A Phase III, Open-label, Extension Trial of ECU-NMO-301 to Evaluate the Safety and Efficacy of Eculizumab in Patients with Relapsing Neuromyelitis Optica (NMO)

Unique Protocol ID:	ECU-NMO-302
NCT Number:	NCT02003144
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Date of Protocol:	22 March 2018

ECULIZUMAB

ECU-NMO-302

A PHASE III, OPEN-LABEL, EXTENSION TRIAL OF ECU-NMO-301 TO EVALUATE THE SAFETY AND EFFICACY OF ECULIZUMAB IN PATIENTS WITH RELAPSING NEUROMYELITIS OPTICA (NMO)

IND 116,207

EudraCT Number: 2013-001151-12

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Amendment 3 – Global 01 June 2015
Amendment 4 – Global 03 August 2016
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Amendment 6 – Global 22 March 2018

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Phase III, Open-Label, Extension Trial of ECU-NMO-301 to Evaluate the Safety and Efficacy of Eculizumab in Patients with Relapsing Neuromyelitis Optica (NMO)

PROTOCOL NUMBER: ECU-NMO-302

PPD

27 Mar 2018

Date

PPD Medical Monitor
Alexion Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase III, Open-Label, Extension Trial of ECU-NMO-301 to Evaluate the Safety and Efficacy of Eculizumab in Patients with Relapsing Neuromyelitis Optica (NMO)

PROTOCOL NUMBER: ECU-NMO-302

I have received and read the Investigator's Brochure for eculizumab. I have read the ECU-NMO-302 protocol and agree to conduct the trial as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to conduct the trial in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Trial	Name	Address and Telephone Number
Clinical Trial Leader	PPD	Alexion Pharma GmbH Giesshübelstrasse 30, 8045 Zürich, Switzerland Tel: PPD Mobile: PPD Email: PPD
Responsible Physician (Medical Monitor)	PPD	Alexion Pharmaceuticals, Inc. 33 Hayden Ave., Lexington, MA 02421, USA Tel: PPD Mobile: PPD Fax: PPD Email:PPD
Drug Safety Physician	PPD	Alexion Pharmaceuticals, Inc. 33 Hayden Ave, Lexington MA 02421, USA Tel: PPD Mobile: PPD Email: PPD
24-Hour Emergency Contact	24 Hour Telephone Number	North America Tel: PPD Europe Tel: PPD Australia: Tel: PPD
Serious Adverse Event Reporting	Alexion Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc. 100 College Street New Haven, CT 06510 Email: PPD Fax Number: PPD
Investigational Product Supply	Almac Clinical Services	USA: Almac Clinical Services 4204 Technology Drive Durham, NC 27704 Tel: PPD Fax: PPD Europe: Almac Clinical Services 9 Charlestown Road Seagoe Industrial Estate Portadown BT63 5PW United Kingdom Tel: PPD

Role in Trial	Name	Address and Telephone Number
Clinical Laboratory	ACM Medical Laboratory	North America and Latin America: ACM Medical Laboratory 160 Elmgrove Park Rochester, NY 14624 Tel: PPD Fax: PPD Europe: ACM Global Central Laboratory Limited 23 Hospital Fields Road York, YO10 4DZ, UK Tel: PPD Fax: PPD Asia-Pacific: Dorevitch Pathology 18 Banksia Street Heidelberg, VIC 3084, Australia Tel: PPD

2. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc.	
Name of Investigational Product: Eculizumab	
Name of Active Ingredient: h5G1.1-mAb	
Title of Trial: A Phase III, Open-Label, Extension Trial of ECU-NMO-301 to Evaluate the Safety and Efficacy of Eculizumab in Patients with Relapsing Neuromyelitis Optica (NMO)	
Trial center(s): Approximately 80 centers in North America, South America, Europe, and Asia-Pacific.	
Principal Investigator: TBD **Investigators:** A list containing all Investigators will be provided when site selection is completed.	
Studied period (years): Actual date first patient enrolled: 12 Jan 2015 Estimated date last patient completed: 30 Jun 2020	**Phase of development:** 3

Objectives:

Primary:

- Evaluate the long-term safety of eculizumab in patients with relapsing NMO.

Secondary:

- Evaluate the long-term efficacy of eculizumab in patients with relapsing NMO as measured by annualized relapsing rate (ARR)
- Evaluate long-term efficacy of eculizumab by additional efficacy measures including:
  - Disability
  - Quality of life (QOL)
  - Neurologic functions
- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in relapsing NMO patients.

Methodology:

This is an open-label trial. All NMO or NMO Spectrum Disorder (NMOSD) patients who have completed the double-blind, randomized, placebo-controlled ECU-NMO-301 (PREVENT) trial may be eligible to participate in this extension trial. Prior to initiating any extension trial procedures, an informed consent form must be signed and inclusion/exclusion criteria must be obtained, evaluated, and met. Throughout this protocol, the term NMO refers to both NMO and NMOSD.

Patients who exit the ECU-NMO-301 trial due to relapse will have their first extension trial visit once the Week 6 Follow-up Relapse Evaluation Visit is completed and no later than 2 weeks (14 days ±2 days) after the last investigational product (IP) dose; patients who exit the ECU-NMO-301 trial due to trial completion will have their first extension trial visit once the End of Study (EOS) Visit is completed and no later than 2 weeks (14 days ±2 days) after the last IP administration in the ECU-NMO-301 trial. Patients who have been unblinded in ECU-NMO-301 may not continue in ECU-NMO-302.

Blind Induction Phase (Visits 1 – 4)

To preserve the blinded nature of ECU-NMO-301 trial, all patients must undergo a blind induction phase prior to entering the open-label phase of this trial (ie, all patients will receive 4 vials of blinded IP weekly for 4 doses). Patients who were randomized to the placebo arm in the ECU-NMO-301 trial will start with the induction dose (ie, they will receive blinded IP [3 vials/900 mg eculizumab plus 1 vial placebo] at Visits 1 to 4). Patients who were randomized to the eculizumab arm in the ECU-NMO-301 trial will continue with the maintenance dose (ie, they will receive blinded IP [4 vials/1200 mg eculizumab every 2 weeks (±2 days) at Visits 1 and 3 and 4 vials of placebo at Visits 2 and 4]). All patients will receive 4 vials/1200 mg eculizumab open-label at Visit 5 and onward throughout the trial.

