Randomized, double-masked, placebo-controlled trial of inebilizumab in neuromyelitis optica spectrum disorder

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Disclosures

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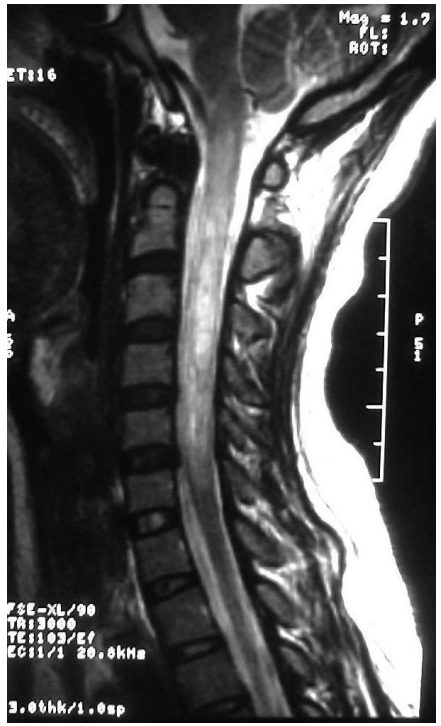
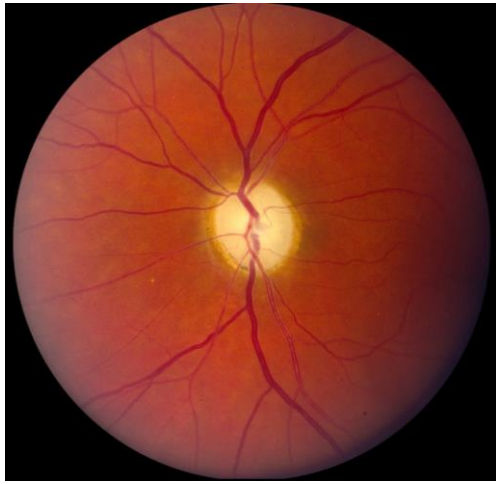
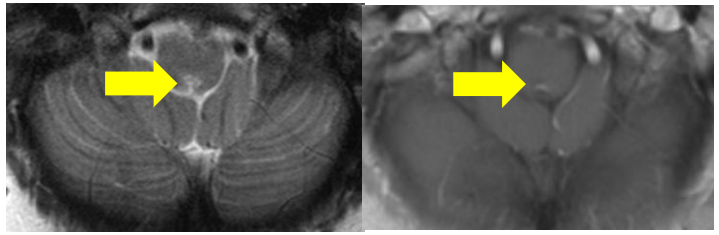
Neuromyelitis optica spectrum disorder (NMOSD)

- Chronic, autoimmune disease of the CNS (also known as Devic's disease)
  - recurrent optic neuritis and acute transverse myelitis
  - prevalence 0.5–4.4 per 100 000[1,2]
  - no approved therapies
- Multiple lines of evidence suggest that NMOSD is a B-cell-mediated disorder,[3] resulting from:
  - pathologic auto-antibody production
  - pro-inflammatory cytokine secretion
  - B cell antigen presentation







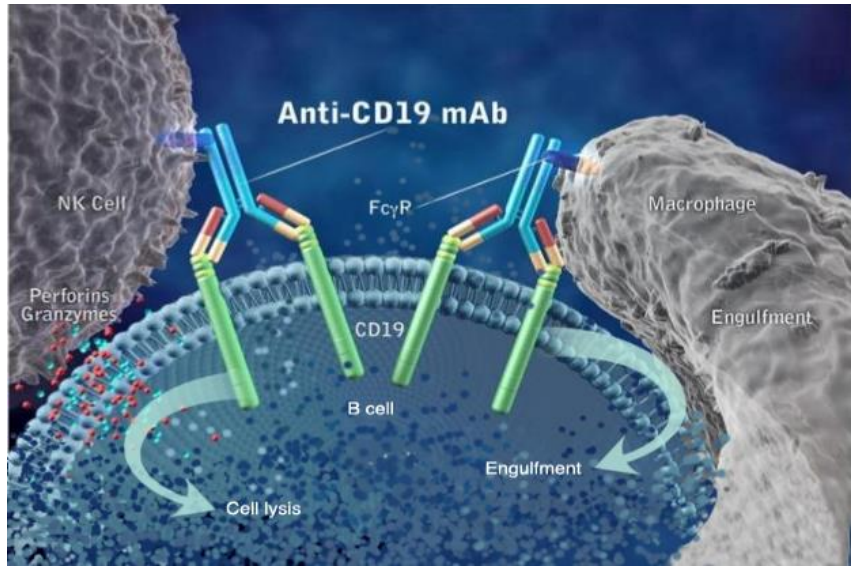
- Highly specific serum autoantibodies, AQP4-IgG, are detected in about 80% of patients and are likely pathogenic[4]
  - AQP4 autoantibodies induce CNS damage through complement activation and antibody-mediated cytotoxicity[5,6]

