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

Sean J. Pittock,[1] Friedemann Paul,[2] Romain Marignier,[3] Ho Jin Kim,[4] Jeffrey L. Bennett,[5] Brian G. Weinshenker,[1] Dean Wingerchuk,[6] Ari J. Green,[7,8] Kazuo Fujihara,[9] Gary Cutter,[10] Orhan Aktas,[11] Hans-Peter Hartung,[11] Jorn Drappa,[12] John N. Ratchford,[12] Dewei She,[12] Daniel Cimbora,[12] Eliezer Katz,[12] and Bruce A.C. Cree,[7] on behalf of the N-MOmentum study investigators

[1]Mayo Clinic, Rochester, MN, USA; [2]Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, Berlin, Germany; [3]Centre de Référence des Maladies Inflammatoires Rares du Cerveau et de la Moelle (MIRCEM), Service de Neurologie, Sclérose en Plaques, Pathologies de la Myéline et Neuro-inflammation – Hôpital Neurologique Pierre Wertheimer Hospices Civils de Lyon, Lyon, France; [4]Research Institute and Hospital of National Cancer Center, Goyang, Republic of Korea; [5]University of Colorado, School of Medicine, Anschutz Medical Campus, Aurora, CO, USA; [6]Mayo Clinic, Scottsdale, AZ, USA; [7]UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, CA, USA; [8]UCSF Weill Institute for Neurosciences, Department of Ophthalmology, University of California San Francisco, San Francisco, CA, USA; [9]Department of Multiple Sclerosis Therapeutics, Fukushima Medical University and Multiple Sclerosis and Neuromyelitis Optica Center, Southern Tohoku Research Institute for Neuroscience, Koriyama, Japan; [10]University of Alabama at Birmingham, Birmingham, AL, USA; [11]Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [12]Viela Bio, Gaithersburg, MD, USA.

Disclosures

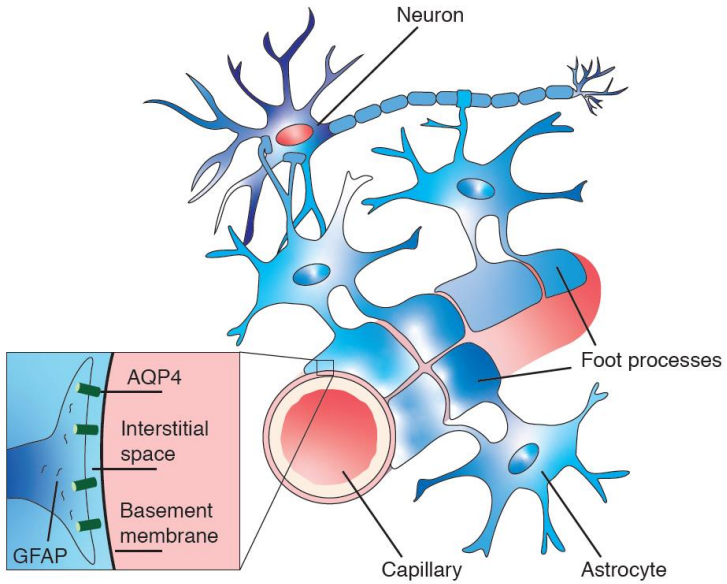
- **S.J. Pittock** reports consulting fees and/or research support paid to the institution from Alexion, Autoimmune Encephalitis Alliance, Euroimmun, Grifols, the Guthy–Jackson Charitable Foundation, MedImmune/Viela Bio and NIH RO1 NS065829-01; and is a named inventor on filed patents that relate to functional AQP4/neuromyelitis optica-IgG assays and neuromyelitis optica-IgG as a cancer marker.

