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Clinical trial

AQP4-IgG-seronegative patient outcomes in the N-MOmentum trial of inebilizumab in neuromyelitis optica spectrum disorder

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ABSTRACT

Background: The N-MOmentum trial, a double-blind, randomized, placebo-controlled, phase 2/3 study of inebilizumab in neuromyelitis optica spectrum disorder (NMOSD), enrolled participants who were aquaporin-4-immunoglobulin G (AQP4-IgG)-seropositive (AQP4+) or -seronegative (AQP4−). This article reports AQP4− participant outcomes.

Methods: AQP4-IgG serostatus was determined for all screened participants by a central laboratory, using a validated, fluorescence-observation cell-binding assay. Medical histories and screening data for AQP4− participants were assessed independently by an eligibility committee of three clinical experts during screening. Diagnosis of NMOSD was confirmed by majority decision using the 2006 neuromyelitis optica criteria. Myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG-IgG) serology (using a clinically validated, flow cytometry assay) and annualized attack rates (AARs) were evaluated *post hoc*. Efficacy outcomes were assessed by comparing pre-study and on-study AARs in treated participants.

Results: Only 18/50 AQP4− screened participants (36%) were initially considered eligible for randomization; 16 were randomized and received full treatment, 4 to placebo (1 MOG-IgG-seropositive [MOG+]) and 12 to inebilizumab (6 MOG+). The most common reason for failure to pass screening among prospective AQP4−

Abbreviations: AAR, annualized attack rate; AQP4, aquaporin-4; AQP4−, AQP4-IgG-seronegative; AQP4+, AQP4-IgG-seropositive; CSF, cerebrospinal fluid; CNS, central nervous system; EC, eligibility committee; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MOG−, MOG-IgG-seronegative; MOG+, MOG-IgG-seropositive; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; OLP, open-label period; ON, optic neuritis; RCP, randomized controlled period; TEAE, treatment-emergent adverse event.

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participants was failure to fulfill the 2006 NMO MRI criteria. In inebilizumab-treated AQP4− participants, on-study AARs (95% confidence interval [CI]) calculated from treatment initiation (whether from randomization or when received at the start of the open-label period) to the end of study were lower than pre-study rates: for all AQP4− participants ($n = 16$), mean (95% CI) AAR was 0.048 (0.02–0.15) versus 1.70 (0.74–2.66), respectively. For the subset of AQP4−/MOG+ participants ($n = 7$), AAR was 0.043 (0.006–0.302) after treatment versus 1.93 (1.10–3.14) before the study. For the subset of AQP4−/MOG− participants ($n = 9$), post-treatment AAR was 0.051 (0.013–0.204) versus 1.60 (1.02–2.38). Three attacks occurred during the randomized controlled period in the AQP4− inebilizumab group and were of mild severity; no attacks occurred in the AQP4− placebo group. The low number of participants receiving placebo ($n = 4$) confounds direct comparison with the inebilizumab group. No attacks were seen in any AQP4− participant after the second infusion of inebilizumab. Inebilizumab was generally well tolerated by AQP4− participants and the adverse event profile observed was similar to that of AQP4+ participants.

Conclusion: The high rate of rejection of AQP4− participants from enrollment into the study highlights the challenges of implementing the diagnostic criteria of AQP4− NMOSD. An apparent reduction of AAR in participants with AQP4− NMOSD who received inebilizumab warrants further investigation.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, severe, autoimmune, inflammatory central nervous system (CNS) disease (Cree et al., 2016). NMOSD is characterized by recurrent attacks, thought to be antibody-meditated (Bennett et al., 2015; Marignier et al., 2010), typically of optic neuritis (ON) or longitudinally extensive transverse myelitis (LETM), and less commonly affecting the brain/brain stem. Attacks are cumulatively responsible for most of the ambulatory, visual, and other disabilities that result from NMOSD (Bennett et al., 2015; Cree et al., 2016; Fujihara et al., 2012).

An important feature of NMOSD is the presence of serum immunoglobulin G (IgG) autoantibodies against aquaporin-4 (AQP4), a water channel protein expressed on astrocytes in the CNS. These AQP4-IgG autoantibodies are detected in up to 90% of patients with NMOSD (Jarius and Wildemann, 2010). The cell-based assay for AQP4-IgG is 99.9% specific for NMOSD (Pittock et al., 2014) and, together with clinical symptoms and the exclusion of alternatives, an AQP4-IgG-positive serostatus (AQP4+) is sufficient to confirm a diagnosis of NMOSD (Wingerchuk et al., 2015). Diagnosis is less precise in AQP4-IgG-seronegative (AQP4−) patients owing to clinical overlap of NMOSD with multiple sclerosis (MS) and other neuroinflammatory disorders. A subset of AQP4− patients are positive for autoantibodies against myelin oligodendrocyte glycoprotein (MOG), further complicating characterization of AQP4− NMOSD (Narayan et al., 2018). The patients who are AQP4− and MOG-IgG-seropositive (MOG+) notably differ in disease manifestation [MOG+ disease affecting men and women with equal prevalence (Salama et al., 2020), with an earlier onset of symptoms (Höftberger et al., 2015; Salama et al., 2020; Weber et al., 2018), and increased incidence of ON] compared with AQP4+ patients (Weber et al., 2018). Currently, there are no approved therapies for MOG+ disease or AQP4− NMOSD. Autoantibody status also affects attack rate and severity (Höftberger et al., 2015; Salama et al., 2020), and informs treatment approaches (Salama et al., 2020).

In 2006, diagnostic criteria were developed for AQP4− neuromyelitis optica (NMO) (Wingerchuk et al., 2006). To receive an NMO diagnosis, AQP4− patients must have had a history of ON and LETM, and a brain magnetic resonance imaging (MRI) scan not meeting diagnostic criteria for MS. This evaluation placed an emphasis on clinical judgment when diagnosing NMO in AQP4− patients. Moreover, the clinical criteria for AQP4− NMO, which require occurrence of both ON and LETM, contrast with the diagnostic criteria for NMOSD in AQP4+ patients who may have experienced only a single attack limited to one of the typical areas of CNS involvement in NMOSD, such as the optic nerves or spinal cord.

The N-MOmentum study was a randomized, placebo-controlled, double-blind, phase 2/3 trial assessing the efficacy and safety of inebilizumab, an anti-CD19, B-cell-depleting antibody, in 230 participants with AQP4+ or AQP4− NMOSD from 99 sites around the world (Cree et al., 2019). The N-MOmentum study started in 2014, when only the 2006 criteria were available for the diagnosis of NMO in AQP4− participants. This manuscript describes the process for enrolling AQP4− participants into the N-MOmentum study and reports the outcomes of AQP4− participants in the trial.

2. Methods

The methods of the N-MOmentum trial (ClinicalTrials.gov identifier: NCT02200770) were reported previously (Cree et al., 2019). In brief, eligible participants aged 18 years or older with NMOSD were randomized (3:1) to intravenous inebilizumab 300 mg or placebo administered on days 1 and 15 of the randomized controlled period (RCP). Participants continued in the RCP for a maximum of 28 weeks or until the occurrence of an adjudicated attack, after which they could participate in an optional open-label period (OLP) of inebilizumab treatment lasting at least 2 years. All participants in the OLP received intravenous inebilizumab 300 mg every 6 months. An institutional review board or ethics committee at each study site approved the protocol, and written informed consent was obtained from all participants (Cree et al., 2019).

The N-MOmentum inclusion criteria allowed the enrollment of both AQP4+ and AQP4− participants to capture a broad spectrum of participants. To be eligible for inclusion, all participants had to have an Expanded Disability Status Scale (EDSS) score of 8.0 or lower and a documented history of at least one attack requiring rescue therapy in the previous year or at least two attacks requiring rescue therapy in the previous 2 years. Participants who were AQP4− at screening had to meet the clinical threshold for NMO according to the 2006 criteria (**Table 1**) (Wingerchuk et al., 2006).

To apply the 2006 diagnostic criteria consistently for AQP4− participants, historical and screening data for each participant were reviewed by an independent eligibility committee (EC), consisting of three NMOSD experts (R.M., S.J.P., and F.P.) experienced in evaluating and treating patients with NMOSD. AQP4-IgG serostatus was determined by the central laboratory (Mayo Clinic, Rochester, MN, USA) using a validated, fluorescence-observation cell-binding assay (**Fig. 1A**) (Pittock et al., 2014; Takahashi et al., 2006). Information regarding demographic data, date and type of previous attacks, clinical data supporting diagnosis and treatment of previous attacks, previous and ongoing symptoms of NMOSD, full neuro-axis MRI scans from the screening visit (with and without gadolinium-enhancing agents), historical radiologist reports and historical spinal, optic nerve, and brain MRI scans, and a consensus report on the screening MRI prepared by the central MRI vendor (NeuroRx, Montreal, QC, Canada) were provided to the EC. EC members could request other historical data or pose questions as necessary to make their determination; majority agreement was based on independent decisions without communication among EC members. The MOG-IgG serostatus of AQP4− participants was determined retrospectively from samples that were prospectively acquired at participant

screening and was assessed by Mayo Clinic Neuroimmunology Laboratory (central laboratory) using an in-house, clinically validated, live cell flow cytometry assay (Mayo Clinic Laboratories; Sechi et al., 2021); cerebrospinal fluid (CSF) samples were not taken from participants for MOG-IgG measurements and MOG-IgG results were not available during EC evaluations.

The role of the EC was protocol-defined, independent from the study sponsor, and governed by a separate charter. To maintain objectivity and to avoid bias, EC members were not permitted to review data of participants enrolled at their own sites, were not included on other N-MOmentum study committees, communicated only with designated contacts, did not have a direct interest in knowing or influencing the trial outcome, did not have a financial or intellectual interest in the outcome of the trial, and were required to disclose all potentially relevant financial interests.

A *post hoc* analysis was undertaken to assess possible differences in EC decisions following the updated 2015 diagnostic criteria for NMOSD. Six randomly chosen cases (two positively adjudicated using the 2006 guidance) were re-reviewed by the EC using the 2015 diagnostic criteria. This review was performed after the end of enrollment and the completion of the RCP.

Efficacy outcomes for AQP4− participants were measured in accordance with the study protocol (Cree et al., 2019), and included annualized NMOSD attack rates (AARs), data permitting. AAR outcomes are reported for the 'any inebilizumab' AQP4− group, consisting of all participants who received inebilizumab at any time, with day 1 for the AAR calculation being the day on which inebilizumab treatment was initiated. For other efficacy outcomes (EDSS scores, cumulative total active MRI lesions and NMO-/NMOSD-related inpatient hospitalizations), results from the AQP4− group were compared with the AQP4− placebo group and, owing to the low number of participants in the former, a combined placebo group comprising AQP4+ and AQP4− participants. Pharmacokinetic exposure was assessed as areas under the 'inebilizumab in blood' concentration–time curve and maximum observed concentrations after the second dose in the RCP. Pharmacodynamic (B-cell counts) and safety outcomes (treatment-emergent adverse events [TEAEs]) were also recorded. AARs before enrollment were calculated for AQP4− participants from medical histories and then compared with on-study AARs. To contextualize these findings, treatment effects were compared between the AQP4− and AQP4+ inebilizumab-treated groups. AAR was calculated for participants who were AQP4− but MOG+ and for those who were AQP4− and seronegative for MOG-IgG (AQP4−/MOG−).

The N-MOmentum study was not powered to assess outcomes in the AQP4− group; the results presented here are not controlled for multiplicity and are for hypothesis generation only. Too few AQP4− participants were randomized to placebo for between-group comparisons to be clinically meaningful; results are presented descriptively.

3. Results

3.1. Inclusion of AQP4− participants in N-MOmentum

The EC reviewed cases for 50 AQP4− participants and determined that 18 participants (36.0%) met the 2006 criteria and were eligible, 10 of whom were confirmed unanimously. Several factors contributed to the exclusion of AQP4− participants, including insufficient participant history of previous ON or myelitis attacks, missing/unclear historical MRI images, lack of evidence for LETM, inaccuracy of historical AQP4-IgG test results or seroconversion. Possible alternative diagnosis (e.g., MS, sarcoidosis, infection, or lymphoma) was another reason for exclusion (**Fig. 1B**). Lack of LETM on MRI was the most common reason for exclusion and was present in 75% of those excluded (24/32).

The EC performed a *post hoc* re-evaluation of six (33.3%) of the eligible cases against the 2015 diagnostic criteria, after the RCP: The review of these cases by the EC resulted in no change in eligibility.

Overall, 16/18 AQP4− participants were randomized and received full study treatment; 12 participants were randomized to inebilizumab and 4 to placebo. The remaining AQP4− participants were both randomized to inebilizumab but were excluded from the analysis for

Table 1
Criteria for the diagnosis of NMO/NMOSD.

2006 diagnostic criteria for NMO		2015 diagnostic criteria for NMOSD			
		with AQP4-IgG		with negative or unknown AQP4-IgG serostatus	
Criteria	Description	Criteria	Description	Criteria	Description
1	ON	1	At least one core clinical characteristic[b]	1	At least two core clinical characteristics[b], occurring as a result of one or more clinical attacks and meeting all of the following requirements: • at least one core clinical characteristic must be ON, acute myelitis with LETM, or area postrema syndrome. • dissemination in space (two or more difference core clinical characteristics) • fulfillment of additional MRI requirements, as applicable
2	Acute myelitis	2	Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)	2	Negative test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) or testing unavailable
3	At least two of the following: • contiguous spinal cord MRI lesion extending over ≥ 3 vertebral segments • brain MRI not meeting diagnostic criteria for MS • AQP4-IgG seropositive status[a]	3	Exclusion of alternative diagnoses	3	Exclusion of alternative diagnoses

AQP4, aquaporin-4; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis lesions; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuromyelitis optica; NMO-IgG, neuromyelitis optica immunoglobulin G (later termed aquaporin-4 IgG); ON, optic neuritis.

[a] Because 'AQP4-IgG-seropositive' status is not applicable to seronegative patients, the other supportive criteria **MUST** be met for NMO diagnosis and to have been eligible for the N-MOmentum study.

[b] Core clinical characteristics: ON; acute myelitis; area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting); acute brain stem syndrome (symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD typical diencephalic MRI lesions); symptomatic cerebral syndrome with NMOSD typical brain lesions.

different reasons: one had an NMOSD attack before receiving their first dose and was subsequently removed from the study; the other was found to be AQP4+ on further analysis and discontinued before receiving the second inebilizumab dose on day 15. Of the 12 participants randomized to inebilizumab, 6 were AQP4−/MOG+ and 6 were AQP4−/MOG−. Of the 4 participants randomized to placebo, 1 was AQP4−/MOG+ and 3 were AQP4−/MOG−.

