The N-MOmentum trial of inebilizumab for neuromyelitis optica spectrum disorder: long-term, open-label efficacy and safety update

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Disclosures

B.A.C. Cree reports personal fees for consulting from Akili, Alexion, Autobahn, EMD Serono, Novartis, Sanofi, TG Therapeutics and Therini and grant support from Genentech **J.L. Bennett** reports payment for study design/consultation from MedImmune/Viela Bio; personal fees from AbbVie, Alexion, Chugai, Clene Nanomedicine, Genentech, Genzyme, Mitsubishi-Tanabe, Reistone Bio and Roche; grants and personal fees from EMD Serono and 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 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. **D. Wingerchuk** reports personal fees from Arcus Medica, Biogen, Celgene, Genentech, MedImmune, Novartis, Reistone Biopharma, TG Therapeutics and Third Rock Ventures; research support paid to the Mayo Clinic by Alexion and Terumo BCT; and serves on a clinical trial adjudication committee for MedImmune and Viela Bio. **F. 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Pittock** reports grants, personal fees and non-financial support from Alexion Pharmaceuticals, Inc.; grants from Autoimmune Encephalitis Alliance and Grifols; grants, personal fees, non-financial support and other from MedImmune and Viela Bio; consulting support from Astellas; personal fees for consulting services from UCB; 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”. **K. Fujihara** serves on scientific advisory boards for Alexion, Bayer Schering, Biogen Idec, Chugai, MedImmune, Merck Serono, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Novartis, Ono and Viela Bio; has received funding for travel and speaker fees from Asahi Kasei Medical, Astellas, Bayer Schering, Biogen Idec, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Novartis and Takeda; and research support from Asahi Kasei Medical, Bayer Schering, Biogen Idec, Chemo-Sero-Therapeutic Research Institute, Chugai, Genzyme Japan, the Ministry of Education, Culture, Sports, Science and Technology of Japan, the Ministry of Health, Welfare and Labor of Japan, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Ono, Teijin and Teva. **G.R. 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Background

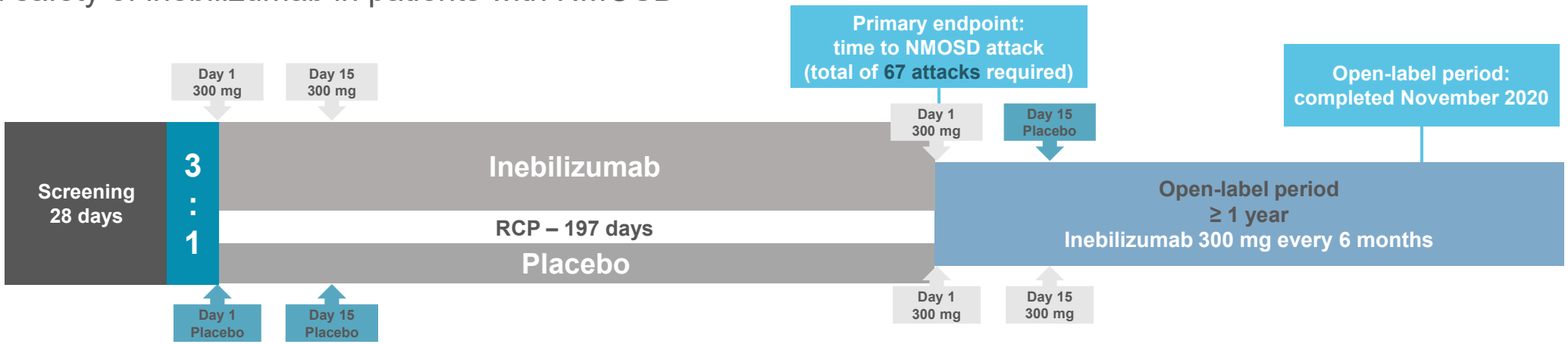
- Inebilizumab, an anti-CD19, B-cell-depleting antibody, has been approved in the USA for aquaporin 4 (AQP4)-immunoglobulin G (IgG) seropositive neuromyelitis optica spectrum disorder (NMOSD), based on the N-MOmentum trial[1]
  - N-MOmentum was the largest randomized placebo-controlled study in NMOSD
  - Only prospective randomized controlled trial (RCT) in NMOSD that conducted full neuroaxis MRI
  - Independent committees adjudicated attack status and study eligibility, and monitored data/safety to ensure the robustness of the study
- Results from the randomized controlled period (RCP) of the trial (up to 197 days after commencing treatment) were reported previously[1]
  - Compared with placebo, inebilizumab reduced the risk of an NMOSD attack
  - Inebilizumab also has significant benefits versus placebo on secondary endpoints, including Expanded Disability Status Scale (EDSS) score worsening from baseline, cumulative total number of active magnetic resonance imaging (MRI) lesions and cumulative number of NMOSD-related inpatient hospitalizations
  - Inebilizumab appeared to be well tolerated during the RCP
- Long-term follow-up is vital to understand fully the durability of efficacy and the safety profile of treatment
- Here, interim data from the open-label period (OLP) are presented, including attack risk and safety outcomes, with up to 4 years of treatment exposure to inebilizumab

