Inebilizumab reduces worsening of disability in neuromyelitis optica spectrum disorder: outcomes from the N-MOmentum randomized, placebo-controlled, double-masked trial

P1604

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INTRODUCTION

- Inebilizumab is a monoclonal antibody that targets CD19, an antigen expressed on immune cells of the B cell lineage.[1]
  - Inebilizumab can deplete antibody-secreting plasmablasts and some plasma cells that are CD20 negative.[1]
- Inebilizumab was assessed in N-MOmentum, a randomized, placebo-controlled, double-masked trial in patients with neuromyelitis optica spectrum disorder (NMOSD).[2]
  - N-MOmentum met its primary endpoint of time to NMOSD attack in the randomized controlled period (RCP); inebilizumab significantly reduced the risk of NMOSD attack compared with placebo (relative risk reduction 72.8% overall, 77.3% for the aquaporin 4 [AQP4]-immunoglobulin [Ig] G+ subgroup).
  - The number needed to treat to prevent one attack at 6.5 months was 3.7 for the overall population and 3.2 for the AQP4-IgG+ subgroup.

OBJECTIVE

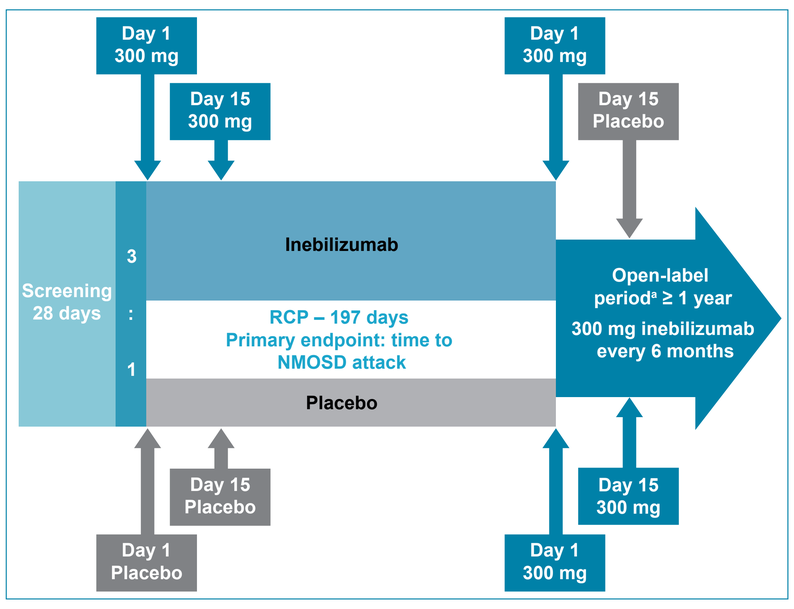
- To assess the effects of inebilizumab on disability in N-MOmentum study participants and to determine if the severity of pre-existing disability influenced efficacy.

METHODS

Study design

- Adults with NMOSD and an Expanded Disability Status Scale (EDSS) score of 8 or lower were randomly assigned (3:1) to receive intravenous inebilizumab 300 mg or placebo on days 1 and 15 (**Figure 1**). Both AQP4-IgG+ and AQP4-IgG– patients were included.
- The RCP for each participant was up to day 197 or until occurrence of an adjudication committee-determined attack.

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.

Evaluation of disability outcomes in patients with NMOSD

- EDSS score was evaluated periodically by a qualified and trained independent rater.
  - The proportion of patients with disability worsening (EDSS score increase ≥ 2 from a baseline of 0, ≥ 1 from a baseline of 1–5, or ≥ 0.5 from a baseline of ≥ 5.5) was assessed by logistic regression.
  - Pre-specified subgroup analyses of risk of EDSS score worsening were performed for baseline EDSS score (< 5 vs ≥ 5), number of prior NMOSD relapses (< 2 vs ≥ 2) and disease duration (< 5 vs ≥ 5 years) using Cox proportional hazards regression.
- Modified Rankin Scale (mRS) score was assessed periodically by the study investigator (see **Table 1** for mRS description).
  - Changes from baseline in mRS scores were analysed by the Wilcoxon–Mann–Whitney odds approach.
- Pre-specified subgroup analysis of the primary outcome (time to adjudicated attack) was performed using Cox proportional hazards regression, grouping patients by baseline EDSS score (< 5 vs ≥ 5).