Demographics and baseline characteristics of AQP4− participants were different from the AQP4+ population, with proportionally more men, shorter disease duration, and lower EDSS scores in the AQP4− group (Table 2).

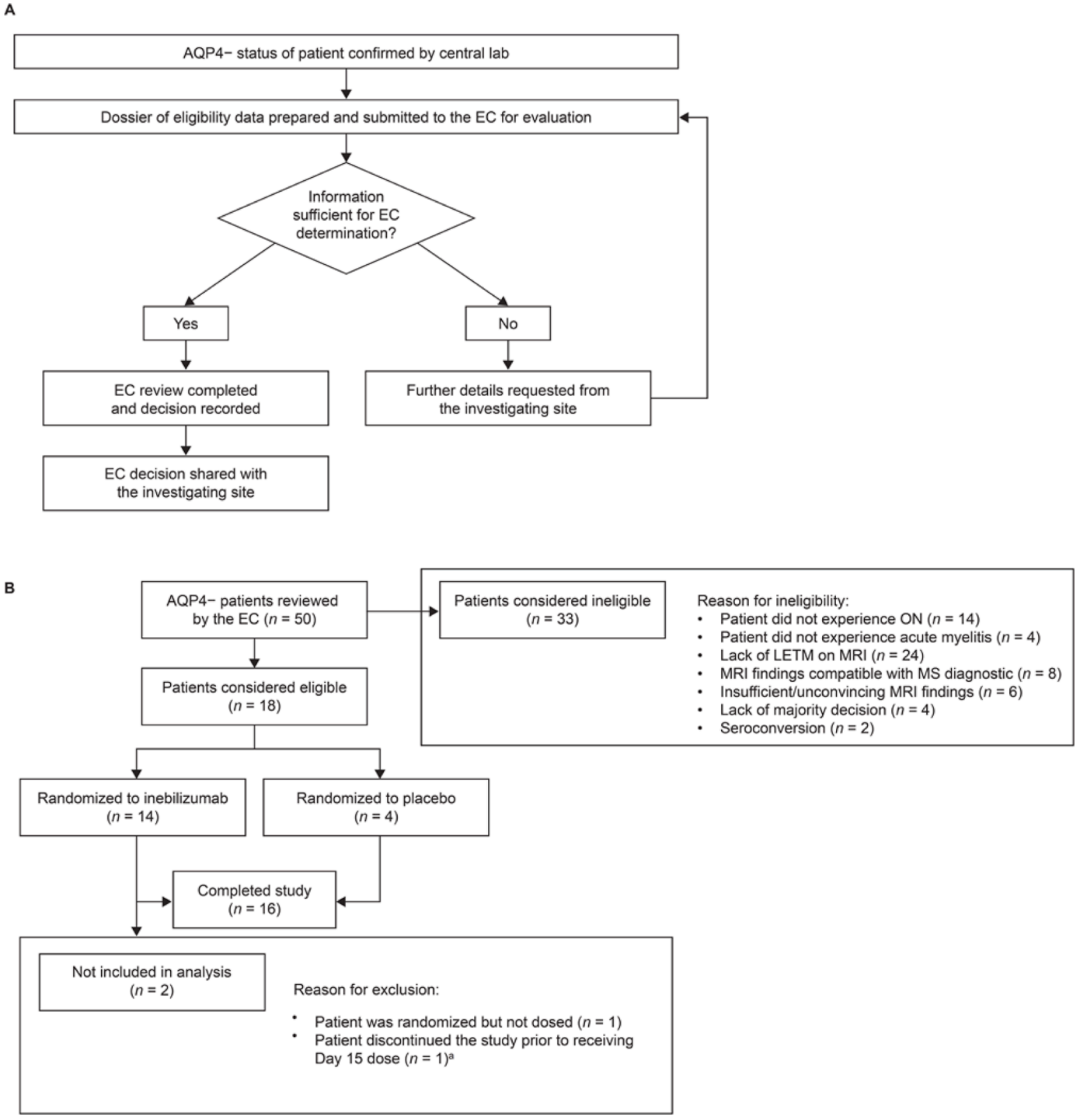


Fig. 1. A) AQP4− participant eligibility and B) participant flowchart.
AQP4, aquaporin-4; AQP4−, AQP4-IgG-seronegative; EC, eligibility committee; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; ON, optic neuritis. [a]One participant discontinued from further involvement in the study owing to an error in determining serostatus. The participant reported a negative AQP4-IgG test at screening, following historical positive tests for AQP4-IgG serostatus. As a result, the EC requested a retest of AQP4-IgG serostatus, which was initially reported as positive. On this basis, the participant was randomized to receive inebilizumab. The retest result was subsequently revised to negative. Owing to the revised result, the participant no longer fulfilled the 2006 diagnostic criteria and was discontinued from the study before receiving the day 15 inebilizumab dose.

Table 2
Demographics and baseline characteristics (ITT population).

Criteria	AQP4+ $N = 213$	AQP4− $N = 17$[a]	AQP4−placebo $N = 4$	AQP4−inebilizumab $N = 13$[a]
Age, years				
Mean (SD)	43.0 (12.3)	41.7 (10.6)	44.8 (7.7)	40.8 (11.4)
Sex				
Female	200 (93.9%)	9 (52.9%)	1 (25.0%)	8 (61.5%)
Male	13 (6.1%)	8 (47.1%)	3 (75.0%)	5 (38.5%)
Race[b]				
White	110 (51.6%)	10 (58.8%)	4 (100.0%)	6 (46.2%)
Asian	45 (21.1%)	2 (11.8%)	0 (0.0%)	2 (15.4%)
American Indian or Alaskan Native	16 (7.5%)	3 (17.6%)	0 (0.0%)	3 (23.1%)
Black or African American	19 (8.9%)	1 (5.9%)	0 (0.0%)	1 (7.7%)
Other	23 (10.8%)[c]	1 (5.9%)	0 (0.0%)	1 (7.7%)
Ethnicity				
Hispanic or Latino	40 (18.8%)	3 (17.6%)	0 (0.0%)	3 (23.1%)
Disease duration, years				
Mean (SD)	2.59 (3.42)	1.23 (1.43)	0.78 (0.66)	1.37 (1.59)
Median (range)	1.13 (0.1–22.2)	0.87 (0.2–5.5)	0.57 (0.3–1.7)	0.91 (0.2–5.5)
Time since first relapse, years				
Mean (SD)	5.19 (5.84)	3.44 (3.99)	0.87 (0.51)	4.23 (4.27)
Median (range)	3.01 (0.2–27.4)	1.60 (0.3–14.6)	0.71 (0.5–1.6)	3.15 (0.3–14.6)
Type of most recent attack[d]				
Myelitis	126 (59.2%)	7 (41.2%)	2 (50.0%)	5 (38.5%)
Optic neuritis	96 (45.1%)	10 (58.8%)	2 (50.0%)	8 (61.5%)
Brain or brain stem	14 (6.6%)	4 (23.5%)	2 (50.0%)	2 (15.4%)
Gadolinium-enhancing lesions				
Mean (SD)	1.1 (1.1)	0.6 (0.9)	1.0 (1.4)	0.5 (0.8)
Median (range)	1.0 (0–5)	0.0 (0–3)	0.5 (0–3)	0.0 (0–2)
EDSS score				
Mean (SD)	3.9 (1.8)	3.4 (2.2)	2.13 (0.85)	3.85 (2.3)
Median (range)	3.5 (0–8)	3.5 (0–7.5)	2.25 (1–3)	4 (0–7.5)

AQP4, aquaporin-4; AQP4−, AQP4-IgG-seronegative; AQP4+, AQP4-IgG-seropositive; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; ITT, intent-to-treat; SD, standard deviation.
Data are n (%) unless otherwise stated.
[a] One participant was declassified before the second dose owing to a change in serostatus results.
[b] Each race category counts participants who selected only that category. Race was self-reported by participants; 'other' indicates the participant did not identify with the categories presented; multiple categories checked counts participants who selected more than one race category.
[c] Includes one participant who selected multiple categories.
[d] Most recent attack can include more than one domain.

