Supplementary material

Supplement to: BG Weinshenker, DM Wingerchuk, AJ Green, et al.
**Attack adjudication in neuromyelitis optica spectrum disorder: substantiation of criteria by magnetic resonance imaging and biomarkers in N-MOmentum**

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

|  |  |  |
| --- | --- | --- |
| **Criteria** | **Type** | **Definition** |
| **Optic neuritisa** | Clinical | *Symptomsb: Blurred vision, loss of vision, eye pain* |
| 1 | Clinical | >15-character drop in high-contrast LCBRC from last visit as measured in a previously affected eye and no other ophthalmological explanation |
| 2 | Clinical | Reduction of ≥2 stepsc in CF to NLP from last visit as measured in a previously affected eye and no other ophthalmological explanation |
| 3 | Clinical | Reduction of ≥7 characters in low-contrast LCBRC from last visit as measured in either eye alone (monocular) **AND** a new RAPD in affected eye |
| 4 | Clinical | Reduction of ≥7 characters in low-contrast LCBRC from last visit as measured in either eye alone (monocular) **AND** loss of a previously documented RAPD in fellow eye |
| 5 | Clinical | Reduction of ≥5 characters in high-contrast LCBRC from last visit as measured in either eye alone (monocular) **AND** a new RAPD in affected eye |
| 6 | Clinical | Reduction of ≥5 characters in high-contrast LCBRC from last visit as measured in either eye alone (monocular) **AND** loss of a previously documented RAPD in fellow eye |
| 7 | Clinical | Reduction of ≥1 stepd in CF to NLP from last visit as measured in a previously affected eye **AND** a new RAPD in affected eye |
| 8 | Clinical | Reduction of ≥1 stepd in CF to NLP from last visit as measured in a previously affected eye **AND** loss of a previously documented RAPD in fellow eye |
| 9 | MRI-dependent | Reduction of ≥7 characters in low-contrast LCBRC from last visit as measured in either eye alone (monocular) **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve |
| 10 | MRI-dependent | Reduction of ≥5 characters in high-contrast LCBRC from last visit as measured in either eye alone (monocular) **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve |
| 11 | MRI-dependent | Reduction of ≥1 stepd in CF to NLP from last visit as measured in a previously affected eye **AND** a newGd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nervee |
| **Myelitisa, f** | Clinical | *Symptomsb: Deep or radicular pain, extremity paraesthesia, weakness, sphincter dysfunction, Lhermitte’s sign (not in isolation)* |
| 12 | Clinical | Worsening of ≥2 point in ≥1 of the relevant (pyramidal, bladder/bowel, sensory) FSS compared with last visit  |
| 13 | Clinical | Worsening of ≥1 point in EDSS score compared with last visit if previous EDSS score ≥5.5 |
| 14 | MRI-dependent | Worsening of ≥1 point in in ≥2 of the relevant (pyramidal, bladder/bowel, sensory) FSS compared with last visit when the last visit score ≥1 **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord |
| 15 | MRI-dependent | Worsening of ≥0.5 point in EDSS score compared with last visit if previous EDSS score ≥5.5 **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord |
| **Brain/brainstema** | Clinical | *Symptomsb: Nausea, intractable vomiting**intractable hiccups, other neurological signsg (e.g. double vision, dysarthria, dysphagia, vertigo, oculomotor palsy, weakness, nystagmus, other cranial nerve abnormality), encephalopathy, hypothalamic dysfunction* |
| 16 | MRI-dependent | Isolated (not present at last visit) intractable nausea, vomiting, and/or hiccups lasting ≥48 hours **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem |
| 17 | MRI-dependent | Worsening of ≥2 points in ≥1 of the relevant (brainstem, cerebellar) FSS compared with last visit **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem |
| 18 | MRI-dependent | Worsening of ≥2 points in ≥1 of the relevant (cerebral, sensory, pyramidal) FSS (with a score of ≥3 at the current visit) compared with last visit **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the brain consistent with the clinical presentation |

The criteria highlighted in gray indicate MRI-dependent criteria.
aFour major areas of the body may be affected by an attack: the optic nerve, resulting in optic neuritis; the spinal cord, resulting in myelitis; the brainstem, resulting in several outcomes; and the brain.
bSymptoms listed are examples and are not inclusive of all neuromyelitis optica spectrum disorder symptoms.
cA decrease of ≥2 steps can be due to any of the following worsening: on LCBRC to HM, LP, or NLP; CF to LP or NLP; HM to NLP.
dA decrease of ≥1 step can be due to any of the following worsening: on LCBRC to CF, HM, LP, or NLP; CF to HM or LP or NLP; HM to LP or NLP; LP to NLP.
eLesions seen in the optic chiasm also count towards these criteria.
fA 1-point change in a single FSS without a change in EDSS score, with or without a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord, is not considered a clinically significant change and does not count as an attack per this protocol.
gOther neurological signs include double vision, dysarthria, dysphagia, vertigo, oculomotor palsy, weakness, nystagmus, or other cranial nerve abnormality.