Open-Label Maintenance Phase

All patients will receive open-label eculizumab (4 vials/1200 mg) every 2 weeks during the maintenance phase. All patients must be present at the trial site, as applicable per Schedule of Assessments, for visit-specific procedures/assessments including IP administration. For other visits, patients may have an opportunity to receive IP administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Principal Investigator (PI) and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. These visits will be conducted by a qualified staff member from the medical facility near the patient's home or by home-care health professionals who are under the supervision of the Investigator. The trial medication will be prepared and administered at the patient's home or at the medical facility. During a remote dosing visit, information on adverse events (AEs), concomitant medications, and signs or symptoms of NMO relapses will be collected and sent to the Investigator's site for evaluation on the day of the visit. Patients must go to the trial site for evaluation if the patient reports any signs or symptoms that suggest a serious adverse event (SAE) or NMO relapse.

Supportive immunosuppressive therapy (IST) for relapse prevention is allowed during this extension trial at the Treating Physician's discretion. Change in IST or its dose/schedule will be allowed if due to relapse, intolerance, or medically indicated at the discretion of the Treating Physician. However, use of rituximab, mitoxantrone, or other biologic agents such as tocilizumab is prohibited during the trial. Patients may continue participation in this trial and receive the IP until the product is registered and available to treat patients diagnosed with relapsing NMO (in accordance with country specific regulations) or for a maximum of 5.5 years from the time the first patient was enrolled, whichever occurs first.

Relapse Evaluation

Identification of potential relapse is critical for patient safety and for the integrity of the trial. Patients will receive a Patient Education Card that details signs and symptoms of a potential relapse and instructions to contact the study site at the first sign or symptom of a potential relapse. The Investigator or his/her designee should review, in detail, this information and any additional warning signs of a relapse specific to that patient's clinical picture at each visit. Patients should be evaluated within 24 hours of notification of the Investigator of a possible relapse, and no later than 48 hours. All reports of possible relapses and actions taken for the possible relapse must be documented in the patient's source documents and recorded on the electronic case report form (eCRF).

At the Relapse Evaluation Visit, a blinded Expanded Disability Status Scale (EDSS) Rater will perform the Kurtzke neurologic assessment to determine the Functional System scores (FSS) and Expanded Disability Status Scale (EDSS) score. The Treating Physician will perform a complete neurologic examination and document the Optic-Spinal Impairment Score (OSIS). The Treating Physician or appropriately trained designee will perform the visual acuity (VA) test (Snellen Chart) and Hauser Ambulatory Index (HAI) as outlined in the Relapse Evaluation Period section (Section 7.1.3). The Treating Physician will make the decision as to whether the clinical signs, symptoms and the neurologic change (objective findings on neurologic examination) meet the definition of an On-Trial Relapse (Section 7.2.1). If the event is confirmed as an On-Trial Relapse, the patient may be treated according to the recommended Standardized On-Trial Relapse Treatment Plan. Relapse treatment is at the Treating Physician's discretion. The treatment with IP will be continued per the specified dose administration schedule for the patient.

Follow-up Relapse Evaluation Visits to monitor the course of the relapse will be performed at 1, 4 and 6 weeks after the onset of relapse. Additional (unscheduled) Follow-up Relapse Evaluation Visits outside the specified time points will be made at the discretion of the Treating Physician. Patients may continue the trial participation if the patient and the Treating Physician decide that it is appropriate to continue to receive eculizumab treatment.

Adjudication of On-Trial Relapse Events

An independent Relapse Adjudication Committee will confirm all On-Trial Relapse events using objective and consistent clinical criteria described in a Relapse Endpoint Adjudication Charter. The Adjudication Committee will consist of three independent medical experts in neurology/neuroophthalmology who are each experienced in the management of patients with NMO. The Adjudication Committee will decide by majority vote whether each On-Trial Relapse (as determined by the treating PI) meets the pre-defined objective criteria for an adjudicated On-Trial Relapse, as described in the Relapse Adjudication Charter.

Safety Follow-Up Period (8 weeks)
If a patient withdraws from this extension trial or discontinues eculizumab treatment at any time after receiving any amount of IP, the patient will be required to complete an Early Termination (ET) Visit at the time of the withdrawal and a safety Follow-up Visit, 8 weeks after the last dose of IP administration. If a patient is discontinued due to an adverse event (AE), the event will be followed until it is resolved or in the opinion of the Investigator is determined medically stable. Patients who withdraw from this extension trial and transition to treatment with commercially available eculizumab will not be required to complete a Follow-Up Visit.

Post-Treatment Follow-up (a Maximum of 2 years):
The Sponsor may seek to collect follow-up information concerning NMO status in patients who have prematurely discontinued from the trial for up to a maximum of 2 years from the last dose of eculizumab.

Number of patients (planned):
This is an extension trial to the ECU-NMO-301 trial. A maximum of 132 patients will be enrolled in the ECU-NMO-301 trial. Patients who complete the ECU-NMO-301 trial may potentially enter this extension trial.

Diagnosis and main criteria for inclusion:
Inclusion Criteria:

1. Patient completed the ECU-NMO-301 trial (ie, completed either Week 6 Follow-up Relapse Evaluation Visit or End of Study Visit)
2. Patient has given written informed consent
3. Patient is willing and able to comply with the protocol requirements for the duration of the trial
4. Female patients of child-bearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]). All patients must practice an effective, reliable, and medically approved contraceptive regimen during the trial and for up to 5 months following discontinuation of treatment.

