Safety and efficacy of inebilizumab for the treatment of neuromyelitis optica spectrum disorder: end-of-study results from the open-label period of the N-MOmentum trial

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Summary

Background Inebilizumab, an anti-CD19 B-cell-depleting antibody, demonstrated safety and efficacy in neuromyelitis optica spectrum disorder in the randomised controlled period of the N-MOmentum trial. Here, end-of-study data, including the randomised controlled period and open-label extension period, are reported.

Methods In the double-blind, randomised, placebo-controlled, phase 2/3 N-MOmentum trial, adults aged 18 years and older with an neuromyelitis optica spectrum disorder diagnosis, Expanded Disability Status Scale score of 8·0 or less, and history of either at least one acute inflammatory attack requiring rescue therapy in the past year or two attacks requiring rescue therapy in the past 2 years, were recruited from 81 outpatient specialty clinics or hospitals in 24 countries. Eligible participants were randomly assigned (3:1), using a central interactive voice system or interactive web response system, and a permuted block randomisation scheme (block size of 4), to receive intravenous inebilizumab (300 mg) or identical placebo on days 1 and 15 of the randomised period, which lasted up to 197 days. Participants and all study staff were masked to treatment assignment. The primary endpoint of the randomised period of the trial was time to onset of adjudicated neuromyelitis optica spectrum disorder attack on or before day 197. Participants in the randomised controlled period who had an adjudicated attack, completed 197 days in the study, or were in the randomised controlled period when enrolment stopped, could voluntarily enter the open-label period. In the open-label period, participants either initiated inebilizumab if assigned placebo (receiving 300 mg on days 1 and 15 of the open-label period) or continued treatment if assigned inebilizumab (receiving 300 mg on day 1 and placebo on day 15, to maintain B-cell depletion and masking of the randomised controlled period). All participants subsequently received inebilizumab 300 mg every 6 months for a minimum of 2 years. The end-of-study analysis endpoints were time to adjudicated attack and annualised attack rate (assessed in all participants who received inebilizumab at any point during the randomised controlled period or open-label period [any inebilizumab population] and the aquaporin-4 [AQP4]-IgG seropositive subgroup [any inebilizumab-AQP4-IgG seropositive population]) and safety outcomes (in all participants who were exposed to inebilizumab, analysed as-treated). This study is registered with ClinicalTrials.gov, NCT02200770, and is now complete.

Findings Between Jan 6, 2015, and Sept 24, 2018, 467 individuals were screened, 231 were randomly assigned, and 230 received at least one dose of inebilizumab (n=174) or placebo (n=56). Between May 19, 2015, and Nov 8, 2018, 165 (95%) of 174 participants in the inebilizumab group and 51 (91%) of 56 in the placebo group entered the open-label period (mean age 42·9 years [SD 12·4], 197 [91%] of 216 were female, 19 [9%] were male, 115 [53%] were White, 45 [21%] were Asian, 19 [9%] were American Indian or Alaskan Native, and 19 [9%] were Black or African American). As of data cutoff for this end of study analysis (Dec 18, 2020; median exposure 1178 days [IQR 856–1538], total exposure of 730 person-years) 225 participants formed the any inebilizumab population, and 208 (92%) participants were AQP4-IgG seropositive. Overall, 63 adjudicated neuromyelitis optica spectrum disorder attacks occurred in 47 (21%) of 225 treated participants (60 attacks occurred in 44 [21%] of 208 in the AQP4-IgG seropositive subgroup); 40 (63%) of 63 attacks occurred in 34 (15%) of 225 treated participants during the first year of treatment. Of individuals who had an adjudicated attack while receiving inebilizumab, 36 (77%) of 47 were subsequently attack-free at the end of 4 years. Annualised attack rates decreased year-on-year, with end-of-study adjusted annualised attack rates being similar in the any inebilizumab-AQP4-IgG seropositive subgroup (0·097 [95% CI 0·070–0·14]) and any inebilizumab populations (0·092 [0·067–0·13]). Overall, 208 (92%) of 225 participants who received any inebilizumab had at least one treatment-emergent adverse event, the most frequent of which were urinary tract infection (59 [26%]), nasopharyngitis (47 [21%]), and arthralgia (39 [17%]). Infection rates did not increase over 4 years. Three (1%) of 225 participants in the any inebilizumab population died during the open-label period (one each due to a CNS event of unknown cause and pneumonia, respiratory insufficiency resulting from an neuromyelitis optica spectrum disorder attack and viral pneumonia related to COVID-19), all of which were deemed to be unrelated to treatment.

Interpretation Data from the end-of-study analysis of the N-MOmentum trial showed continued and sustained clinical benefits of long-term inebilizumab treatment in individuals with neuromyelitis optica spectrum disorder, which supports the role of inebilizumab as a CD19+ B-cell-depleting therapy in neuromyelitis optica spectrum disorder.

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Introduction

Neuromyelitis optica spectrum disorder is a rare, severe autoimmune disease characterised by acute inflammatory attacks affecting the optic nerves and spinal cord, and sometimes the brainstem or cerebrum.[1] Attacks are recurrent in most people with neuromyelitis optica spectrum disorder and are linked to irreversible accumulation of neurological disability and worsening quality of life.[2] Neuromyelitis optica spectrum disorder is thought to be driven by pathogenic autoantibodies against aquaporin-4 (AQP4) in 90% of individuals.[3–5] Binding of anti-AQP4 autoantibodies to AQP4 on astrocytes activates the classical complement pathway, as well as complement-independent mechanisms of cytotoxicity, leading to astrocyte death, demyelination, and neuronal loss.[6–9] In addition to secreting antibodies to AQP4, B cells contribute to neuromyelitis optica spectrum disorder pathophysiology by driving T-cell responses through pro-inflammatory cytokine secretion and antigen presentation.[3,6]

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2019 (the start of the year that the primary N-MOmentum manuscript was published) and June 30, 2023, using the search terms "neuromyelitis" OR "NMO" OR "NMOSD" OR "Devic's disease" and retrieved 2844 articles. Results from clinical trials and systematic reviews were identified. Internet searches were also conducted for relevant congress presentations (Americas Committee for Treatment and Research in Multiple Sclerosis, European Committee for Treatment and Research in Multiple Sclerosis, American Academy of Neurology, Consortium of Multiple Sclerosis; performed with the same date restrictions above). In addition to the publication of the primary results and several subgroup analyses of the phase 2/3 N-MOmentum trial, we identified two phase 3 clinical trials and their extension phases that reported the safety and efficacy of the anti-IL-6 receptor antibody satralizumab in the treatment of neuromyelitis optica spectrum disorder; a phase 3 clinical trial and extension study showed the benefits of the anti-complement C5 antibody eculizumab in neuromyelitis optica spectrum disorder; another anti-complement C5 antibody, ravulizumab, was efficacious in a phase 3 clinical trial; phase 2 clinical trial results were reported for the IL-6 receptor inhibitor tocilizumab; and phase 2/3 results reported for the anti-CD20 monoclonal antibody rituximab in individuals with neuromyelitis optica spectrum disorder. Phase 1 studies reported on the safety and tolerability of batoclimab, a neonatal Fc receptor antagonist, and the anti-CD20 monoclonal antibody ublituximab as add-on therapies in neuromyelitis optica spectrum disorder. Several non-systematic and systematic reviews of evidence for these different treatments in neuromyelitis optica spectrum disorder were published, although differences in trial design complicate their direct comparison. The pivotal studies prompted US Food and Drug Administration (FDA) approval of eculizumab, inebilizumab, and satralizumab for the treatment of neuromyelitis optica spectrum disorder in adults in 2019. Rituximab and tocilizumab are currently used off-label for the treatment of neuromyelitis optica spectrum disorder.

Added value of this study

N-MOmentum was a double-blind, randomised, placebo-controlled, phase 2/3 study with an open-label extension period assessing the safety and efficacy of inebilizumab in individuals with neuromyelitis optica spectrum disorder. Among the three FDA-approved therapies for neuromyelitis optica spectrum disorder, inebilizumab is the only B cell-depleting therapy and targets the B cell-specific membrane protein CD19, a novel therapeutic target in neuromyelitis optica spectrum disorder. This end-of-study analysis of data, for which participants were recruited from 81 outpatient specialty clinics or hospitals in 24 countries, captures 730 person-years of exposure to inebilizumab throughout the N-MOmentum randomised controlled period and open-label period. The safety profile of B-cell depletion with inebilizumab and the therapeutic effect of inebilizumab on attack risk, disability worsening, MRI lesion activity, and hospitalisations in individuals with neuromyelitis optica spectrum disorder over the longer term is reported.

Implications of all the available evidence

Across the randomised controlled period and open-label period of N-MOmentum, we found sustained clinical benefits of long-term treatment with inebilizumab in individuals with neuromyelitis optica spectrum disorder, thereby supporting the use of this drug as a CD19+ B cell-depleting therapy in neuromyelitis optica spectrum disorder.