CF: counting fingers; EDSS: Expanded Disability Status Scale; FSS: Functional Systems Score; Gd: gadolinium; HM: hand motion; LCBRC: Landolt C Broken Ring Chart; LP: light perception; MRI: magnetic resonance imaging; NLP: no light perception; RAPD: relative afferent pupillary defect.

**Supplementary Table 2.** Breakdown of on-study NMOSD potential attacks.

|  |  |  |
| --- | --- | --- |
| **Attack outcome, *n* (%)** | **Placebo****(*n* = 56)** | **Inebilizumab****(*n* = 174)** |
| Participant-reported symptomsa | 28 (50.0%) | 36 (20.7%) |
| Investigator-determined attacksa | 25 (44.6%) | 26 (14.9%) |
| AC-adjudicated attacksa | 22 (39.3%) | 21 (12.1%) |
| Isolated attacks according to typeb |
|  Optic neuritis | 8 (36.4%) | 8 (38.1%) |
|  Myelitis | 11 (50.0%) | 11 (52.4%) |
|  Brain/Brainstem | – | – |
| Attacks affecting multiple domainsb |
|  Optic neuritis and myelitis | 2 (9.1%) | 2 (9.5%) |
|  Optic neuritis and brain/brainstem | – | – |
|  Myelitis and brain/brainstem | 1 (4.5%) | 0 |

aPresented as *n* (%) of the number of participants in each treatment arm.
bPresented as *n* (%) of the total number of adjudicated attacks in each treatment arm.

AC: adjudication committee; NMOSD: neuromyelitis optica spectrum disorder.

**Supplementary Table 3.** AC rejection of investigator-determined attacks.

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

AC: adjudication committee; MRI, magnetic resonance imaging; RAPD: relative afferent pupillary defect.

**Supplementary methods**

***Assessment of neuromyelitis optica spectrum disorder attack***

Predefined neuromyelitis optica spectrum disorder (NMOSD) attack criteria were used to diagnose each on-study attack (**Supplementary Table 1**). The 18 attack criteria covered optic neuritis, myelitis, and brain/brainstem domains.1, 2 Ten criteria (8 for optic neuritis and 2 for myelitis) allowed adjudication of an attack if the event reached or exceeded a defined threshold of change in the clinical examination from baseline. The remaining criteria for optic neuritis (*n* = 3), myelitis (*n* = 2), or brain/brainstem (*n* = 3) attacks required less robust change in objective findings from baseline supplemented by detection of a corresponding new/enlarging T2 lesion or a gadolinium-enhancing T1 lesion on MRI to support the clinical findings.1, 2

Potential attacks (i.e. participants presenting with new symptoms or worsening of existing symptoms) were evaluated by an on-site investigator together with independent Expanded Disability Status Scale (EDSS) and ophthalmology assessors (the latter performing high- and low-contrast visual acuity using Landolt C Broken Ring High Contrast [100%] and Low Contrast [2.5%] Charts respectively, and relative afferent pupillary defect assessments). The investigator was responsible for determining if one or more of the predefined criteria were met. A decision to treat the attack was made by investigator independent of the adjudication process. An independent adjudication committee (AC) of three NMOSD expert clinicians2 independently reviewed all potential attacks regardless of the adjudication by the site investigator. The attack assessment data obtained by the investigator and independent assessors determined the investigator-determined attack diagnosis, based on the predefined criteria. Participants reporting symptoms suggestive of a potential attack were evaluated at the clinical site within 72 hours; assessment was completed within 5 days and the AC reached a decision within 17 days of initial evaluation.

The AC was comprised of three physicians (two neurologists and one neuro-ophthalmologist) with extensive NMOSD experience who were not otherwise involved in the study conduct. The AC functioned independently with oversight by the data monitoring committee and was governed by a separate charter. Based on data provided, protocol-defined criteria for an attack, and clinical judgment, members of the AC determined whether an event met the definition of an NMOSD attack.

AC members were provided with a narrative consisting of the participant’s presenting symptoms and their time course, examination findings recorded by the site investigator, results of EDSS and Functional Systems Score ratings, and ophthalmological examination results. Determinations in each case were made independently by the three AC members. When a majority of AC members agreed that an attack criterion was met and identified the neuroanatomic site of the attack, the attack was considered positively adjudicated. A full committee meeting was called by the chair to achieve consensus when members had concerns on the adequacy or interpretation of the data, or otherwise requested group discussion. The AC was masked to information regarding attack treatment, the investigator’s decision as to whether attack criteria were met, and all other potential information that might have caused bias. Inter-member reliability was assessed by reviewing agreement between the three adjudicators. To assess intra-member reliability, approximately half of the positively and negatively adjudicated events were selected randomly and resubmitted to the AC. Resubmitted events were presented as potential attacks without informing the AC that cases had been previously reviewed.

***MRI assessment***

Participants received a full neuroaxis MRI (spinal cord, optic nerve, and brain) at screening, at the end of the randomized controlled period, and at the time of an attack assessment visit. All MRI scans were performed at the study site, in accordance with local practice and in line with general guidelines on MRI scanner settings and procedures provided by the independent central reader (NeuroRx, Montreal, QC, Canada). Specific MRI protocols differed across sites according to the local practice, for example in the scanner model and field strength. Quality assessments on the scans were performed by the independent central reader to ensure that all MRI scans were of acceptable quality. All MRI images from the site were dated and time stamped, sent to the central imaging vendor, and read by two independent neuro‑radiologists. In the event of a discrepancy between the readers, a consensus read was performed. Of note, images of the optic nerve were obtained during acquisition of brain scans.

Although CNS MRI (optic nerves, brain, and spinal cord) was performed as part of attack assessments, the investigator and the AC members were allowed to review MRI data of only the *relevant* neuroanatomic region when the selected attack criteria required MRI review (criteria 9–11, 14–17, Supplementary Table 1). In special circumstances, MRI review could be requested by AC members on any case of a patient-reported neurological event when clinical data were deemed inconclusive or potentially inconsistent to be able to positively adjudicate an attack despite meeting clinical criteria that might normally not have required MRI review (e.g. major change in gait without corresponding motor or sensory system findings, or when pain was a potential confounding factor). In such circumstances, an independent request for MRI review by the majority of AC members resulted in MRI images of the relevant domain being provided to all AC members. For the analyses presented herein, the MRI was considered reviewed by the AC when attack criteria required MRI review or when the majority of AC members believed MRI review was required by special circumstances. An MRI lesion was considered to be domain-specific when it correlated with reported attack-related symptoms.

All domain-specific MRI findings were retrospectively reviewed for all AC-adjudicated attacks, investigator-determined attacks, and participant-reported symptoms.

***Data availability***

Access to anonymized, individual, and trial-level data (analysis data sets) may be granted upon reasonable request to qualified researchers for independent scientific research, provided the trials are not part of an ongoing or planned regulatory submission (including clinical trial data for unlicensed products and indications). Clinical trial data can be requested by submitting a research proposal and statistical analysis plan to Horizon Therapeutics plc, Gaithersburg, MD, USA. Data will be provided following review and approval of the plan and execution of a data-sharing agreement. For more information, or to submit a request, please email medicalinformation@horizontherapeutics.com.

**Supplementary references**

1. Cree BA, Bennett JL, Sheehan M, et al. Placebo-controlled study in neuromyelitis optica-Ethical and design considerations. Mult Scler 2016;22:862-872.

2. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 2019;394:1352-1363.

**Appendix 1**

***Attack adjudication narratives***

*Case 1*

A 32-year-old Arab woman with aquaporin-4 (AQP4)-seronegative neuromyelitis optica spectrum disorder (NMOSD) complained of new-onset blurred vision in her left eye with eye pain aggravated by eye movement. There was a new relative afferent pupillary defect and visual field defect but no change in visual acuity on ophthalmological exam (Landolt C Broken Ring Chart, high-contrast visual acuity [HCVA], or low-contrast visual acuity [LCVA]). The site principal investigator (PI) determined that she met criteria for an optic neuritis (ON) attack. All three members of the adjudication committee (AC) suspected ON attack; however, she deemed that she did not meet criteria. Retrospective analysis of MRI revealed gadolinium-enhancing lesions of both optic nerves.

*Case 2*

A 27-year-old Asian woman with AQP4-seropositive NMOSD presented with new-onset abdominal paresthesias and tightness; found to have minimally decreased pinprick in the right T9–T11 dermatomes. Although pyramidal functional systems increased by 2 points, this was primarily because of weakness in the left upper extremity and was thought to be unrelated to presenting symptoms. There was new constipation, and the bowel/bladder score increased by 1. The site PI and AC determined that she did not meet attack criteria. The AC reached a negative decision with a split vote (2:1). The member of the AC who adjudicated the event as an attack cited criterion 14 which requires MRI review. MRI demonstrated a lesion of the right optic nerve and in the thoracic cord.

*Case 3*

A 46-year-old Caucasian woman with AQP4-seropositive NMOSD complained of a painless visual scotoma of the left eye and worsening tonic spasms in the right hand. There were no changes in formal ophthalmological testing. Exam was notable for decrease in right hip flexor strength from 5/5 to 4/5. There was no change in any Functional Systems Score or Expanded Disability Status Scale (EDSS) score. The site PI determined that conditions were not met for any attack criteria. The AC independently reviewed the dossier and unanimously reached a negative decision. Retrospective review of the MRI revealed a gadolinium-enhancing lesion of the left optic nerve.

*Case 4*

A 51-year-old Asian man with AQP4-seropositive NMOSD complained of worsening gait and spasticity without changes in bowel/bladder function. Changes in the exam were primarily increased spasticity and hyper-reflexia with mild worsening in vibration sense in both lower extremities. Pyramidal functional score increased by 1 (from 1 to 2). The site PI and AC independently determined that none of the established attack criteria were met. Retrospective review of the MRI revealed gadolinium-enhancing lesions of the left ON and thoracic spine.

*Case 5*

A 36-year-old Asian woman with AQP4-seropositive NMOSD complained of new back pain followed 3 days later by right leg weakness and left leg numbness. The treating physician indicated that there was objective evidence of reduced pinprick and temperature perception in the left leg but this was not reflected in the scores recorded. In fact, there was recorded improvement and vibration sense, leading to a 2-point decrease in the sensory functional score. Failure to confirm the findings of the examining neurologist (confirmed on query of the site neurologist) potentially obscured a real observation about worsening sensory function. Only one member of the AC requested MRI for review by special circumstances such that the MRI was not reviewed at the time of adjudication. After reviewing assessment results, the PI and AC independently concluded that conditions were not met for any attack criteria. Retrospective review of the MRI revealed gadolinium-enhancing T1 and T2 lesions of the thoracic spine.

*Case 6*

A 56-year-old Caucasian man with AQP4-seronegativeNMOSD presented with new blurred vision of his right eye and nausea. With regard to the blurred vision, HCVA deteriorated by 3 characters and LCVA did not change in the symptomatic eye, although 0 characters could be perceived on LCVA. With regard to possible area postrema lesion, vomiting did not persist longer than 24 hours and there were no hiccups. MRI scan flair axial images of the brainstem were reviewed. The AC felt there may be a suggestion of a possible lesion in the area postrema, although this could not be confirmed on other sequences including sagittal T1 gadolinium-enhanced images. Request for re-review by the neuro-radiologist confirmed that there may be a lesion on the fluid-attenuated inversion recovery (FLAIR) sequence. In accordance with the AC charter, the AC deferred to the radiologist who did not feel there was adequate evidence of a lesion on the FLAIR sequence. Accordingly, criteria for a brainstem attack were not satisfied. Retrospective review of the brain MRI revealed gadolinium-enhancing lesions of the bilateral ONs and spine (C6–T5) as well as a T2 lesion of the spine (C6–T7).

*Case 7*

A 23-year-old Hispanic woman with AQP4-seropositive NMOSD presented with new subjective extremity paresthesias with a sensory level at C3. Some minor changes in vibration were noted on exam without motor findings or changes in bowel and/or bladder. There were no changes in any Functional Systems Score or EDSS score. The PI and AC independently concluded that no attack criterion was met. Retrospective review of the MRI demonstrated gadolinium-enhancing T1 as well as T2 lesions of the cervical spinal cord.

**Appendix 2**

***Co-investigators***

The following co-investigators served as principal site investigators for the N-MOmentum study and administered the trial.

**Australia:** Neil Shuey, MD (Melbourne, VIC); **Bulgaria:** Ivan Milanov, MD (Sofia), Ara Kaprelyan, MD (Varna), Ivaylo Tarnev, MD (Sofia), Lyubomir Haralanov, MD (Sofia); **Canada:** Robert Carruthers, MD (Vancouver); **Colombia:** Mario Muñoz, MD (Bogotá), Jairo Quiñones, MD (Cali), Jose Vargas, MD (Barranquilla), Jesus Rodriguez, MD (Bogotá); **Czech Republic:** Petra Nytrova, MD (Praha), Marta Vachova, MD (Teplice), Jan Mares, MD (Olomouc); **Estonia:** Sulev Haldre, MD (Tartu), Katrin Gross-Paju, MD (Tallinn); **Germany:** Tjalf Ziemssen, MD (Dresden), Uwe Klaus Zettl, MD (Rostock), Luisa Klotz, MD (Münster), Florian Then Bergh, MD (Leipzig); **Hong Kong:** Alexander Lau, MD (Sha Tin); **Hungary:** Peter Dioszeghy, MD (Nyiregyhaza), Mária Sátori, MD (Esztergom), László Vécsei, MD (Szeged); **Israel:** Anat Achiron, MD (Ramat-Gan), Arnon Karni, MD (Tel Aviv), Adi Vaknin-Dembinsky, MD (Jerusalem); **Japan:** Takahiko Saida, MD (Kyoto), Tatsuro Misu, MD (Sendai), Masayuki Baba, MD (Aomori), Akira Tamaoka, MD (Tsukuba City), Chiyoko Nohara, MD (Tokyo), Kazumasa Yokoyama, MD (Bunkyo); **Korea, Republic of:** Byoung Joon Kim, MD (Seoul), Sung Min Kim, MD (Seoul), Jee Young Oh, MD (Seoul); **Mexico:** Freddy Castro Farfan, MD (Mexico City), Daniel San Juan Orta, MD (Tlalnepantla De Baz), Ildefonso Rodríguez, MD (San Luis Potosi), Juan Gongora Rivera, MD (Monterrey); **Moldova, Republic of:** Olesea Odainic, MD (Chisinau); **New Zealand:** Ernest Willoughby, MD (Auckland); **Peru:** Edwin Pretell Alva, MD (Callao), Julio Perez Villegas, MD (Lima); **Poland:** Anna Czlonkowska, MD (Warszawa), Krzysztof Selmaj, MD (Lodz), Andrzej Tutaj, MD (Olsztyn), Stanislaw Rusek, MD (Kraków), Beata Zakrzewska-Pniewska, MD (Warszawa), Maciej Maciejowski, MD (Katowice), Konrad Rejdak, MD (Lublin); **Russian Federation:** Anna Belova, MD (Nizhny Novgorod), Denis Sazonov, MD (Novosibirsk), Farit Khabirov, MD (Kazan), Klara Bakhtiyarova, MD (Ufa), Ekaterina Kairbekova, MD (St. Petersburg), Tatiana Shcherbоnosova, MD (Khabarovsk), Zhanna Chefranova, MD (Belgorod), Alexey Boyko, MD (Moscow), Alexey Rozhdestvenskiy, MD (Omsk), Dmitry Pokhabov, MD (Krasnoyarsk), Maria Zakharova, MD (Moscow); **Serbia:** Jelena Drulovic, MD (Belgrade); **South Africa:** Edward Bernard Leepan, MD (Cape Town), Franclo Henning, MD (Cape Town); **Spain:** Celia Oreja-Guevara, MD (Madrid); **Taiwan, Province of China:** Chou-Ching Lin, MD (Tainan City), Shey-Lin Wu, MD (Changhua City), An-Bang Liu, MD (Hualien City); **Thailand:** Somsak Tiamkao, MD (Khon Kaen), Surat Tanprawate, MD (Chiang Mai), Naraporn Prayoonwiwat, MD (Bangkok); **Turkey:** Aksel Siva, MD (Istanbul), Kadriye Agan Yildirim, MD (Istanbul), Muhtesem Gedizlioglu, MD (Izmir), Murat Terzi, MD (Samsun), Aysun Soysal, MD (Istanbul); **United States:** Michael Levy, MD (Baltimore, MD), Adil Javed, MD (Chicago, IL), Benjamin Greenberg, MD (Dallas, TX), Evanthia Bernitsas, MD (Detroit, MI), George Hutton, MD (Houston, TX), Mark Tullman, MD (Saint Louis, MO), William Honeycutt, MD (Maitland, FL), John Scagnelli, MD (Raleigh, NC), Michelle Apperson, MD (Sacramento, CA), Sharon Lynch, MD (Kansas City, MO), Khurram Bashir, MD (Birmingham, AL), Mary Rensel, MD (Cleveland, OH), John Lindsey, MD (Houston, TX), Sarah Wesley, MD (North Haven, CT), Eoin Flanagan, MD (Rochester, MN), Aram Zabeti, MD (Cincinnati, OH), Geoffrey Eubank, MD (Columbus, OH), Warren Felton III, MD (Richmond, VA).