- **F. 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); has received travel reimbursement from Guthy–Jackson Charitable Foundation; and serves on the steering committee of the OCTIMS study sponsored by Novartis.
- **R. Marignier** serves on scientific advisory boards for MedImmune and Viela Bio; and has received funding for travel and fees from Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva and Viela Bio.
- **H.J. Kim** reports personal fees from Alexion, Aprilbio, Celltrion, Eisai, HanAll BioPharma, Merck Serono, Novartis, Sanofi Genzyme, Teva-Handok and Viela Bio; grants from the National Research Foundation of Korea; and other financial relationships (associate editor/co-editor) with the Journal of Clinical Neurology and the Multiple Sclerosis Journal.
- **J.L. Bennett** reports payment for study design/consultation from MedImmune/Viela Bio; personal fees from AbbVie, Alexion, Chugai, Clene Nanomedicine, Equillium, Frequency Therapeutics, Genentech, Mitsubishi Tanabe, Reistone-Bio and Roche; grants and personal fees from Novartis; grants from the Guthy–Jackson Charitable Foundation, Mallinckrodt and the National Institutes of Health; and has a patent for Aquaporumab issued.
- **B.G. Weinshenker** receives payments for serving as chair of attack adjudication committees for clinical trials in NMOSD for Alexion, MedImmune and Viela Bio; has consulted with Mitsubishi Tanabe Pharma regarding clinical trial design for NMOSD; and has a patent neuromyelitis optica-IgG for diagnosis of neuromyelitis optica with royalties paid by Hospices Civils de Lyon, MVZ Labor PD Dr Volkmann und Kollegen GbR, Oxford University and RSR Ltd.
- **D. Wingerchuk** reports personal fees from BrainStorm Therapeutics, Caladrius Biosciences, Celgene, MedImmune, Novartis and Ono Pharmaceutical; research support paid to Mayo Clinic by Alexion Pharmaceuticals, the Guthy–Jackson Charitable Foundation and Terumo BCT; serves on a clinical trial adjudication committee for MedImmune and Viela Bio; and has served as a consultant to Chugai Pharmaceutical.
- **A.J. Green** reports grants from the Conrad N. Hilton Foundation and the 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, Mylan, Synthon and Trims Pharma; and personal fees from and other financial relationships with Pipeline Therapeutics.
- **K. Fujihara** serves on scientific advisory boards for Alexion, Biogen Idec, Chugai, MedImmune, Merck Serono, Mitsubishi Tanabe, Novartis and Viela Bio; has received funding for travel and speaker fees from Asahi Kasei Medical, Astellas, Biogen Idec, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Mitsubishi Tanabe, Novartis and Takeda; and research support from the Ministry of Education, Culture, Sports, Science and Technology of Japan.
- **G. Cutter** has received personal fees for participation on Data and Safety Monitoring Boards from AMO Pharma, BioLineRx, Horizon Pharmaceuticals, Merck, Merck/Pfizer, Neurim, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee), OPKO Biologics, Orphazyme, Reata Pharmaceuticals, Receptos/Celgene, Sanofi-Aventis and Teva Pharmaceuticals; personal fees for consulting or advisory board participation from Argenix, Atara Biotherapeutics, Axon, Biogen, Biotherapeutics, Brainstorm Cell Therapeutics, Charleston Laboratories, Inc., Click Therapeutics, Genentech, Genzyme, GW Pharma, Klein Buendel, Inc., MedDay, MedImmune, Novartis, Roche, SciFluor, Somahlution, Teva Pharmaceuticals, TG Therapeutics and UTHealth Houston; a grant from Teva Neuroscience; and is employed by the University of Alabama at Birmingham, AL, USA and President of Pythagoras, Inc.
- **O. Aktas** reports grants from the German Research Foundation (DFG) and the German Ministry of Education and Research (BMBF); grants and personal fees from Bayer HealthCare, Biogen, Genzyme, Novartis, Teva and Viela Bio; and personal fees from Almirall, MedImmune, Merck Serono and Roche.
- **H.-P. Hartung** has received fees for consulting, speaking and serving on steering committees from Bayer Healthcare, Biogen Idec, Celgene Receptos, CSL Behring, GeNeuro, Genzyme, MedDay, MedImmune, Merck Serono, Novartis, **Roche, Sanofi**, TG Therapeutics and Viela Bio with approval from the Rector of Heinrich Heine University Düsseldorf.
- **J. Drappa**, **J.N. Ratchford**, **D. She**, **D. Cimbora** and **E. Katz** are employees of Viela Bio.
- **B.A.C. Cree** reports personal fees for consulting from Akili, Alexion, Atara, Biogen, EMD Serono, Novartis and TG Therapeutics.