RESULTS

Participants

- Of the 467 participants screened, 231 were enrolled, with 175 randomized to inebilizumab and 56 to placebo.
- Baseline demographics and characteristics were generally similar between treatment groups (**Table 2**).

Disability outcomes in patients with NMOSD

- The median (range) baseline EDSS score for patients receiving inebilizumab (n = 174) was 3.5 (0–8) compared with 4.0 (1–8) for those receiving placebo (n = 56) (**Table 2**).

Table 1. Modified Rankin Scale.

mRS score	Score definition
0	No symptoms
1	No significant disability; able to carry out all usual activities despite some symptoms
2	Slight disability; able to look after own affairs without assistance but unable to carry out all previous activities
3	Moderate disability; requires some help, but able to walk unassisted
4	Moderately severe disability; unable to attend to own bodily needs without assistance and unable to walk unassisted
5	Severe disability; requires constant nursing care and attention, bedridden, incontinent
6	Dead

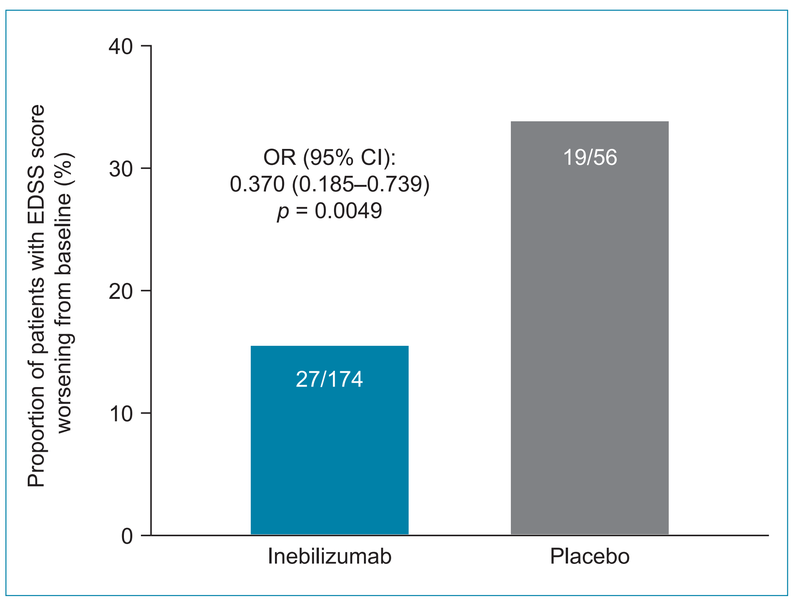
mRS, modified Rankin Scale.

Table 2. Summary of baseline demographics and characteristics (intent-to-treat population).

Demographic/characteristic	Placebo n = 56	Inebilizumab n = 174
Age, years (mean [SD])	42.6 (13.9)	43.0 (11.6)
Sex, women	50 (89.3)	159 (91.4)
Race		
American Indian/Alaskan Native	5 (8.9)	14 (8.0)
Asian	8 (14.3)	39 (22.4)
Black or African American	5 (8.9)	15 (8.6)
White	28 (50.0)	92 (52.9)
Other/multiple categories checked	10 (17.9)	14 (8.0)
Disease duration, years (mean [SD])	2.8 (3.5)	2.4 (3.3)
Most recent attack		
Optic neuritis	21 (37.5)	85 (48.9)
Myelitis	34 (60.7)	99 (56.9)
Brain/brainstem	10 (17.9)	8 (4.6)
Number of Gd+ lesions (mean, [SD])	0.9 (0.9)	1.2 (1.2)
EDSS score (median, [range])	4.0 (1.0–8.0)	3.5 (0–8.0)
EDSS category		
0	0	4 (2.3)
< 5	40 (71.4)	129 (74.1)
≥ 5	16 (28.6)	41 (23.6)
Modified Rankin Scale (median, [range])	2 (0.5)	2 (0.5)
Number of prior relapses		
<2	14 (25.0)	25 (14.4)
≥2	42 (75.0)	149 (85.6)

Data are n (%) unless stated otherwise.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SD, standard deviation.