Exclusion Criteria:

1. Patient withdrew from the ECU-NMO-301 trial as a result of an AE related to IP
2. Female patients who are pregnant, breastfeeding, or intend to conceive during the course of the trial
3. Any medical condition or circumstances that, in the opinion of the Investigator, might interfere with the patient's participation in the trial, pose any added risk for the patient, or confound the assessment of the patient.

Investigational product, dosage and mode of administration:
IP (eculizumab or placebo during the blind-induction phase), will be given by intravenous (IV) administration over approximately 35 minutes.
Blind Induction Phase: To maintain the blind of the ECU-NMO-301 trial, all patients will undergo a blind induction phase. IP will be administered weekly for 4 weeks during the induction phase according to the following schedule:

ECU-NMO-301 (PREVENT) Cohort	Dose	Visit #
Eculizumab arm	4 vials IP (eculizumab 1200 mg)	1, 3
	4 vials IP (placebo)	2, 4
Placebo arm	4 vials IP (3 vials eculizumab 900 mg + 1 vial placebo)	1, 2, 3, 4

Open-label Maintenance Phase: All patients will receive 4 vials eculizumab (1200 mg) every 2 weeks (±2 days) from Visit 5 and onward throughout the trial.

Supplemental Dose: If a patient undergoes plasmapheresis or plasma exchange (PE) for an On-Trial Relapse during the Study Period, a supplemental dose of IP must be administered after each PE session, preferably within 1-2 hours. If the relapse occurs during the blinded induction phase, and the PE coincides with the day of a regularly

scheduled IP infusion:

- For Visit 1 (Day1) and Visit 3 (Week 2), administer the scheduled 4 vials of blinded IP
- For Visit 2 (Week 1) and Visit 4 (Week 3) administer only a supplemental IP dose, ie, 2 vials eculizumab (600 mg)

If the relapse occurs during the open-label maintenance phase, and the PE coincides with the day of a regularly scheduled IP infusion, administer the scheduled IP dose (4 vials/1200 mg eculizumab). In all other cases, administer only a supplemental IP dose, ie, 2 vials eculizumab (600 mg).

After receiving the supplemental dose, patients are to continue IP infusion according to the protocol-specified dosing regimen.

Duration of treatment:
The maximum total trial duration is 5.5 years from the time the first patient was enrolled. Trial duration for an individual patient will vary depending on when the patient enters the trial; participation may continue until the product is registered and available to treat patients with NMO (in accordance with country specific regulations) or until the trial ends, whichever occurs first.

Reference therapy, dosage and mode of administration:
Not applicable.

Criteria for evaluation:
Efficacy:
Duration of treatment commences with the first IP infusion (eculizumab).

- On-Trial Relapses will be monitored closely throughout the trial and evaluated as described in the above section "Study Period, Relapse Evaluation". PI-determined On-Trial Relapses will be adjudicated by the Adjudication Committee and if confirmed by the Adjudication Committee, will be used for the ARR assessment.
- Disability will be assessed by the EDSS and modified Rankin Scale (mRS) scores comparing the change from baseline. The EDSS Rater, who is blinded to all other trial data, as well as all other patient clinical data, will be responsible for performing the Kurtzke neurological assessments throughout the trial at the protocol-specified time points as well as at the Relapse Evaluation Visits. The Treating Physician or designee will perform the mRS throughout the trial at the protocol-specified time points.
- Neurologic function will be assessed based on the EDSS FSS. Ambulatory function will be assessed by HAI scale and visual function will be measured by VA using the Snellen chart. In addition, the EDSS visual (optic) FSS will be used for statistical analysis of changes in VA. Neurologic function evaluation will be assessed at the protocol-specified time points as well as at the On-Trial Relapse Evaluation Visit(s).
- QOL will be assessed by the patient self-assessment using both the EuroQoL (EQ-5D) and Short Form Health Survey (SF-36) instruments at the protocol-specified time points.

Safety:

- The safety of eculizumab will be assessed based on treatment emergent AEs (TEAEs), SAEs, and changes from baseline through trial completion in vital signs (VS), routine clinical laboratory tests (chemistry and hematology), Columbia-Suicide Severity Rating Scale (C-SSRS), and pregnancy tests for female patients of childbearing potential.
- Immunogenicity: Blood samples will be collected for evaluation for human-anti-human antibodies (HAHA) at specified time points to describe the presence or absence of an immune response to eculizumab and to evaluate, if antibodies are detected, whether the antibodies neutralize the activity of eculizumab.
- The same independent Data Monitoring Committee (DMC) that will conduct the monitoring of safety data for ECU-NMO-301 trial will be used in this extension trial. Since its primary function will be to ensure patient safety, the DMC will have access to all safety data. The DMC may make recommendations to the Sponsor regarding safety issues, trial conduct, and modifying, extending or stopping the trial. A separate DMC Charter will document all DMC procedures and processes for the trial. Data and analysis for the DMC will be prepared by an independent statistical group.

Biomarker

- Blood samples and cerebrospinal fluid (CSF) samples for NMO-IgG (AQP4-Ab) will be measured at

protocol-specified time points and during the On-Trial Relapse Evaluation Period. CSF samples will be obtained only from patients who have provided consent for lumbar puncture to obtain CSF samples.

PK and PD

- The population PK analysis of eculizumab in NMO patients will be performed to assess the concentration of eculizumab versus time. PK parameters such as maximum concentration as well as trough and peak eculizumab concentration during the induction and maintenance treatment phases will be reported. Clearance and terminal half-life will be estimated. PD analysis will be performed to assess pre- and post-treatment serum hemolytic activity and therefore C5 complement activity inhibition. Free C5 concentration also may be measured.
- CSF samples for PK and free C5 from patients who have opted to provide consent will be measured at protocol-specified time points and during the On-Trial Relapse Evaluation Period.

Statistical methods:
Analyses will be produced using the data from this trial alone as well as combined analyses that will include data from the ECU-NMO-301 trial. The analyses will include safety, efficacy, and PK/PD analyses. The statistical analysis plan will cover both the stand-alone trial analyses and the combined ECU-NMO-301 and ECU-NMO-302 trial analyses.