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Neuromyelitis optica spectrum disorder treatment involves management of acute inflammatory attacks and long-term prevention of further attacks with immunotherapies.[10] Inebilizumab is a humanised monoclonal antibody that binds to the B-cell surface antigen CD19, and it is now approved in Brazil, China, the EU, Japan, South Korea, and the USA for the treatment of adults with AQP4-IgG seropositive neuromyelitis optica spectrum disorder.[11] As an anti-CD19 antibody, inebilizumab might have the added benefit of targeting a wider range of B cells than anti-CD20 antibodies.[12] Indeed, inebilizumab treatment has been found to provide deep and sustained depletion of B cells, including plasmablasts and some plasma cells.[11,13,14] In the 6·5-month randomised controlled period of the N-MOmentum study, inebilizumab (300 mg intravenous infusion) was well tolerated and reduced the risk of adjudicated neuromyelitis optica spectrum disorder attacks by 77% in the AQP4-IgG seropositive population versus placebo (hazard ratio [HR] 0·227 [95% CI 0·12–0·42]).[13] Disability worsening based on changes in Expanded Disability Status Scale (EDSS) score affected proportionally fewer participants receiving inebilizumab (16%) than placebo (35%).[15] Inebilizumab was also associated with significant reductions in neuromyelitis optica spectrum disorder-related hospitalisations and MRI lesion formation.[15] Overall incidences of adverse events were similar in both treatment groups.[13] A separate analysis of data from N-MOmentum examined the association between disease activity in neuromyelitis optica spectrum disorder and serum concentrations of glial fibrillary acidic protein (GFAP; a biomarker of astrocyte damage) that are elevated in individuals with neuromyelitis optica spectrum disorder. Post-baseline GFAP concentrations in serum were lower in the inebilizumab group than in the placebo group, even during an neuromyelitis optica spectrum disorder attack when serum GFAP concentrations typically increase (median fold-change from baseline: inebilizumab, 1·1 [IQR 0·8–24·6], p>0·05; placebo, 20·2 [4·4–98·3], p=0·001).[16]

Owing to the clear demonstration of inebilizumab efficacy in N-MOmentum and the unethical nature of continuing to expose placebo-treated participants to further risk of attacks, the Independent Data Monitoring Committee recommended that the randomised controlled period be stopped early.[13] Participants in the randomised controlled period who had an adjudicated attack, completed 28 weeks in the study, or were in the randomised controlled period when enrolment stopped could voluntarily enter an open-label extension period for at least 2 years. During the open-label period, after initial dosing, all participants received inebilizumab 300 mg every 6 months. This end-of-study analysis reports the efficacy outcomes and safety and tolerability profile of long-term treatment with inebilizumab in individuals with neuromyelitis optica spectrum disorder who participated in N-MOmentum.

See Online for appendix

Methods

Study design and participants

The N-MOmentum trial design and full inclusion and exclusion criteria have been previously reported.[13] Briefly, in this double-blind, randomised, placebo-controlled, phase 2/3 study, participants were recruited from 81 outpatient specialty clinics or hospitals in 24 countries. Eligible participants were aged 18 years or older with a diagnosis of neuromyelitis optica spectrum disorder, EDSS score of 8·0 or less, and history of at least one attack requiring rescue therapy in the past year or two attacks requiring rescue therapy in the past 2 years. AQP4-IgG seropositive and AQP4-IgG seronegative individuals were eligible, but individuals who were AQP4-IgG seronegative had to fulfil additional entry criteria.[17] Full eligibility criteria are provided in the appendix (pp 15–17).

All participants provided written informed consent before any protocol-related procedures. Institutional review boards or ethics committees at each study site approved the protocol. The randomised controlled period and open-label period were conducted in accordance with the provisions of the International Conference on Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki in its currently applicable version. This study is registered with ClinicalTrials.gov, NCT02200770.

Randomisation and masking

After a screening period, eligible participants were randomly assigned (3:1), using a central interactive voice system or interactive web response system, and a permuted block randomisation scheme (block size of 4), to receive inebilizumab 300 mg or identical placebo on days 1 and 15 of the randomised controlled period. All participants, investigators, sponsor, adjudication committee, and staff involved in the running of the trial were masked to the treatment received.

Procedures

After randomisation, intravenous inebilizumab (Horizon Therapeutics Ireland DAC, Dublin, Ireland; now part of Amgen) or placebo (saline) was administered on days 1 and 15 (the total dose of inebilizumab in the randomised controlled period was 600 mg, with no further doses occurring after day 15 in this period of the study). All participants received oral corticosteroids between days 1 and 14, tapered to day 21, to minimise the risk of attack (eg, caused by discontinuation of immunosuppressive therapies) during the initial phase of B-cell depletion. No other immunosuppressant use was permitted during the randomised controlled period or the open-label period. The randomised controlled period for each participant was up to 197 days or until the occurrence of an adjudicated attack or until enrolment was stopped. Visits were conducted on days 1, 8, 15, 29, 57, 85, 113, 155, and 197 of the randomised controlled period.

Participants in the randomised controlled period who had an adjudicated attack, completed 28 weeks in the study, or were in the randomised controlled period when enrolment stopped could voluntarily enter the open-label period. During the open-label period, inebilizumab 300 mg was administered intravenously to all participants on day 1. On day 15, participants who had been randomly assigned to the placebo group during the randomised controlled period received a second dose of inebilizumab to establish B-cell depletion, whereas those originally assigned to inebilizumab received placebo to maintain masking of the randomised controlled period. Subsequently, all participants received inebilizumab 300 mg every 26 weeks for a minimum of 2 years; the open-label period was designed to continue for a maximum of 3 years after the last participant entered. Follow-up assessments[13] were conducted at weeks 2, 4, 13, 26, and 39 of the open-label period, and every 26 weeks thereafter. Attack assessments were performed when a participant had one or more new or worsening neuromyelitis optica spectrum disorder symptoms. An independent committee performed attack adjudication using protocol-defined criteria, as reported previously (also described in the appendix [pp 22–25]).[13,18] Participants receiving inebilizumab in the randomised controlled period or the open label period could continue in the trial irrespective of whether they had an attack while receiving treatment. Treatment was discontinued if participants withdrew consent or if the investigator identified an adverse event that precluded further dosing, including an elevated liver aminotransferase concentration, severe anaphylaxis, a hypersensitivity reaction, an infusion reaction, or neutropenia, or if the participant became pregnant. After the last dose, participants transitioned into a safety follow-up period of 12 months. Sex and race and ethnicity were self-reported at baseline.

Treatment-emergent adverse events (referred to hereafter as adverse events) were coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities version 23.1. Severity of adverse events were categorised from grade 1 to 5 (1 being mild, 2 being moderate, 3 being severe, 4 being life-threatening, and 5 being fatal). Serious adverse events included those of grade 4 or 5 severity, those requiring or prolonging hospitalisation, and those resulting in persistent or significant incapacity. Adverse events were assessed at each study visit, and association of an adverse event to study drug was determined by the investigator and reviewed by the study medical monitor and Independent Data Monitoring Committee

Blood samples for total Ig, IgM, IgG, IgA, and IgE assessments were collected at day 1, week 12, and week 28 (or at early discontinuation visit) during the randomised controlled period, and at weeks 13, 26, 39, 52, and every 26 weeks thereafter (or at early discontinuation visit) during the open label period. Laboratory testing was done at a central clinical laboratory (Covance Central Laboratory Services, Indianapolis, IN, USA). Additionally, AQP4-IgG serostatus was determined at screening by testing conducted by a central laboratory (Mayo Medical Laboratories, Rochester, MN, USA) using a modified commercially available visual fluorescence-observation cell-binding assay (CA1128-0502, EUROIMMUN, Lübeck, Germany) that has been validated to Clinical Laboratory Improvement Amendment/College of American Pathologists standards.

MRI examinations were done at screening and week 28 (or at the early discontinuation visit) in the randomised controlled period, then on day 1 of the open label period (only if participant experienced an neuromyelitis optica spectrum disorder attack during the randomised controlled period and had an incomplete examination at that time) and yearly thereafter (or at the early discontinuation visit). EDSS was completed at day 1, week 12 and week 28 (or at the early discontinuation visit) in the randomised controlled period, and at weeks 13, 26, 39, 52, and every 26 weeks thereafter (or at the early discontinuation visit) in the open label period. The 36-item Short Form survey (SF-36) version 2 health survey was completed at day 1, week 12 and week 28 (or at the early discontinuation visit) in the randomised controlled period, and at weeks 13, 26, 39, 52, and every 26 weeks thereafter (or at the early discontinuation visit) in the open-label period.

Outcomes

Outcomes assessed during the randomised controlled period of N-MOmentum have been described previously.[13] The primary endpoint was time (in days) from day 1 to the onset of an neuromyelitis optica spectrum disorder attack (as determined by the adjudication committee), on or before day 197. An attack was defined as the presence of a new symptom or symptoms or worsening of an existing symptom or symptoms related to neuromyelitis optica spectrum disorder that met at least one of the protocol-defined criteria for an attack on neurological evaluation. Key secondary endpoints were worsening of EDSS score from baseline, change from baseline in low-contrast visual acuity binocular score, cumulative total number of active MRI lesions, and number of neuromyelitis optica spectrum disorder-related inpatient hospitalisations longer than an overnight stay.

