Sensitivity analyses of time to adjudicated attacks in the N-MOmentum study: a randomized, placebo-controlled, double-masked trial in patients with neuromyelitis optica spectrum disorder

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INTRODUCTION

- Neuromyelitis optica spectrum disorder (NMOSD) is a severe, autoimmune, inflammatory disease of the central nervous system characterized by repeated attacks of optic neuritis, transverse myelitis or brain/brainstem encephalitis, which causes disability or death.[1]
- N-MOmentum is a prospective, randomized, placebo-controlled, double-masked trial of inebilizumab, an anti-CD19 monoclonal B-cell-depleting antibody, in patients with NMOSD.[2]
- In N-MOmentum the risk of an adjudicated NMOSD attack was significantly reduced with inebilizumab compared with placebo.[2]

OBJECTIVE

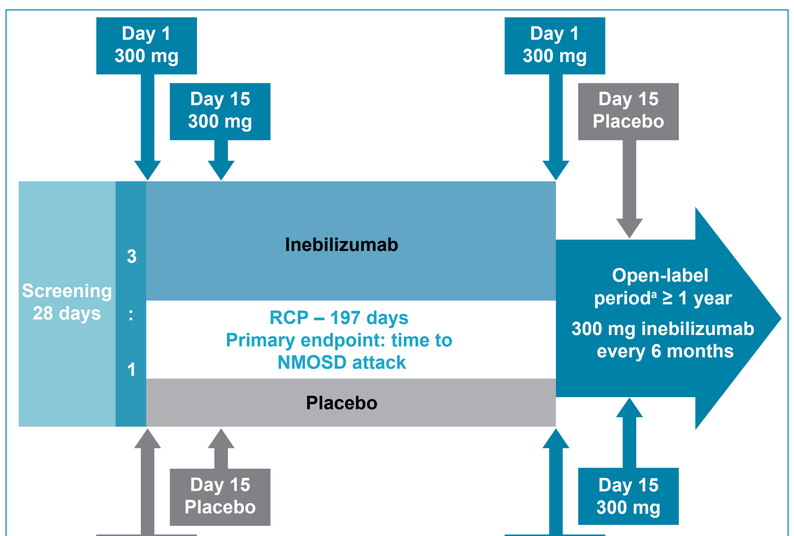
- To assess the robustness of the primary endpoint in N-MOmentum, the time to an adjudicated NMOSD attack, using pre-planned sensitivity and subset analyses.

METHODS

Study design

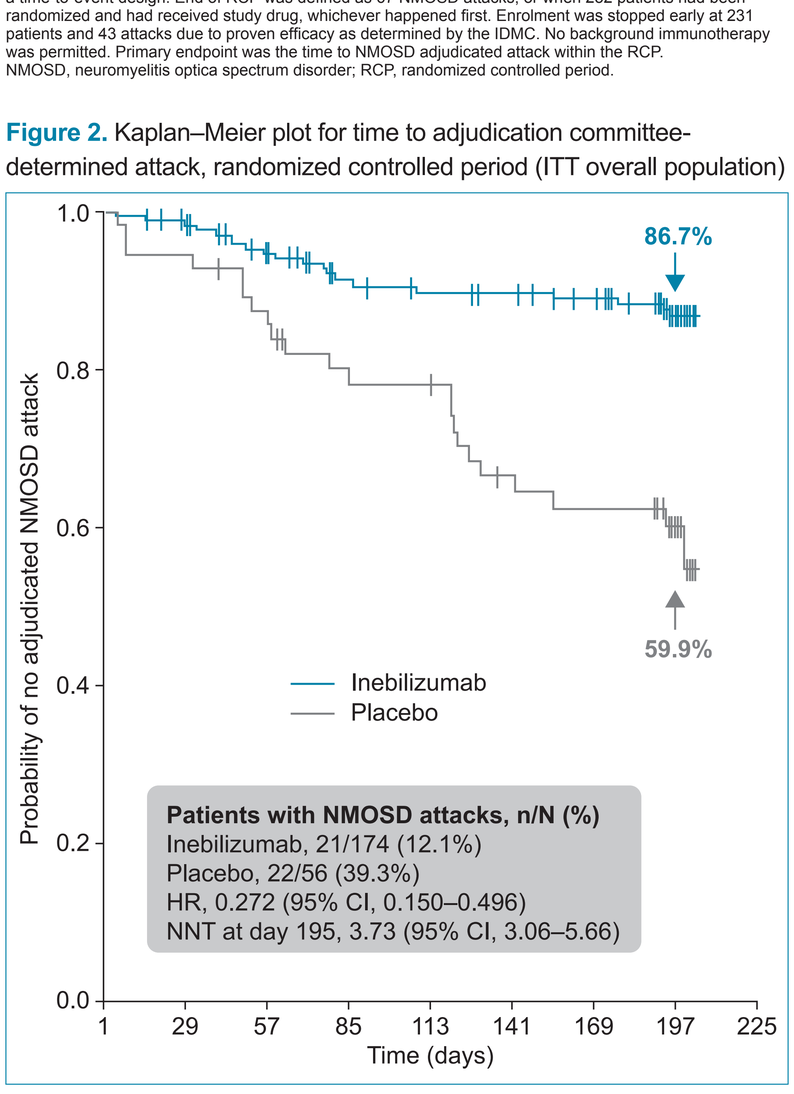
- Adults with NMOSD and an Expanded Disability Status Scale score of ≤ 8 were randomly assigned (3:1) to receive intravenous inebilizumab 300 mg or placebo on days 1 and 15, with no other treatments allowed (**Figure 1**).
  - Participants could be aquaporin 4 (AQP4)-IgG seropositive or seronegative.
- The randomized controlled period was 28 weeks or up to an adjudicated attack.
  - Attacks were evaluated using predefined attack diagnosis criteria, which were developed specifically for this study.
  - Each attack was assessed by study investigators and an independent adjudication committee (AC) composed of three members.
- Only attacks confirmed by an AC majority (2/3) were used for the primary endpoint analysis.
- Sensitivity and subset analyses were performed to assess whether the primary endpoint remained significant when considering attacks as reported by unanimous AC decisions, by investigators or by patients.
- Subsets of the primary endpoint defined by attack type or the inclusion of patients who discontinued prematurely were also assessed.