Table 3
Anti-MOG antibody titers in AQP4−/ MOG+ participants.

Participant identifier	Treatment arm	Anti-MOG antibody titer (screening)	Last RCP draw	MOG titers (last RCP draw)	Last draw in study	MOG titers (last draw)
20,027,850,003	Inebilizumab	1:320	D197 RCP	1:320	D197 RCP	1:320
20,031,420,012	Inebilizumab	1:320	D197 RCP	1:160	D29 RCP	1:160
20,005,150,001	Inebilizumab	1:160	D85 RCP	1:160	Attack assessment D1206 OLP	1:80
20,005,930,005	Inebilizumab	1:40	D197 RCP	1:20	D183 OLP	1:20
20,006,180,010	Inebilizumab	1:20	D197 RCP	Negative	D92 OLP	Negative
20,006,200,003	Inebilizumab	1:160	None	None	W104 OLP	1:40
20,005,850,001	Placebo	1:20	D197 RCP	Negative	W104 OLP	Negative

AQP4, aquaporin-4; AQP4−, AQP4-IgG-seronegative; D, day; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MOG+, MOG-IgG-seropositive; OLP, open-label period, RCP, randomized controlled period; W, week.

3.2. MOG-IgG titers

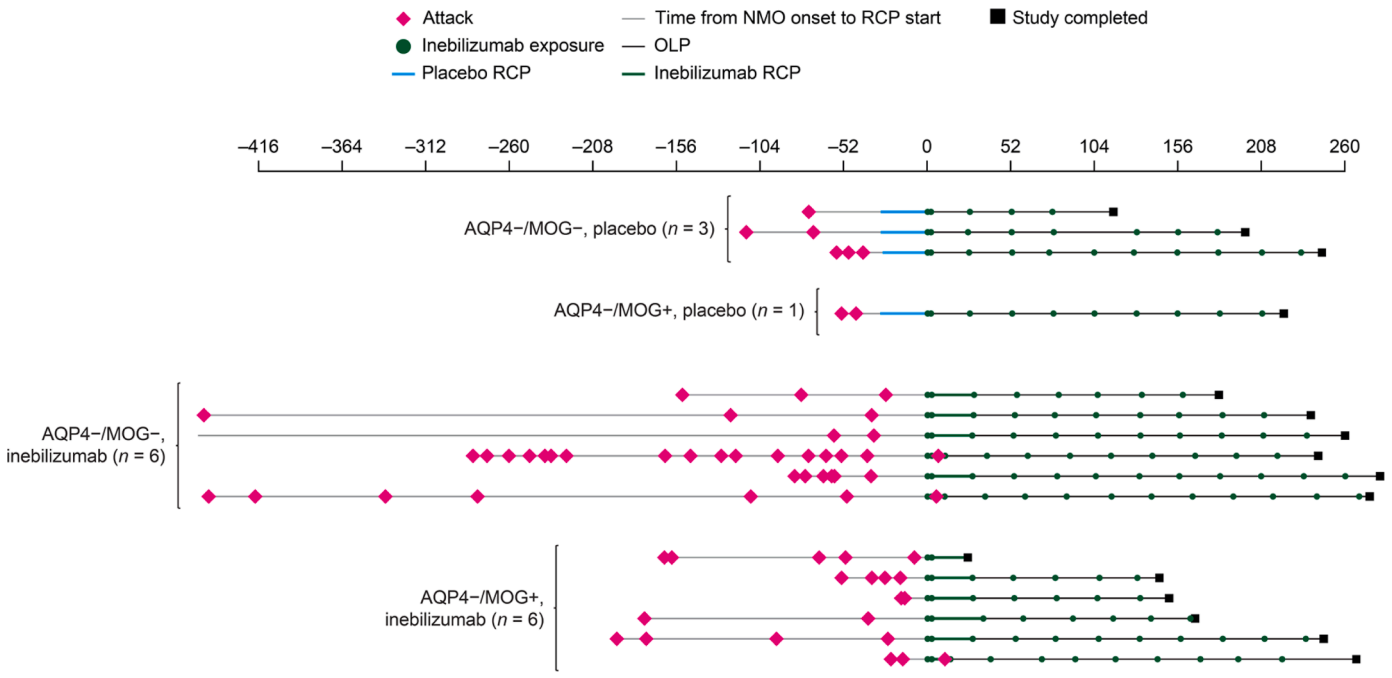
For the six inebilizumab-treated participants who were AQP4−/ MOG+ at screening, MOG-IgG titers ranged from 1:20 to 1:320 (Table 3). MOG-IgG titers decreased in four of these six participants by day 197 of the RCP. A fifth participant did not have a reduction in MOG-IgG titers during the RCP but showed a twofold reduction at the last sample draw at day 1206 of the OLP. The AQP4−/MOG+ placebo-treated participant was persistently negative for MOG-IgG titers in all RCP draws following screening. Sample draws from this participant continued to be negative for MOG-IgG titers after initiation of inebilizumab treatment in the OLP (Table 3).

None of the seven participants who were AQP4−/MOG+ at screening tested positive for anti-AQP4 antibody titers in any sample drawn during the study. None of the AQP4−/MOG− participants at screening tested positive for either autoantibody throughout the study.

3.3. AARs

In the AQP4− group, 3/12 inebilizumab-treated participants (25.0%) had an adjudication committee-determined NMOSD attack during the RCP; none of the four AQP4− participants receiving placebo had an attack in the RCP and no further attacks were seen in the OLP, including among those who received placebo in the RCP (Fig. 2**A**). The three attacks seen during the RCP happened during the first treatment window and were minor (participant 1: minor ON and myelitis 78 days after first dose; participant 2: minor myelitis attack 44 days after first dose; participant 3: minor ON attack 49 days after first dose). EDSS and

