EFFECTS OF INEBILIZUMAB ON ATTACK SEVERITY AND BIOMARKERS OF DISEASE ACTIVITY IN NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD): N-MOMENTUM STUDY

JL Bennett[1], M. Smith[2], BG Weinshenker[3]

[1]University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, USA; [2]Horizon Therapeutics, Gaithersburg, MD, USA; [3]University of Virginia, Charlottesville, VA, USA

Background

- Neuromyelitis optica spectrum disorder (NMOSD), an autoimmune neuroinflammatory disorder can present with frequent attacks on the optic nerve, spinal cord and brain stem. These optic neuritis (ON) and transverse myelitis attacks can result in accumulated, irreversible disability and blindness.[1]
- Attacks may be severe or mild; however, consensus criteria to assess the severity of attacks are lacking.
- About 90% of patients with NMOSD have autoantibodies to the aquaporin-4 protein on the surface of astrocytes.[2] Destruction of the astrocytes releases proteins including glial fibrillary acidic protein (GFAP).[3] Neuroaxonal damage can result in the release of neurofilament light chain (NfL).[4]
- Inebilizumab is an anti-CD19 antibody, FDA-approved for treatment of adults with NMOSD who are seropositive for AQP4 autoantibodies.
- Previous post hoc analyses from N-MOmentum showed that sGFAP levels were correlated with the severity of attacks. During attacks, sGFAP levels were elevated in participants receiving placebo; they also rose in some inebilizumab-treated subjects.[6]

Objectives

- Examine the relationship of attack severity with sGFAP and sNfL in ON attacks during the N-MOmentum trial
- Assess the effect of inebilizumab on attack severity and serum biomarkers

Methods

Study Design

- N-MOmentum was a double-masked, placebo-controlled, randomized phase 2/3 trial that assessed the efficacy and safety of inebilizumab in adults with NMOSD.[5]
- The study had a time-to-event design with a 28-week randomized controlled period (RCP) (**Figure 1**). Participants were randomized (3:1) to receive intravenous inebilizumab 300 mg or placebo on days 1 and 15. RCP duration was up to 197 days or to an adjudicated attack.
- Participants who had an attack or completed the RCP could receive inebilizumab every 6 months in an open-label period (OLP) for ≥2 years.
- Participants had received treatment for ≥1 attack in the past year or ≥2 attacks in the past 2 years with an Expanded Disability Status Scale (EDSS) score ≤8.0.
- **Primary endpoint:** Time to adjudicated NMOSD attack in the RCP (defined as the presence of new or worsening NMOSD-related symptoms that met at least one prespecified criterion upon neurological evaluation.
  - All attacks were confirmed by an independent adjudication committee (AC).
- **Attack severity:** The severity of adjudicated attacks were graded by a modified opticospinal impairment scale (OSIS, **Table 1**) which uses domain-specific scores for neurological function, and characterizes attacks as major or minor based on the magnitude of changes in these scores at the attack assessment visit relative to the previous assessment.[7,8] For ON and myelitis attacks:
  - If subscale score at pre-attack visit is <2, attack was classified as Minor if score was <3 at the time of attack; Major if score was ≥3 at the time of attack
  - If subscale score at pre-attack visit is ≥2, attack was classified as Minor if score increased by 1 point at the time of attack; Major if score increased by ≥2 points at the time of attack
- **Biomarker analysis:** sGFAP and sNfL concentrations were measured in blood samples collected during RCP visits at baseline (Day 1) and on Days 15, 29, 57, 85, 113, 155, and 197. Blood samples were collected within a window of 1 week before/after an attack for assessment of sGFAP and sNfL. Concentrations were determined using the single-molecule arrays (SIMOA) assay (Quanterix, Lexington, MA, USA). Elevated concentrations were defined by being ≥2 standard deviations (SD) above the healthy donor mean concentration (≥170 pg/mL for sGFAP or >16 pg/ml for sNfL).

Analysis Population

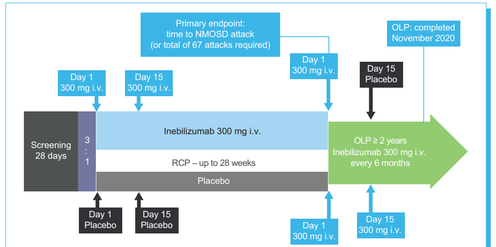
- All efficacy and safety analyses were conducted *post hoc* in the group of participants in the intent-to-treat (ITT) population in N MOmentum. The numbers and severity of attacks were also assessed in AQP4-seropositive patients.

Table 1. Subscale Scores by Domain of NMOSD Attack

Domain	Subscale Score	Description
Optic Nuritis (VA)	0	Normal
	1	Scotoma but VA ≥ 50 characters
	2	VA ≥ 35–49 characters
	3	VA ≥ 20–34 characters
	4	VA ≥ 1–19 characters
	5	Counting fingers only
	6	Light perception only
	7	No light perception
Myelitis (motor function)	0	Normal
	1	Abnormal signs (hyperreflexia, Babinski sign) without weakness
	2	Mild weakness (MRC grade 5– or 4+) in affected limb(s)
	3	Moderate weakness (MRC grade 3 or 4) in 1 or 2 UMN muscles in affected limb(s)
	4	Moderate weakness (MRC grade 3 or 4) in 3 UMN muscles in affected limb(s)
	5	Severe weakness (MRC grade 2) in 1 or more muscles in affected limb(s)
	6	Some plegic (MRC grade 0 or 1) muscles in 1 or more limbs
	7	Plegia (MRC grade 0 or 1) of all muscles in 1 or more limbs
Brain	0	Normal
	1	Drowsiness or mood changes only
	2	Mild confusion/disorientation (able to manage all self-care functions); mild focal impairment (mild aphasia, apraxia, agnosia, anorexia, or drowsiness)
	3	Moderate confusion/disorientation (able to manage some self-care functions); moderate focal impairment (moderate aphasia, apraxia, agnosia, anorexia, or drowsiness)
	4	Severe confusion/disorientation (unable to manage self-care functions); severe focal impairment (aphasia such that is unable to comprehend simple 1-step commands or speak 5-word sentences; severe apraxia, agnosia, anorexia, or drowsiness)
	5	Stupor or coma
Brainstem	0	Normal
	1	Signs only (unsustained nystagmus, impaired saccadic pursuit, ocular dysmetria, mild facial weakness, or sensory loss)
	2	Sustained conjugate nystagmus, incomplete INO, moderate facial weakness or sensory loss, or other mild disability; mild nausea and vomiting for 48 hours or longer without other explanation, with vomiting not more than 3 times per day; intractable hiccups occurring more than 20 times per hour for less than 6 hours per day
	3	Dysconjugate nystagmus (INO) or severe extraocular weakness, loss of facial sensation or facial paralysis (unilateral or bilateral), moderate dysarthria or dysphagia; moderate nausea and vomiting lasting 48 hours or longer without other explanation, with vomiting between 3 and 7 times per day; intractable hiccups occurring more than 20 times per hour for 6–12 hours per day
	4	Severe dysarthria or dysphagia, almost complete ophthalmoplegia, or other severe disability of a cranial nerve/nerves; severe nausea and vomiting lasting 48 hours or longer without other explanation, with vomiting occurring more than 7 times per day; intractable hiccups occurring more than 20 times per hour for more than 12 hours per day
	5	Inability to swallow or speak because of bulbar dysfunction; respiratory failure requiring intubation because of brainstem lesion

VA represents corrected visual acuity based on high-contrast Landolt Broken Ring C-chart.

Figure 1. N-MOmentum Study Design



Participants were eligible for the open-label period at the end of the RCP or after an adjudicated attack.
NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized control period.

Results

- In the N-Momentum trial, 174 participants received inebilizumab and 56 received placebo. At baseline, characteristics were similar between groups; 91% were female.[5]
- A total of 43 AC-determined attacks occurred during the RCP in 22/56 (39.3%) of the placebo-treated and 21/174 (12.1%) of participants in the inebilizumab-treated group (**Table 2**).