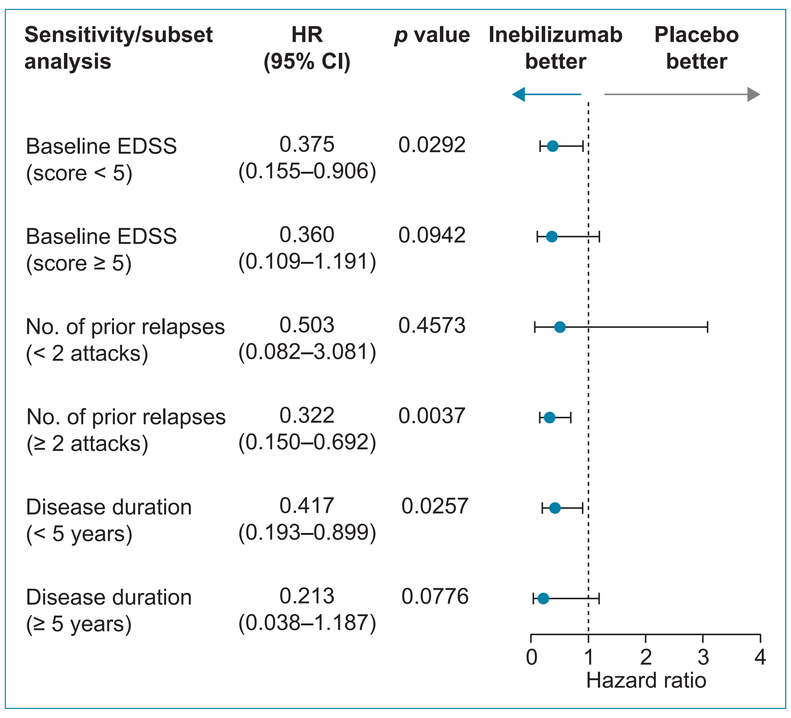
Figure 2. Proportion of patients with EDSS score worsening from baseline to end of the RCP.



Subjects with missing data are imputed as 'worsening', the denominator represents the total number of subjects in each treatment group with baseline score.
CI, confidence interval; EDSS, Expanded Disability Status Scale; OR, odds ratio; RCP, randomized controlled period.

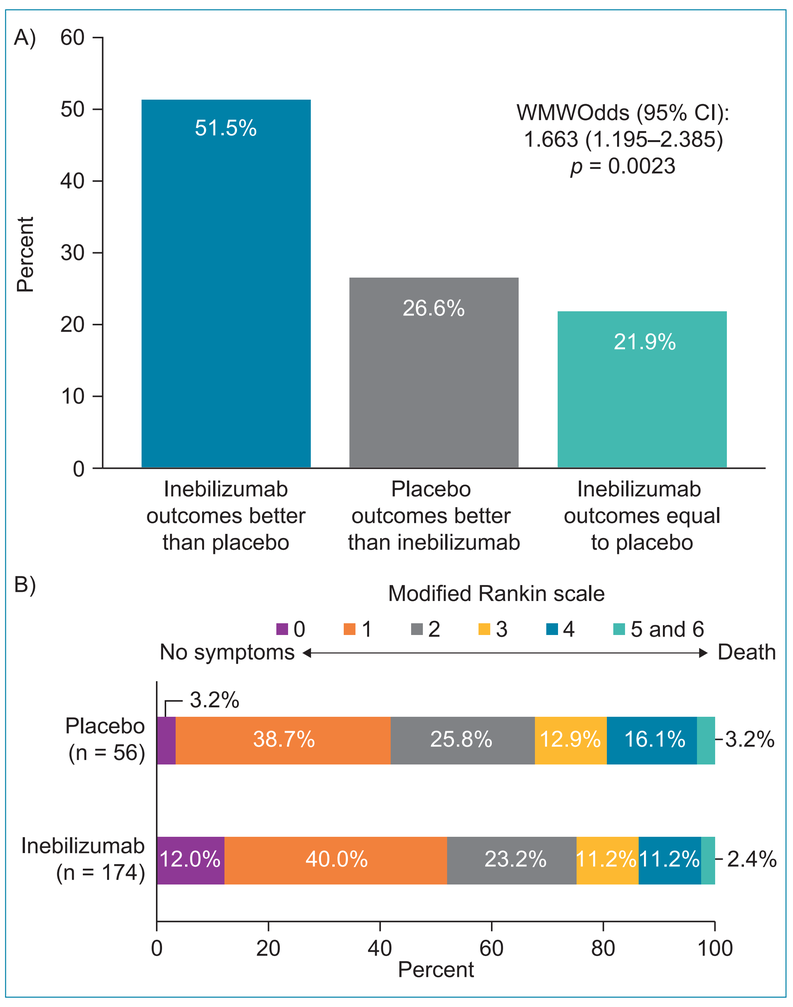
- A lower proportion of patients in the inebilizumab group than in the placebo group had a worsening in EDSS score at the end of the RCP (15.5% vs 33.9%).
  - Odds ratio (95% confidence interval [CI]): 0.370 (0.185–0.739); $p = 0.0049$ (**Figure 2**).
  - The number needed to treat to prevent one EDSS score worsening at 6.5 months was 6.
- Pre-specified subgroup analyses of risk of worsening EDSS score showed a consistent trend of reduced risk with inebilizumab compared with placebo, regardless of baseline EDSS score category, number of prior NMOSD relapses and disease duration (**Figure 3**).
- The median (range) baseline mRS score was 2 (0–5) for both the inebilizumab and placebo groups (**Table 2**).
- For 9632 paired comparisons, mRS outcomes at the end of the RCP were better with inebilizumab than placebo in 51.5% of cases and were equal in 21.9% of cases.
  - Patients receiving inebilizumab were 66.3% more likely to report less disability than those on placebo; odds ratio (95% CI): 1.663 (1.195–2.385); $p = 0.0023$ (**Figure 4**).
- Compared with placebo, inebilizumab reduced the risk of attack in patients with baseline EDSS score in the lower half (< 5) or the upper half (≥ 5) of the 10-point scale.
  - Hazard ratios (95% CI): 0.257 (0.120–0.552); $p = 0.0005$ and 0.367 (0.137–0.981); $p = 0.0456$, respectively.
  - The treatment effect was not significantly different between the EDSS groups; interaction test, $p = 0.6363$ (**Figure 5**).

