Quiescent MRI activity in neuromyelitis optica spectrum disorder: results from the N-MOmentum randomized placebo-controlled trial

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

[1]Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Mayo Clinic, Scottsdale, AZ, USA; [3]Mayo Clinic, Rochester, MN, USA; [4]University of Colorado, School of Medicine, Anschutz Medical Campus, Aurora, CO, USA; [5]Research Institute and Hospital of National Cancer Center, Goyang, Republic of Korea; [6]Department of Multiple Sclerosis Therapeutics, Fukushima Medical University and Multiple Sclerosis and Neuromyelitis Optica Center, Southern Tohoku Research Institute for Neuroscience, Koriyama, Japan; [7]University of Alabama at Birmingham, Birmingham, AL, USA; [8]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; [9]Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [10]UCSF Weill Institute for Neurosciences, Department of Neurology and Department of Ophthalmology, University of California San Francisco, San Francisco, CA, USA; [11]Viela Bio, Gaithersburg, MD, USA; 12UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, CA, USA.

Disclosures

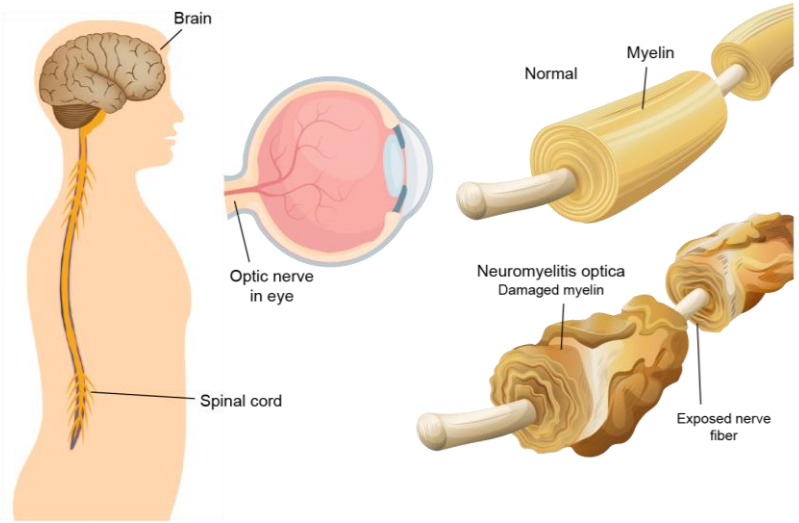
- **F. Paul** has received research support, speaker fees and travel reimbursement from Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme and Teva; is supported by the German Competence Network for Multiple Sclerosis and the German Research Council (DFG Exc 257); has received travel reimbursement from the Guthy–Jackson Charitable Foundation; and serves on the steering committee of the OCTIMS study sponsored by Novartis.

- **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.
- **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; 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, Oxford University and RSR Ltd.
- **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.
- **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*.
- **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.
- **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 honoraria 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; is employed by the University of Alabama at Birmingham, AL, USA and President of Pythagoras, Inc.
- **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.
- **O. Aktas** reports grants from the German Ministry of Education and Research (BMBF) and the German Research Foundation (DFG); 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.
- **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.
- **J. Drappa**, **M. A. Smith, W.A. Rees, J.N. Ratchford, D. She**, **D. Cimbora, D. Stefani-Hunyady** 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.

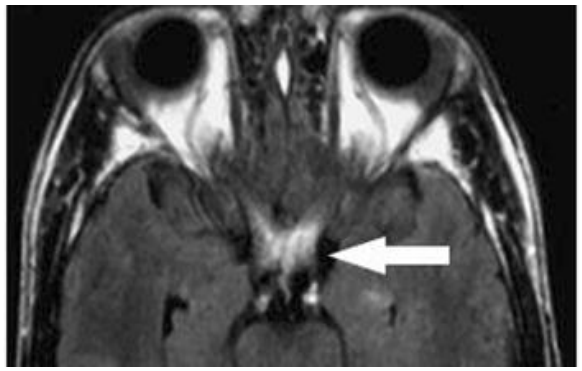
- The N-MOmentum study was funded by Viela Bio and MedImmune

Background

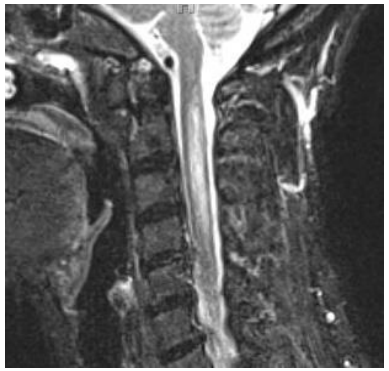
- Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease, characterized by recurrent inflammation of the optic nerve (optic neuritis), spinal cord (transverse myelitis), brain or brainstem.[1]
- Magnetic resonance imaging (MRI) can be used to both aid in the diagnosis of NMOSD and the adjudication of attacks.
- Longitudinal magnetic resonance imaging (MRI) findings in patients with NMOSD have not previously been studied with data from a randomized, controlled study with a large number of patients.