SAFETY:
Safety analyses will be performed on the Extension Safety Population and the Combined Safety Population from both studies. The Extension Safety Population includes all patients who receive at least 1 dose of eculizumab in this trial. The Combined Safety Population includes all patients who receive at least 1 dose of eculizumab in the ECU-NMO-301 trial or this trial.

Note: Baseline for the extension trial alone analyses is defined as the last available assessment prior to starting treatment with eculizumab in the extension trial. Baseline for the combined trial safety analyses is defined as the last available assessment prior to starting treatment with eculizumab in ECU-NMO-301 or in this trial for patients who have received placebo in the ECU-NMO-301 trial.

Safety Analyses:
For the extension trial alone, AEs onset on or after the first dose date for eculizumab in the extension trial will be summarized by incidence, system organ class (SOC), preferred term, (PT), seriousness, severity, and relationship to treatment. Concomitant medications taken during the extension trial will be summarized. Changes in IST usage (ie, increases, decreases, switching ISTs, etc) will be summarized.
For the Combined Safety Population, AEs that occurred on or after the first dose of eculizumab whether in the ECU-NMO-301 or this extension trial will be summarized by incidence, SOC, PT, seriousness, severity, and relationship to treatment. Concomitant medications taken during eculizumab treatment regardless of the trial will be summarized.

Changes from baseline in laboratory assessments (chemistry and hematology) will be summarized for the extension trial alone as well as for the two studies combined. Likewise, shift tables (L [low], N [normal], H [high]) will be produced for clinical laboratory tests for the extension trial alone as well as for the two studies combined. Pregnancy tests will be summarized in patient listings. Electrocardiogram (ECG) data will be summarized for the extension trial. Shift tables for the C-SSRS will be produced for the extension trial.

Immunogenicity as measured by HAHA will be summarized in tabular form as well as a patient listing for the extension trial alone as well as for the two studies combined.

EFFICACY:
Efficacy analyses will be performed on the Extension Trial Full Analysis Set (Extension FAS) population as well as the Extension Trial Per-Protocol (Extension PP) population. In addition, efficacy analyses will be performed on the Combined Full Analysis Set (Combined FAS) population as well as the Combined Per-Protocol (Combined PP) population from the combined ECU-NMO-301 trial and the extension trial.

Extension FAS Population: The population on which primary, secondary, and tertiary efficacy analyses will be performed consists of all patients who have received at least 1 dose of eculizumab in this extension trial and have a

post-IP infusion efficacy assessment.

Extension PP Population: A subset of the Extension FAS population, excluding patients with major extension trial protocol deviations. The Extension PP population will include all patients who:

- Have no major protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy
- Patients who took at least 80% of the required eculizumab doses during participation in the extension trial

Combined FAS Population: The population on which primary, secondary, and tertiary efficacy analyses will be performed consists of all patients who have received at least 1 dose of eculizumab in either ECU-NMO-301 or this trial and have a post-IP infusion efficacy assessment.

Combined PP Population: A subset of the Combined FAS population, excluding patients with major protocol deviations from either the ECU-NMO-301 or extension trial. The Combined PP population will include all patients who:

- Have no major protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy
- Patients who took at least 80% of the required eculizumab doses during participation in ECU-NMO-301 and/or this trial

The Extension PP population as well as the Combined PP population will be determined prior to database lock.

Primary Efficacy Analysis:
The primary efficacy endpoint is ARR including all relapses as identified by the Investigator. Baseline ARR for all patients will be calculated starting 1 year prior to enrollment in the ECU-NMO-301 trial. Baseline ARR will be compared to rates calculated for the time period that patients are on eculizumab in ECU-NMO-302. The trial will be considered to have met its primary efficacy endpoint if a statistically significant p-value (< 0.05) is observed for the change in ARR between the baseline ARR and the On-Trial ARR when on eculizumab treatment in ECU-NMO-302 using a Wilcoxon signed rank test. Confidence intervals (95%) for the change and percentage change in the ARR will be presented. The percentage of patients who are relapse-free based on On-Trial Relapse events while on eculizumab treatment in ECU-NMO-302 along with 95% confidence intervals will be computed using the Kaplan-Meier method. A sensitivity analysis will be performed for the change in ARR between the baseline ARR and the adjudicated On-Trial ARR when on eculizumab treatment in ECU-NMO-302 using a Wilcoxon signed rank test. The percentage of patients who are relapse-free while on eculizumab treatment in ECU-NMO-302 along with 95% confidence intervals will also be computed using the Kaplan-Meier method for the adjudicated On-Trial relapses.

Additional analyses will be performed on the combined data from ECU-NMO-301and ECU-NMO-302 trials. Baseline ARR for all patients will be calculated starting 1 year prior to enrollment in the ECU-NMO-301 trial and will include all On-Trial attacks (as identified by the Investigator) that occur in the ECU-NMO-301 trial for patients randomized to placebo. Baseline ARR for patients who were randomized to eculizumab in the ECU-NMO-301 trial will be calculated starting one year prior to enrollment in the ECU-NMO-301 trial. Baseline ARR will be compared to rates calculated for the time period that patients are on eculizumab. For patients who are treated in the placebo arm of the ECU-NMO-301 trial, the ARR for comparison with baseline will be calculated once the patient transitions to eculizumab treatment. A Wilcoxon signed rank test will be used to assess the change in ARR between the baseline ARR and the On-Trial ARR when on eculizumab treatment. Confidence intervals (95%) for the change and percentage change in the ARR will be presented. The percentage of patients who are relapse-free based on On-Trial Relapse events while on eculizumab treatment along with 95% confidence intervals will be computed using the Kaplan-Meier method. A sensitivity analysis will be performed for the change in ARR between the baseline ARR and the adjudicated On-Trial ARR when on eculizumab treatment using a Wilcoxon signed rank test. The percentage of patients who are relapse-free while on eculizumab treatment along with 95% confidence intervals will also be computed using the Kaplan-Meier method for the adjudicated On-Trial relapses.