Table 2. Type of Attacks in the Placebo and Inebilizumab Arm by Domain (ITT) in the RCP

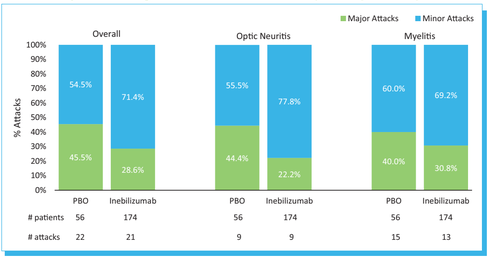
Attack Outcome, n (%)	Placebo (n=56)	Inebilizumab (n=174)
AC- determined attacks, (n [%] of the number of patients in each arm		
	22 (39.3%)	21 (12.1%)
Isolated attacks according to type, (n [%] of number of attacks in each arm)		
Optic neuritis	7 (31.8%)	8 (38.1%)
Myelitis	11 (50.0%)	11 (52.4%)
Brain/Brainstem	—	—
Attacks affecting multiple domains		
Optic neuritis and myelitis	2 (9.1%)	2 (9.5%)
Optic neuritis and brain/brainstem	1 (4.5%)	0
Myelitis and brain/brainstem	1 (4.5%)	0

The type of attack is based on investigator reported criteria.

Severity of AC-Determined Optic Neuritis and Myelitis Attacks

- A smaller proportion of attacks in the inebilizumab group were major compared to the placebo group (**Table 3**, **Figure 2**) (p=0.35).
  - In the placebo group 10/22 (45%) attacks were major and 12 (55%) were minor.
  - In the inebilizumab group, 6/21 (29%) were major and 15/21 (71%) were minor.
- Fewer major attacks occurred in the inebilizumab group for both optic neuritis and myelitis (**Table 3**, **Figure 2**).

Figure 2. Adjudication Committee-Determined NMOSD Attacks Based on Severity According to the OSIS in the RCP (ITT Population)



The type of attack is based on investigator reported criteria.

Table 3. Severity of AC-determined Optic Neuritis and Myelitis Attacks in the RCP (ITT and AQP4+); n (%) of Overall Attacks

	Placebo (22 attacks); ITT N=56	Inebilizumab (21 attacks); ITT N=174	Placebo (22 attacks); AQP4+ N=52	Inebilizumab (18 attacks); AQP4+ N=161
Overall				
Major	10 (45.5)	6 (28.6)	10 (45.5)	6 (33.3)
Minor	12 (54.5)	15 (71.4)	12 (54.5)	12 (66.6)
Optic Neuritis				
Major	4 (18.2)	2 (9.5)	4 (18.2)	2 (11.5)
Minor	5 (22.7)	7 (33.3)	5 (22.7)	5 (27.8)
Myelitis				
Major	6 (27.3)	4 (19.0)	6 (27.3)	4 (22.2)
Minor	9 (40.9)	9 (42.9)	9 (40.9)	8 (44.2)

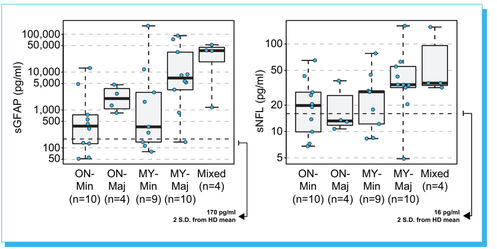
The type of attack is based on investigator reported criteria.

- Among AQP4-seropositive participants, 22/52 (42.3%) in the placebo group and 18/161 (11.2%) in the Inebilizumab group had AC-determined attacks. Similar to the ITT population, in the inebilizumab group a smaller proportion of attacks were major compared to the placebo group (**Table 3**).

Correlation of sGFAP and sNfL with Attack Severity by OSIS

- Levels of sGFAP were significantly higher during major vs minor attacks (p=0.023). The median fold change [IQR] from baseline for major attacks was 34.32 [8.72–107.53], and 1.06 [0.85–7.43] for minor attacks.
- For ON attacks, a trend toward increased sGFAP during major attacks was observed (p=0.06) (**Figure 3**).
- Increased levels of sGFAP were also observed during major myelitis attacks.
- Levels of sNfL trended with severity of myelitis attacks but not of ON attacks.