AQP4, aquaporin 4, EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder; OLP, open-label period; RCP, randomized controlled period; RCT, randomized controlled trial

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

Study design, methods and objectives

- N-MOmentum was a multicenter, double-blind, randomized, placebo-controlled, phase 2/3 study assessing the efficacy and safety of inebilizumab in patients with NMOSD[1]



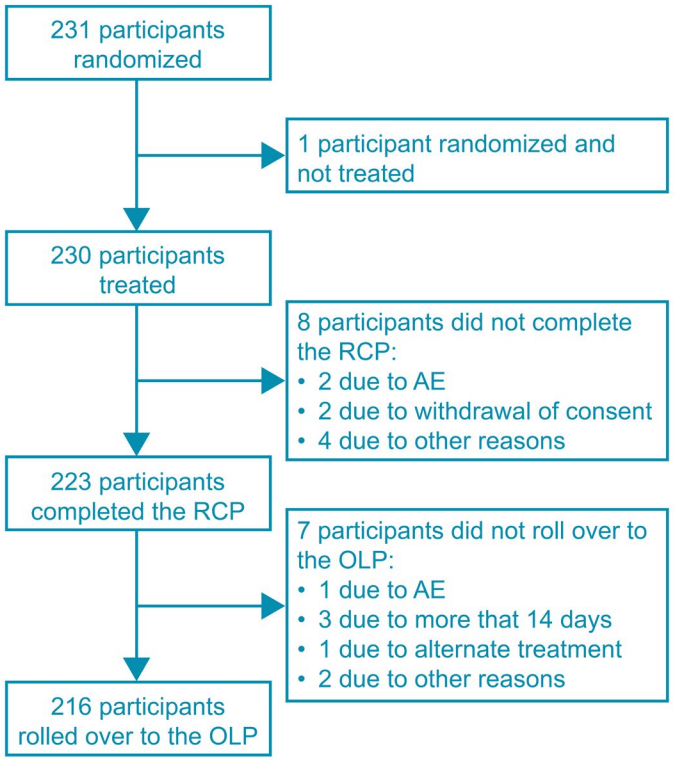
- Following the RCP, patients could enter the OLP for ≥ 2 years
- Patients were grouped for analysis as follows
  - RCP inebilizumab/OLP inebilizumab group: Patients previously receiving inebilizumab before entering the OLP
  - RCP placebo/OLP inebilizumab group: Patients previously receiving placebo before entering the OLP
  - 'Any inebilizumab' group: All patients who received inebilizumab at any time of the study, regardless of when treatment started.

Objective	To report interim efficacy and safety analyses of longer-term inebilizumab treatment in NMOSD

NMOSD, neuromyelitis optica spectrum disorder; OLP, open-label period; Q; quartile;
1. Cree BAC, *et al*. *Lancet* 2019;394:1352–63