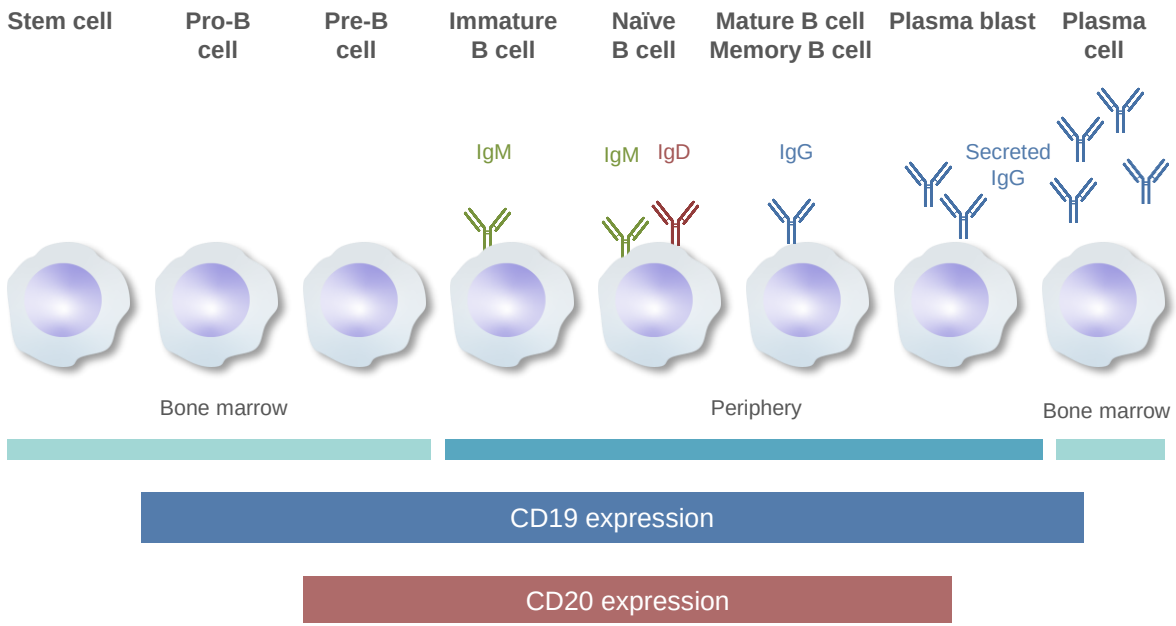
AQP4, aquaporin-4; CNS, central nervous system; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.

1. Marrie RA, *et al. Int J MS Care* 2013;15:113–18; 2. Pandit L, *et al. Mult Scler* 2015;21:845–53; 3. Bennett JL, *et al. Neurol Neuroimmunol Neuroinflamm* 2015;2:e104; 4. Hamid SHM, *et al. J Neurol* 2017; 264:2088–94; 5. Bennett JL, *et al. Ann Neurol* 2009;66:617–29; 6. Saadoun S, *et al. Brain* 2010;133:349–61

Inebilizumab – mechanism of action

- CD19 is a potential therapeutic target in NMOSD
  - CD19 is expressed widely throughout B cell development (more widely than CD20)
- Inebilizumab is a humanized IgG1-κ mAb with high affinity for CD19
- Interaction with effector cells causes ADCC- and ADCP-mediated B cell death
  - Shown to thoroughly and durably deplete B cells in pre-clinical and clinical studies[1–5]
  - Also directly depletes plasmablasts and depletes some plasma cells, which are not directly targeted by anti-CD20 mAbs[1]





ADCC, antibody-dependent cellular cytotoxicity; ADCP antibody-dependent cellular phagocytosis; CD19, B-lymphocyte antigen CD19; CD20, B-lymphocyte antigen CD20; FcγR, immunoglobulin Fcγ receptor; Ig, immunoglobulin; mAb, monoclonal antibody; NK, natural killer.

1. Chen D, *et al. J Clin Med* 2016;5:107; 2. Herbst R, *et al. J Pharmacol Exp Ther* 2010;335:213–22; 3. Gallagher S, *et al. Arthritis Rheumatol* 2016;68:965–76;
4. Schiopu E, *et al. Arthritis Res Ther* 2016;18:131;5. https://clinicaltrials.gov/ct2/show/NCT01585766

Study eligibility

1) Age ≥ 18 years

2) AQP4-IgG positive or negative (AQP4-IgG seronegative eligibility confirmed by committee using Wingerchuk 2006 critieria[1])

3) ≥ 1 NMOSD attack treated in the past year, or ≥ 2 in the past 2 years[a]