Figure 1. N-MOmentum study design



[a]Patients eligible for the open-label period at the end of the RCP or after an adjudicated attack.
N-MOmentum was a double-masked, placebo-controlled study at 99 medical centres in 25 countries, with a time-to-event design. End of RCP was defined as 67 NMOSD attacks, or when 252 patients had been randomized and had received study drug, whichever happened first. Enrolment was stopped early at 231 patients and 43 attacks due to proven efficacy as determined by the IDMC. No background immunotherapy was permitted. Primary endpoint was the time to NMOSD adjudicated attack within the RCP.
NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period.

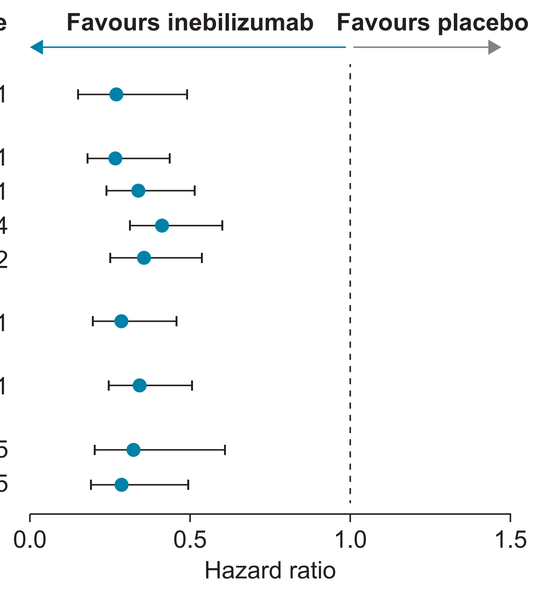
Figure 2. Kaplan–Meier plot for time to adjudication committee-determined attack, randomized controlled period (ITT overall population)



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

Figure 3. Sensitivity and subset analyses for primary variable (time to adjudicated attack; overall population)

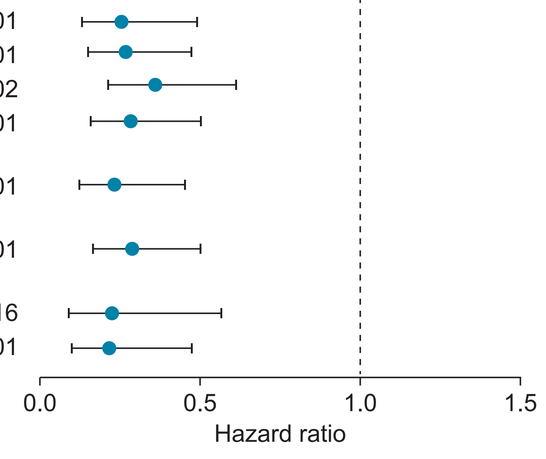
Sensitivity/subset analysis	Number of patients with an attack: Placebo (n = 56)	Inebilizumab (n = 174)	HR (95% CI)	*p* value
AC-determined NMOSD attacks (primary analysis)	22 (39.3%)	21 (12.1%)	0.272 (0.150–0.496)	< 0.0001
Unanimous AC decisions	18 (32.1%)	16 (9.2%)	0.248 (0.126–0.486)	< 0.0001
Investigator-determined attacks	23 (41.1%)	26 (14.9%)	0.323 (0.184–0.568)	< 0.0001
Patient-reported attacks	25 (44.6%)	34 (19.5%)	0.393 (0.235–0.660)	0.0004
Attacks including patients who prematurely discontinued the study	22 (39.3%)	26 (14.9%)	0.338 (0.191–0.597)	0.0002
Attacks based on only clinical criteria and not requiring MRI confirmation	19 (33.9%)	18 (10.3%)	0.267 (0.140–0.509)	< 0.0001
Combined attacks or use of rescue therapy	25 (44.6%)	29 (16.7%)	0.327 (0.191–0.558)	< 0.0001
Optic neuritis attacks	10 (17.9%)	10 (5.7%)	0.288 (0.120–0.694)	0.0055
Spinal cord attacks	14 (25%)	13 (7.5%)	0.262 (0.123–0.558)	0.0005



Based on Cox regression method, with placebo as the reference group.
AC, adjudication committee; CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging.

Figure 4. Sensitivity and subset analyses for primary variable (time to adjudicated attack; AQP4-IgG seropositive population)

Sensitivity/subset analysis	Number of patients with an attack: Placebo (n = 52)	Inebilizumab (n = 161)	HR (95% CI)	*p* value
AC-determined NMOSD attacks (primary analysis)	22 (42.3%)	18 (11.2%)	0.227 (0.121–0.423)	< 0.0001
Unanimous AC decisions	18 (34.6%)	16 (9.9%)	0.248 (0.126–0.486)	< 0.0001
Investigator-determined attacks	23 (44.2%)	22 (13.7%)	0.262 (0.146–0.470)	< 0.0001
Patient-reported attacks	24 (46.1%)	30 (18.6%)	0.354 (0.207–0.607)	0.0002
Attacks including patients who prematurely discontinued the study	22 (42.3%)	22 (13.7%)	0.275 (0.152–0.498)	< 0.0001
Attacks based on only clinical criteria and not requiring MRI confirmation	19 (36.5%)	16 (9.9%)	0.231 (0.119–0.450)	< 0.0001
Combined attacks or use of rescue therapy	24 (46.2%)	25 (15.5%)	0.285 (0.163–0.500)	< 0.0001
Optic neuritis attacks	10 (19.2%)	8 (5.0%)	0.222 (0.088–0.565)	0.0016
Spinal cord attacks	14 (26.9%)	11 (6.8%)	0.214 (0.097–0.472)	0.0001



Based on Cox regression method, with placebo as the reference group.
AC, adjudication committee; AQP4-IgG; aquaporin 4 immunoglobulin G; CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging.

RESULTS

Participants

- Of the 467 participants screened, 230 were randomized and dosed, with 175 randomly assigned to inebilizumab (with one patient not dosed) and 56 to placebo (overall population).
  - In the subset of patients who were AQP4-IgG seropositive, 161 were randomized to inebilizumab and 52 to placebo.
- Baseline demographics and characteristics were generally similar between treatment groups in the overall population and in AQP4-IgG seropositive participants.

Primary analysis of time to adjudicated attacks

- According to majority AC decision, 21/174 patients (12.1%) who received inebilizumab and 22/56 (39.3%) who received placebo experienced attacks.
  - The risk reduction for inebilizumab versus placebo was 72.8%; hazard ratio, 0.272 (95% confidence interval, 0.150–0.496), $p < 0.0001$ (**Figure 2**).

Sensitivity and subset analyses of time to adjudicated attack

- **The reduction in the risk of attack with inebilizumab versus placebo was significant in all sensitivity and subset analyses (Figure 3).**
- These analyses included:
  - only unanimous AC decisions, to account for any potential uncertainty in adjudication by censoring any attacks that were adjudicated by a majority decision
  - investigator-determined attacks, to control for any potential bias introduced by remote attack adjudication or the AC process
  - patient-reported attacks, including all events for which patients reported a potential attack, irrespective of whether the investigators or the AC later confirmed the attack
  - attacks in patients who prematurely discontinued the study without experiencing an attack, thus adjusting for any attrition in patient numbers
  - attacks based on only clinical criteria and not requiring magnetic resonance imaging confirmation, controlling for the use of imaging tools in attack diagnosis
  - AC-determined attacks or use of rescue therapy (intravenous corticosteroids, intravenous immunoglobulin and/or plasma exchange), broadening the definition of attacks to include events that required clinical intervention, even though they may not have fully met the attack criteria
  - only optic neuritis attacks, indicating that the treatment effect was significant for this specific subset of attacks
  - only brainstem/spinal cord attacks, indicating that the treatment effect was significant for this specific subset of attacks.
- The reduction in the risk of attack with inebilizumab versus placebo was also significant in all sensitivity and subset analyses in the AQP4-IgG seropositive population (**Figure 4**).
- These results suggest that the result of the primary endpoint was robust and insensitive to any of these potential confounders.

CONCLUSIONS

- In N-MOmentum, inebilizumab consistently provided a statistically significant reduction in the risk of attacks compared with placebo, regardless of who evaluated or reported attacks, whether decisions were based on only clinical criteria, and also when considering individual attack types separately.
- These results confirm the robustness of the primary endpoint in the N-MOmentum study in both the AQP4-IgG seropositive and the overall populations.

References

1. Cree BAC *et al. Mult Scler* 2016;22:862–72.
2. Cree BAC *et al. Lancet.* Forthcoming, September 2019.

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