Patient disposition and demographics

- Baseline demographics of the RCP and OLP groups remained similar



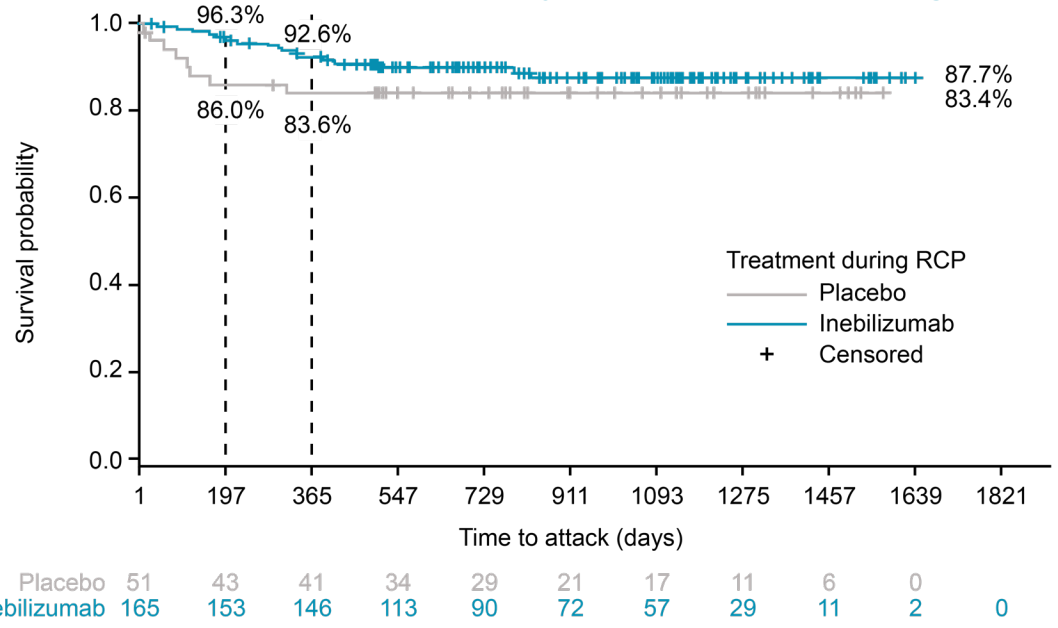
		RCP (N = 230)	OLP (N = 216)
Age, years	Mean (SD)	42.9 (12.2)	42.9 (12.4)
	Median (range)	43.0 (18–74)	43.0 (18–74)
Sex	Women	209 (90.9%)	197 (91.2%)
	Men	21 (9.1%)	19 (8.8%)
Race	American Indian or Alaskan Native	19 (8.3%)	19 (8.8%)
	Asian	47 (20.4%)	45 (20.8%)
	Black or African American	20 (8.7%)	19 (8.8%)
	White	120 (52.2%)	115 (53.2%)
	Other	23 (10.0%)	17 (7.9%)
	Multiple categories checked	1 (0.4%)	1 (0.5%)
Ethnicity	Hispanic or Latino	43 (18.7%)	38 (17.6%)
Disease duration, years	Mean (SD)	2.5 (3.33)	2.5 (3.40)
	Median (range)	1.10 (0.1–22.2)	1.10 (0.1–22.2)
Type of most recent attack	Optic neuritis	106 (46.1%)	98 (45.4%)
	Myelitis	133 (57.8%)	126 (58.3%)
	Brain or brainstem	18 (7.8%)	16 (7.4%)
Gadolinium-enhancing lesions (overall)	Mean (SD)	1.1 (1.1)	1.1 (1.1)
	Median (range)	1 (0–5)	1.0 (0–5)
EDSS score	Mean (SD)	3.90 (1.78)	3.9 (1.75)
	Median (range)	3.5 (0–8)	3.5 (0–8)
Prior NMO/NMOSD medications and/or therapies	Any therapy	227 (98.7%)	213 (98.6%)
	Plasmapheresis	94 (40.9%)	89 (41.2%)
	IVIg	11 (4.8%)	11 (5.1%)
AQP4-IgG serostatus	Seropositive	213 (92.6%)	201 (93.1%)
	Seronegative	17 (7.4%)	15 (6.9%)

AE, adverse event; EDSS, Expanded Disability Status Scale; IVIg, intravenous immunoglobulin; NMO, neuromyelitis optica; NMOSD, NMO spectrum disorder; OLP, open-label period; RCP, randomized controlled period; SD, standard deviation