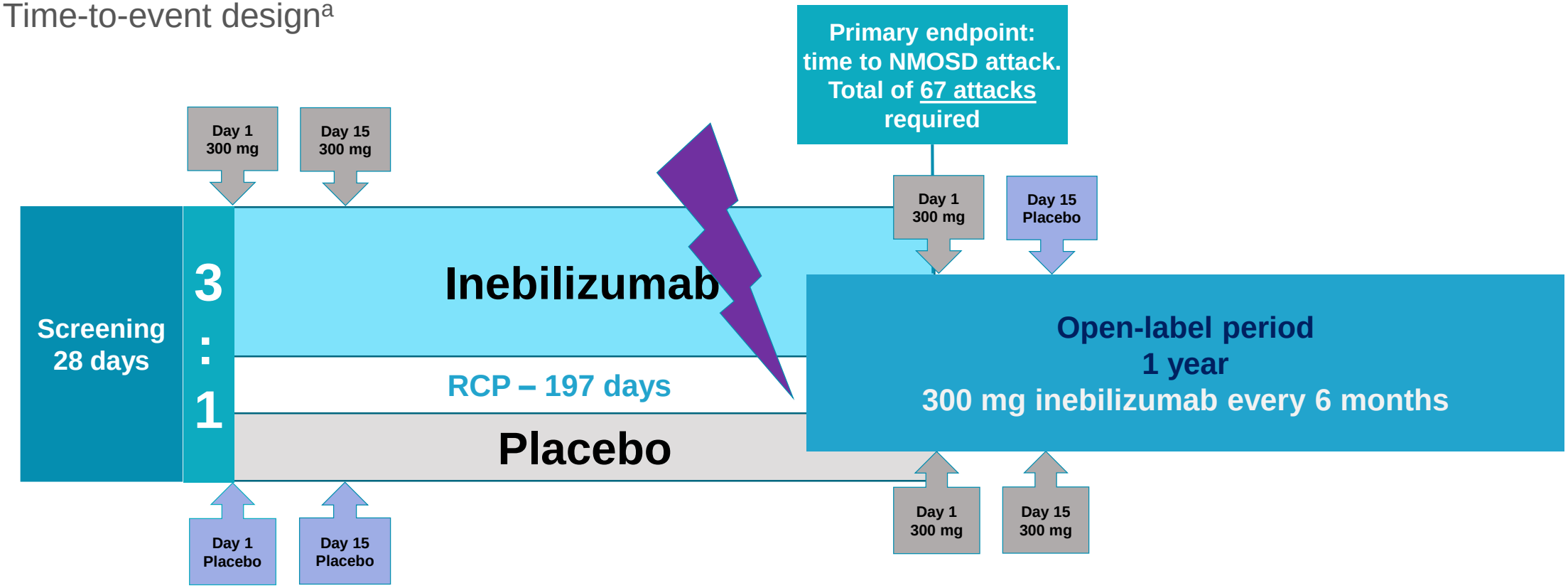
4) EDSS score ≤ 8.0

AQP4-IgG, aquaporin-4 immunoglobulin G; EDSS, Expanded Disability Status Scale; NMOSD, neuromyelitis optica spectrum disorder.
[a]Attacks were defined as a new symptom or worsening of an existing symptom meeting ≥ 1 protocol-defined attack criterion, and occurring up to day 197.
1. Wingerchuk DM, *et al. Neurology* 2006;66:1485–9

N-MOmentum: a global, pivotal study

Efficacy and safety of inebilizumab in adults with NMOSD[1]

- Double-masked, placebo controlled study at 99 medical centers in 24 countries
- **Monotherapy (no background immunotherapy permitted)**
- Time-to-event design[a]



[a]Study end defined as 67 NMOSD attacks, or when 252 patients had been randomized and received study drug.

1. Cree BAC, *et al. Mult Scler* 2015;22:862–72; NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period

N-MOmentum: independent oversight and objectivity

Independent Eligibility Committee

- Reviewed and confirmed eligibility of AQP4-IgG seronegative patients

Masked Adjudication Committee

- Provided expert, objective, independent and real-time adjudication of NMOSD attacks

Independent Data Monitoring Committee

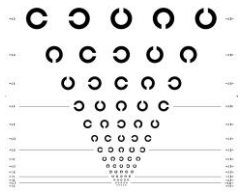
- Ongoing review of patient safety and ethical conduct of study[1]

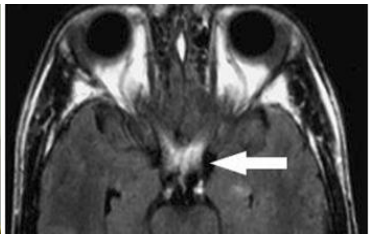
AQP4, aquaporin-4; Ig, immunoglobulin; NMOSD, neuromyelitis optica spectrum disorder.

1. Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees; Food and Drug Administration: 2006. Accessed on 2 April 2019 at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm127073.pdf

Pre-defined, clinically significant attack diagnosis criteria

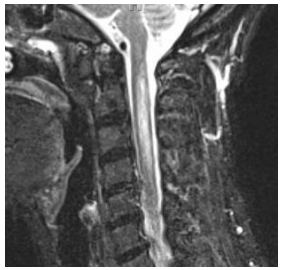
Optic neuritis



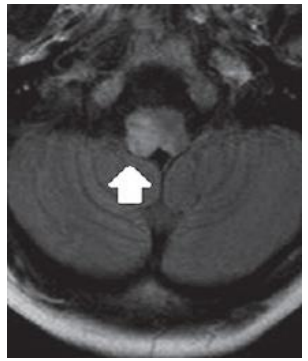


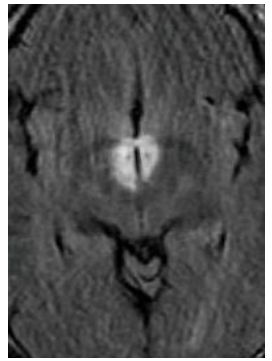
Myelitis

The Expanded Disability Status Scale (EDSS)



Brain/brainstem





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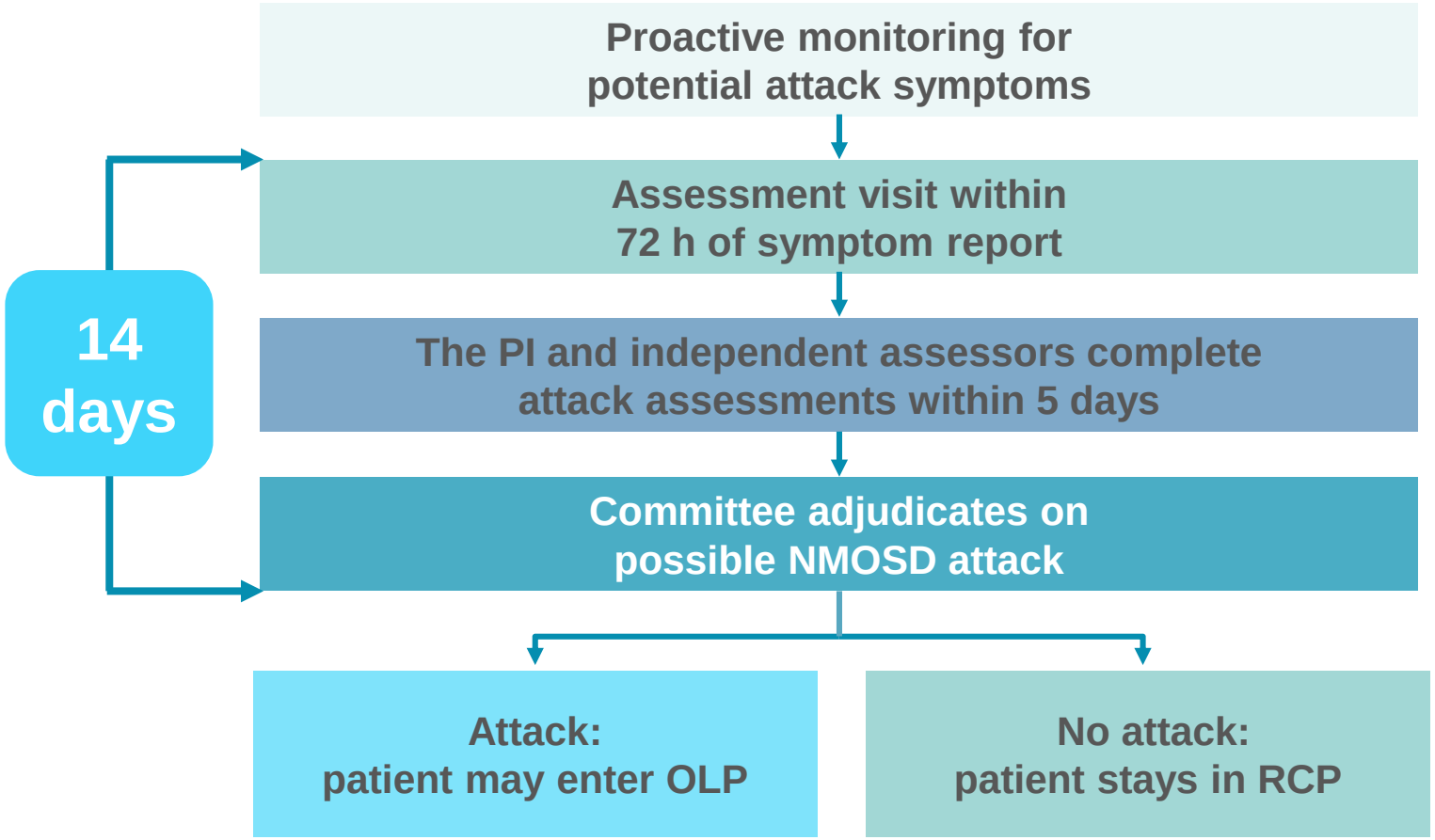
10 criteria representing overt clinical change + Adjudication committee confirmation = **NMOSD ATTACK**