Figure 3. Subgroup analyses of risk of EDSS score worsening from baseline to end of RCP.



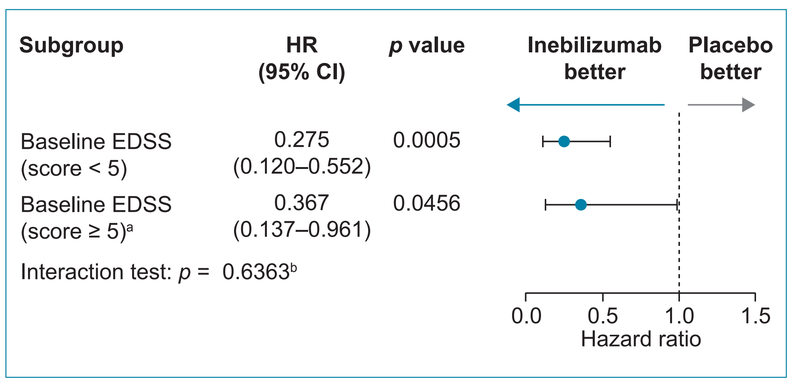
EDSS, Expanded Disability Status Scale; HR, hazard ratio; RCP, randomized controlled period.

Figure 4. A) Treatment effect based on mRS score during the RCP; B) distribution of mRS during the RCP.



CI, confidence interval; mRS, modified Rankin Scale; WMWOdds, Wilcoxon–Mann–Whitney odds ratio; RCP, randomized controlled period.

Figure 5. Subgroup analysis of the risk of attack (primary endpoint) by EDSS category.



[a]Based on Kaplan–Meier method. [b]Based on Cox regression method, with placebo as the reference group.
CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio.

CONCLUSIONS

- In N-MOmentum, disability outcomes were significantly better with inebilizumab than with placebo, as measured by EDSS and mRS.
  - The number needed to treat with inebilizumab to prevent one EDSS score worsening at 6.5 months was 6.
- Subgroup analyses demonstrated a consistent trend in the reduction in risk of EDSS score worsening in the inebilizumab group, regardless of baseline disability status, relapse history or disease duration.
- Compared with placebo, inebilizumab reduced the risk of attack in patients with NMOSD irrespective of the level of pre-existing disability.
- These data underline the positive effect of inebilizumab on disabilty in patients with NMOSD.

References

1. Chen D *et al. J Clin Med* 2016:5:107.
2. Cree BAC *et al. Lancet.* Forthcoming, September 2019.

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