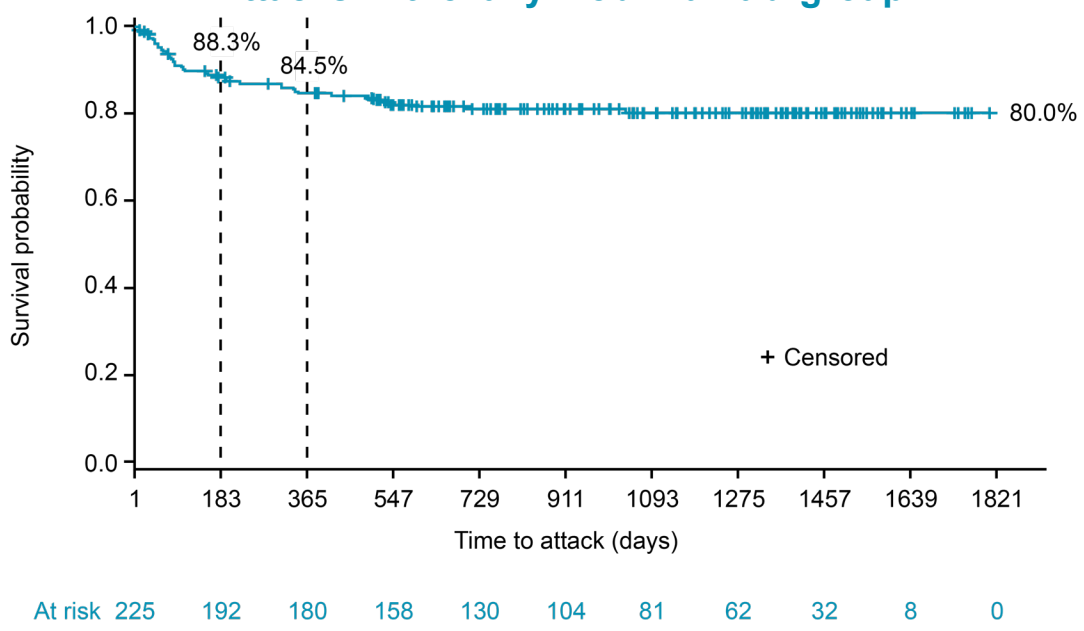
Attack risk during the OLP

- A sustained, long-term effect on attack risk was observed during the OLP
  - Fewer attacks occurred following prolonged treatment exposure. The proportions of participants remaining attack-free were as follows
    - RCP inebilizumab/OLP inebilizumab group: 96.3% at 6 months, 92.6% at 1 year and 87.7% at over 4 years
    - RCP placebo/OLP inebilizumab group: 86.0% at 6 months, 83.6% at 1 year and 83.4% at over 4 years
    - Any inebilizumab group:[a] 88.3% at 6 months, 84.5% at 1 year and 80.0% at over 4 years

Attacks in the OLP: by RCP randomization group



Attacks in the 'any inebilizumab' group[b]



[a]Any inebilizumab group includes all patients who received inebilizumab at any time of the study, regardless of when treatment started; [b]Day 1 represents initiation of inebilizumab treatment, whether in RCP or OLP
OLP, open-label period; RCP, randomized controlled period;

Treatment-emergent adverse events (TEAEs) in the OLP

- TEAE incidences per person-year in the OLP were 2.51 (RI) and 3.05 (RP)
- Infusion-related reactions occurred in 5.5% of RCP inebilizumab/OLP inebilizumab and 13.7% of RCP placebo/OLP inebilizumab participants, compared with 11.6% in the RCP
- Two participants in the OLP died: one from complications of a severe NMOSD attack and the other from a CNS event of unclear etiology

Participants with:[a]	RCP placebo/ OLP inebilizumab (OLP population) N = 51 n (%)	RCP inebilizumab/ OLP inebilizumab (OLP population) N = 165 n (%)	'Any inebilizumab' population[d] N = 225 n (%)
At least one event	45 (88.2%)	140 (84.8%)	207 (92.0%)
At least one investigational product-related event	18 (35.3%)	46 (27.9%)	88 (39.1%)
At least one event of ≥ grade 3 severity[b]	15 (29.4%)	28 (17.0%)	51 (22.7%)
At least one investigational product-related serious[c] event	4 (7.8%)	5 (3.0%)	11 (4.9%)
At least one event leading to discontinuation of investigational product	1 (2.0%)	4 (2.4%)	7 (3.1%)