Figure 3. Concentrations of sGFAP and sNfL Biomarkers During Major and Minor Optic Neuritis and Transverse Myelitis Attacks According to OSIS in the RCP (ITT Population)

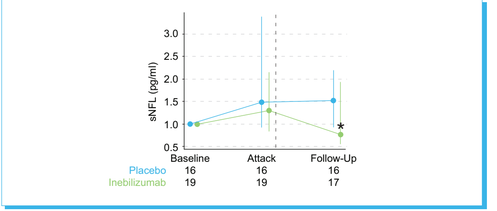


sGFAP and sNfL concentrations are presented on log and linear scales respectively. ON, optic neuritis attacks; MY, myelitis attacks.

Changes in sGFAP and sNfL Concentrations During Attacks and with Treatment

- An increase from baseline in sGFAP concentrations was observed during attacks, most notably in placebo-treated participants (median fold change from baseline [IQR]: 20.2 [4.4–98.3]; p=0.001), but sGFAP was not significantly elevated in inebilizumab-treated participants (1.1 [0.8–24.6]; p>0.05) (**Figure 4**). Similar trends were seen in patients experiencing ON.
- Though concentrations of sNfL did trend with severity of myelitis attacks, they did not appreciably change from baseline during an attack for placebo-treated participants (1.49 [0.93-3.37]) or inebilizumab-treated participants (1.3 [0.84-2.14]).
- While sNfL was not different during attacks for inebilizumab vs placebo (p=0.40), in participants who had an attack during the RCP, sNfL was higher for placebo vs inebilizumab treatment at follow-up (week 26, p=0.03) (**Figure 5**).

Figure 5. Concentrations of sNfL at Baseline, During Attacks and Post-Attack in Placebo and Inebilizumab-Treated Participants in the RCP (ITT Population)

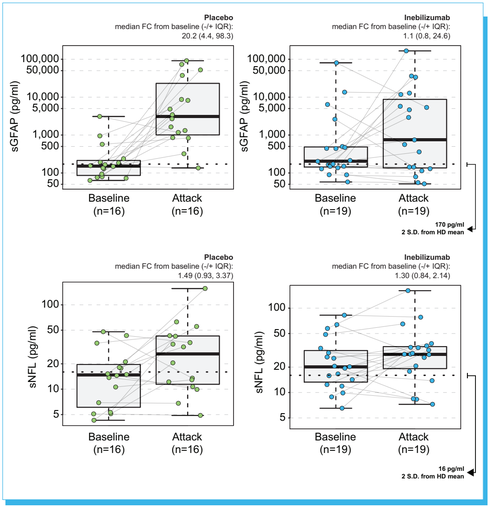


*p=0.03

Data in this poster have been previously presented in full at NANOS; February 12-17, 2022; Austin, TX, USA; Poster #227.

Presented at the Consortium of Multiple Sclerosis Centers (CMSC) 2022 Annual Meeting), National Harbor, Maryland, June 1–4, 2022.

Figure 4. Concentrations of sGFAP and sNfL Biomarkers at Baseline and During Attacks in Placebo and Inebilizumab-Treated Participants in the RCP (ITT Population)



Presents concentrations where matched samples available at baseline and at attack.

Conclusions

- There were fewer severe attacks in participants receiving inebilizumab compared to placebo.
- Increased concentrations of sGFAP were observed during major versus minor attacks, both for ON and myelitis. Increases from baseline in sGFAP concentrations occurred only in the placebo but not the inebilizumab group.
- sNfL concentrations did not show a correlation with attack severity for ON, although they trended with severity of myelitis attacks.
- In participants that had an attack during the RCP, sNfL was higher for placebo vs inebilizumab treatment at follow-up (week 26).

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DISCLOSURES

JL Bennett reports payment for study design/consultation from MedImmune; personal fees from AbbVie, Alexion, Chugai, Clene Nanomedicine, Genentech and Genzyme; grants and personal fees from EMD Serono and Novartis; and grants from the National Eye Institute. In addition, Dr Bennett has a patent 'Compositions and methods for the treatment of neuromyelitis optica' issued.

BG Weinshenker received payments for serving as chair of attack adjudication committees for clinical trials in NMOSD for Alexion, Horizon Therapeutics and MedImmune and UCB Biosciences; has consulted with Chugai, Genentech, Mitsubishi Tanabe Pharma, Roche Pharmaceuticals and UCB Biosciences regarding clinical trial design; 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, Oxford University and RSR.

M Smith is an employee of Horizon and owns stock.

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