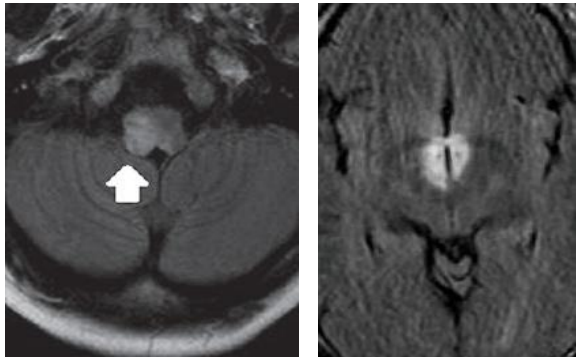
Optic neuritis



Myelitis

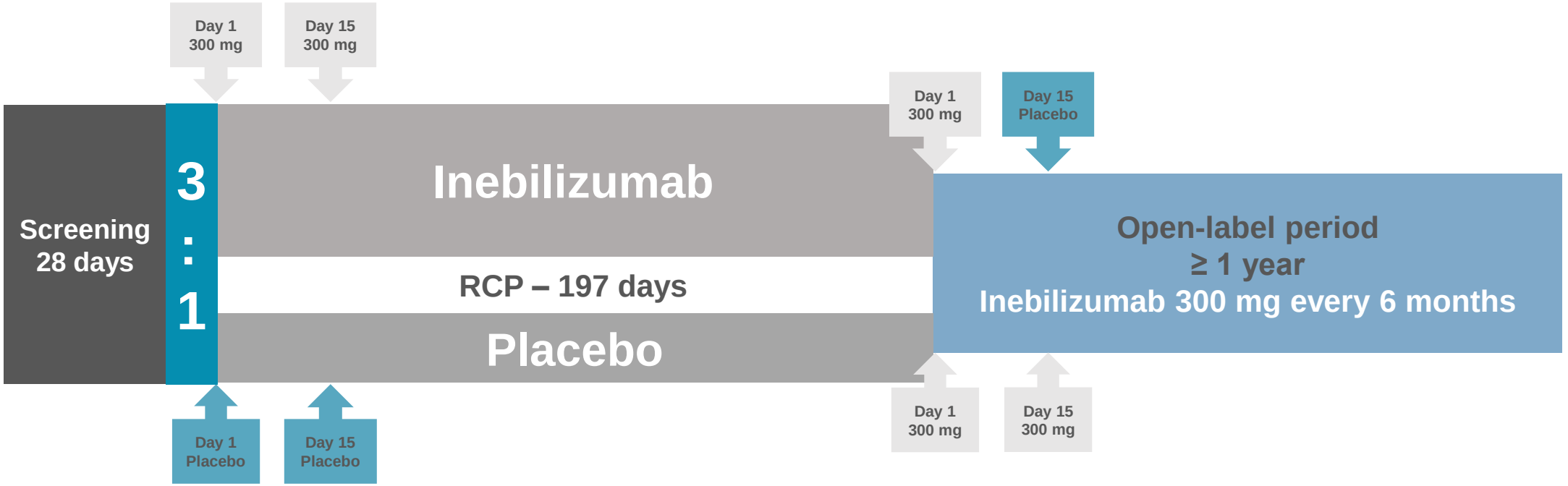


Brain/brainstem



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

Study design



- N-MOmentum is a multicenter, double-blind, randomized, placebo-controlled, phase 2/3 study assessing the efficacy and safety of inebilizumab in patients with NMOSD[1]
  - The trial was designed to be acceptable to patients, physicians, ethics boards and regulatory authorities, with safety a key consideration
  - It included independent assessment of patient eligibility, study oversight and objective adjudication of NMOSD attacks according to predefined criteria

NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period

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

Methods and objectives

- MRI data for the spinal cord, optic nerve and brain were obtained as part of the N-MOmentum trial, at 3 timepoints:
  - Baseline
  - Within 8 days of an NMOSD attack
  - At the end of the RCP (6.5 months after trial start)
- MRIs were read centrally for new Gd-T1 enhancment events
  - MRI read by two independent, treatment-blinded neuroradiologists
- NMOSD attacks were adjudicated by an expert committee

Objective:	To characterize MRI findings in patients with NMOSD in the N-MOmentum study of inebilizumab.

Gd, gadolinium; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period .