A. Attacks in all AQP4− participants in N-MOmentum, including the pre-study period, the RCP and the OLP.



B. Changes related to attack in AQP4− participants during N-MOmentum.

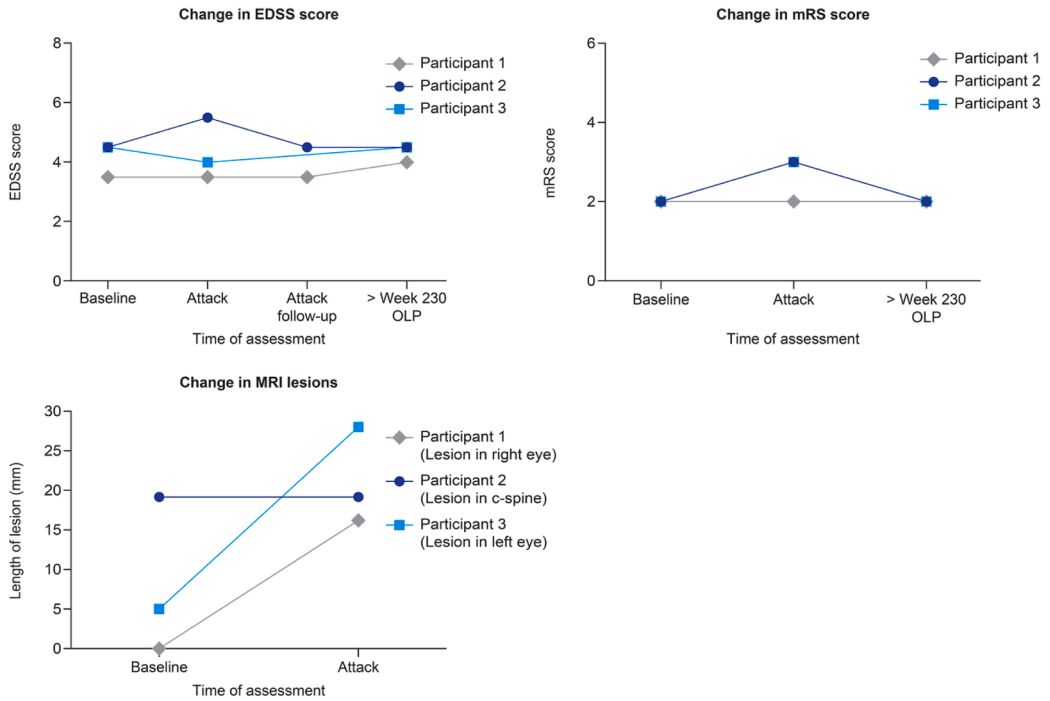


Fig. 2. Summary of attacks in AQP4− participants in N-MOmentum. A) Attacks in all AQP4− participants in N-MOmentum, including the pre-study period, the RCP, and the OLP. B) Changes related to attack in AQP4− participants during N-MOmentum.
AQP4, aquaporin-4; AQP4−, AQP4-IgG-seronegative; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MOG−, MOG-IgG-seronegative; MOG+, MOG-IgG-seropositive; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NMO, neuromyelitis optica; OLP, open-label period; RCP, randomized controlled period.

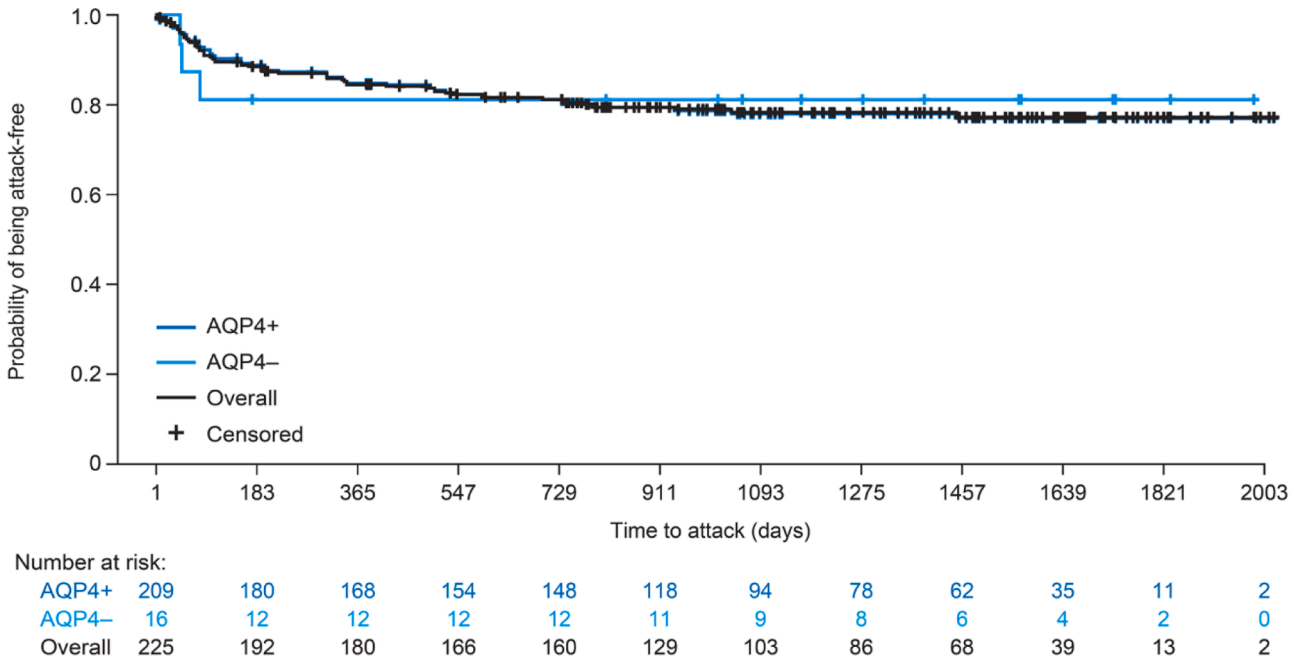


Fig 3. Probability to remain attack-free over time with inebilizumab treatment according to AQP4 serostatus.
AQP4, aquaporin-4; AQP4+, AQP4-IgG-seropositive; AQP4–, AQP4-IgG-seronegative; IgG, immunoglobulin G.

modified Rankin Scale scores generally increased at the time of attack, although scores recovered to near baseline levels in follow-up assessments; 2/3 participants had a new or enlarged MRI lesion at attack assessment (Fig. 2**B**).

The effect of inebilizumab on the probability of remaining attack-free was similar between AQP4– and AQP4+ participants and remained stable with multiple dosing (Fig. 3). Given the low number of participants in the placebo group and the absence of attacks, a hazard ratio could not be calculated for the primary endpoint in the AQP4– population.

The overall mean AAR for all 16 AQP4– participants in the 24 months before first dose was 1.7 (95% confidence interval [CI]: 0.74–2.66; Table 4). For the 7 AQP4–/MOG+ participants, mean pre-study AAR was 1.93 (95% CI: 1.10–3.14); for the 9 AQP4–/MOG– participants, mean pre-study AAR was 1.60 (95% CI: 1.02–2.38). Among AQP4+ participants, mean AAR was 1.35 (95% CI: 1.15–1.54).

Mean AARs were similar for all participant groups with inebilizumab exposure (Table 4). At the end of the OLP, mean AAR for the 16 AQP4– participants was 0.048 (95% CI: 0.015–0.148; 62.8 person-years of exposure), and AARs for the 7 AQP4–/MOG+ and 9 AQP4–/MOG– participants were 0.043 (95% CI: 0.006–0.302; 23.5 person-years of exposure) and 0.051 (95% CI: 0.013–0.204; 39.3 person-years of exposure), respectively. By comparison, the corresponding AAR in the AQP4+ inebilizumab-treated group was 0.097 (95% CI: 0.07–0.136; 667.6 person-years of exposure); in the 52 AQP4+ placebo-treated participants, the pre-study AAR was 1.10 (95% CI: 0.71–1.49) and their on-study AAR during the RCP was 1.11 (95% CI: 0.89–1.36; 24.18 person-years of exposure).

Table 4
AARs in AQP4+ and AQP4– participants.