Secondary Efficacy Analysis for the Trial Period:
Baseline for the extension trial alone is defined as the last available assessment prior to starting treatment with eculizumab in the extension trial. Baseline for the combined trial efficacy analyses is defined as the last available assessment prior to starting treatment with eculizumab in ECU-NMO-301 or this trial for all patients.
Changes from baseline for the various secondary efficacy endpoints will be summarized over the applicable visits.

1. Change from baseline in EDSS score
2. Change from baseline in EQ-5D
3. Change from baseline in mRS score
4. Change from baseline in HAI in patients with abnormal baseline ambulatory function
5. Change from baseline in VA in patients with abnormal baseline visual function

The primary analysis for the change from baseline in EDSS score at a particular visit will be based on the repeated measures model with effects for baseline EDSS and visit. Changes from baseline in the HAI, VA, EQ-5D index score, EQ-5D visual analog scale, and mRS will be analyzed in a similar manner as changes in EDSS score using the baseline and visit as covariates in the modeling. In addition, summary statistics for the changes from baseline in the mRS score will be produced by visit. Likewise, shift tables from baseline in the mRS score will be produced by visit. By-patient listings of the secondary endpoints assessments and changes from baseline in the secondary endpoints will be produced.

For the secondary endpoints, some summaries by subgroups will be produced. Patients will belong to one of four possible subgroups:
(a) patients randomized to eculizumab who did not have relapses in the ECU-NMO-301 trial,
(b) patients randomized to eculizumab who did have relapses in the ECU-NMO-301 trial,
(c) patients randomized to placebo who did not have relapses in the ECU-NMO-301 trial, and
(d) patients randomized to placebo who did have relapses in the ECU-NMO-301 trial.

For the patients in sub-group (a), baseline is defined as the baseline assessment (last available assessment) prior to dosing in the ECU-NMO-301 trial. For the patients in sub-group (c), baseline is defined as the last available assessment prior to dosing with eculizumab in this trial. For the patients in subgroups (b) and (d), baseline for these subgroup analyses is defined as the last available assessment prior to eculizumab dosing in this extension trial in consideration of neurologic changes and recoveries as a result of relapse in the ECU-NMO-301 trial. Changes from baseline for the various secondary efficacy endpoints will be summarized separately for the 4 subgroups of patients over the applicable visits. Missing secondary endpoint assessments will not be imputed.

Tertiary Efficacy Analysis for the Trial Period:
Like the secondary efficacy endpoint, the tertiary endpoint analyses will be based on changes from baseline.

1. Change from baseline in HAI score
2. Change from baseline in VA
3. Change from baseline in the SF-36
4. Change from baseline in the EDSS FSS

Changes from baseline in the HAI score and VA will be analyzed in a similar manner to the secondary endpoint analyses described for HAI with abnormal baseline ambulatory function and VA with abnormal baseline visual function using repeated measures models.

Change from baseline in QOL will be summarized as appropriate to the QOL instrument and analyses will be performed as specified in the statistical analysis plan (SAP).

Changes from baseline in the EDSS FSS will be analyzed in a similar manner to the secondary endpoint analyses described for the EDSS score using repeated measures models.

In addition, summaries of changes from baseline like those for the secondary efficacy endpoints will also be created for the tertiary efficacy endpoints for the 4 subgroups of patients from the ECU-NMO-301 trial who are treated in the extension trial.

Other Efficacy Analyses: On-Trial Relapses:
For patients with a PI-determined On-Trial relapse(s), summary tables of the types of relapses and the severity of the relapses will be produced. Summary tables will also be produced only for those patients with adjudicated On-Trial relapse(s). A by-patient listing of the PI-determined On-Trial relapses, including the subsequent adjudication outcome will be produced. The severity of a relapse will be determined using the OSIS scale. Severity will be assessed at the time of the relapse.

Changes from baseline to all of the trial-collected time-points after a relapse (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and VA. Changes from the last assessment prior to the relapse to all trial collected time-points after a relapse (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and VA. Likewise, changes from the assessment 1 week after the relapse to all trial collected time-points after that time point (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and VA. These summaries will be produced for patients with a PI-determined On-Trial relapse(s) as well as for only those patients with adjudicated On-Trial relapse(s). Patient listings for the EDSS, HAI, and VA assessments before and after a relapse will be created for the patients with all On-Trial relapses as determined by the PI(s), including the subsequent adjudication outcome.

Biomarker Analysis for the Trial Period:
Changes from baseline for NMO-IgG assessments will be summarized and patient listings for the NMO biomarker data will be created.

PK/PD for the Trial Period:
Population PK analysis of eculizumab in NMO patients will be performed to assess the concentration of eculizumab versus time. PK parameters such as maximum concentration as well as trough and peak eculizumab concentration during the induction and maintenance treatment phases will be reported. Clearance and terminal half-life will be estimated. PD analysis will be performed to assess pre- and post-treatment serum hemolytic activity and therefore C5 complement activity inhibition. Free C5 concentration also may be measured.

Rationale for Number of Patients:
This is an extension trial to ECU-NMO-301 trial. A maximum of 132 patients are planned to be enrolled in the ECU-NMO-301 trial. This extension trial will be open to all patients who have completed the ECU-NMO-301 trial and meet the eligibility criteria.