In the present analysis of long-term data from N-MOmentum covering the randomised controlled period and the open-label period, the prespecified endpoints were time to neuromyelitis optica spectrum disorder attack, annualised attack rates, and safety outcomes, including investigator-reported treatment-emergent adverse events, serious adverse events, adverse events of special interest (including infusion-related reactions and infections), and IgA, IgM, and IgG concentrations.

Statistical analysis

The study was designed to detect a relative reduction (inebilizumab *vs* placebo) of 60% in time to onset of an

adjudicated neuromyelitis optica spectrum disorder attack on or before day 197 of the randomised controlled period, with at least 90% power and a two-sided significance level of 5%. With an assumption of 3:1 randomisation, 67 adjudicated attacks were predicted among 212 enrolled participants, on the basis of estimated attack rates and expected relative reduction from open-label cohort studies.[13] After a protocol amendment (amendment 1, July 1, 2014), the enrolment target was changed. On the basis of the observed overall attack rate for the first 78 participants enrolled, a new target enrolment of 252 participants was implemented to provide 90% probability of reaching 67 adjudicated attacks. Enrolment was planned to stop following 67 adjudicated attacks, random allocation and dosing of 252 participants, or a data-monitoring committee recommendation (whichever occurred first). Additional details of the sample size and statistical considerations are in the appendix (pp 26–28).

Statistical analyses of the primary and key secondary endpoints in the randomised controlled period were described previously.[13,19] For the current end-of-study analysis, outcomes were analysed, when possible, in all participants who received inebilizumab at any point during the randomised controlled period or the open-label period (referred to hereafter as the any inebilizumab population), which included both AQP4-IgG seropositive and seronegative participants, and in the subgroup of AQP4-IgG seropositive participants within this any inebilizumab population (referred to hereafter as the any inebilizumab-AQP4-IgG seropositive population). Data for the subgroup of AQP4-IgG seronegative participants only have been reported separately[20] owing to the small number of participants enrolled in N-MOmentum who were AQP4-IgG seronegative, and because increasing data have suggested this population might have divergent responses to immunotherapy. Furthermore, N-MOmentum was not powered to demonstrate efficacy in the AQP4-IgG seronegative subgroup. A detailed analysis of B-cell depletion with inebilizumab treatment observed across N-MOmentum has also been reported separately.[14]

We used the Kaplan–Meier methodology to assess time to first attack. Participants who completed the day 197 visit of the randomised controlled period or who discontinued the study before day 197 for reasons other than an adjudicated attack were censored in this model at day 197 or their discontinuation visit. We estimated annualised attack rates and corresponding 95% CIs as unadjusted rates (calculated as the total number of attacks divided by total person-years) and adjusted rates (calculated using a negative binomial model based on the total number of adjudication committee-determined neuromyelitis optica spectrum disorder attacks normalised by the total person-years of exposure). We did a sensitivity analysis in which we imputed attacks for participants who discontinued due to investigator decision or death, participants coming for assessments but not for treatments, and participants requiring steroid treatment, all of which we determined to be potential indicators of a paucity of efficacy. We estimated significance for all efficacy analyses using a two-sided test at the 5% significance level. Where appropriate, model-based estimates were presented with their two-sided 95% CIs and p values. Categorical data analyses were done with Pearson's χ^2 test or with Fisher's exact test if more than 20% of expected contingency table cell counts were below the 5% significance level.

Safety was assessed in the as-treated any inebilizumab population, which for the end-of-study analysis included all participants who received at least one dose of inebilizumab at any time. Adverse events were summarised using descriptive statistics and as incidence per person-year. Overall incidence of adverse events of special interest, including infusion-related reactions and infections, was reported, alongside infection incidence over 4 years, for the any inebilizumab population. Correlations between IgA, IgM, and IgG concentrations and incidence of infection and incidence of grade 3 or worse infection were assessed using Fisher's exact test.

Post-hoc assessments in the any inebilizumab group were: annualised rate of new or enlarging T2-hyperintense MRI lesions across the optic nerve, brain, brainstem, and spinal cord; the annualised rate of neuromyelitis optica spectrum disorder-related hospitalisations longer than an overnight stay; changes in the SF-36 score. Additionally, change in EDSS score was reported for participants according to their randomly assigned groups for the randomised controlled period and the open label period, with baseline being day 1 of the respective study periods.

Post hoc, we compared the long-term efficacy of inebilizumab to the natural course of the disease by assessing time to neuromyelitis optica spectrum disorder attack in the any inebilizumab-AQP4-IgG seropositive subgroup with that of a historical, pooled, untreated group constructed from published studies of individuals with neuromyelitis optica spectrum disorder with attack data from a total of 106 untreated individuals and a follow-up of 50 months.[19,21–23] For this analysis, HRs were estimated using a Cox proportional hazards regression, with the historical untreated group as the reference group. The proportional hazards assumption was tested and met (appendix p 30). Attacks were analysed using parametric and flexible survival (spline) models. Models were fit to the any inebilizumab-AQP4-IgG seropositive subgroup and the historical untreated data. Further details regarding the individuals in the historical control group, the model, and the diagnostics used are in the appendix (p 30).

Significance for all efficacy and safety analyses was estimated using a two-sided test at 5% significance level. Statistical analyses were done using SAS (version 9.04).

Role of the funding source
The funders of the study (MedImmune, Viela Bio/Horizon Therapeutics [now Amgen]) had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Jan 6, 2015, and Sept 24, 2018, 467 individuals were screened, of whom 231 were randomly assigned as part of the randomised controlled period of the trial (n=175 to the inebilizumab group and n=56 to the placebo group). When the randomised controlled period was stopped (Sept 7, 2018), 230 participants had received their assigned treatment (n=174 in the inebilizumab group and n=56 in the placebo group). Between May 19, 2015, and Nov 8, 2018, 165 (95%) of 174 participants in the inebilizumab group and 51 (91%) of 56 in the placebo group entered the open-label period, of whom 154 (93%) from the original inebilizumab group and 47 (92%) from the original placebo group were AQP4-IgG seropositive (figure 1). Baseline demographics of participants in the randomised controlled period and the open-label period were similar (table 1). In the open-label population, mean age was 42·9 years (SD 12·4), 197 (91%) of 216 participants were female, 19 (9%) were male, 115 (53%) were White, 45 (21%) were Asian, 19 (9%) were American Indian or Alaskan Native, 19 (9%) were Black or African American, and 17 (8%) were other races. By the end of the study (date of data cutoff Dec 18, 2020; median exposure per participant in the any inebilizumab population was 1178 days [IQR 856–1538], and total exposure was 730 person-years; appendix p 3), 225 participants had received inebilizumab across the randomised controlled period and the open-label period (any inebilizumab population), 208 (92%) of whom were AQP4-IgG seropositive (any inebilizumab-AQP4-IgG seropositive population). Details of the reasons for participant discontinuation during the open-label period of the study are provided in the appendix (pp 4–5). In the any inebilizumab population, 204 (91%) participants had over 1 year, 191 (85%) had over 2 years, 125 (55%) had over 3 years, and 81 (36%) had over 4 years of inebilizumab exposure. After the last dose of study drug, all participants transitioned to a 12-month safety follow up, among whom only one did not complete this follow up. The reduced proportion of participants with longer exposures was mainly attributable to the study design, with the time-to-event randomised controlled period and extended recruitment schedule contributing to the variation in exposure time for those completing the open-label period.

Notably, the randomised controlled period discontinuation dates for two participants changed from those previously reported[13,19] (from Jan 7 to Feb 7, 2017, and from May 20 to June 21, 2018), with a minor effect on two of the key secondary endpoints (EDSS score worsening and neuromyelitis optica spectrum disorder-related hospitalisations) that did not alter the significance or interpretation of the results. Final analyses for the primary and secondary endpoints in the randomised controlled period are presented in the appendix (p 6).

The history of attacks among participants during N-MOmentum and the period preceding randomisation is shown in the appendix (p 8). A significant reduction in risk of attack with inebilizumab versus placebo was seen during the randomised controlled period, which was also seen in those who were AQP4-IgG seropositive, and the risk of attack decreased progressively over time with continued treatment.[13] Over the randomised controlled

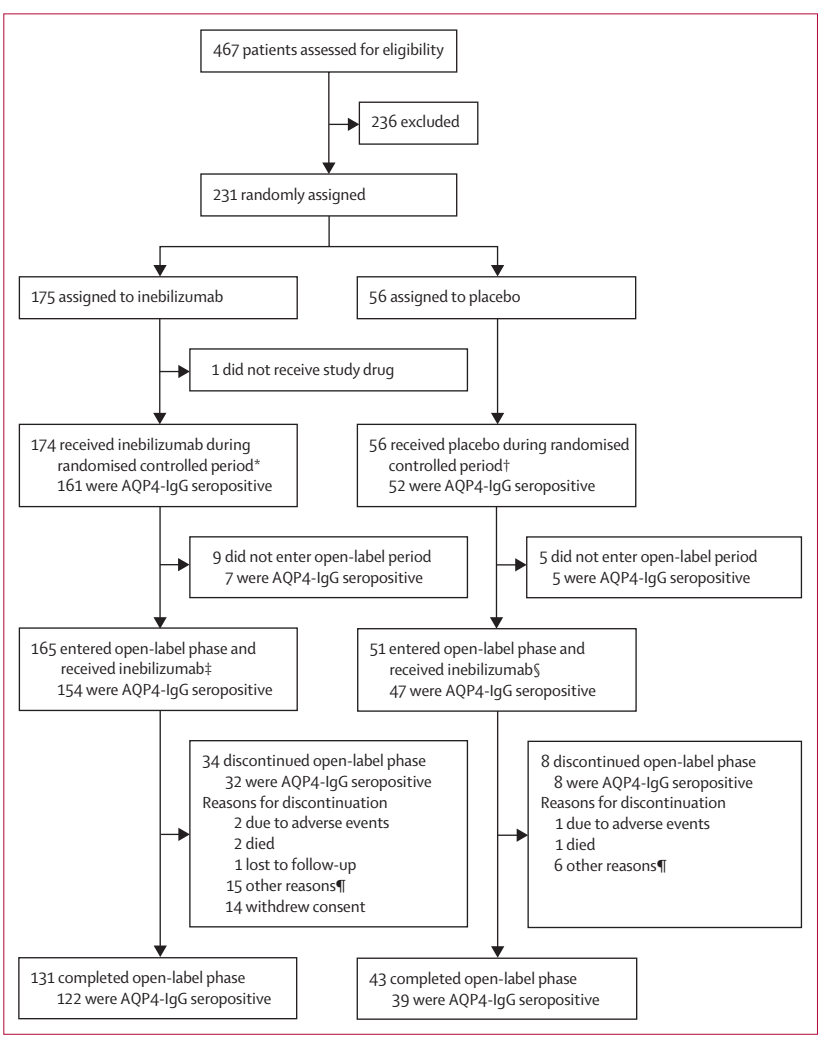


Figure 1: **Trial profile**
For participants randomly assigned to inebilizumab who did not enter the open-label period, treatment exposure during the randomised controlled period was still included in the any inebilizumab data set; likewise, for those who discontinued the open-label period, any treatment exposure before discontinuation was included in the any inebilizumab dataset. AQP4=aquaporin-4. ITT=intention-to-treat. *Exposure for ITT population, 82·55 person-years and for AQP4-IgG seropositive subgroup, 76·91 person-years.†Exposure for ITT population, 26·41 person-years, and for AQP4-IgG seropositive subgroup, 24·18 person-years. ‡Exposure for ITT population, 491·97 person-years, and for AQP4-IgG seropositive subgroup, 449·80 person-years. §Exposure for ITT population, 26·41 person-years and for AQP4-IgG seropositive subgroup, 24·18 person-years. ¶Reasons for reporting 'other' were physician, investigator, or participant decisions; unwillingness to receive investigational product; withdrawing after worsening of neuromyelitis optica spectrum disorder; decision to change therapy; and pregnancy.

	Randomised controlled period*		Open-label period	
	All participants (n=230)	AQP4-IgG seropositive subgroup (n=213)	All participants (n=216)	AQP4-IgG seropositive subgroup (n=201)
Age, years	42·9 (12·2)	43·0 (12·3)	42·9 (12·4)	43·0 (12·5)
Sex				
Female	209 (91%)	200 (94%)	197 (91%)	189 (94%)
Male	21 (9%)	13 (6%)	19 (9%)	12 (6%)
Race				
American Indian or Alaskan Native	19 (8%)	16 (8%)	19 (9%)	16 (8%)
Asian	47 (20%)	45 (21%)	45 (21%)	43 (21%)
Black or African American	20 (9%)	19 (9%)	19 (9%)	18 (9%)
White	120 (52%)	110 (52%)	115 (53%)	106 (53%)
Other	23 (10%)	22 (10%)	17 (8%)	17 (9%)
Ethnicity				
Hispanic or Latino	43 (19%)	40 (19%)	38 (18%)	35 (17%)
Not Hispanic or Latino	187 (81%)	173 (81%)	178 (82%)	166 (83%)
Disease duration, years	2·49 (3·33)	2·59 (3·42)	2·50 (3·40)	2·59 (3·48)
Type of most recent attack				
Optic neuritis	106 (46%)	96 (45%)	98 (45%)	89 (44%)
Myelitis	133 (58%)	126 (59%)	126 (58%)	119 (59%)
Brain or brainstem	18 (8%)	14 (7%)	16 (7%)	13 (7%)
Annualised attack rate	1·69 (1·51)	1·63 (1·46)	1·72 (1·54)	1·67 (1·49)
EDSS score	3·90 (1·78)	3·94 (1·75)	3·90 (1·75)	3·91 (1·73)
Previous NMO or NMOSD treatment†				
Any therapy	227 (99%)	210 (99%)	213 (99%)	198 (99%)
Plasmapheresis	94 (41%)	84 (39%)	89 (41%)	80 (40%)
Intravenous immunoglobulin	11 (5%)	11 (5%)	11 (5%)	11 (6%)

Data are mean (SD) or n (%). AQP4=aquaporin. EDSS=Expanded Disability Status Scale. NMO=neuromyelitis optica. NMOSD=neuromyelitis optica spectrum disorder. *Includes patients treated with both placebo and inebilizumab. †Patients could receive more than one type of previous treatment.

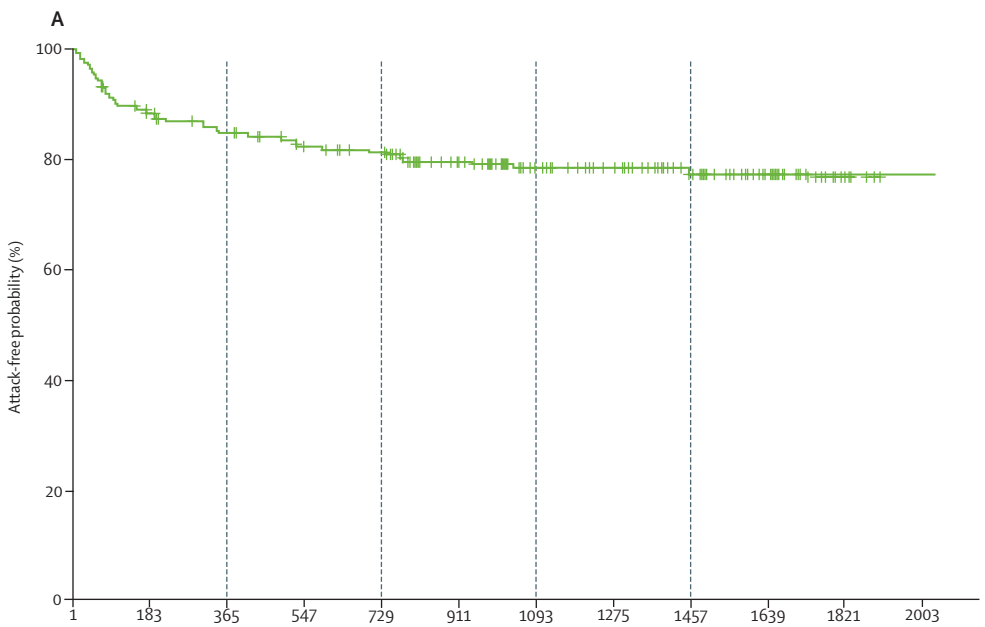
Table 1: **Baseline demographic and clinical characteristics of participants in the N-MOmentum study**

period and the open-label period combined, 63 adjudication committee determined attacks occurred in 47 (21%) of 225 participants in the any inebilizumab population, of which 60 attacks occurred in 44 (21%) of 208 participants in the any inebilizumab AQP4-IgG seropositive subgroup. Overall, 40 (63%) of 63 attacks happened in 34 (15%) of 225 participants in the first year, and progressively fewer attacks occurred with continued inebilizumab treatment (figure 2A; appendix pp 7–8). Of the participants who had an attack, 36 (77%) did not have a subsequent attack, eight (17%) had two attacks, two (4%) had three attacks, and one (2%) had five attacks. Of the recurrent attacks, six (38%) occurred in the first year of inebilizumab treatment, five (31%) in the second year, four (25%) in the third year, and one (6%) in the fourth year.

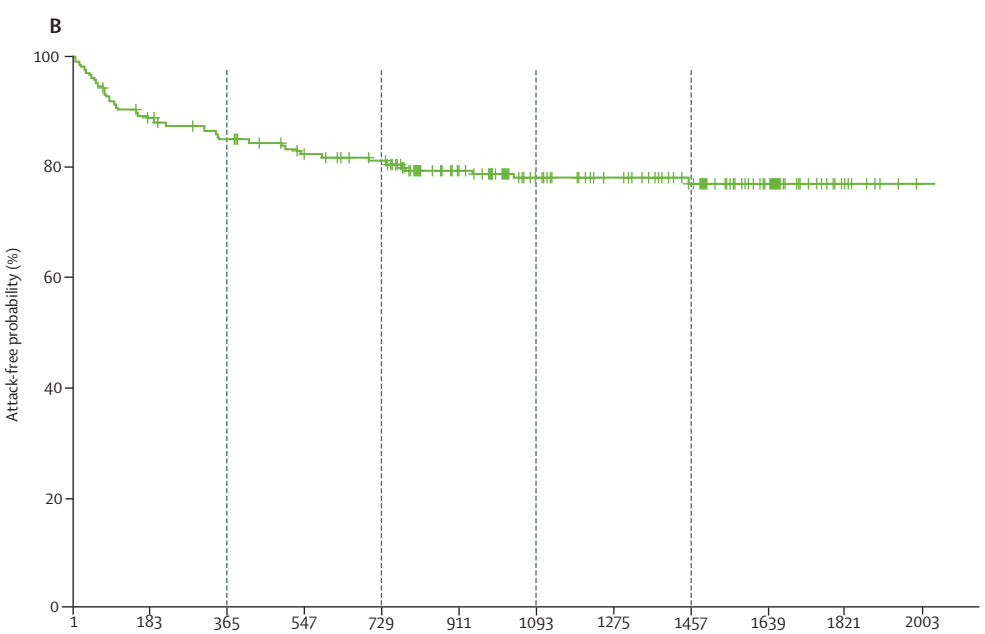
Of the 225 participants in the any inebilizumab population, the probability of being attack free was 85% after 1 year of inebilizumab treatment, and the probability of being attack free was 77% after 4 years of inebilizumab treatment (figure 2A). Similar results were seen in the any inebilizumab AQP4-IgG seropositive subgroup (figure 2B). Unadjusted annualised attack rates were lower with inebilizumab than with placebo during the randomised controlled period (inebilizumab, 0·26 [95% CI 0·14–0·48]; placebo, 1·03 [0·65–1·54]). Annualised attack rates continued to decline year-on-year during the open-label period and across the 4 year study period, for both the any inebilizumab population and the any inebilizumab AQP4-IgG seropositive subgroup (figure 2C). End-of-study unadjusted and adjusted annualised attack rates were 0·086 (95% CI 0·066–0·11) and 0·092 (0·067–0·13) for the any inebilizumab population and 0·090 (0·069–0·12) and 0·097 (0·070–0·14) for the any inebilizumab AQP4-IgG seropositive subgroup, respectively. A sensitivity analysis that imputed attacks for the four participants who discontinued for reasons possibly related to paucity of efficacy (reasons captured for discontinuation were investigator decision, death, participant coming for assessments but not for treatments, and required steroid treatment; appendix pp 4–5) generated unadjusted annualised attack rates of 0·20 (95% CI 0·14–0·27) for year 1 and 0·095 (0·056–0·15) for year 2 and so did not affect interpretation of the results.

In post-hoc analyses, compared with the placebo group during the randomised controlled period, the any inebilizumab population had fewer neuromyelitis optica spectrum disorder-related hospitalisations, lower annualised rates of new or enlarging T2-hyperintense MRI lesions, and improvements in the physical component, but not in the mental component of the SF-36 (summary of the SF-36 is in the appendix [pp 2, 6, 10]; full results will be reported elsewhere). Similarly, compared with the placebo group during the randomised controlled period, participants receiving inebilizumab had better stabilisation of EDSS scores whether they started inebilizumab in the randomised controlled period or in the open label period. These benefits were sustained over time with prolonged inebilizumab treatment. In further post-hoc assessments, when compared with the historical untreated control group, participants in the any inebilizumab-AQP4-IgG seropositive subgroup had a substantially lower attack risk, which decreased further with long-term inebilizumab treatment (appendix pp 13–14). The historical group showed a parallel trajectory of clinical attacks when compared with the randomised controlled period placebo group during the 6·5 months of the placebo-controlled study (appendix pp 2, 20).

Long-term inebilizumab treatment was generally well tolerated. The adverse event profile for the any inebilizumab population (the as-treated group) was similar to that for the participants in the randomised controlled period who were exposed to inebilizumab (table 2); adverse events in the any inebilizumab as-treated AQP4-IgG seropositive subgroup were also similar to those in the any inebilizumab group (data not shown). In the any inebilizumab population, at least one



Any ineblilizumab population												
Number at risk	225	192	180	166	160	129	103	86	68	39	13	2
(number censored)	(225)	(199)	(191)	(186)	(184)	(181)	(179)	(179)	(178)	(178)	(178)	(178)
Attack-free probability			146 (85%)		153 (81%)		98 (78%)		67 (77%)			
Participants with attacks (n=47)			34 in year 1		7 in year 2		5 in year 3		1 in year 4			
Total number of attacks (n=68)			40 in year 1		12 in year 2		9 in year 3		2 in year 4			



Any inebilizumab AQP4-IgG seropositive subgroup												
Number at risk	208	180	168	154	148	118	94	78	62	35	11	2
(number censored)	(208)	(185)	(177)	(172)	(170)	(167)	(165)	(165)	(164)	(164)	(164)	(164)
Attack-free probability			137 (85%)		141 (81%)		89 (78%)		61 (77%)			
Participants with attacks (n=44)			31 in year 1		7 in year 2		5 in year 3		1 in year 4			
Total number of attacks (n=60)			37 in year 1		12 in year 2		9 in year 3		2 in year 4			

(Figure 2 continues on next page)

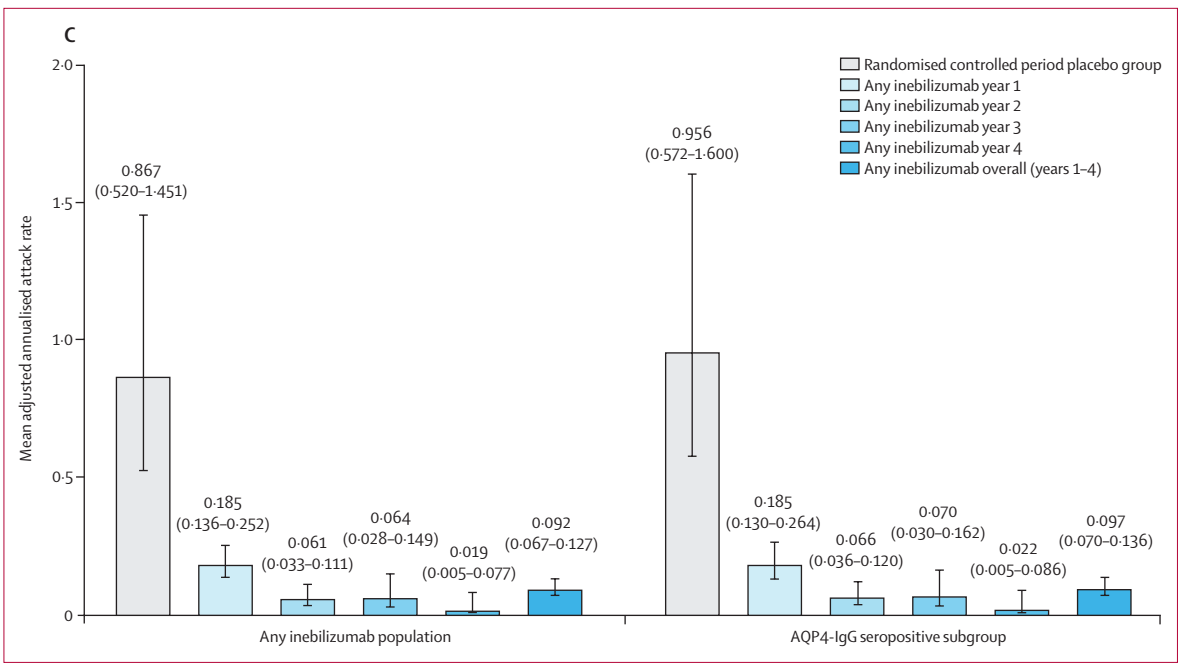


Figure 2: **Time to first attack and annualised attack rates during the N-MOmentum study**
Kaplan–Meier plots are for the any inebilizumab population (A) and the any inebilizumab AQP4-IgG seropositive subgroup (B), including total number of investigator and adjudication committee determined attacks at each timepoint. Vertical dotted lines in (A) and (B) denote years 1, 2, 3, and 4. Bar chart (C) shows adjusted annualised attack rates, with bars indicating mean estimates and whiskers indicating 95% CIs. AQP4=aquaporin-4.

treatment-emergent adverse event was reported by 208 (92%) of 225 participants, and 89 (40%) reported at least one inebilizumab-related treatment-emergent adverse event. The most commonly reported treatment-emergent adverse events in the any inebilizumab population were urinary tract infection (59 [26%]), nasopharyngitis (47 [21%]), arthralgia (39 [17%]), upper respiratory tract infection (35 [16%]), headache (34 [15%]), back pain (31 [14%]), and infusion-related reaction (29 [13%]; table 2). The rate of neoplasms was low, with a mean incidence rate of 0·012 (95% CI 0·0056–0·023) per person-year. Overall, 46 (20%) of 225 participants in the any inebilizumab population reported at least one serious adverse event, with ten (4%) having at least one inebilizumab-related serious treatment-emergent adverse event. Among these ten individuals, seven had infections; one had a CNS event of unclear cause, post-cardiac-arrest syndrome, and pneumonia; one had neutropenia; and one had an infusion-related reaction. Across both the randomised controlled period and the open-label period, seven (3%) of 225 participants permanently discontinued treatment owing to inebilizumab-related treatment-emergent adverse events: two during the randomised controlled period (one each of atypical pneumonia and myasthenia gravis) and five during the open-label period (one each of neutropenia, steroid-withdrawal syndrome unrelated to neuromyelitis optica spectrum disorder attack, hepatic steatosis, pneumonia, liver function test worsened, and female breast cancer).

In the any inebilizumab population, most individuals had grade 1 adverse events (59 [26%] of 225) or grade 2 adverse events (91 [42%]). During the open-label period, there were proportionally more life-threatening (grade 4) and fatal (grade 5) events among participants who were previously in the placebo group (four [8%] of 51 participants had a grade 4 event and one [2%] had a grade 5 event) than among those who continued to receive inebilizumab (four [2%] of 165 participants had grade 4 events and two [1%] had grade 5 events). Two of the three deaths have been previously reported.[13] The first previously reported death was a 67-year-old woman who was taking inebilizumab during the randomised controlled period who had a CNS event of unknown cause. Differential diagnoses included progressive multifocal leukoencephalopathy (PML), acute disseminated encephalomyelitis, and atypical neuromyelitis optica spectrum disorder attack. Ultrasensitive PCR testing of CSF at the National Institutes of Health (Bethesda, MD, USA) did not detect JC virus DNA, rendering a PML diagnosis unlikely. The participant died from hospital-acquired, ventilator-associated pneumonia on study day 245, after 244 days of inebilizumab exposure. The family declined an autopsy, so the cause of this CNS event could not be definitively determined. The second previously reported death was a 31-year-old man who had previously been in the placebo group and moved onto inebilizumab in the open-label period who died from complications of a severe neuromyelitis optica spectrum disorder attack

	Any inebilizumab population (n=225)		Population exposed to inebilizumab during the randomised controlled period (n=174)	
	Participants, n (%)	Mean (95% CI) incidence per person-year	Participants, n (%)	Mean (95% CI) incidence per person-year
At least one treatment-emergent adverse event	208 (92%)	0·28 (0·25–0·33)	127 (73%)	1·50 (1·30–1·80)
At least one adverse event graded as severe	55 (24%)	0·075 (0·057–0·098)	15 (9%)	0·18 (0·10–0·30)
At least one serious adverse event	46 (20%)	0·063 (0·046–0·084)	9 (5%)	0·11 (0·050–0·21)
Permanently discontinued due to treatment-related adverse event	7 (3%)	0·0096 (0·0039–0·020)	2 (1%)	0·024 (0·0029–0·088)
Death	3 (1%)	0·0041 (0·00085–0·012)	0	NA
Most frequent treatment-emergent adverse events*				
Urinary tract infection	59 (26%)	0·081 (0·061–0·10)	20 (11%)	0·24 (0·15–0·37)
Nasopharyngitis	47 (21%)	0·064 (0·047–0·086)	13 (7%)	0·16 (0·084–0·27)
Arthralgia	39 (17%)	0·053 (0·038–0·073)	18 (10%)	0·22 (0·13–0·34)
Upper respiratory tract infection	35 (16%)	0·048 (0·033–0·067)	5 (3%)	0·061 (0·020–0·14)
Headache	34 (15%)	0·047 (0·032–0·065)	14 (8%)	0·17 (0·093–0·28)
Back pain	31 (14%)	0·042 (0·029–0·060)	13 (7%)	0·16 (0·084–0·27)
Infusion-related reaction	29 (13%)	0·040 (0·027–0·057)	16 (9%)	0·19 (0·11–0·31)
Adverse events of special interest				
At least one adverse event of special interest	179 (80%)	0·25 (0·21–0·28)	83 (48%)	1·0 (0·80–1·20)
Infusion-related reaction	29 (13%)	0·040 (0·027–0·057)	16 (9%)	0·19 (0·11–0·31)
Infection	168 (75%)	0·23 (0·20–0·27)	68 (39%)	0·82 (0·64–1·0)
Herpes simplex	1 (<1%)	0·0014 (0·000035–0·0076)	0	NA
Herpes virus infection	2 (1%)	0·0027 (0·00033–0·0099)	0	NA
Herpes zoster	3 (1%)	0·0041 (0·00085–0·012)	0	NA
Opportunistic infection	2 (1%)	0·0027 (0·00033–0·0099)	0	NA
Fungal respiratory tract infection	1 (<1%)	0·0014 (0·000035–0·0076)	0	NA
Hepatic function abnormality	16 (7%)	0·022 (0·013–0·036)	8 (5%)	0·097 (0·042–0·19)
Neoplasms, benign, malignant, and unspecified	9 (4%)	0·012 (0·0056–0·023)	2 (1%)	0·024 (0·0029–0·088)
Benign ovarian tumour	1 (<1%)	0·0014 (0·000035–0·0076)	1 (1%)	0·012 (0·00031–0·067)
Breast cancer (female)	1 (<1%)	0·0014 (0·000035–0·0076)	0	NA
Colon cancer	1 (<1%)	0·0014 (0·000035–0·0076)	0	NA
Fibroadenoma of breast	1 (<1%)	0·0014 (0·000035–0·0076)	0	NA
Meningioma	1 (<1%)	0·0014 (0·000035–0·0076)	0	NA
Benign pituitary tumour	1 (<1%)	0·0014 (0·000035–0·0076)	1 (1%)	0·012 (0·00031–0·067)
Tumour pain	1 (<1%)	0·0014 (0·000035–0·0076)	0	NA
Uterine leiomyoma	2 (1%)	0·0027 (0·00033–0·0099)	0	NA

Safety endpoints were analysed as-treated in all participants who received at least one dose of inebilizumab at any time. Mean incidence data are presented to two significant figures. NA=not applicable. *Adverse events that occurred in >10% of participants in the any inebilizumab population.

Table 2: **Adverse events in all participants exposed to inebilizumab during the N-MOmentum study**

resulting in respiratory insufficiency due to chest mobility impairment. This death occurred on study day 62, after 9 days of inebilizumab exposure. No infection or fever was noted around the time of death, and the investigator reported the death as unrelated to study drug. The third death was a 58-year-old woman who died on study day 1226, after 1225 days of inebilizumab exposure, from viral pneumonia related to COVID-19; the association between this event and inebilizumab treatment could not be determined. There was no evidence for increased risk of death with increased duration of inebilizumab treatment.

Among treatment-emergent adverse events of special interest in the any inebilizumab population, the incidence of infusion-related reactions was 11·1 (95% CI 8·8–13·8) per 100 person-years (equivalent to 0·04 [95% CI 0·027–0·057] per person-year). All infusion-related reactions were of grade 1 or grade 2 severity. The overall proportion of participants with infusion-related reactions in the open-label period was 17 (8%) of 216. Infusion-related reactions were less frequent in participants who had received inebilizumab throughout the study (ten [6%] of 165) than in those who had previously been in the placebo group (seven [14%] of 51). The incidence of infections in the any inebilizumab population was 78·0 (95% CI 71·8–84·7) per 100 person-years (table 3). The rate of infections did not increase with duration of inebilizumab treatment (table 3). In the any inebilizumab

	Any inebilizumab population (n=225)
Overall	
Number of infections	570
Total person-years of exposure	730·4
Incidence (95% CI) per 100 person-years	78·0 (71·8–84·7)
Year 1	
Number of infections	252
Total person-years of exposure	216·6
Incidence (95% CI) per 100 person-years	116·3 (102·4–131·6)
Year 2	
Number of infections	136
Total person-years of exposure	199·6
Incidence (95% CI) per 100 person-years	68·1 (57·2–80·6)
Year 3	
Number of infections	98
Total person-years of exposure	158·3
Incidence (95% CI) per 100 person-years	61·9 (50·3–75·5)
Year 4	
Number of infections	57
Total person-years of exposure	103·4
Incidence (95% CI) per 100 person-years	55·1 (41·7–71·4)

Safety endpoints were analysed as-treated in all participants who received at least one dose of inebilizumab at any time.

Table 3: **Incidence of infections in the any inebilizumab population**

	Participants with any infection		Participants with at least grade 3 infection		Any inebilizumab population (n=225)
	Yes (n=173)	No (n=52)	Yes (n=30)	No (n=195)	
Worst IgG concentration*					
Normal (≥700 mg/dL)	91 (53%)	29 (56%)	13 (43%)	107 (55%)	120 (53%)
Mild (500 to <700 mg/dL)	49 (28%)	16 (31%)	7 (23%)	58 (30%)	65 (29%)
Moderate (300 to <500 mg/dL)	27 (16%)	5 (10%)	8 (27%)	24 (12%)	32 (14%)
Severe (<300 mg/dL)	6 (3%)	2 (4%)	2 (7%)	6 (3%)	8 (4%)
Worst IgM concentration*					
Normal (>30 mg/dL)	98 (57%)	34 (65%)	13 (43%)	119 (61%)	132 (59%)
Low (≤30 mg/dL)	75 (43%)	18 (35%)	17 (57%)	76 (39%)	93 (41%)
Worst IgA concentration*					
Normal (≥70 mg/dL)	112 (65%)	38 (73%)	21 (70%)	129 (66%)	150 (67%)
Low (<70 mg/dL)	61 (35%)	14 (27%)	9 (30%)	66 (34%)	75 (33%)

Data are n (%). Safety endpoints were analysed as-treated in all participants who received at least one dose of inebilizumab at any time. For IgG, Fisher's exact p=0·76 for any infection and p=0·10 for infections that were grade 3 or worse. For IgM, Fisher's exact p=0·34 for any infection and p=0·075 for infections that were grade 3 or worse. For IgA, Fisher's exact p=0·32 for any infection and p=0·84 for infections that were grade 3 or worse. *The worst or most severely reduced concentrations of the respective immunoglobulin reported at any time during the study.

Table 4: **IgG, IgM, and IgA concentrations, stratified by occurrence of infection, in the any inebilizumab population**

population, 25 (11%) of 225 participants had an infection-related treatment-emergent adverse event of grade 3 severity or worse. Of these events, only urinary tract infection (eight [4%]) and pneumonia (five [2%]) occurred in more than one participant. There was no evidence of a correlation between IgG concentrations (normal, mild, moderate, or severe) and the incidence of any infection (p=0·76) or an infection that was of grade 3 severity or worse (p=0·10; table 4). Similar results were found for IgM and IgA concentrations (table 4).

Discussion

This end-of-study analysis of data from the N-MOmentum trial, with mean exposure to inebilizumab of more than 3 years and a total exposure of more than 730 person-years, provides evidence for the safety and efficacy of inebilizumab in the long-term treatment of neuromyelitis optica spectrum disorder. Prolonged inebilizumab exposure did not raise any additional safety concerns and reduced the frequency of neuromyelitis optica spectrum disorder attacks over time, disability worsening (measured by EDSS score), MRI T2 lesion activity, and disease-related hospitalisations. Most neuromyelitis optica spectrum disorder attacks occurred in the first year, with incidence declining rapidly thereafter with multiple dosing, suggesting improving efficacy with ongoing treatment. The significant reduction in attack risk and disability progression with inebilizumab compared with placebo in the N-MOmentum randomised controlled period,[13] together with the demonstration of increasing and sustained clinical benefits in the end-of-study analysis provide robust support for inebilizumab as a therapeutic option in people with neuromyelitis optica spectrum disorder and those with AQP4-IgG-seropositive disease. Data for the subgroup of participants who were AQP4-IgG seronegative were not included in the analysis because the group was too small to be adequately powered to demonstrate efficacy. Furthermore, data for the AQP4-IgG seronegative subgroup have been reported separately,[20] as well as a detailed analysis of B-cell depletion with inebilizumab treatment observed across N-MOmentum.[14]

Molecular characterisation of neuromyelitis optica spectrum disorder disease activity remains an important topic of investigation. Although CD19+ B cells are known to have an important role in neuromyelitis optica spectrum disorder attacks, B-cell concentrations have not been found to be elevated during neuromyelitis optica spectrum disorder attacks relative to concentrations measured during other routine assessments. However, the extent of B-cell depletion in participants treated with inebilizumab in N-MOmentum has been inversely correlated with attack risk.[13] An investigation into the potential correlation between plasma cell signature and AQP4-IgG titres and attacks has shown that both are significantly increased during attacks, and that AQP4-IgG titres are decreased in participants treated with inebilizumab (unpublished data; Bennett JL, Pittock SJ, Paul F, et al). Nevertheless, in an unpublished analysis with data from the N-MOmentum study, we found no strong associations between IgG, IgM, IgA, or IgE

concentrations and neuromyelitis optica spectrum disorder disease activity. Investigations into the levels of biomarkers related to CNS damage during the course of neuromyelitis optica spectrum disorder have found that GFAP, tau, UCH-L1, and NfL are increased during neuromyelitis optica spectrum disorder attacks, but only GFAP might be a predictor of attack risk; increases in GFAP and NfL during attacks occur to a lesser extent in individuals treated with inebilizumab than in those treated with placebo.[16,24] These analyses improve understanding of the mechanisms behind neuromyelitis optica spectrum disorder activity and suggest that the clinical effect of inebilizumab treatment in neuromyelitis optica spectrum disorder is linked to decreased CD19+ B-cell counts and less severe attacks. Although not a perfect replacement, in the absence of long-term placebo data, we compared outcomes of inebilizumab with the natural history of the disease using historical data pooled from untreated participants and placebo controls from contemporaneous clinical trials. This historical untreated group showed similarities with the placebo group from the randomised controlled period of N-MOmentum, suggesting that the historical untreated group, at least initially, behaved similarly to the population under study and, therefore, could be compared with long-term inebilizumab data. Model diagnostics, assumption testing, and sensitivity analyses contributed to the robustness of the analyses. The differences observed between the any inebilizumab-AQP4-IgG seropositive subgroup and the historical untreated group (which largely comprised AQP4-IgG-seropositive participants) suggested that the significant decrease in attack risk related to inebilizumab observed during the randomised controlled period[13] was not only sustained but appeared to improve with long-term treatment. Additionally, the use of a historical untreated group, with a follow-up period of 50 months, allowed for a comparison over a period that would not have been possible otherwise owing to the ethical issues of prolonged placebo-controlled studies in severe diseases such as neuromyelitis optica spectrum disorder.

The long-term safety profile of inebilizumab was similar to that previously reported in the randomised controlled period, with urinary tract infections, nasopharyngitis, and arthralgia being the most common treatment-emergent adverse events.[13] B-cell-depleting therapies were previously linked to increased risks of malignancies and infections, including viral (eg, PML and herpes-related infections), bacterial, and fungal infections.[25–27] Over the long term in N-MOmentum, there were single cases of breast cancer and colon cancer but no confirmed cases of PML, the overall infection rate was no higher with inebilizumab than with placebo during the randomised controlled period,[13] and there was no increase in the rate of infections associated with long-term treatment. Moreover, no clear correlation was established between IgG or other immunoglobulin concentrations and risk of infection. This finding suggests that even individuals with low immunoglobulin concentrations might be able to continue inebilizumab treatment with no increased risk of infections, although close monitoring and longer-than-usual follow-up periods remain essential. There were three deaths during the N-MOmentum study, with no increase in mortality over time with inebilizumab treatment.

The frequency of infusion-related reactions during the randomised controlled period was similar with inebilizumab and placebo (9% with inebilizumab; 11% with placebo), as was the frequency in the open-label period among those initiating inebilizumab (12%). Such reactions seem to be most common at first infusion, becoming less frequent at subsequent infusions, as seen during the open-label period among those continuing inebilizumab (6%). However, in the context of B-cell-depleting infusible therapies generally, the initial rates with inebilizumab are low: infusion-related reaction rates of 11–32% were reported with rituximab, an anti-CD20 B-cell-depleting monoclonal antibody used in rheumatoid arthritis, multiple sclerosis, and empirically in neuromyelitis optica spectrum disorder.[25] Similarly, ocrelizumab had infusion-related reaction rates of 34–40% in multiple sclerosis,[26] and rates with infusion of intravenous ocrelizumab for rheumatoid arthritis were 19–28%.[28] Data from studies of ublituximab in multiple sclerosis indicate there might also be high rates, with approximately half of participants reporting infusion-related reactions.[29]

Our study has some limitations. Some exclusion criteria specified for safety reasons might have restricted representation of the real-world neuromyelitis optica spectrum disorder population, and the absence of a parallel comparator as well as the open-label follow-up could potentially lead to unconscious reporting bias, therefore limiting causal inferences on long-term treatment effects and safety. Continued expert and independent adjudication through the open-label period by the committee might have mitigated the effect of unblinding on attack assessment. Reduced participant numbers later in the open-label period potentially introduced confirmation bias. Several participants received inebilizumab for longer than 5 years, but the time-to-event study design and extended enrolment period meant that despite completing the open-label period, other participants only received treatment for approximately 2 years. However, the drop-out rate in the N-MOmentum study was low and discontinuation due to potential absence of efficacy was rare in the open-label period, and a sensitivity analysis discounted any notable effect on annualised attack rates. Nonetheless, because scant descriptive data were captured when participants withdrew consent or were lost to follow-up, no conclusions can be drawn regarding whether these discontinuations were related to lack of efficacy, or on how these discontinuations during the open-label period

potentially affected the results. With regard to the majority of attacks occurring in the first year of treatment, notably, another study showed that approximately half of attacks seemed to occur during the 12 months after the last clinical attack.[30] Additionally, rapid tapering of oral corticosteroids is associated with an increased risk of neuromyelitis optica spectrum disorder attacks.[31] Because participants with a recent history of attacks were enrolled and the monotherapy study design required tapering of concomitant corticosteroid use in the first 3 weeks of N-MOmentum, these design elements could have contributed to the attack frequency in the first 12 months, with clustered attacks manifesting more easily in this initial phase of the study. Use of concomitant immunosuppressive therapy (eg, daily prednisone) during inebilizumab initiation might mitigate risk of attack in the early phase of treatment. Further investigations into prospective therapeutic combinations are needed. Finally, in modelling the historical untreated group, several assumptions were made and thus results must be interpreted cautiously; populations, designs, attack definitions, and capture of historical attacks varied between trials and could account for observed differences.

This analysis of the long-term safety and efficacy of inebilizumab showed continued and sustained clinical benefits and supports the role of CD19+ B-cell-depleting therapy and inebilizumab in the neuromyelitis optica spectrum disorder therapeutic landscape. These results, together with our previously published data on the reduction of attack risk in participants regardless of disease history, demographics, or previous therapies,[32] including participants with a history of breakthrough attacks with anti-CD20+ B-cell depletion (eg, rituximab),[33] highlight the efficacy of targeting and depleting CD19+ B-cell lymphocytes when treating neuromyelitis optica spectrum disorder.

Contributors

As members of the N-MOmentum steering committee or the Horizon team, all authors were involved in the design or conceptualisation of the study, interpretation of data, and revising the manuscript for intellectual content. BACC, HJK, BGW, SJP, DMW, KF, FP, GRC, RM, AJG, OA, H-PH, and JLB were involved with the acquisition of data; BACC, DS, DC, WR, and MS directly accessed and verified study data and underlying data reported in the manuscript. BACC, JLB, MS, DC, and EK developed the first draft of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. MedImmune (Gaithersburg, MD, USA) developed the study design in collaboration with the N-MOmentum steering committee and in consultation with regulatory agencies and bioethicists. Viela Bio (Gaithersburg) assumed ownership of inebilizumab and regulatory responsibilities in March 2018. Data were collected by investigators and, after database lock, analysed by the sponsor. Viela Bio and the steering committee reviewed the results. All authors, including those employed by Horizon Therapeutics, had full access to the data and guarantee the accuracy and completeness of the data, analyses, reporting of adverse events, and protocol adherence. Employees of MedImmune and Viela Bio/Horizon Therapeutics participated in the design and conduct of the study, data collection, management, analysis, and interpretation, and in writing the report. No authors were paid to write this article by a pharmaceutical company or other agency.

Declaration of interests

BACC reports personal fees for consulting from Alexion, Atara, Autobahn, Avotres, Biogen, Boston Pharma, EMD Serono, Gossamer Bio, Hexal/Sandoz, Horizon Therapeutics, Neuron23, Novartis, Sanofi, Siemens, TG Therapeutics, and Therini Bio, and has received research support from Genentech. HJK has received a grant from the National Research Foundation of Korea and research support from AprilBio, Eisai, and UCB; consultancy or speaker fees from Alexion, Altos Biologics, AstraZeneca, Biogen, Daewoong Pharmaceutical, Eisai, GC Pharma, Handok Pharmaceuticals, Kaigene, Kolon Life Science, MDimune, Merck Serono, Mitsubishi Tanabe Pharma, Roche, and Sanofi Genzyme; serves on a steering committee for MedImmune/Viela Bio; and is a co-editor for the *Multiple Sclerosis Journal* and an associate editor for the *Journal of Clinical Neurology*. BGW receives payments for serving as chair of attack adjudication committees for clinical trials in neuromyelitis optica spectrum disorder for Alexion, MedImmune, UCB Bioscience, and Viela Bio/Horizon Therapeutics; has consulted with CANbridge Pharmaceuticals, Chugai, Genentech, Horizon Therapeutics, Mitsubishi Tanabe Pharma, and Roche Pharmaceuticals; has received payments for speaking for Genentech, Horizon Therapeutics, and Roche; 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, RSR Limited, and the University of Oxford. SJP reports grants, personal fees, and non-financial support from Alexion; grants from Autoimmune Encephalitis Alliance and Grifols; grants, personal fees, and non-financial support from MedImmune and Viela Bio/Horizon Therapeutics; consulting support from Astellas, Genentech, and Sage Therapeutics; personal fees for consulting services from for F Hoffman-La Roche AG, Genentech, and UCB; and has a patent #9,891,219 (Application#12-573942) "Methods for Treating Neuromyelitis Optica (NMO) by Administration of Eculizumab to an individual that is Aquaporin-4 (AQP4)-IgG Autoantibody positive". DMW reports personal fees from Alexion, AstraZeneca, Bristol Myers Squibb, Genentech, Horizon Therapeutics, Imcyse, Merck, Novartis, and Reistone Biopharma; serves on a clinical trial adjudication committee for MedImmune, Viela Bio/Horizon Therapeutics, and UCB Pharma; and serves on a data and safety monitoring board for Alexion and Abscuro. KF serves on scientific advisory boards for Alexion, Bayer Schering, Biogen, Chugai, MedImmune, Merck Serono, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Novartis, Ono Pharmaceutical, and Viela Bio/Horizon Therapeutics; has received funding for travel and speaker fees from Asahi Kasei Medical, Astellas, Bayer Schering, Biogen, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Novartis, and Takeda; and research support from Asahi Kasei Medical, Bayer Schering, Biogen, Chemo-Sero-Therapeutic Research Institute, Chugai, Genzyme Japan, the Ministry of Education, Culture, Sports, Science, and Technology of Japan, the Ministry of Health, Welfare, and Labor of Japan, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Ono Pharmaceutical, Teijin, and Teva. FP has received research support, speaker fees, and travel reimbursement from Bayer, Biogen, Merck Serono, Novartis, Sanofi Genzyme, and Teva; is supported by the German Competence Network for Multiple Sclerosis and the German Research Council (DFG Exc 257); has received travel reimbursement from the Guthy–Jackson Charitable Foundation; and serves on the steering committee of the OCTiMS study sponsored by Novartis. GRC has received personal fees for participation on data and safety monitoring boards from AI Therapeutics, AMO Pharma, Applied Therapeutics, AstraZeneca, Avexis Pharmaceuticals, BioLineRx, Brainstorm Cell Therapeutics, Bristol Myers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Green Valley Pharma, Horizon Therapeutics, Immunic Therapeutics, Karuna Therapeutics, Mapi Pharma, Merck, Mitsubishi Tanabe Pharma, the National Heart, Lung, and Blood Institute (US; Protocol Review Committee), Novartis, OPKO Biologics, Prothena Biosciences, Reata Pharmaceuticals, Regeneron, Sanofi-Aventis, Teva Pharmaceuticals, the University of Texas Southwestern, the University of Pennsylvania, and Visioneering Technologies; personal fees for consulting or advisory board participation from Alexion, Antisense Therapeutics, Biogen, Clinical Trial Solutions, Entelexo Biotherapeutics, Genentech, Genzyme, GW Pharmaceuticals, Immunic Therapeutics, Immunosis, Klein Buendel, Merck/Serono, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Protalix

BioTherapeutics, Recursion/CereXis, Regeneron, Roche, and SAB Biotherapeutics. GRC is employed by the University of Alabama at Birmingham and is President of Pythagoras, a private consulting company based in Birmingham, AL, USA. RM serves on scientific advisory boards for MedImmune and Viela Bio/Horizon Therapeutics; and has received funding for travel and fees from Alexion, Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva, and Viela Bio/Horizon Therapeutics. AJG reports grants from the Conrad N Hilton Foundation and the Tom Sherak MS Hope Foundation; other financial relationships for activities as expert witness, associate editor, advisory board or steering committee participation, and endpoint adjudication with Bionure, Inception Sciences, *JAMA Neurology*, MedImmune/Viela Bio, Mylan, Synthon, and Trims Pharma; and personal fees from Pipeline Therapeutics. OA reports grants from the German Ministry of Education and Research (known as BMBF) and the German Research Foundation (known as DFG); grants and personal fees from Bayer HealthCare, Biogen, Genzyme, Novartis, Teva, and Viela Bio/Horizon Therapeutics; and personal fees from Alexion, Almirall, Horizon Therapeutics, Merck Serono, Roche, and Zambon. H-PH has received fees for consulting, speaking, and serving on steering committees from Bayer HealthCare, Biogen, Celgene Receptos, CSL Behring, GeNeuro, Genzyme, MedDay, MedImmune, Merck Serono, Novartis, Roche, Sanofi, TG Therapeutics, and Viela Bio with approval by the Rector of Heinrich Heine University Düsseldorf. DS, WR, MS, and DC hold stock or are employees of Viela Bio/Horizon Therapeutics, or both. EK was an employee of Viela Bio/Horizon Therapeutics during the preparation of this manuscript. JLB reports payment for study design or consultation from MedImmune/Viela Bio; personal fees from AbbVie, Alexion, Antigenomycs, BeiGene, Chugai, Clene Nanomedicine, EMD Serono, Genentech, Genzyme, Horizon Therapeutics, Mitsubishi Tanabe Pharma, Novartis, Reistone Biopharma, Roche, and TG Therapeutics; grants and personal fees from Novartis; grants from Alexion, the Guthy–Jackson Charitable Foundation, Mallinckrodt, and the National Institutes of Health; and has a patent for aquaporumab issued (US10654916B2: Compositions and methods for the treatment of neuromyelitis optica).

Data sharing

There is a plan to share data. This may include de-identified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and (1) this product and indication (or other new use) have been granted marketing authorisation in both the USA and Europe, or (2) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study or studies in scope, endpoints or outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researchers. In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. A committee of internal advisors reviews requests. If not approved, requests might be further arbitrated by a Data Sharing Independent Review panel. Requests that pose a potential conflict of interest or an actual or potential competitive risk might be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymised individual patient data or available supporting documents, or both, containing fragments of analysis code where provided in analysis specifications. Further details are available online. For more information, or to submit a request, please email medinfo@amgen.com.

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