8 criteria representing moderate clinical change & New MRI lesion + Adjudication committee confirmation = **NMOSD ATTACK**

NMOSD attack adjudication in ‘real time’



- **Only adjudication committee-validated attacks were included in primary analysis**

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; OLP, open-label period; PI, principal investigator; RCP, randomized controlled period

Study key efficacy endpoints

Overall population and AQP4-IgG seropositive subgroup

Primary endpoint

Time from Day 1 to adjudicated NMOSD attack[a] within the RCP

Secondary endpoints

Worsening of EDSS score[a]

Change in low-contrast visual-acuity binocular score[b]

Cumulative active MRI lesions[c]

NMOSD-related inpatient hospitalizations[d]

AQP4-IgG, aquaporin-4 immunoglobulin G; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period

[a]Score increase of ≥ 2 from a baseline of 0, of ≥ 1 from 1–5 or of ≥ 0.5 from ≥ 5.5; [b]Assessed by low-contrast Landolt C Broken Ring Chart; [c]Gd+ and new/enlarging T2 lesions; [d]Hospital stay > 1 night.

1. Wingerchuk DM, *et al. Neurology* 2015;85:177–89

Patient disposition and baseline characteristics

Treatment groups were generally well matched

	Placebo (n = 56)	Inebilizumab (n = 174)	Overall population (N = 230)
Number of attacks at study entry (%)			
1	25.0	14.4	17.0
≥ 2	75.0	85.6	83.0
Mean number of attacks prior to screening	4.3	4.4	4.3
Prior immune suppressants (%)	58.9	61.5	60.9

Enrollment to the RCP was stopped at 231 patients and 43 adjudicated attacks based on IDMC recommendation

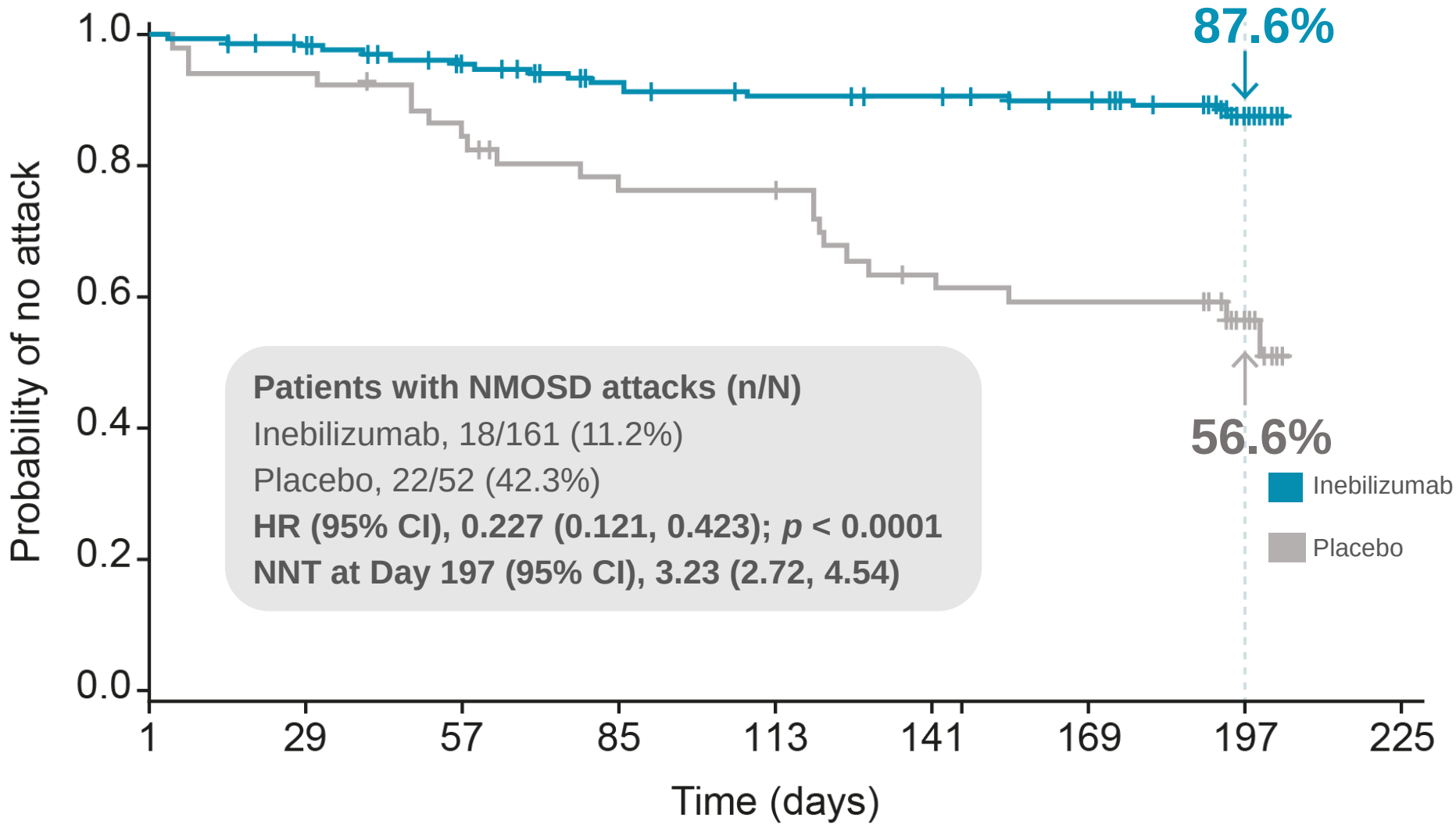
a, b: 1 patient randomized but not dosed

IDMC, independent data monitoring committee; ITT, intent-to-treat; RCP, randomized controlled period.

Primary endpoint: time from day 1 to adjudicated NMOSD attack

Inebilizumab reduced the risk of NMOSD attacks by 77.3% relative to placebo

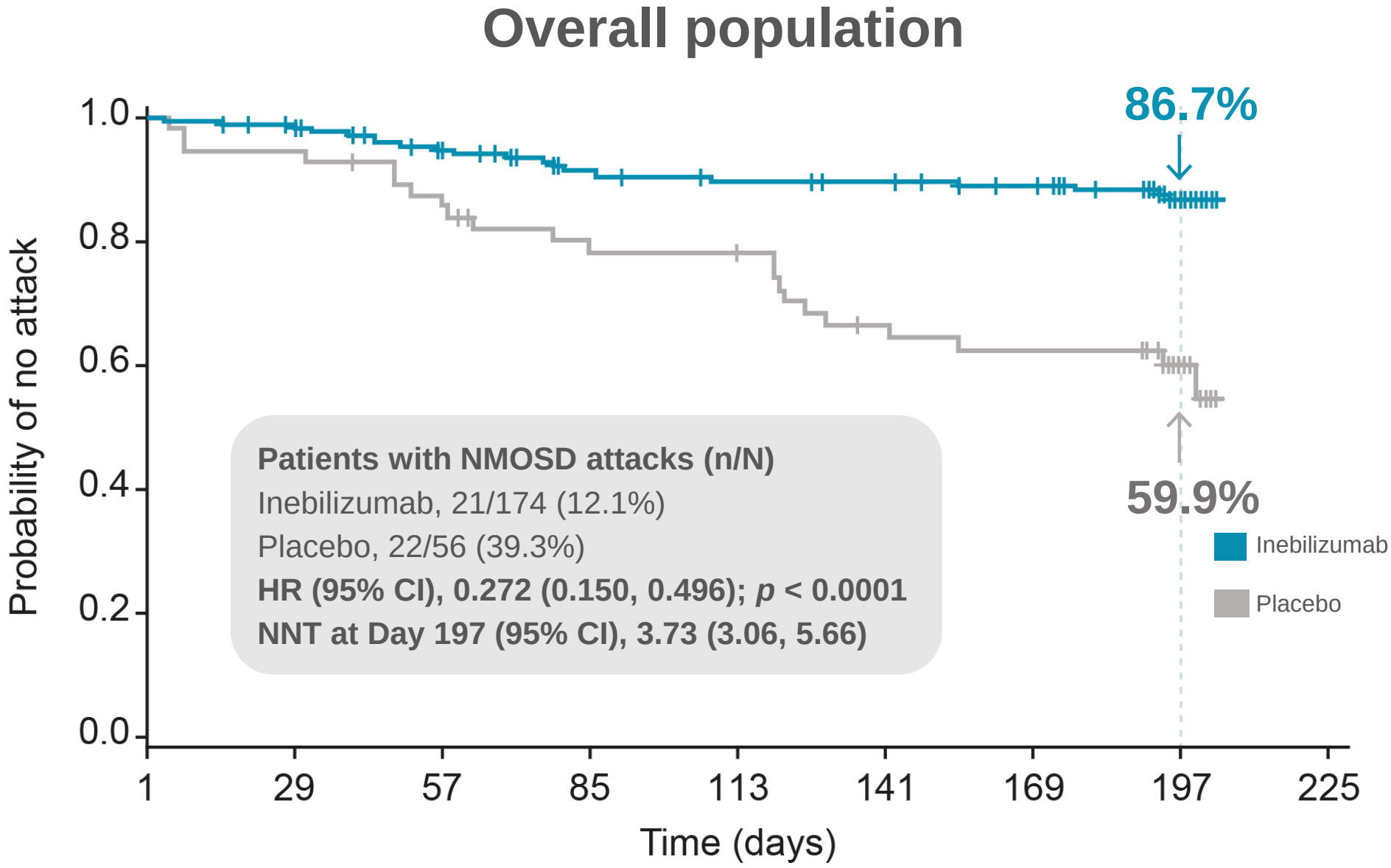
AQP4-IgG seropositive population



AQP4-IgG, aquaporin-4 immunoglobulin G; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat; NMOSD, neuromyelitis optica spectrum disorder