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LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this trial protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ARR	Annualized Relapsing Rate
AQP4-Ab	Aquaporin-4 Antibody
AZA	Azathioprine
BP	Blood Pressure
C5	Complement Protein 5
CNS	Central Nervous System
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed Tomography
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EIU	Exposure in-utero
EOS	End of Study
EQ-5D	EuroQol
ET	Early Termination
FAS	Full Analysis Set
FSS	Functional System Scores
GCP	Good Clinical Practice
HAHA	Human Anti-human Antibody
HAI	Hauser Ambulation Index
HCG	Human Chorionic Gonadotropin
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IRB	Institutional Review Board
IST	Immunosuppressant Therapy
IV	Intravenous
IVIg	Intravenous Immunoglobulin
IVMP	Intravenous Methylprednisolone
IXRS	Interactive voice or web Response System
mAb	Monoclonal Antibody
MMF	Mycophenolate Mofetil
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NMO	Neuromyelitis Optica
NMO-IgG	Neuromyelitis Optica antibody
OAE	Other Significant Adverse Event

Abbreviation or Specialist Term	Explanation
OSIS	Optic Spinal Impairment Score
PD	Pharmacodynamics
PE	Plasmapheresis Or Plasma Exchange
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
QOL	Quality Of Life
RR	Respiration Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	Short Form Health Survey
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
VA	Visual Acuity
VS	Vital Signs

5. INTRODUCTION

Neuromyelitis Optica (NMO) or NMO Spectrum Disorder (NMOSD), also known as Devic's Disease, is a rare, severe disabling autoimmune inflammatory disorder of the central nervous system (CNS) that predominately affects the optic nerves and spinal cord, and is often characterized by a relapsing course (1;2). Currently there are no approved therapies for the treatment of NMO. Complement activation is a key element in the development of CNS lesions in NMO. Eculizumab (h5G1.1-mAb) is a terminal complement inhibitor that blocks conversion of C5 to C5a and C5b thus blocking terminal complement activation. The mechanism of action of eculizumab as a terminal complement inhibitor suggests that it may provide therapeutic benefit in the management of NMO by reducing NMO relapses and thus reducing disability (see the Investigator's Brochure (IB) for more information).

A phase 3 clinical trial, Protocol ECU-NMO-301, to evaluate the safety and efficacy of eculizumab in the treatment of relapsing NMO, has been initiated. Protocol ECU-NMO-302 is an extension trial designed to provide the patients who have participated in the ECU-NMO-301 trial an opportunity to continue receiving eculizumab and to collect clinical data that will provide long term safety and efficacy information on eculizumab in patients with relapsing NMO. Throughout this document, the term NMO refers to both NMO and NMOSD.

Refer to Protocol ECU-NMO-301 and to the current IB for additional information on the safety and efficacy data of eculizumab.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

- Evaluate the long-term safety of eculizumab in patients with relapsing NMO.

6.2. Secondary Objectives

- Evaluate the long-term efficacy of eculizumab in patients with relapsing NMO as measured by annualized relapsing rate (ARR)
- Evaluate long-term efficacy of eculizumab by additional efficacy measures including:
    - Disability
    - Quality of life (QOL)
    - Neurologic functions
- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in relapsing NMO patients.

7. INVESTIGATIONAL PLAN

7.1. Overall Trial Design

This is an open-label trial. All patients who have completed the trial ECU-NMO-301 may be eligible to participate in this extension trial. Prior to initiating any extension trial procedures, an Informed Consent Form (ICF) must be signed and inclusion/exclusion criteria must be obtained, evaluated and met. Patients who exit the ECU-NMO-301 trial due to a relapse will have their first extension trial visit once the Week 6 Follow-up Relapse Evaluation Visit is completed and no later than 2 weeks (14 days ±2 days) after the last IP dose; patients who exit the ECU-NMO-301 trial due to trial completion will have their first extension trial visit once the End of Study (EOS) Visit is completed and no later than 2 weeks (14 days ±2 days) after the last IP administration in the ECU-NMO-301 trial.

Due to the length of this extension trial, patients may need to be revaccinated for *N meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.

Patients who have been unblinded in ECU-NMO-301 may not continue in ECU-NMO-302.

7.1.1. Blind Induction Phase (Visits 1 – 4)

To preserve the blinded nature of the ECU-NMO-301 trial, all patients must undergo a blind induction phase prior to entering the open-label phase of this trial, ie, all patients will receive 4 vials of blinded investigational product (IP) weekly (±2 days) for 4 doses. Patients who had been randomized to the placebo arm in the ECU-NMO-301 trial will start with the induction dose (ie, they will receive blinded IP [3 vials/900 mg eculizumab plus 1 vial placebo] at Visits 1 to 4). Patients who were randomized to the eculizumab arm in the ECU-NMO-301 trial will continue with the maintenance dose (ie, they will receive blinded IP [4 vials/1200 mg eculizumab every two weeks (±2 days) at Visits 1 and 3 and 4 vials of placebo at Visits 2 and 4]). All patients will receive open-label 4 vials/1200 mg eculizumab at Visit 5 and onward.

7.1.2. Open-Label Maintenance Phase

All patients will receive open-label eculizumab (4 vials/1200 mg) every 2 weeks (±2 days) during the maintenance phase. The end of the trial occurs a maximum of 5.5 years after the first patient was enrolled in this study, therefore for each individual patient the number of visits and the relative timing of the EOS Visit will vary.

All patients must be present at the trial site, as applicable, for visit-specific procedures/assessments including IP administration (see Schedule of Assessments in Section 7.5). For other visits, patients may have an opportunity to receive IP administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. These visits will be conducted by a qualified staff member from the medical facility near the patient's home or by home-care health professionals, who are under the direct supervision of the Investigator. The trial medication will be prepared and administered at the patient's home or at the medical facility. During a remote

dosing visit, information on adverse events (AEs), concomitant medications, and signs or symptoms of NMO relapses will be collected and sent to the Investigator's site for evaluation on the day of the visit. Patients must go to the trial site for evaluation if the patient reports any signs or symptoms that suggest a serious adverse event (SAE) or NMO relapse.

Supportive immunosuppressive therapy (IST) for relapse prevention is allowed during the extension trial at the Treating Physician's discretion. However, use of rituximab, mitoxantrone, or other biologic agents such as tocilizumab is prohibited during the trial.

Patients may continue participation in this trial and receive the IP until the product is registered and available to treat patients diagnosed with relapsing NMO (in accordance with country specific regulations) or for a maximum of 5.5 years from the time the first patient was enrolled, whichever occurs first.

7.1.3. Relapse Evaluation

Identification of potential relapse is critical for patient safety and for the integrity of this trial. Patients will receive a Patient Education Card that details signs and symptoms of a potential relapse and instructions to contact the study site at the first sign or symptom of a potential relapse. The Investigator or his/her designee should review, in detail, this information and any additional warning signs of a relapse specific to that patient's clinical picture at each visit. Patients should be evaluated within 24 hours of notification of the Investigator of a possible relapse, and no later than 48 hours. All reports of possible relapses and actions taken for the possible relapse must be documented in the patient's source documents and recorded on the electronic case report forms (eCRFs).

At the Relapse Evaluation Visit, a blinded Expanded Disability Status Scale (EDSS) Rater will perform the Kurtzke neurologic assessment and document the Functional System scores (FSS) to determine the EDSS score. The Treating Physician will perform a complete neurologic examination and document the Optic-Spinal Impairment Score (OSIS). Treating Physician or appropriately trained designee will perform the visual acuity (VA) test (Snellen Chart) and Hauser Ambulatory Index (HAI) as outlined in the Relapse Evaluation Period (section 7.6.2).

The Treating Physician will make the decision as to whether the clinical signs, symptoms and neurologic change (objective findings on neurologic examination) meet the definition of an On-Trial Relapse (Section 7.2.1). The blinded EDSS Rater will complete the Kurtzke neurologic assessment and document the FSS and EDSS scores. If the event is confirmed as an On-Trial Relapse, the patient may be treated according to the recommended Standardized On-Trial Relapse Treatment Plan (Section 9.2.1.3). Relapse treatment is at the Treating Physician's discretion. The IP administration will be continued as scheduled every 1 week (if during the induction phase) or every 2 weeks (if during the maintenance phase) until the EOS.

Follow-up Relapse Evaluation visits to monitor the course of the relapse will be performed at 1, 4 and 6 weeks after the onset of relapse. Additional (unscheduled) Follow-up Relapse Evaluation Visits outside the specified time points will be made at the discretion of the Treating Physician. Following a relapse, a patient may continue in the trial if the patient and the Treating Physician decide that it is appropriate to continue to receive eculizumab treatment.

All reports of possible relapses and actions taken for the possible relapse must be documented in the patient's source documents and recorded in the eCRF.

An independent Relapse Endpoint Adjudication Committee will confirm all On-Trial Relapse events using objective and consistent clinical criteria described in a Relapse Endpoint Adjudication Charter. The Adjudication Committee will consist of three independent medical experts in neurology/neuroophthalmology who are each experienced in the management of patients with NMO. The Adjudication Committee will decide by majority vote whether each relapse meets the pre-defined objective criteria for an adjudicated On-Trial Relapse, as described in the Relapse Adjudication Charter.

7.1.4. Safety Follow-up Period (Post-Treatment)

If a patient withdraws from this extension trial at any time after receiving any amount of IP, the patient will be required to complete an Early Termination (ET) Visit at the time of the withdrawal and a safety Follow-up Visit, 8 weeks after the last IP administration. If a patient is discontinued due to an AE, the event will be followed until it is resolved or, in the opinion of the Principal Investigator (PI), is determined medically stable. Patients who withdraw from the extension trial and transition to treatment with the commercially available eculizumab will not be required to complete a safety Follow-up Visit.

7.1.5. Post-Treatment Follow-up (a Maximum of 2 Years)

The Sponsor may seek to collect follow-up information concerning NMO status in patients who have prematurely discontinued from the trial for a maximum of 2 years from the last dose of eculizumab (refer to Appendix 11).

7.2. Standard Protocol Definitions

7.2.1. On-Trial Relapse

On-Trial Relapses are acute attacks that occur during the trial. For this protocol, On-Trial Relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persists for more than 24 hours as confirmed by the Treating Physician. The signs and symptoms must be attributed to NMO, ie, not caused by an identifiable cause such as infection, excessive exercise, or excessively high ambient temperature. Isolated changes on magnetic resonance imaging (MRI) or other imaging investigation with no related clinical findings is not considered an On-Trial Relapse. The relapse must be preceded by at least 30 days of clinical stability. The Treating Physician is not required to wait 24 hours prior to initiating treatment for the relapse.

All PI-determined relapses will be reviewed by the Adjudication Committee; to determine if they meet protocol-defined criteria for an On-Trial relapse event.

7.2.2. Severity of Relapse

Severity of an On-trial Relapse will be measured by OSIS. The OSIS Visual Acuity (VA) Subscale Scores will be used to categorize the severity of optic neuritis relapse. The OSIS Motor Subscale Scores and Sensory Subscale Scores will used to categorize the severity of transverse myelitis. OSIS scores will be assessed by the Treating Physician at the time of the relapse as in Table 3 below.

Table 3: Relapse Severity as Measured by OSIS

Optic Neuritis		
Visual Acuity (VA) Subscale Score		**Relapse Descriptor**
Pre-Relapse	**Post Relapse**	
0-1	0-2	Minor
0-1	3+	Major
2-7	Increase by 1 point	Minor
2-7	Increase by ≥2 points	Major
Transverse Myelitis		
Motor Subscale Score		
Pre-Relapse	**Post Relapse**	**Relapse Descriptor**
0-1	0-2	Minor
0-1	3+	Major
2-6	Increase by 1 point	Minor
2-6	Increase by ≥2 points	Major
Sensory Subscale Score		
Based on proprioceptive loss only	Severe loss in one or more limbs with prior normal function or mild proprioceptive loss	Major

7.2.3. The Treating Physician

The Treating Physician is the PI or the Sub-Investigator for the trial, and will be responsible for overall patient management including patient eligibility evaluation, the supervision of the blinded (induction phase) and open label (maintenance phase) IP administration, the recording and treating of AEs and the monitoring of safety assessment. In addition, the Treating Physician or an appropriately trained designee will perform mRS and C-SSRS assessments. At the time of a relapse the Treating Physician will perform a complete neurologic exam and determine if a patient experiences an On-Trial Relapse, determine relapse severity by OSIS, assess VA test (Snellen Chart), ambulation (HAI), have the patient complete EQ-5D and SF-36, and may treat the patient's relapse at his/her discretion, according to the recommended Standardized On-Trial Relapse Treatment plan (section 9.2.1.3). Treatment for On-Trial Relapse and any changes in the ISTs are at the discretion of the Treating Physician.

