)	1612.9; 2 (100.0)	0.0; 0 (0.0)	104.1; 2 (100.0)	52.0; 1 (50.0)	0.0; 0 (0.0)
Previous rituximab	Eculizumab (n = 26; 38.4 PY)	934.6; 24 (92.3)	411.3; 16 (61.5)	18.2; 5 (19.2)	177.0; 18 (69.2)	734.1; 24 (92.3)	5.2; 2 (7.7)	39.1; 8 (30.8)	5.2; 2 (7.7)	7.8; 2 (7.7)
	Placebo (n = 20; 17.2 PY)	1159.9; 20 (100.0)	156.6; 12 (60.0)	29.0; 3 (15.0)	336.4; 12 (60.0)	794.5; 19 (95.0)	0.0; 0 (0.0)	63.8; 9 (45.0)	11.6; 2 (10.0)	11.6; 2 (10.0)

ISTs were used concomitantly throughout the trial, except rituximab. Patients previously receiving rituximab could be included in the trial if they had not received rituximab in the 3 months before screening. Data include all physician-reported NMOSD relapses that met the definition of a serious AE. *One patient receiving eculizumab and concomitant azathioprine died during the trial. *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). *Two patients receiving placebo discontinued owing to an AE: one in the azathioprine subgroup and one in the other ISTs subgroup. AE, adverse event; IST, immunosuppressive therapy; NMOSD, neuromyelitis optica spectrum disorder; PY, patient-years.

Figure 2. Analyses of time to first adjudicated relapse according to IST use



Panel A 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.

Please scan QR code to download four additional figures showing the analyses of time to first adjudicated relapse in subgroups receiving concomitant corticosteroids only (Figure 2B), concomitant azathioprine \pm corticosteroids (Figure 2C) and concomitant mycophenolate mofetil \pm corticosteroids (Figure 2D) during the trial, and in those previously receiving rituximab⁹ (Figure 2E).

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. p values are based on an unstratified log-rank test. *Patients previously receiving rituximab could be included in the trial if they had not received rituximab in the 3 months before screening. *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.

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CONCLUSIONS

- The clinically meaningful treatment effect of eculizumab on relapse risk reduction in subgroups of patients was consistent with that for the overall population.
 - The robust effect of eculizumab on time to first adjudicated relapse compared with placebo was observed regardless of: whether it was used as a monotherapy or with concomitant ISTs (corticosteroids alone, azathioprine, mycophenolate mofetil); previous IST use (including rituximab); geographical region; age; sex; and race.
- The safety profile of eculizumab was consistent across all IST subgroups in this trial and with those in other indications for which eculizumab has been approved.^{10–14}

Disclosures

RA, AP and MY – employees of and hold stock in Alexion; KPF – formerly an employee of Alexion and holds stock in Alexion. AB – compensation for clinical trials received by his institution from Alexion Pharmaceuticals, Biogen, Novartis Pharmaceuticals, Roche, Sanofi Genzyme and Teva Pharmaceuticals; personal fees and non-financial support from Bayer Healthcare, Biogen, Merck Serono, Mylan, Novartis Pharmaceuticals, Roche and Sanofi Genzyme. KF – consultancy/speaker fees from Alexion Pharmaceuticals, Asahi Kasei Medical, Biogen, Chugai, Eisai, Mitsubishi-Tanabe Pharma, Nihon, Novartis Pharmaceuticals, ONO Pharmaceutical, Takeda and Teijin. HJK – research support from Merck Serono, the Ministry of Science and ICT, Sanofi Genzyme, Teva-Handok and UCB; consultancy/speaker fees from Celltrion, Eisai, HanA BioPharma, MedImmune, Merck Serono, Novartis, Sanofi Genzyme, Teva-Handok and UCB; serves on a steering committee for MedImmune/Viola Bio; is co-editor for the *Multiple Sclerosis Journal – Experimental, Translational and Clinical*, and associate editor for the *Journal of Clinical Neurology*. ML – partly funded by highly specialized services to run a national congenital myasthenia service and a neuromyelitis service; support for scientific meetings and fees for advisory work from Abide, Alexion, ARGENTX, Bayer Schering, Biogen Idec, Chugai Pharma, Euroimmun, MedDay, MedImmune, Merck Serono, Novartis, Roche, Sanofi Genzyme and Teva; grants from Abide, Bayer Schering, Biogen Idec, Merck Serono, Novartis and Teva; grants from EDEN, GMSI, the Gutty-Jackson Charitable Foundation, the John Fell Fund, the Medical Research Council, the MS Society, National Institute for Health Research and the Oxford Health Services Research Committee for research studies. SJP – grants, personal fees and non-financial support from Alexion Pharmaceuticals; grants from the Autoimmune Encephalitis Alliance and Grifols; grants, personal fees, non-financial support and honoraria from MedImmune, Inc; patient # 9,891,219 (application # 12-573942) "Methods for treating neuromyelitis optica (NMO) by administration of eculizumab to an individual that is aquaporin-4 (AQP4)-IgG antibody positive". MT, SV and K-CW have nothing to disclose. NT – personal fees from Bayer, Janssen, Merck, Receptos, Inc., Roche, Sanofi Genzyme and Teva; grants and personal fees from Actelion, BIOCAD (Russia) and Novartis; grants from Genzyme, DMW – grants from Alexion Pharmaceuticals during the conduct of the study; personal fees from Biogen, BrainStorm Therapeutics, Caladrius, Celgene, MedImmune, Novartis and ONO Pharmaceutical.