Results: MRI data quality

- Complete MRI data was available for 192 (83%) of 230 participants
  - 42 patients had adjudicated attack data
    - 22 myelitis
    - 14 optic neuritis
    - 6 multi-domain
- 38 (17%) patients did not have valid post-baseline MRI scans available
- Inter-rater agreement between the two neuroradiologists for Gd+ lesions was 98% for brain, 95% for spinal cord and 90% for optic nerve.

Gd, gadolinium; MRI, magnetic resonance imaging;

MRI enhancement during adjudicated NMOSD attack

- New Gd-T1 MRI enhancements corresponding to the affected clinical domain were observed in the majority of attacks

Acute optic neuritis

new Gd-T1 MRI enhancement in 11/14 attacks (79%)

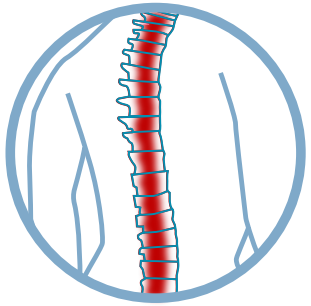
Simultaneous asymptomatic Gd-T1 MRI enhancement

4/14 MRIs (29%)

1/14 MRIs (7%)

Acute myelitis

new Gd-T1 MRI enhancement 19/22 attacks (84%)



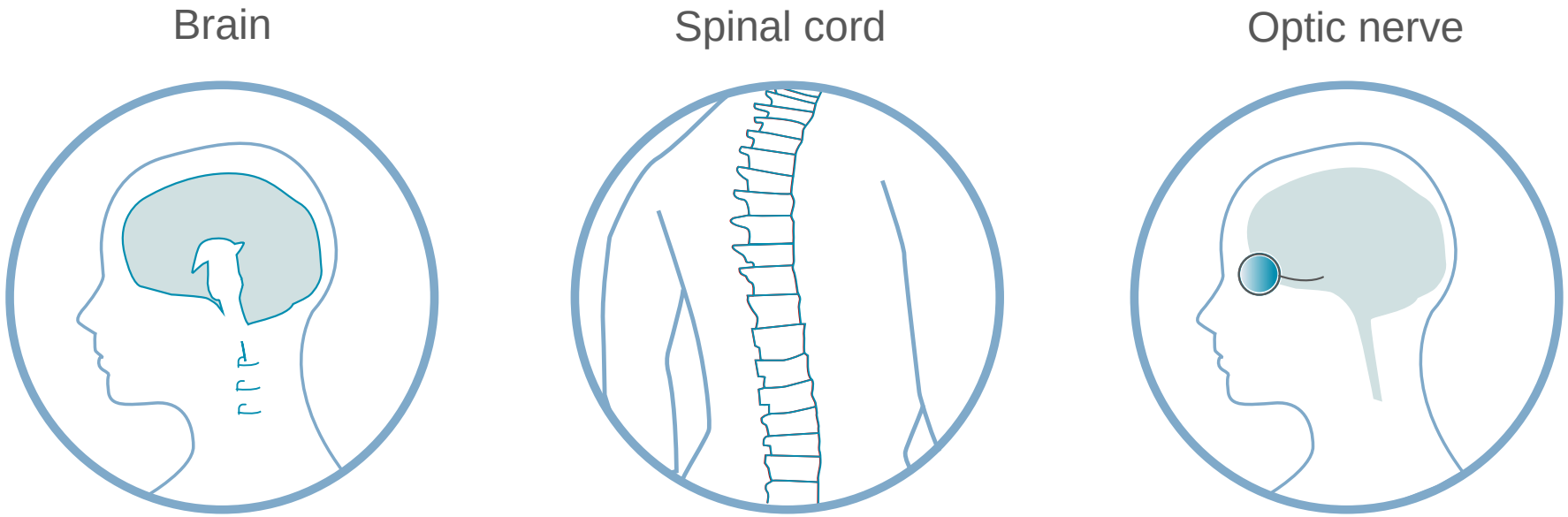
6/22 MRIs (29%)

3/22 MRIs (14%)

Gd, gadolinium; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder

MRI enhancement in absence of adjudicated attacks

- 150 participants had MRI data in absence of an adjudicated attack
- New Gd-T1 MRI enhancements from baseline were observed in brain, spinal cord and optic nerve



% new Gd-T1 MRI enhancement	3%	18%	51%

Gd, gadolinium; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder.

Conclusions

- **MRI enhancements were highly correlated to the clinical presentations at the time of attack**
  - **Asymptomatic Gd-T1 enhancements were detected outside of symptomatic attacks in ~1/3 of cases**
- **Subclinical Gd-T1 enhancements were observed in many patients who did not experience clinically overt attacks**
- **Subclinical blood–brain barrier breakdown, particularly in the optic nerve, may be a frequent phenomenon in patients with active NMOSD.**

Gd, gadolinium; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder.