Diagnosis, severity, and recovery of attacks in the N-MOmentum study of inebilizumab in neuromyelitis optica spectrum disorder

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Brian G Weinshenker,[1] Dean Wingerchuk,[2] Ari Green,[3] Jeffrey L Bennett,[4] Ho Jin Kim,[5] Sean J Pittock,[1] Kazuo Fujihara,[6] Friedemann Paul,[7] Gary Cutter,[8] Romain Marignier,[9] Orhan Aktas,[10] Hans-Peter Hartung,[10] Jorn Drappa,[11] Gerard Barron,[12] Soraya Madani,[11] John N Ratchford,[11] Dewei She,[11] Daniel Cimbora,[11] Eliezer Katz,[11] Bruce AC Cree,[13] on behalf of the N-MOmentum study investigators

[1]Mayo Clinic, Rochester, MN, USA; [2]Mayo Clinic, Scottsdale, AZ, USA; [3]UCSF Weill Institute for Neurosciences, Department of Neurology and Department of Ophthalmology, University of California San Francisco, San Francisco, CA, USA; [4]University of Colorado, School of Medicine, Anschutz Medical Campus, Aurora, CO, USA; [5]Research Institute and Hospital of National Cancer Center, Seoul, South 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]Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, Berlin, Germany; [8]University of Alabama at Birmingham, Birmingham, AL, USA; [9]Lyon University Hospital, Lyon, France; [10]Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [11]Viela Bio, Gaithersburg, MD, USA; [12]Viela Bio, Cambridge, UK; [13]UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA.

INTRODUCTION

- Neuromyelitis optica spectrum disorder (NMOSD) is a severe, autoimmune, inflammatory central nervous system (CNS) disease.[1]
- NMOSD is characterized by recurrent attacks, typically of optic neuritis or transverse myelitis and less commonly affecting the brain/brainstem.
  - Attacks are thought to be antibody meditated,[2] and are cumulatively responsible for most of the ambulatory, visual and other impairments that result from NMOSD.[1,3]
- Accurate and objective diagnosis of attacks can be difficult, particularly when patients present early in the course of an attack and when severity may be mitigated by immunotherapy; precise definitions are lacking for all types of NMOSD attacks.[1]
- The N-MOmentum study is a randomized, placebo-controlled, double-blind, phase 2/3 trial in 231 patients enrolled from 99 sites around the world. This study assessed the efficacy and safety of inebilizumab, an anti-CD19, B-cell depleting antibody, in patients with NMOSD.[4]
- N-MOmentum met the primary endpoint of time to onset of an adjudication committee (AC)-determined NMOSD attack in the randomized controlled period (RCP); inebilizumab significantly lowered the risk of attack compared with placebo (relative risk reduction, 72.8%).[4]
- Using time to attack as the primary endpoint required the development of attack criteria to permit the uniform recognition of attacks in this international study.
  - A set of 18 attack criteria was developed in collaboration with a panel of NMOSD experts, and with advice from the US Food and Drug Administration before the study,[1] and used to diagnose on-study attacks[4] (**Table 1**).
- All attacks were assessed by an AC of three physicians with extensive knowledge of and experience in evaluating and treating patients with NMOSD, to verify that attack criteria were consistently applied and that no confounding explanation for an event was missed; the decision of the AC was determined by majority vote.
- Attack severity and recovery were also evaluated.

OBJECTIVE

- To assess attack diagnosis in N-MOmentum, including AC performance and agreement with investigators, to characterize the attacks diagnosed according to the predefined attack criteria, and to describe the effect of inebilizumab on attack severity and recovery.

METHODS

Study design

- Predefined attack criteria were used to assess each on-study attack[1,4] (**Table 1**).

Table 1. Protocol-defined criteria for an attack with criteria-based severity.

Criteria	Definition
Optic neuritis[a]	Symptoms[b]: blurred vision, loss of vision, eye pain
1	> 15-character drop in high-contrast LCBRC from last visit as measured in a previously affected eye and no other ophthalmological explanation
2	Reduction of ≥ 2 steps[c] in CF to NLP from last visit as measured in a previously affected eye and no other ophthalmological explanation
3	Reduction of ≥ 7 characters in low-contrast LCBRC from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye
4	Reduction of ≥ 7 characters in low-contrast LCBRC from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye
5	Reduction of ≥ 5 characters in high-contrast LCBRC from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye
6	Reduction of ≥ 5 characters in high-contrast LCBRC from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye
7	Reduction of ≥ 1 step[d] in CF to NLP from last visit as measured in a previously affected eye AND a new RAPD in affected eye
8	Reduction of ≥ 1 step[d] in CF to NLP from last visit as measured in a previously affected eye AND loss of a previously documented RAPD in fellow eye
9	Reduction of ≥ 7 characters in low-contrast LCBRC from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve[e]
10	Reduction of ≥ 5 characters in high-contrast LCBRC from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve[e]
11	Reduction of ≥ 1 step[d] in CF to NLP from last visit as measured in a previously affected eye AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve[e]
Myelitis[a,f]	Symptoms[b]: deep or radicular pain, extremity paraesthesia, weakness, sphincter dysfunction, Lhermitte's sign (not in isolation)
12	Worsening of ≥ 2 points in at least one of the relevant (pyramidal, bladder/bowel, sensory) FSS compared with last visit
13	Worsening of ≥ 1 point in EDSS score compared with last visit if previous EDSS score ≥ 5.5
14	Worsening of ≥ 1 point in at least two of the relevant (pyramidal, bladder/bowel, sensory) FSS compared with last visit when last visit score ≥ 1 AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord
15	Worsening of ≥ 0.5 points in EDSS score compared with last visit if previous EDSS score ≥ 5.5 AND a new GD-enhancing or new/enlarging T2 MRI lesion in the spinal cord
Brain/ brainstem[a]	Symptoms[b]: nausea, intractable vomiting, intractable hiccups, other neurological signs[g], encephalopathy, hypothalamic dysfunction
16	Isolated (not present at last visit) intractable nausea, vomiting, and/or hiccups lasting > 48 hours AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem
17	Worsening of ≥ 2 points in at least one of the relevant (brainstem, cerebellar) FSS compared with last visit AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem
18	Worsening of ≥ 2 points in at least one of the relevant (cerebral, sensory, pyramidal) FSS (with a score of ≥ 3 at the current visit) compared with last visit AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brain consistent with the clinical presentation

The teal criteria indicate MRI-dependent criteria. [a]Four major areas of the body may be affected by an attack: the optic nerve, resulting in optic neuritis; the spinal cord, resulting in myelitis; the brainstem, resulting in several outcomes; and the brain; [b]Symptoms listed are examples and are not inclusive of all neuromyelitis optica spectrum disorder symptoms; [c]A decrease of ≥ 2 steps can be due to any of the following worsening: on Landolt C Broken Ring Chart to HM, LP, or NLP; CF to LP or NLP; HM to NLP; [d]A decrease of ≥ 1 step can be due to any of the following worsening: on Landolt C Broken Ring Chart to CF, HM, LP, or NLP; CF to HM or LP or NLP; HM to LP or NLP; LP to NLP; [e]Lesions seen in the optic chasm also count towards these criteria; [f]A 1-point change in a single FSS without a change in EDSS score, with or without a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord, is not considered a clinically significant change and does not count as an attack per this protocol; [g]Other neurological signs include double vision, dysarthria, dysphagia, vertigo, oculomotor palsy, weakness, nystagmus or other cranial nerve abnormality.
CF, counting fingers; EDSS, Expanded Disability Status Scale; FSS, functional system score; Gd, gadolinium; HM, hand motion; LCBRC, Landolt C Broken Ring Chart; LP, light perception; MRI, magnetic resonance imaging; NLP, no light perception; RAPD, relative afferent pupillary defect.

Table 2. Breakdown of on-study AC-determined attacks.

Attack outcome	Placebo n = 56	Inebilizumab n = 174
AC-determined attacks[a]	22 (39.3%)	21 (12.1%)
Attacks according to type[b]		
Optic neuritis	10 (45.5%)	10 (47.6%)
Myelitis	14 (63.6%)	13 (61.9%)
Brain/brainstem	2 (9.1%)	0
Attacks affecting multiple domains		
Optic neuritis and myelitis	2 (9.1%)	2 (9.5%)
Optic neuritis and brain/brainstem	1 (4.5%)	0
Brain/brainstem and myelitis	1 (4.5%)	0

[a]Presented as n (%) of the number of patients in each treatment arm; [b]Presented as n (%) of the total number of adjudicated attacks in each treatment arm. An attack may appear in more than one category.
AC, adjudication committee.

Table 3. Relationship between investigator and AC attack determinations.

		AC		Total
		Attack	Non-attack	
Investigator	**Attack**	43	8	51
	Non-attack	0	13	13
	Total	43	21	64

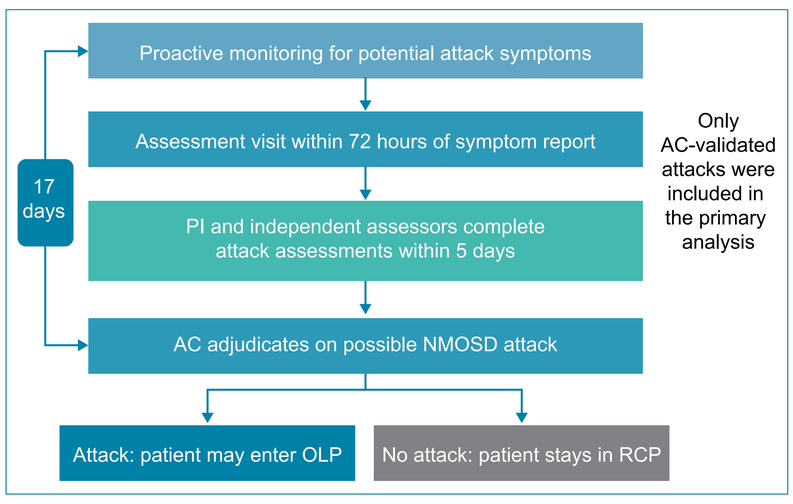
AC, adjudication committee.

Table 4. AC rejection of investigator-determined attacks.

Subject	Domain affected	Criteria met per investigator	AC decision	Basis for AC rejection (summary)
1	Myelitis	12	Unanimous	Minor clinical changes with no supporting MRI findings
2	Myelitis	12	Unanimous	Minor clinical changes with no supporting MRI findings
3	Optic neuritis	1	Unanimous (following full AC discussion)	No new/worsening visual symptoms; visual changes only noted upon ophthalmology assessment
4	Optic neuritis	3	Unanimous (2:0)	Minor clinical changes with no supporting MRI findings
5	Myelitis	12	Unanimous	Substantial clinical changes, but inconsistencies and atypical findings led to request for MRI by exceptional circumstance; negative MRI indicated not an attack
6	Myelitis	12	Split (2:1)	Substantial clinical changes, but inconsistencies and atypical findings led to request for MRI by exceptional circumstance; negative MRI indicated not an attack
7	Myelitis	13	Unanimous	Concerns about evaluation findings and concurrent UTI led to request for MRI by exceptional circumstance; negative MRI indicated not an attack
8	Optic neuritis	5	Unanimous	Changes limited to visual field and new RAPD, but no visual acuity loss. Clinical criteria for optic neuritis attack not met

AC, adjudication committee; MRI, magnetic resonance imaging; UTI, urinary tract infection; RAPD, relative afferent pupillary defect.

Figure 1. Attack evaluation and adjudication process.



AC, adjudication committee; 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.

- Eligible participants were adults with a diagnosis of NMOSD and an Expanded Disability Status Scale (EDSS) score no greater than 8, and a history of either at least one attack requiring rescue therapy in the year before screening or at least two attacks requiring rescue therapy in the 2 years before screening.
- Participants were randomly assigned 3:1 to intravenous inebilizumab 300 mg or placebo, with dosing on days 1 and 15; the RCP was 197 days or until an AC-determined attack occurred.

Evaluation of attacks

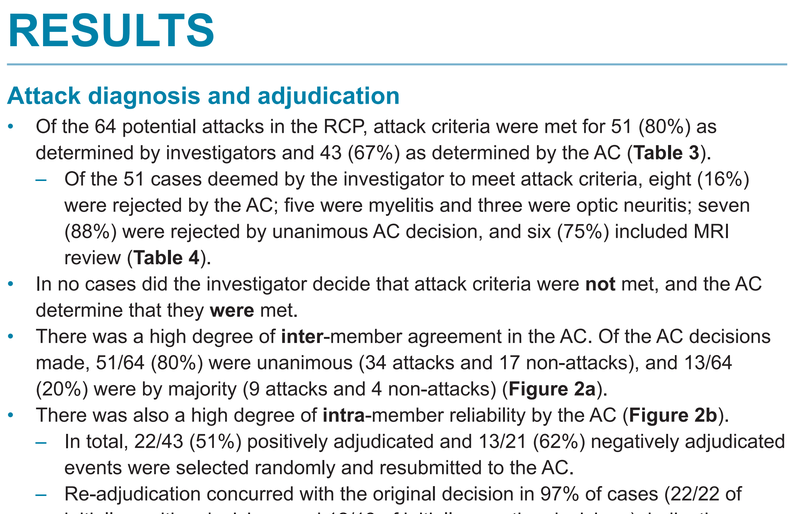
- Potential attacks were evaluated by an on-site investigator together with independent EDSS and ophthalmology assessors; results were adjudicated by the independent AC of three NMOSD expert clinicians.[4]
  - Participants reporting a potential attack were evaluated at the clinical site by the investigator within 72 hours; the AC reached a decision within 17 days of initial evaluation (**Figure 1**).
  - The AC was masked from information regarding treatment, the investigator's determination, and all other potentially unmasking information.
- Attack diagnosis required new/worsening NMOSD symptoms, ophthalmological and/or EDSS score changes that met at least one criterion, and supportive magnetic resonance imaging (MRI) findings for cases in which clinical criteria were considered indeterminate.[1,4] The attack criteria covered optic neuritis, myelitis, and brain/brainstem domains (**Tables 1** and **2**).
- In order to assess intra-rater reliability, approximately half of the positively and negatively adjudicated events were randomly resubmitted to the AC.
  - Resubmitted events were presented as potential attacks; the AC was masked in the normal fashion, without notification that these were re-adjudications or knowledge of their previous decisions.
- Attack severity was graded according to the optico-spinal index,[5] an exploratory, predefined scale based on the degree of domain-specific neurological deficit since the last assessment.
- Attack recovery was graded according to an exploratory predefined scale (major, minor or no recovery), based on the degree of domain-specific neurological improvement within 35 days of the attack assessment.
- The outcomes of attack diagnosis, severity and recovery were exploratory;[4] as such, these data are reported descriptively.

RESULTS

Attack diagnosis and adjudication

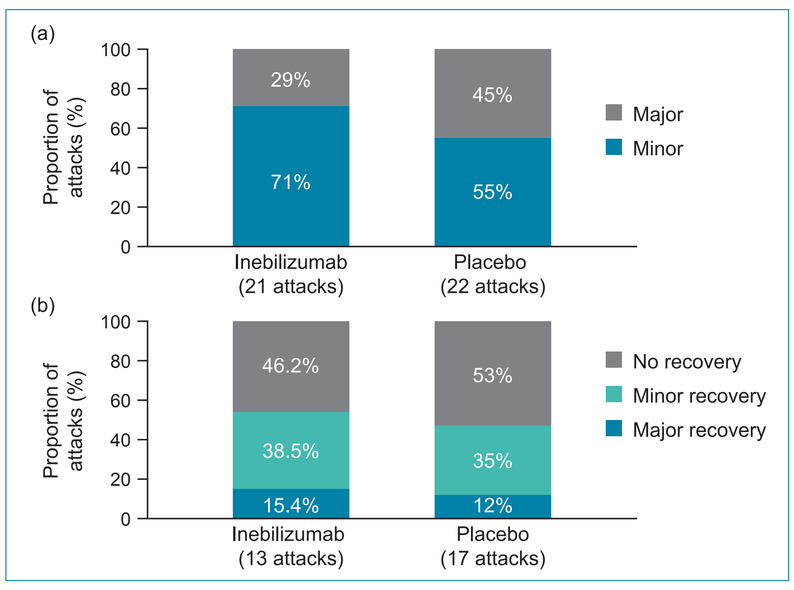
- Of the 64 potential attacks in the RCP, attack criteria were met for 51 (80%) as determined by investigators and 43 (67%) as determined by the AC (**Table 3**).
  - Of the 51 cases deemed by the investigator to meet attack criteria, eight (16%) were rejected by the AC; five were myelitis and three were optic neuritis; seven (88%) were rejected by unanimous AC decision, and six (75%) included MRI review (**Table 4**).
- In no cases did the investigator decide that attack criteria were **not** met, and the AC determine that they **were** met.
- There was a high degree of **inter**-member agreement in the AC. Of the AC decisions made, 51/64 (80%) were unanimous (34 attacks and 17 non-attacks), and 13/64 (20%) were by majority (9 attacks and 4 non-attacks) (**Figure 2a**).
- There was also a high degree of **intra**-member reliability by the AC (**Figure 2b**).
  - In total, 22/43 (51%) positively adjudicated and 13/21 (62%) negatively adjudicated events were selected randomly and resubmitted to the AC.
  - Re-adjudication concurred with the original decision in 97% of cases (22/22 of initially positive decisions and 12/13 of initially negative decisions), indicating a high degree of overall AC reliability.
    - A single adjudicator's re-review decision differed from the original in only three of the 35 cases (9%), reflecting a high degree of intra-rater reliability by AC members; in each of these three cases, the overall AC majority decision remained unchanged.

Figure 2. Breakdown of (a) inter-member and (b) intra-member AC decisions.



'Unanimous' = decisions made with the agreement of all committee members. 'Majority' = decisions made with the agreement of two out of three committee members.
AC, adjudication committee.

Figure 3. Characterization of attacks in N-MOmentum by (a) severity and (b) recovery.



(a) Attack severity was graded as minor or major, according to a predefined scale based on domain-specific neurological changes since the last assessment. (b) The level of recovery (major, minor or no recovery) was graded based on the degree of domain-specific neurological improvement 30 days after the attack assessment.

Attack characteristics

- Of the 43 AC-determined attacks, 20 were optic neuritis, 27 myelitis, and two brain/brainstem attacks, with six attacks affecting more than one domain (**Table 2**).
  - MRI was required in order to meet protocol-defined attack criteria in 16 (37%) of these attacks, indicating the importance of MRI in attack diagnosis.

Attack severity and recovery from attacks

- The severity profile of attacks in N-MOmentum was more favourable in the inebilizumab group than in the placebo group (**Figure 3a**).
  - Of the 21 AC-determined attacks in the inebilizumab-treated group, six (29%) were major and 15 (71%) were minor.
  - Of the 22 AC-determined attacks in the placebo group, 10 (45%) were major and 12 (55%) were minor.
- When compared with the placebo group, a nominally greater proportion of participants in the inebilizumab group showed signs of recovery following an attack (**Figure 3b**).
  - In the inebilizumab group, follow-up data were available for 13 attacks. Six patients (46%) exhibited no recovery and seven patients (54%) showed partial recovery: five (38%) minor and two (15%) major.
  - In the placebo group, follow-up data were available for 17 attacks. Nine patients (53%) exhibited no recovery and eight patients (47%) showed partial recovery: six (35%) minor and two (12%) major.

CONCLUSIONS

- This study helps to demonstrate that an independent AC using defined attack criteria may increase the stringency of attack diagnosis; the inter-rater and intra-rater agreement by the AC members was extremely high.
  - The lower rate of positive attack adjudication by the AC versus individual investigators highlights the difficulty in accurately diagnosing an attack even with defined criteria, and emphasizes the need for expert adjudication of attacks in NMOSD clinical studies.
- A substantial proportion (37%) of events did not meet attack criteria based solely on clinical changes, and required MRI to support adjudication, highlighting the importance of MRI in attack diagnosis.
- In addition to significantly reducing the risk of attack, inebilizumab may reduce the severity of attacks and improve recovery from NMOSD attacks compared with placebo.
- By implementing consistent processes for the diagnosis and adjudication of attacks, the N-MOmentum study provides reliable, important information on the positive effects of inebilizumab and the natural history of NMOSD attacks with respect to untreated patients.

References

1. Cree BAC *et al. Mult Scler* 2016;22:862–72.
2. Bennett JL *et al. Neurol Neuroimmunol Neuroinflamm* 2015;2:e104.
3. Fujihara K *et al. Clin Exp Neuroimmunol* 2012;3:58–73.
4. Cree BAC *et al. Lancet* forthcoming, September 2019.
5. Wingerchuk DM *et al. Neurology* 1999; 53:1107–14.

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