- The N-MOmentum study was funded by Viela Bio and MedImmune

Background

- Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease, characterized by recurrent inflammation of the optic nerve, spinal cord, brain or brainstem[1,2]
- An autoantibody against aquaporin-4 (AQP4), a water channel expressed on astrocytes, is detected in up to 90% of patients with NMOSD[3]
  - AQP4-IgG is produced by CD19 positive (CD19+) B-lineage plasmablasts,[4] and the presence of these plasmablasts correlates with disease activity in NMO.[4,5,6]

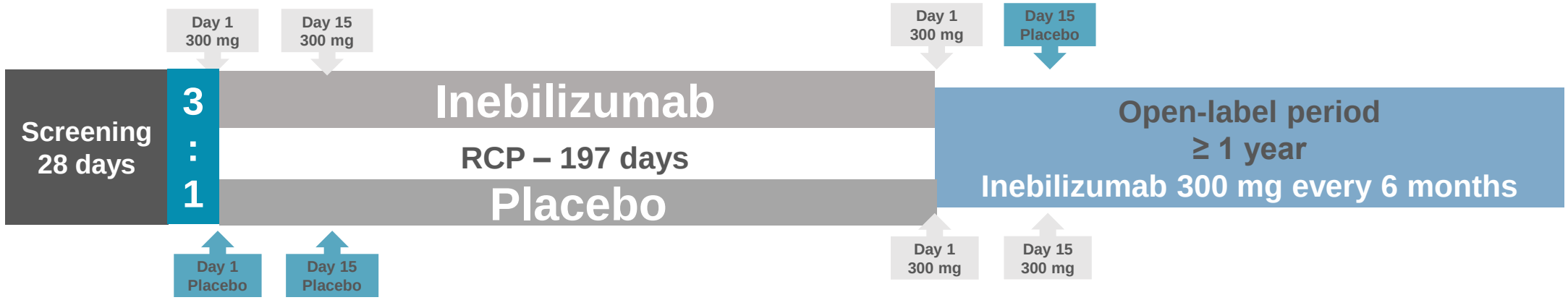


- The remaining patients are AQP4-IgG seronegative; there are relatively few studies in this patient population
  - Recent studies have identified a subset of AQP4-IgG seronegative NMOSD patients who are positive for antibodies against myelin-oligodendrocyte glycoprotein (MOG), a protein expressed on the outer surface of the myelin sheath and oligodendrocytes[7,8]

1. Lucchinetti CF, et al. Brain Pathol 2014;24:83–97. 2. Cree BAC, et al. Mult Scler 2016;22:862–72. 3. Jarius S and Wildemann B. Nat Rev Neurol 2010;6:383–92. 4. Chihara N, et al. Proc Natl Acad Sci USA 2011;108(9):3701–6. 5. Kim W, et al. J Clin Neurol 2011;7(3):115–27. 6. Greenberg BM, et al. Mult Scler 2012;18(7):1022–6. 7. Kitley J, et al. Neurology 2012;79(12):1273–7. 8. Mader, et al. J Neuroinflamm 2011;8:184.

Study design, methods and objectives

- The N-MOmentum study was a randomized, placebo-controlled, double-blind, phase 2/3 trial in 231 patients enrolled from 99 sites around the world[1]
- The study assessed the efficacy and safety of IV inebilizumab, an anti-CD19, B-cell depleting antibody, in patients with NMOSD, including **AQP4-IgG seropositive** and **AQP4-IgG seronegative** patients



- The primary efficacy endpoint of the main study was the time (days) from Day 1 to onset of an AC-determined NMO/NMOSD attack on or before the end of RCP

Objective:	To report AQP4−IgG seronegative patient outcomes in N-MOmentum (post hoc analysis).

1. Cree BAC, et al. Lancet 2019;394:1352–63

Abbreviations: AQP4, aquaporin-4; AC, NMO, neuromyelitis optica; DMC, data monitoring committee; IV, intravenous; NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized-controlled period;

Detailed methods

- Medical histories and screening data for AQP4-IgG seronegative patients were assessed independently by 3 clinical experts before enrollment
  - A majority decision confirmed NMOSD diagnoses using the 2006 criteria:

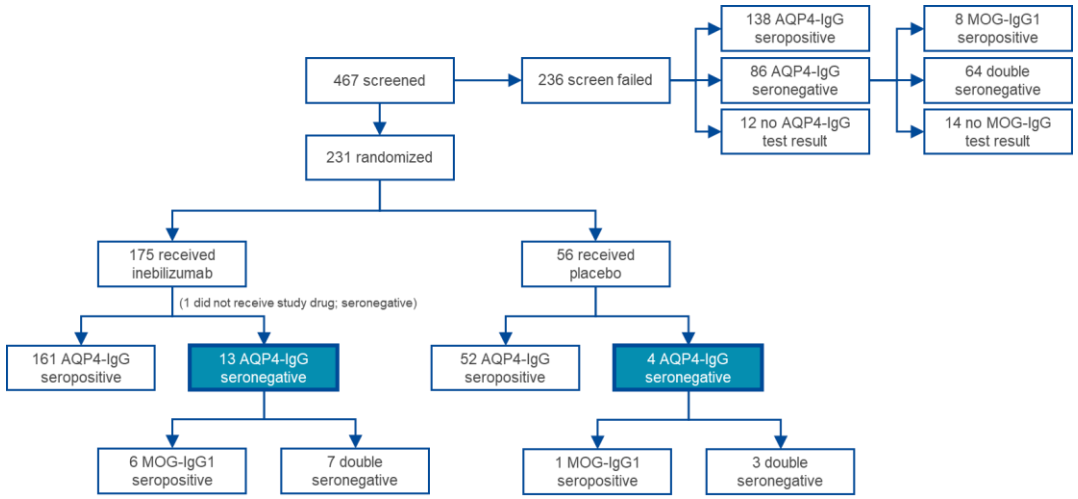
Criteria	Description
1	Optic neuritis
2	Acute myelitis
3	At least 2 of 3 of the following: • Contiguous spinal cord MRI lesion extending over ≥ 3 vertebral segments • Brain MRI not meeting diagnostic criteria for MS • NMO-IgG (AQP4-IgG) seropositive status

- Consistency of treatment effect measured by the primary endpoint was investigated by AQP4-IgG serostatus (positive vs negative) as determined at screening (predefined subgroup analysis)
- MOG-IgG1 serology and AARs were tested ***post hoc***
  - These observations do not account for bias in estimates of effects on the AAR caused by regression to the mean, introduced by inclusion criteria requiring attacks during the 1 to 2 years before study entry

Abbreviations: AARs, annualized attack rates; AC, adjudication committee; AQP4, aquaporin-4; NMO, neuromyelitis optica; DMC, data monitoring committee; IgG, immunoglobulin G; IgG1, immunoglobulin G1; IV, intravenous; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder;

Disposition, demographics and baseline characteristics

- 17 patients(7.4%) who were randomized and received treatment were AQP4-IgG seronegative*
  - 13 inebilizumab (6 MOG-IgG1 seropositive)
  - 4 placebo (1 MOG-IgG1 seropositive)
- 86 prospective AQP4-IgG seronegative patients failed screening by not meeting the 2006 NMOSD diagnosis criteria (primarily due to lacking MRI finding)



- AQP4-IgG seronegative vs. AQP4-IgG seronegative subgroup:
  - Higher proportion of male patients
  - Greater baseline disability based on EDSS

		AQP4-IgG seropositive (n=213)	AQP4-IgG seronegative (n=17)
Age, years	Mean (SD)	43.0 (12.3)	41.7 (10.6)
	Median (range)	43.0 (18-74)	43.0 (22-56)
Sex	Female	200 (93.9%)	9 (52.9%)
	Male	13 (6.1%)	8 (61.5%)
Race	American Indian or Alaskan Native	16 (7.5%)	3 (17.6%)
	Asian	45 (21.1%)	2 (11.8%)
	Black or African American	19 (8.9%)	1 (5.9%)
	White	110 (51.6%)	10 (58.8%)
	Other	22 (10.3%)	1 (5.9%)
	Multiple categories checked	1 (0.5%)	0 (0%)
Ethnicity	Hispanic or Latino	40 (18.8%)	3 (17.6%)
Disease duration, years	Mean (SD)	2.59 (3.42)	1.23 (1.43)
	Median (range)	1.13 (0.1-22.2)	0.87 (0.2-5.5)
Type of most recent attack	Optic neuritis	96 (45.1%)	10 (58.8%)
	Myelitis	126 (59.2%)	7 (41.2%)
	Brain or brainstem	14 (6.6%)	4 (23.5%)
Gadolinium-enhancing lesions	Mean (SD)	1.1 (1.1)	0.6 (0.9)
	Median (range)	1.0 (0-5)	0.0 (0-3)
EDSS score	Mean(SD)	2.9 (2.5)	4.3 (3.1)
	Median (range)	2.0 (1-7)	5.0 (1-7)