Primary endpoint: time from day 1 to adjudicated NMOSD attack

Inebilizumab reduced the risk of NMOSD attacks by 72.8% relative to placebo

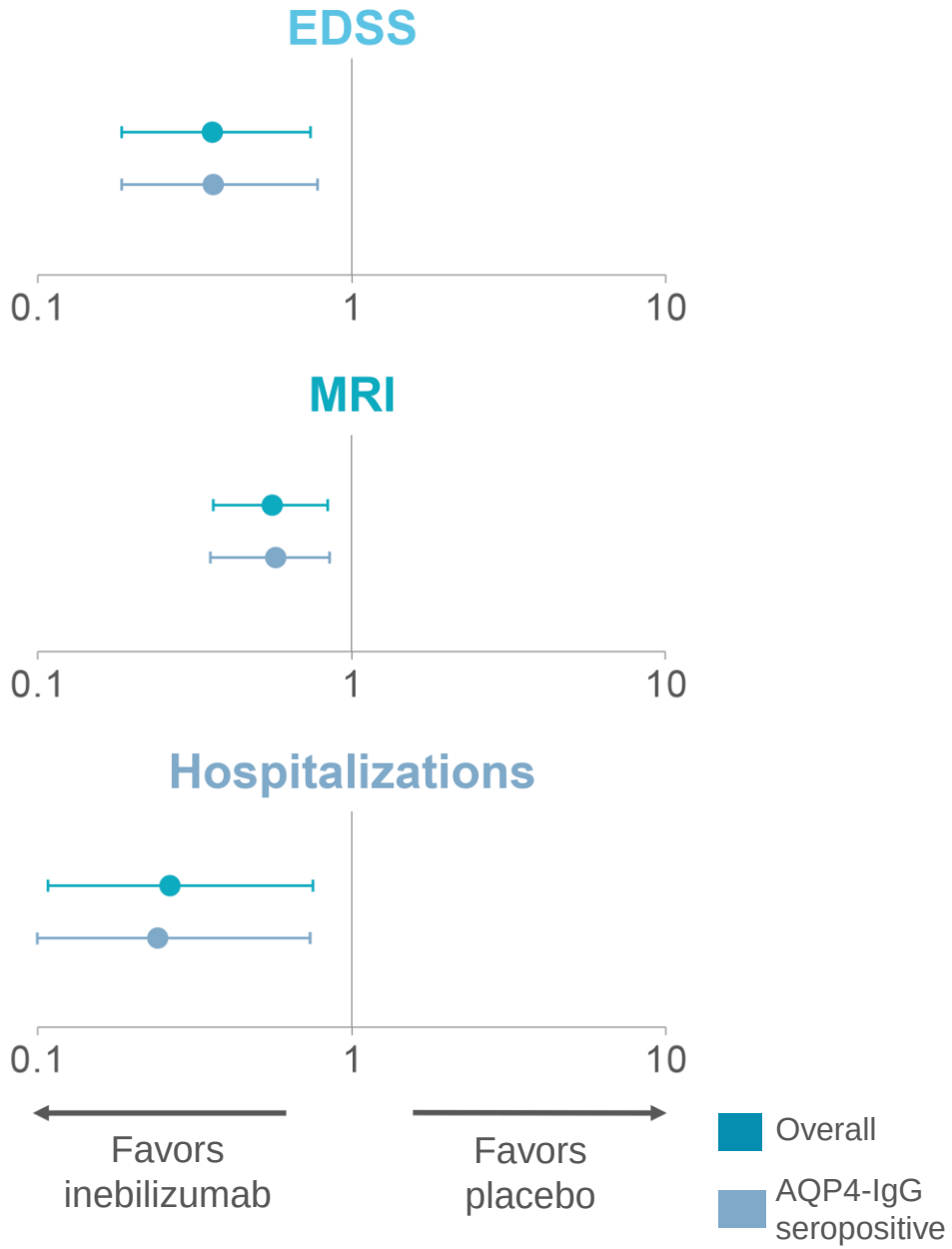


CI, confidence interval; HR, hazard ratio; NNT, number needed to treat; NMOSD, neuromyelitis optica spectrum disorder

Secondary endpoints: disability worsening, MRI lesions and hospitalizations

- Relative to placebo, the inebilizumab group had:
  - proportionally fewer patients with worsening disability
    - placebo 33.9% vs inebilizumab 15.5%
    - 63% reduction in risk
  - 43% fewer new MRI lesions
  - 71% fewer disease-related hospitalizations

- No difference between placebo and inebilizumab groups for low-contrast visual acuity binocular score
  - May be owing to low frequency of optic neuritis attacks, floor effect within placebo arm, or selection of binocular acuity test