	AQP4+	AQP4–		
		All	MOG+	MOG–
During the 24 months before first dose of study treatment				
Participants, *n*	214	16	7	9
Mean AAR	1.35	1.70	1.93	1.60
Total person-years	335.56	23.30	8.28	15.02
95% CI	1.15–1.54	0.74–2.66	1.10–3.14	1.02–2.38
With inebilizumab exposure[a]				
Participants, *n*	208	16	7	9
Mean AAR	0.097	0.048	0.043	0.051
Total person-years	667.6	62.8	23.5	39.3
95% CI	0.07–0.136	0.015–0.148	0.006–0.302	0.013–0.204

AAR, annualized attack rate; AQP4, aquaporin-4; AQP4–, AQP4-IgG-seronegative; AQP4+, AQP4-IgG-seropositive; CI, confidence interval; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MOG+, MOG-IgG-seropositive; OLP, open-label period; RCP, randomized controlled period.

[a] Results reported for the 'any inebilizumab' group, consisting of all participants who received inebilizumab, whether in the RCP or the OLP, with day 1 being the day of inebilizumab initiation.

3.4. MRI, disability, and hospitalization outcomes

The effect of inebilizumab treatment on MRI lesion formation, disability outcomes, and the rate of NMOSD-related hospitalization was assessed in AQP4– participants during the RCP. Given the low number of placebo-controlled participants in the AQP4– subgroup, comparisons were also performed versus a combined placebo group comprising AQP4+ and AQP4– participants. For AQP4– participants receiving inebilizumab, the odds of EDSS score worsening from baseline to end of study were lower than those for the combined placebo group (odds ratio [95% CI]: 0.385 [0.076–1.944]) or for the AQP4– placebo group (odds ratio [95% CI]: 1.108 [0.061–20.043]). The number of participants with active MRI lesions in the AQP4– group was lower than that in the combined placebo group (rate ratio [95% CI]: 0.441 [0.173–1.128]) but higher than that in AQP4– placebo group (rate ratio [95% CI]: 0.583 [0.092–3.701]). Changes were nominal and not statistically significant (Table 5). Similar numbers of participants in the combined placebo group and AQP4– inebilizumab group had an NMOSD-related inpatient hospitalization, although the percentage was higher in the AQP4– placebo group (combined placebo: 18 [14.3%]; AQP4– inebilizumab: 2 [15.4%]; AQP4– placebo: 1 [25.0%]; Table 5).

3.5. Pharmacodynamics, pharmacokinetics, and safety

The pharmacodynamics and pharmacokinetics of inebilizumab treatment were assessed in AQP4– and AQP4+ participants during the RCP. B-cell depletions below the lower limit of normal were seen in all AQP4+ and AQP4– participants after 4 weeks of inebilizumab treatment. The pharmacokinetic profile of inebilizumab was similar for

Table 5
Secondary endpoint outcomes.

	Combined placebo groups[a] $n = 56$	AQP4− placebo group $n = 4$	AQP4− inebilizumab group $n = 12$
EDSS score			
Worsening from baseline	19 (33.9%)	1 (25.0%)	2 (16.7%)
Odds ratio combined placebo group vs AQP4− inebilizumab group (95% CI)			0.385 (0.076–1.944)
p value			0.2480
Odds ratio AQP4− placebo group vs AQP4− inebilizumab group (95% CI)			1.108 (0.061–20.043)
p value			0.9448
Cumulative total active MRI lesions			
Participants with MRI lesions, *n* (%)	32 (57.1%)	1 (25.0%)	5 (41.7%)
Mean (SD)	2.3 (1.3)	4	1.4 (0.9)
Rate ratio combined placebo group vs AQP4− inebilizumab group (95% CI)			0.441 (0.173–1.128)
p value			0.0876
Rate ratio AQP4− placebo group vs AQP4− inebilizumab group (95% CI)			0.583 (0.092–3.701)
p value			0.5675
NMO/NMOSD-related inpatient hospitalizations			
Participants with hospitalization, *n* (%)	8 (14.3%)	1 (25.0%)	2 (15.4%)
Mean (SD)	1.4 (0.7)	1	1 (0)
Rate ratio Combined placebo group vs AQP4− inebilizumab group (95% CI)			0.8485 (0.144–5.009)
p value			0.8561
Rate ratio AQP4− placebo group vs AQP4− inebilizumab group (95% CI)			0.667 (0.060–7.352)
p value			0.7406

AQP4, aquaporin-4; AQP4−, AQP4-IgG-seronegative; AQP4+, AQP4-IgG-seropositive; CI, confidence interval, EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; SD, standard deviation.
[a] Combined placebo includes data from participants who received placebo from both AQP4+ and AQP4− populations.

AQP4− and AQP4+ participants.

The overall adverse event (AE) profile was similar for the AQP4 subgroups. The proportions of participants in the AQP4+ and AQP4− subgroups who had a TEAE were 92.3% and 100%, respectively, whereas 31.3% of participants in both subgroups had serious AEs (Table 6); however, the low number of participants in the AQP4− group precluded further conclusions. Among the participants who experienced AEs in the AQP4− group, 10 had infections and two had an infusion-related reaction; five participants had serious AEs (eye disorders, $n = 1$; infections and infestations, $n = 2$; injury, poisoning, and procedural complications, $n = 1$; musculoskeletal and connective tissue disorders, $n = 2$; nervous system disorders, $n = 1$). TEAEs reported by at least 10% of participants in the 'any inebilizumab' group are presented in Table 7.

Table 6
Summary of TEAEs in participants with any exposure to inebilizumab in N-MOmentum.

	AQP4+ participants $n = 208$	AQP4− participants[a] $n = 16$
At least one AE	192 (92.3%)	16 (100.0%)
At least one treatment-related AE	82 (39.4%)	7 (43.8%)
At least one SAE[b]	65 (31.3%)	5 (31.3%)
At least one treatment-related SAE[b]	10 (4.8%)	0
Death (grade 5 severity)	3 (1.4%)	0

AE, adverse event; AQP4, aquaporin-4; AQP4+, AQP4-IgG-seropositive; AQP4−, AQP4-IgG-seronegative; OLP, open-label period, RCP, randomized controlled period; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Data are shown as number of participants (%).
[a] Results reported for the 'any inebilizumab' group, consisting of all participants who received inebilizumab, whether in the RCP or the OLP, with day 1 being the day of inebilizumab initiation.
[b] SAE criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the participant's offspring).

Table 7
TEAEs reported by ≥ 10% of participants for the 'any inebilizumab' group in N-MOmentum.

Type of TEAE, annualized rates; *n* (%)	AQP4+ participants $n = 208$	AQP4− participants[a] $n = 16$
Eye disorders	0.05; 32 (15.4%)	0.05; 3 (18.8%)
Gastrointestinal disorders	0.10; 70 (33.7%)	0.13; 8 (50.0%)
General disorders and administration site conditions	0.07; 46 (22.1%)	0.10; 6 (37.5%)
Infections and infestations	0.24; 158 (76.0%)	0.16; 10 (62.5%)
Nasopharyngitis	0.07; 44 (21.2%)	0.05; 3 (18.8%)
Upper respiratory tract infection	0.05; 35 (16.8%)	0
Urinary tract infection	0.08; 56 (26.9%)	0.05; 3 (18.8%)
Injury, poisoning, and procedural complications	0.10; 67 (32.2%)	0.08; 5 (31.3%)
Infusion-related reaction	0.04; 27 (13.0%)	0.03; 2 (12.5%)
Investigations	0.05; 35 (16.8%)	0.03; 2 (12.5%)
Metabolism and nutrition disorders	0.04; 25 (12.0%)	0.02; 1 (6.3%)
Musculoskeletal and connective tissue disorders	0.12; 83 (39.9%)	0.11; 7 (43.8%)
Arthralgia	0.05; 36 (17.3%)	0.05; 3 (18.8%)
Back pain	0.04; 26 (12.5%)	0.08; 5 (31.3%)
Nervous system disorders	0.11; 72 (34.6%)	0.11; 7 (43.8%)
Headache	0.05; 33 (15.9%)	0.02; 1 (6.3%)
Psychiatric disorders	0.05; 34 (16.3%)	0.08; 5 (31.3%)
Renal and urinary disorders	0.04; 25 (12.0%)	0.03; 2 (12.5%)
Respiratory, thoracic, and mediastinal disorders	0.06; 43 (20.7%)	0.02; 1 (6.3%)
Cough	0.03; 20 (9.6%)	0.02; 1 (6.3%)
Skin and subcutaneous tissue disorders	0.08; 56 (26.9%)	0.03; 2 (12.5%)