*1 patient (AQP4-IgG seronegative) was randomized to inebilizumab but did not receive treatment
Abbreviations: AQP4, aquaporin-4; EDSS, (Kurtzke) Expanded Disability Status Scale; IgG, immunoglobulin G; IgG1, immunoglobulin G1; MOG, myelin oligodendrocyte glycoprotein

Results: NMOSD attacks during the RCP

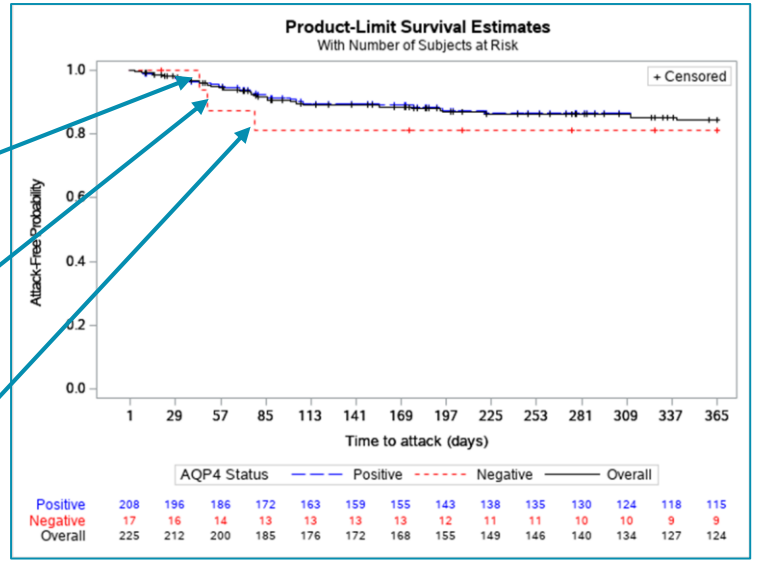
- 3/17 AQP4-IgG seronegative patients had AC-determined NMO/NMOSD attacks during the RCP
- All 3 attacks in AQP4-IgG seronegative patients were in the inebilizumab-treated group and occurred in the first 3 months of the RCP
  - No observed attacks in the remaining 10 inebilizumab-treated or 4 placebo-treated AQP4-IgG seronegative patients through the first 6 months of OLP

	AQP4 Seronegative N = 17	
Primary Endpoint	Placebo N=4	Inebilizumab N=13
# of patients with an AC-determined attack	0	3 (23.1%)

AQP4-/MOG- (Day 43)
Minor OSIS myelitis attack with no new accompanying MRI lesions

AQP4-/MOG- (Day 48)
Minor OSIS ON attack with Gd+ T1 lesion in Optic nerve

AQP4-/MOG+ (Day 77)
Minor OSIS ON attack with Gd+ T1 lesion in Optic nerve)



Abbreviations: AC, adjudication committee; AQP4, aquaporin-4; Gd+, Gadolinium-enhancing; IgG, immunoglobulin G; IgG1, immunoglobulin G1; MOG, myelin oligodendrocyte glycoprotein; NMO/NMOSD, neuromyelitis optica/ neuromyelitis optica spectrum disorder; ON, optic nerve; RCP, randomized-controlled period

Results: Annualized Attack Rates During RCP (Post Hoc Analysis)

- On-study and pre-study AARs for treated patients were compared for treatment effects, due to the limited number of AQP4-IgG seronegative patients who received placebo
- Following inebilizumab treatment, AARs declined in all AQP4-IgG seronegative groups by the end of the RCP
  - Post-inebilizumab AARs for AQP4-IgG seronegative patients were similar to that calculated for AQP4-IgG seropositive patients (0.13; 95% CI: 0.09–0.18)