AQP4-IgG, aquaporin-4 immunoglobulin G; MRI, magnetic resonance imaging

Safety

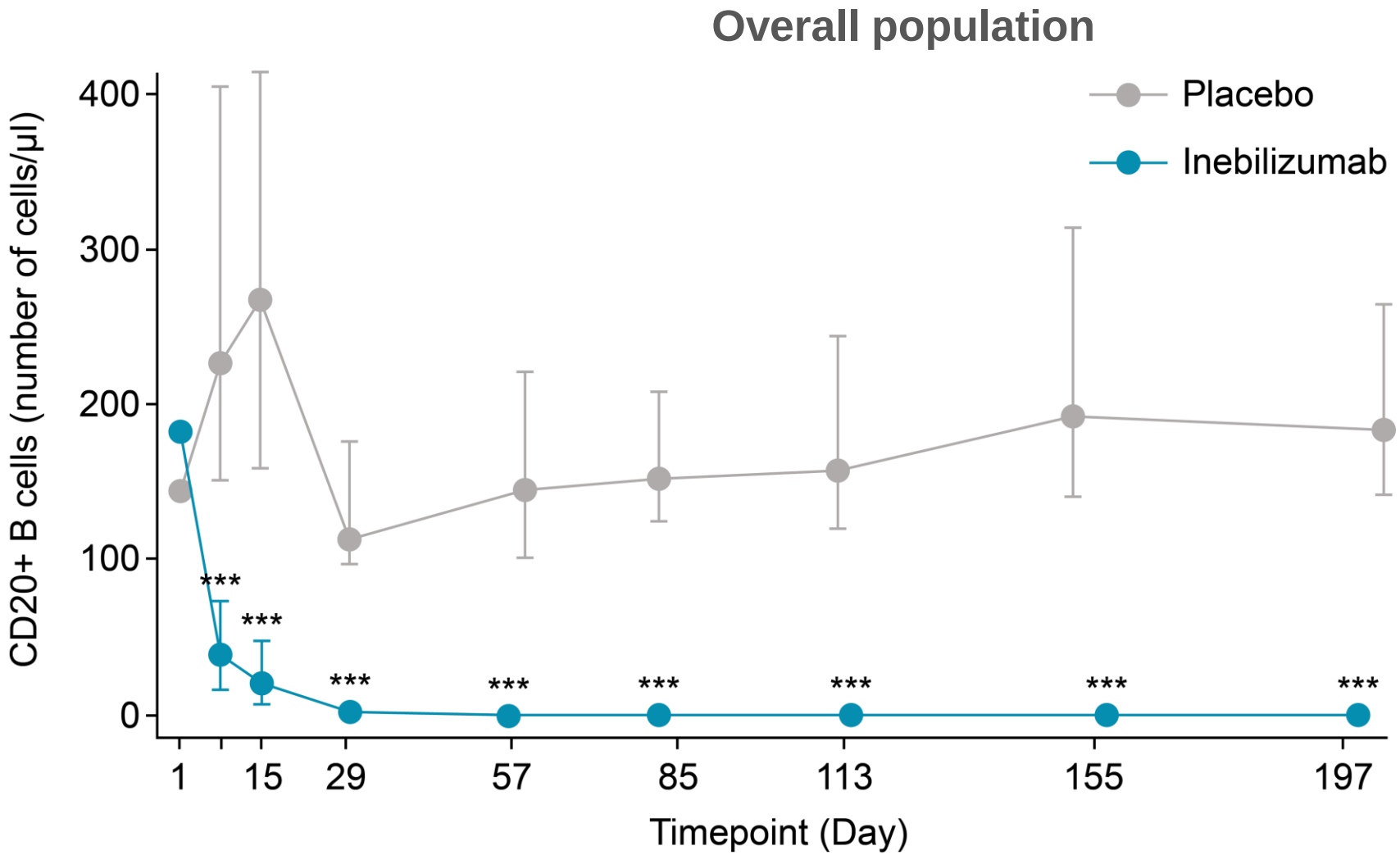
- Similar event rates during RCP
  - AEs: 71.8% (inebilizumab) vs 73.2%[a] (placebo)
  - SAEs: 4.6% (inebilizumab) vs 8.9%[b] (placebo)
- Lower frequency of IRRs than with placebo
  - IRRs: 9.2% vs 10.7%[c]
- No deaths, and no SAEs in > 1 patient, during RCP
- Two deaths during OLP
  - One related to a severe attack
  - The other a brain event of unclear etiology without definite diagnosis

AEs occurring in > 5% of patients in either group (RCP)	Inebilizumab (n = 174)	Placebo N = 56
UTI	11.5%	8.9%
Arthralgia	9.8%	3.6%
IRR	9.2%	10.7%
Back pain	7.5%	3.6%
Headache	7.5%	7.1%
Nasopharyngitis	7.5%	10.7%
Diarrhea	4.6%	5.4%
Nausea	3.4%	5.4%
URTI	2.9%	5.4%
Depression	2.3%	8.9%
Oral herpes	0.6%	5.4%
Pruritus	0.6%	8.9%
Vomiting	0.6%	7.1%

AE, adverse event; IRR, infusion-related reaction; OLP, open-label period; RCP, randomized controlled period; SAE, serious adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.
[a]AEs: inebilizumab, n = 174; placebo, n = 41; [b]SAEs: inebilizumab, n = 8; placebo, n = 5; [c]IRR: inebilizumab, n = 16, placebo, n = 6

Pharmacodynamics: effect of inebilizumab on B cells

- Effect of inebilizumab on B cells (CD20+) observed within 4 weeks
- Mean circulating B cell counts:
  - dropped to below 10% of baseline
  - did not rise above this threshold throughout the RCP



CD20, B-lymphocyte antigen CD20; RCP, randomized controlled period

Conclusions

- Inebilizumab was generally well tolerated
- Inebilizumab treatment induced thorough and durable B cell depletion
- Compared with placebo, inebilizumab significantly reduced the risk of an adjudicated NMOSD attack in both the AQP4-IgG seropositive group and the overall intent-to-treat population (primary endpoint)
- Compared with placebo, in the AQP4-IgG seropositive group and the overall intent-to-treat population, inebilizumab also substantially reduced:
  - disability worsening based on EDSS score
  - MRI lesion activity
  - hospitalizations

AQP4-IgG, aquaporin-4 immunoglobulin G; EDSS, Expanded Disability Status Scale; MRI, magneitic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder

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IDMC, Independent Data Monitoring Committee

AAN 2019 is a big meeting for NMOSD: two other trials will be presented

- Emerging Science Session

  Tuesday, May 7, 11:45 a.m. to 12:45 p.m.

  - Efficacy and safety of eculizumab in aquaporin-4 antibody positive (AQP4-IgG+) neuromyelitis optica spectrum disorder (NMOSD): a phase 3, randomized, double-blind, placebo-controlled, multicenter trial (PREVENT) *Sean Pittock*

- S43: Immunotherapies and Drug Trials in Autoimmune Neurological Disorders

  Wednesday, May 8, 3:30 p.m. to 5:30 p.m.

  - Efficacy of satralizumab (SA237) in subgroups of patients in SAkuraSky: a Phase III double-blind, placebo-controlled, add-on study in patients with neuromyelitis optica spectrum disorder (NMOSD) *Takashi Yamamura*

Back-up

Details of deaths

- No deaths occurred during the randomized controlled period
- Two deaths occurred in the open-label period
  - One not treatment related, the other may have been related although no definite diagnosis

Patient one

- Pneumonia
- Followed by an adjudicated attack, prior to enrollment in the open-label period
- Died at home nine days later, probably from respiratory insufficiency

Patient two

- New onset weakness, aphasia, neurological decline and seizures during the open-label period
- Lesions in white and grey matter on MRI
- Patient had respiratory arrest and died of cardiopulmonary complications
- Inconclusive JCV information

JCV, John Cunningham Virus; MRI, magnetic resonance imaging

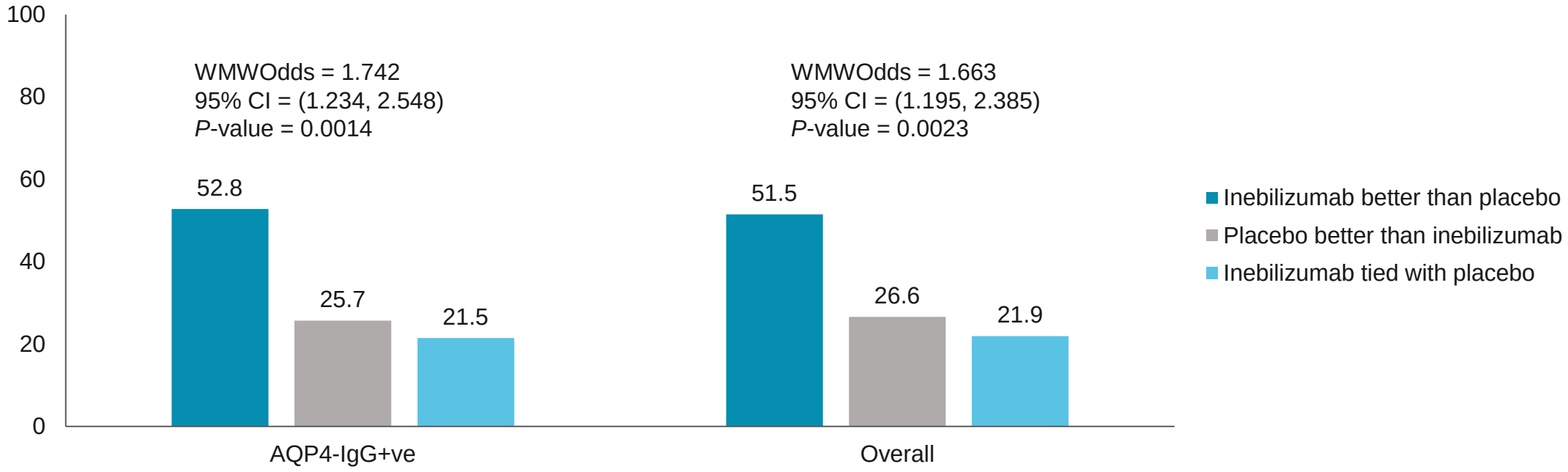
IgG levels during the randomized controlled period

Total IgG summary	AQP4-IgG seropositive population		Overall population	
IgG	**Placebo (N = 52)**	**Inebilizumab (N = 161)**	**Placebo (N = 56)**	**Inebilizumab (N = 174)**
Baseline, mg/dL	1084.6 ± 320.7 (n = 51)	1044.5 ± 310.0 (n = 159)	1067.3 ± 316.4 (n = 55)	1041.1 ± 308.0 (n = 172)
Change from baseline at week 12, %	5.3 ± 22.6 (n = 51)	−1.9 ± 21.5 (n = 156)	4.7 ± 22.2 (n = 55)	−2.5 ± 21.5 (n = 169)
Change from baseline at week 28, %	6.5 ± 30.8 (n = 28)	−3.6 ± 20.4 (n = 122)	6.2 ± 29.3 (n = 32)	−4.0 ± 20.9 (n = 131)

Data are shown as mean ± SD
AQP4, aquaporin-4; IgG, immunoglobulin; SD, standard deviation

Disability: modified Rankin score

- Fewer patients in the inebilizumab group had worsening disability while carrying out daily activities than those in the placebo group
  - AQP4-IgG seropositive subgroup: inebilizumab better than placebo in 52.8% of patients
  - Overall population: inebilizumab better than placebo in 51.5% of patients



AQP4-IgG, aquaporin-4 immunoglobulin G; CI, confidence interval; WMWOdds, Wilcoxon-Mann-Whitney Odds

Attack Adjudication and Characteristics

- Agreement between Investigator and Adjudication Committee in 56/64 potential attacks (92%), Kappa value 0.6859 indicating moderate agreement

		Adjudication Committee		Total
		Attack	Non-attack	
Investigator	Attack	43	8	51
	Non-attack	0	13	13
Total		43	21	64

- Domains affected (based on AC-selected criteria for 43 attacks):
  - 22 (51%) myelitis alone
  - 15 (35%) optic neuritis alone
  - 4 (9%) myelitis + optic neuritis
  - 1 (2%) each myelitis + brainstem, optic neuritis + brainstem
- MRI was required for attack diagnosis in 16/43 (37%) AC-determined attacks
- Attack Severity (determined by adaptation of the Opticospinal Impairment (OSI) scale[1]:
  - Inebiliuzmab group: 6/21 (29%) major, 15/21 (71%) minor
  - Placebo group: 10/22 (46%) major, 12/22 (55%) minor
  -

[1] Wingerchuk DM, Hoogancamp WF, O'Brien PC, Weinshenker BG. Neurology. 1999;53(5):1107-14.

AQP4-IgG Seronegative Subjects

- AQP4-IgG seronegative subjects were permitted to enroll, up to 20% of the total study population (stratified)
- Eligibility required confirmation of the NMOSD diagnosis by a Seronegative Eligibility Committee (SEC), with reference to the 2006 Wingerchuk criteria
- SEC reviewed 50 subjects in screening, and determined that **only 18 (36%)** met 2006 Wingerchuk criteria
  - All of these subjects had an existing diagnosis of NMO/NMOSD at the time of screening → seronegative NMOSD is a diagnostic challenge
- MOG-IgG status: 7/17 (41%) of the randomized AQP4-IgG seronegative subjects were positive at baseline for MOG-IgG