TEAE by frequency	RCP placebo/ OLP inebilizumab (OLP population) N = 51 n (%); mean (SD) events per p/y	RCP inebilizumab/ OLP inebilizumab (OLP population) N = 165 n (%); mean (SD) events per p/y	'Any inebilizumab' population[d] N = 225 n (%); mean (SD) events per p/y
Urinary tract infection	19 (37.3%); 0.19 (0.15)	29 (17.6%); 0.29 (0.07)	58 (25.8%); 0.58 (0.09)
Nasopharyngitis	9 (17.6%); 0.09 (0.07)	28 (17.0%); 0.28 (0.07)	44 (19.6%); 0.44 (0.0.7)
Arthralgia	8 (15.7%); 0.08 (0.06)	14 (8.5%); 0.14 (0.03)	33 (14.7%); 0.33 (0.05)
Upper respiratory tract infection	6 (11.8%); 0.06 (0.05)	23 (13.9%); 0.23 (0.06)	32 (14.2%); 0.32 (0.05)
Headache	5 (9.8%); 0.05 (0.04)	18 (10.9%); 0.18 (0.04)	32 (14.2%); 0.32 (0.05)
Back pain	6 (11.8%); 0.06 (0.05)	14 (8.5%); 0.14 (0.03)	30 (13.3%); 0.3 (0.05)
Infusion-related reaction	7 (13.7%); 0.07 (0.05)	9 (5.5%); 0.09 (0.02)	28 (12.4%); 0.28 (0.05)
Diarrhea	4 (7.8%); 0.04 (0.03)	9 (5.5%); 0.09 (0.02)	20 (8.9%); 0.2 (0.03)

[a]Participants are counted once for each category regardless of the number of events. [b]Grade 3: severe; grade 4: life-threatening; grade 5: fatal. [c]Serious adverse event 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 offspring of the participant). [d]Any inebilizumab exposure. CNS, central nervous system; NMOSD, neuromyelitis optica spectrum disorder, OLP, open-label period; p/y, person-year; RCP, randomized controlled period; SD, standard deviation; TEAE, treatment-emergent adverse event

Treatment-emergent infections following inebilizumab treatment in the OLP

- The rate of treatment-emergent infections did not increase in the OLP with prolonged inebilizumab treatment
- The rate of serious treatment-emergent infections did not increase in the OLP with prolonged inebilizumab treatment

Treatment-emergent infection events Any inebilizumab exposure: N = 225	TEAEs: Infections	Serious TEAEs: Infections
Overall		
Number of infections	516	40
Total person-years	615	615
Incidence per person-year (95% CI)	0.84 (0.77 – 0.92)	0.07 (0.05 – 0.09)
Year 1		
Number of infections	251	18
Total person-years	217	217
Incidence per person-year (95% CI)	1.16 (1.02 – 1.31)	0.08 (0.05 – 0.13)
Year 2		
Number of infections	130	7
Total person-years	186	186
Incidence per person-year (95% CI)	0.70 (0.58 – 0.83)	0.04 (0.02 – 0.08)
Year 3		
Number of infections	77	3
Total person-years	125	125
Incidence per person-year (95% CI)	0.62 (0.49 – 0.77)	0.02 (0.00 – 0.07)
Year 4		
Number of infections	45	2
Total person-years	72	72
Incidence per person-year (95% CI)	0.62 (0.45 – 0.83)	0.03 (0.00 – 0.10)

CI, confidence interval; OLP, open-label period; TEAE, treatment-emergent adverse event

Effect of immunoglobulin concentrations on infection rate

- No correlations between rates of infections and concentrations of IgG or IgM were observed
  - *p* value from Fisher exact test for IgG: 0.8001
  - *p* value from Fisher exact test for IgM: 0.2159

Worst IgG levels	Participants with Infection		Total N = 230
	Yes n = 170	No n = 60	
Normal (≥ 700 mg/dL)	140 (82.4%)	52 (86.7%)	192 (83.5%)
Mild (500–< 700 mg/dL)	0	0	0
Moderate (300–< 500 mg/dL)	24 (14.1%)	6 (10.0%)	30 (13.0%)
Severe (< 300 mg/dL)	6 (3.5%)	2 (3.3%)	8 (3.48)

Worst IgM levels	Participants with Infection		Total N = 230
	Yes n = 170	No n = 60	
Low (≤ 30 mg/dL)	67 (39.4%)	18 (30.0%)	85 (37.0%)
Normal (> 30 mg/dL)	103 (60.6%)	42 (70.0%)	145 (63.0%)

IgG, immunoglobulin G; IgM, immunoglobulin M

Conclusions

- The reduction of NMOSD attack risk with inebilizumab was sustained in the OLP
- No new safety signals were identified with prolonged inebilizumab treatment and inebilizumab-mediated B-cell depletion
  - Common TEAEs were similar in the RCP and OLP periods
  - Rates of infection or serious infection did not increase with prolonged inebilizumab treatment
  - No correlations between rates of infections and concentrations of IgG or IgM were observed

IgG, immunoglobulin G; IgM, immunoglobulin M; NMOSD, neuromyelitis optica spectrum disorder; OL, open-label period; RCP, randomized controlled period; TEAE, treatment-emergent adverse event