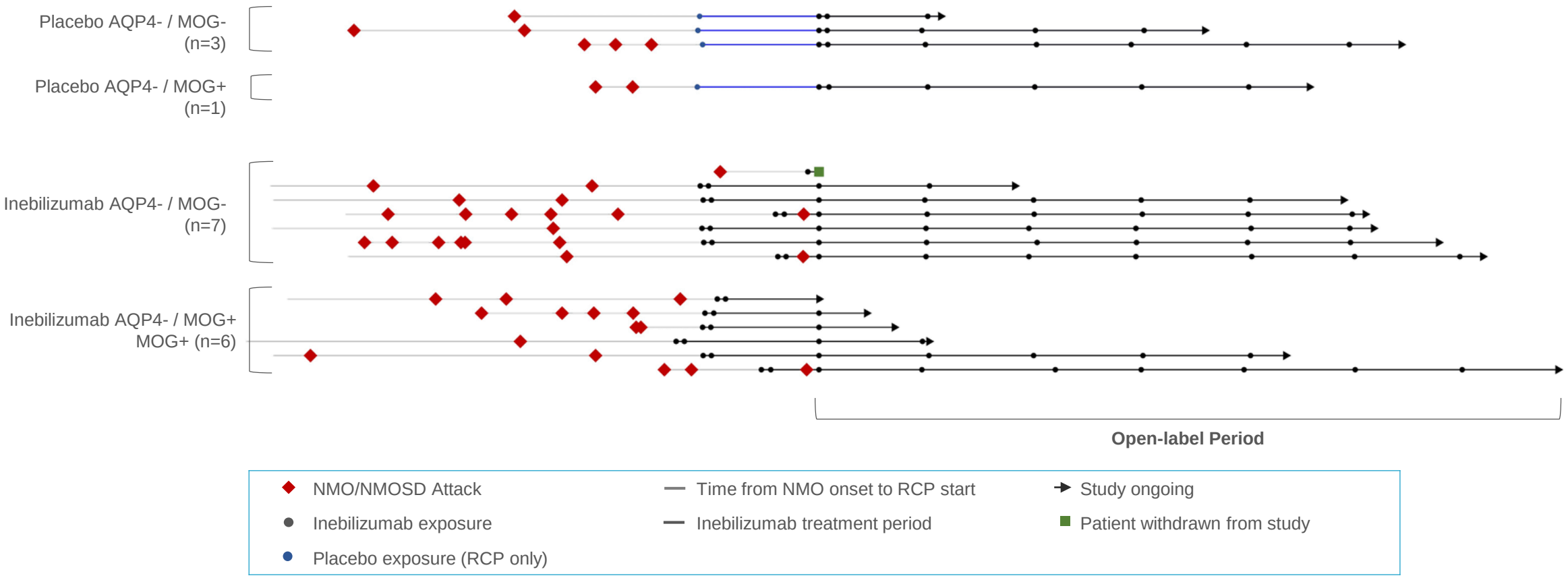
	AQP4-IgG –ve		AQP4-IgG –ve / MOG +ve		AQP4-IgG –ve / MOG –ve	
	Pre-study N=17	Post-inebilizumab N=13	Pre-study N=7	Post inebilizumab N=6	Pre-study N=10	Post inebilizumab N=7
Number of attacks*	40	3	16	1	24	2
Patient years	23	34.2	8.3	12	15	22
AAR (95% CI)	1.72 (1.23–2.33)	0.09 (0.02–0.26)	1.93 (1.11–3.14)	0.08 (0.002–0.464)	1.60 (1.02–2.38)	0.09 (0.011–0.326)

* AC-determined attacks post-inebilizumad

Abbreviations: AQP4, aquaporin-4; CI, confidence interval; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; RCP, randomized-controlled period

Results: Annualized Attack Rates During OLE

- No NMO/NMOSD attacks were seen in any AQP4-IgG seronegative patient during the OLP
- At 120 days into the OLP AAR in AQP4-IgG seronegative patients = 0.069 (95% CI: 0.014-0.202)



Summary

- An AAR of 1.72 (95% CI: 1.23–2.33) was observed during the up to 24-month period prior to the first on-study dosing in the 17 AQP4-IgG seronegative patients who were subsequently treated in the study
- 13 AQP4-IgG seronegative patients received inebilizumab treatment
  - The AAR for the RCP was 0.09 (95% CI: 0.02–0.26) with a similar decline in ARR observed in MOG-IgG1 seropositive and MOG-IgG1 seronegative patients

Conclusions

- **The N-MOmentum trial provides clinically important insight on the difficulty of correctly diagnosing AQP4− NMOSD and suggests that inebilizumab may have a benefit on AAR in these patients.**

Abbreviations: AQP4, aquaporin-4; CI, confidence interval; IgG, immunoglobulin G; IgG1, immunoglobulin G1; MOG, myelin oligodendrocyte glycoprotein; ON, optic nerve; RCP, randomized-controlled period