AQP4, aquaporin-4; AQP4+, AQP4-IgG-seropositive; AQP4−, AQP4-IgG-seronegative; OLP, open-label period, RCP, randomized controlled period; TEAE, treatment-emergent adverse event.
Data are shown as number of participants (%).
[a] Results reported for the 'any inebilizumab' group, consisting of all participants who received inebilizumab, whether in the RCP or the OLP, with day 1 being the day of inebilizumab initiation.

4. Discussion

The adoption of the 2015 international consensus diagnostic criteria for NMOSD highlighted the importance of AQP4-IgG serostatus in NMOSD diagnosis. The identification of the AQP4-IgG marker

demonstrated that AQP4-IgG is involved in the pathogenesis of NMOSD and that it may be predictive of attacks and/or later conversion to multiphasic NMOSD (Jarius et al., 2010; Matiello et al., 2008; Weinshenker et al., 2006). A multicenter study of 175 White patients identified that bilateral ON at onset was more common in AQP4− patients than in AQP4+ patients, as were simultaneous attacks of both ON and myelitis; consequently, AQP4− patients had a shorter time to diagnosis. Furthermore, the disease course was more often monophasic in AQP4− participants (9/38 [23.7%]) than in AQP4+ participants (10/137 [7.3%]) (Jarius et al., 2012).

NMOSD presents as a clinical syndrome composed of pathologically heterogeneous diseases (Cree et al., 2002). Subsets of patients who are not AQP4+ may still meet clinical criteria for the disease by virtue of the simultaneous or sequential presentation of LETM and ON. Despite the use of reliable assays, the presence of confounding and false results cannot be disregarded. False positives can be caused by nonspecific antibody binding: these cases would require additional AQP4-IgG assays to verify serostatus (Fryer et al., 2014). False negative results can be caused by low serum AQP4-IgG levels at the borderline of assay sensitivity, leading to inconclusive results (Prain et al., 2019). Reassuringly, investigation of AQP4-IgG assays reported low false positive rates with high specificity and selectivity in patients with NMOSD (Prain et al., 2019; Waters et al., 2016), with false positives more common in patients with MS (Pittock et al., 2014).

Few AQP4− patients with clinical characteristics of NMOSD have been identified as having detectable serum concentration of antibodies against MOG, a protein expressed on the outer surface of the myelin sheath and oligodendrocytes (Kitley et al., 2012; Mader et al., 2011; Reindl et al., 2020). Multiple clinical, histopathological, and laboratory investigations demonstrated that patients with AQP4−/MOG+ NMOSD have a different underlying pathogenesis from patients with AQP4+ NMOSD (Borisow et al., 2018; Kim et al., 2020; Marignier et al., 2013; Zamvil and Slavin, 2015). It is important to note that, in the present study, one AQP4−/MOG+ participant who was randomized to placebo during the RCP was found to be MOG− in subsequent titers, suggestive of a false positive. There have been rare cases of isolated CSF MOG-IgG seropositivity reported (Mariotto et al., 2019); however, since CSF samples were not routinely collected in N-MOmentum, CSF seropositivity cannot be determined for this case or the other AQP4−/MOG− participants. Before the study, this participant had two successive NMOSD attacks days apart and none thereafter, including during the study. As such, it is possible that this represents a clinically isolated event, potentially indicative of monophasic disease. Although no further conclusions can be drawn regarding this participant, it is a reminder of the potential caveat of studying such low numbers of participants, which may prevent these results from being clinically meaningful.

The N-MOmentum study enrolled both AQP4− and AQP4+ participants to capture the spectrum of this potentially fatal and rare autoimmune disease. It is noteworthy that nearly two-thirds of potential AQP4− participants reviewed by the EC were deemed not eligible for randomization, despite all participants having an existing diagnosis of NMOSD at screening. This finding underscores the ongoing diagnostic dilemma in individuals with NMOSD-like phenotypes and negative AQP4-IgG serology (Jurynczyk et al., 2016). A lack of appropriate information from previous attacks, missing MRI assessments, an inaccurate historical positive AQP4-IgG test or potential seroconversion may explain the high rate of exclusion by the EC. Improved understanding of the pathophysiology and underlying disease mechanisms of AQP4− NMOSD is required (Yeo et al., 2019). Furthermore, some of the historical NMOSD diagnoses in AQP4− patients may be erroneous owing to similarities in presentation to other diseases such as MS, sarcoidosis, infection, and lymphoma (Trebst et al., 2011). The possibility of alternative diagnoses such as these were noted by the EC. Nonetheless, that 24 of 50 seronegative participants did not meet radiographic criteria for LETM underscores the challenges of implementing even seemingly straightforward radiographic criteria.

After N-MOmentum began in early 2014, the diagnostic criteria for NMOSD were revised in 2015 (Wingerchuk et al., 2015), introducing changes to increase the diagnostic sensitivity for AQP4− NMOSD (Bennett, 2016). Using the revised criteria in N-MOmentum may have altered enrollment of AQP4− participants. However, the results of test cases re-reviewed by the EC using the 2015 criteria did not suggest that those originally enrolled would have been ruled out. Furthermore, owing to the increased stringency for AQP4− NMOSD in the 2015 criteria (Wingerchuk et al., 2015), the probability of detecting eligible participants among those ruled out by the 2006 criteria is low. The low rate of seronegative participant eligibility determined by the EC highlights the complexity and ambiguity of NMOSD diagnosis in participants who are AQP4− and underscores the importance of detailed assessment of all available data when a diagnosis of NMOSD is considered in patients with a neurological NMOSD phenotype who are AQP4−. This would be especially true for clinical trials of MOG antibody-associated disease, when the additional complexity of false positive and false negative results for MOG-IgG in addition to AQP4 serostatus would make the role of an expert adjudication committee even more important. Minimizing the rates of misdiagnosis is vital when the rarity of the disease necessitates the design of trials with low participant numbers.

It is speculated that different etiological mechanisms are involved in AQP4− NMOSD. Studies have identified subsets of patients with AQP4− NMOSD who are positive for antibodies against MOG (Kitley et al., 2012; Mader et al., 2011), CV2/CRMP5 (Jarius et al., 2012), and glial fibrillary acidic protein (GFAP) (Yang et al., 2018). Because inebilizumab depletes a broad range of B cells, including plasmablasts/plasma cells, hypothetically it could favorably modulate B-cell functions (such as autoantibody production, cytokine secretion, and antigen presentation) in these disorders, similar to how it does in AQP4+ disease. Although variable levels of efficacy at depleting B cells have been reported with rituximab treatment in AQP4+ and AQP4− patients (Cobo-Calvo et al., 2019; Durozard et al., 2020; Whittam et al., 2020), treatment was found to be uniformly effective, suggesting that serostatus should not influence choice of treatment (Mealy et al., 2018).

This present analysis is limited by the low number of AQP4− participants. With 16 participants randomized in total, only four AQP4− participants were randomized to placebo (owing to the 3:1 inebilizumab:placebo randomization ratio), none of whom had an attack during the RCP; thus, direct interpretation of between-group differences was not possible. Of note, as recently reported, the attacks experienced by the three inebilizumab-treated AQP4− participants were not associated with increases in serum GFAP levels (Aktas et al., 2021), suggesting targets other than astrocytes. In addition, attacks recorded in medical histories were not adjudicated in the same way as on-study attacks. Regression to the mean in the small number of participants could influence the AAR calculations, especially because the inclusion criteria selected individuals who had recently experienced attacks before enrollment. Some patients with AQP4− NMOSD (including MOG+ patients) have a monophasic illness (Jarius et al., 2012), and inclusion of such participants in this study would have confounded the on-study AAR.

Data on participants with AQP4− NMOSD from randomized studies are rare and of clinical interest. In the present analyses, comparison of AARs in the recorded period before inebilizumab treatment with AARs during the 62.8 person-years of inebilizumab exposure for the AQP4− group suggests that AQP4− participants may benefit from inebilizumab treatment. Furthermore, the reduction of AARs in the AQP4− group is similar to that for AQP4+ participants. Further studies are needed to confirm these results. Inebilizumab appeared to be well tolerated in AQP4− participants with NMOSD, and treatment resulted in the anticipated ablation of B-cell counts.

The current analysis is one of few to date reporting findings for AQP4− participants from a phase 3 clinical trial. In two recent randomized, placebo-controlled, phase 3 trials of satralizumab therapy in NMOSD, AQP4− participants constituted approximately one-third of the

study population, with 28 and 31 AQP4− participants included in the add-on (to immunosuppressant treatment) and monotherapy studies, respectively (Traboulsee et al., 2020; Yamamura et al., 2019). However, neither study involved the use of a separate, independent committee to confirm the NMOSD diagnoses for AQP4− participants. In both studies, evidence was lacking for a beneficial effect of satralizumab therapy on the risk of attacks for the AQP4− subgroup, although risk reductions were observed for AQP4+ participants (Traboulsee et al., 2020; Yamamura et al., 2019). The three most recent approvals of NMOSD therapies by the US Food and Drug Administration have been for the treatment of AQP4+ patients (Alexion Pharmaceuticals, 2019; Genentech, 2020; VielaBio, 2020); thus, an unmet need remains for treatment of AQP4− patients.

5. Conclusion

This study highlights some of the core challenges in diagnosing AQP4− NMOSD and treating patients with this diagnosis, and provides limited data on the effects of B-cell depletion with inebilizumab in these participants. This study also shows that thorough review of medical data from such patients can minimize misdiagnosis. In future NMOSD clinical trials of seronegative participants, the use of an independent EC using defined NMOSD diagnostic criteria may increase the accuracy of disease diagnosis and better define the participant population. Despite the low number of AQP4− participants randomized and the lack of attacks in the placebo group during the RCP, longer-term assessment of AARs with open-label inebilizumab appears to suggest a treatment effect. By implementing consistent processes for determining the eligibility of patients, the N-MOmentum study provides reliable, important information on the natural history of NMOSD, the challenges of accurate diagnosis, and the response to B-cell depletion with inebilizumab in AQP4− patients.

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Declaration of Competing Interest

Romain Marignier serves on scientific advisory boards for MedImmune and Viela Bio/Horizon Therapeutics; and has received funding for travel and fees from Alexion Pharmaceuticals, Biogen, Merck, Novartis, Roche, and Viela Bio/Horizon Therapeutics. **Sean J. Pittock** reports grants, personal fees, and nonfinancial support from Alexion Pharmaceuticals; grants from Autoimmune Encephalitis Alliance and Grifols; grants, personal fees, nonfinancial support, and other from MedImmune and Viela Bio/Horizon Therapeutics; consulting support from Astellas; personal fees for consulting services from UCB; personal fees for consulting services from Genentech/Roche; and has a patent # 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 Autoantibody positive". **Friedemann Paul** has received research support, speaker fees and travel reimbursement from Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, and Teva; is supported by the German Competence Network for Multiple Sclerosis and the German Research Council (DFG Exc 257); received travel reimbursement from Guthy–Jackson Charitable Foundation; and serves on the steering committee of the OCTI*MS* study sponsored by Novartis. **Ho Jin Kim** has received a grant from the National Research Foundation of Korea; consultancy/speaker fees or research support from Alexion Pharmaceuticals, AprilBio, Celltrion, Daewoong Pharmaceutical, Eisai, GC Pharma, HanAll BioPharma, MDimune, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva Handok, UCB, and Viela Bio/Horizon Therapeutics; serves on a steering committee for MedImmune/Viela Bio/Horizon Therapeutics; and is a coeditor for the *Multiple Sclerosis Journal* and an associated editor for the *Journal of Clinical Neurology*. **Jeffrey L. Bennett** reports payment for study design/consultation from MedImmune/Viela Bio/Horizon Therapeutics; personal fees from AbbVie, Alexion Pharmaceuticals, Chugai, Clene Nanomedicine, Genentech, Genzyme, Mitsubishi Tanabe Pharma, Reistone Biopharma, and Roche; grants and personal fees from Novartis, Mallinckrodt, and the National Institutes of Health; and has a patent for Aquaporumab issued. **Brian G. Weinshenker** receives payments for serving as chair of attack adjudication committees for clinical trials in NMOSD for Alexion Pharmaceuticals, MedImmune, UCB Biosciences and Viela Bio/Horizon Therapeutics; has consulted with Chugai, Genentech, Mitsubishi Tanabe Pharma, and Roche Pharmaceuticals regarding clinical trial design for NMOSD; and has a patent for NMO-IgG for diagnosis of neuromyelitis optica, with royalties paid by Hospices Civils de Lyon, MVZ Labor PD Dr. Volkmann und Kollegen GbR, RSR, and the University of Oxford. **Dean M. Wingerchuk** reports personal fees from Arcus Medica, Biogen, Celgene, Genentech, MedImmune, Novartis, Reistone Biopharma, TG Therapeutics, and Third Rock Ventures; research support paid to Mayo Clinic by Alexion Pharmaceuticals and Terumo BCT; and serves on a clinical trial adjudication committee for MedImmune and Viela Bio/Horizon Therapeutics. **Ari J. Green** reports grants from Conrad N. Hilton Foundation and Tom Sherak MS Hope Foundation; other financial relationships (for activities as expert witness, associate editor, advisory board/steering committee participation, and endpoint adjudication) with Bionure, Inception Sciences, *JAMA Neurology*, MedImmune/Viela Bio/Horizon Therapeutics, Mylan, Synthon, and Trims Pharma; and personal fees from and other financial relationships with Pipeline Therapeutics. **Kazuo Fujihara** serves on scientific advisory boards for Alexion Pharmaceuticals, Bayer Schering, Biogen Idec, Chugai, MedImmune, Merck Serono, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Novartis, Ono Pharmaceutical, and

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Supplementary materials

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