7.2.4. The (Blinded) EDSS Rater

The blinded EDSS Rater will be responsible for performing the EDSS assessments throughout the trial at protocol-specified time points including at the time of a relapse. The EDSS Rater will perform the Kurtzke neurologic assessment (5) and document the FSS and EDSS score. The EDSS Rater shall not be the PI or the Treating Physician, and cannot be directly involved in the trial patient's management. The EDSS Rater must remain blinded to all other trial data as well as

all other patient clinical data. When possible, the EDSS rater should be a physician. If a non-physician EDSS rater (eg, specialized nurse) will be used, the rater must be approved by the Sponsor prior to initiation of the study. For specific requirements for EDSS Rater qualifications, refer to the training materials provided to the sites.

The table below provides roles and responsibilities of Treating Physician and EDSS Rater.

Table 4: Roles and Responsibilities of Treating Physician and EDSS Rater

Treating Physician	EDSS Rater
Blinded to the patient's treatment assignment during the Induction Phase • Determine patient eligibility for the trial • Overall patient management during the trial, including IP administration and safety assessments. • Perform modified Rankin Scale (mRS)* • Perform Columbia-Suicide Severity Rating Scale (C-SSRS)*	Blinded to all other trial data as well as all other patient clinical chart data At protocol-specified time points: • Kurtzke neurologic assessment • Document FSS • Record EDSS score
At relapse evaluation visits: • Initial patient assessment • Have the EDSS Rater record FSS and EDSS score • Perform a complete neurologic examination • Determine if the patient has experienced an On-Trial Relapse • Determine relapse severity by OSIS • Assess VA, Snellen Chart* • Assess ambulation, HAI* • Have the patient complete EuroQoL EQ-5D and Short Form Health Survey (SF-36)* • Treat relapse	At relapse evaluation visits: • Perform Kurtzke neurologic assessment • Document FSS • Record EDSS score

* Can be performed by the Treating Physician or his/her designee.

7.3. Number of Patients

This is an extension trial to the ECU-NMO-301 trial. A maximum of 132 patients are expected to enroll in the ECU-NMO-301 trial. Patients who complete the ECU-NMO-301 trial may potentially enter this extension trial.

7.4. Treatment Assignment

This is an open-label extension trial to the ECU-NMO-301 trial. All patients will be administered intravenous (IV) eculizumab. To maintain the blind of the ECU-NMO-301 trial, all patients will undergo a blind induction phase as described in Section 9.1.

7.5. Schedule of Assessments

The Schedules of Assessments are presented in Table 5 through Table 10. Note that when a patient continues beyond Visit 29 (end of first year), the visit schedule and assessments scheme for the second year and beyond will restart from the equivalent of Visit 30 onward. These visits and assessments in the second year and beyond are included in the Schedule of Assessments in Table 7 .

Table 5: Schedule of Assessments – Visits 1-16

Phase	**Induction**					**Open-label Maintenance**										
Visit Location [Δ]	**In Clinic**					**In Clinic/ Remote**	**In Clinic**	**In Clinic/ Remote**	**In Clinic**	**In Clinic/Remote**						**In Clinic**
Trial Visit Year 1	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**
Trial Week Year 1	**Day 1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Informed Consent	**X**															
Physical exam																**X**
Weight																**X**
Vital Signs	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Electrocardiogram (ECG)																**X**
Concomitant Medication	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse events (AEs)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Clinical Laboratory Tests [1]	**X**				**X**		**X**		**X**							**X**
Pregnancy serum test [2]	**X**				**X**		**X**		**X**							**X**
NMO-IgG (serum)	**X**				**X**		**X**		**X**							**X**
NMO-IgG (CSF) [3]	**See Footnote**								**X**							**X**
PK/PD/Free C5 (serum) [4]	**T/P**				**T/P**		**T/P**		**T/P**							**T/P**
HAHA (serum)	**X**				**X**				**X**							**X**
PK and Free C5 (CSF) [3]	**See Footnote**								**X**							**X**
EuroQol (EQ-5D)	**X**				**X**		**X**		**X**							**X**
Short Form Health Survey (SF-36)	**X**				**X**		**X**		**X**							**X**
Columbia-Suicide Severity Scale (C-SSRS)[7]	**X**				**X**		**X**		**X**							**X**
Expanded Disability Status Scale (EDSS) [5]	**X**				**X**		**X**		**X**							**X**
Modified Rankin Scale (mRS)	**X**				**X**		**X**		**X**							**X**
Patient Education Card and NMO Symptom Evaluation [6]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Neurologic Examination [6]	**X**				**X**		**X**		**X**							**X**
Optic Spinal Impairment Score (OSIS) [6]	**X**															
VA test (Snellen chart) [7]	**X**				**X**		**X**		**X**							**X**
Hauser Ambulation Index (HAI) [7]	**X**				**X**		**X**		**X**							**X**
Medically indicated tests [8]																

Review Inclusion / Exclusion criteria	**X**															
N meningitidis Revaccination [9]	**See Footnote**															
Patient Safety Identification Card [9]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Investigational Product (IP) Infusion [10]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Table 6: Schedule of Assessments – Visits 17-29

Phase	**Open-label Maintenance**												
Visit Location [Δ]	**In Clinic/Remote**						**In Clinic**	**In Clinic/Remote**					**In Clinic**
Trial Visit Year 1	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**
Trial Week Year 1	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**
Physical exam													X
Weight													X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)													X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests [1]							X						X
Pregnancy serum test [2]							X						X
NMO-IgG (serum)							X						X
NMO-IgG (CSF) [3]	***Only to be collected in the event of a relapse***												
PK/PD/Free C5 (serum) [4]							T/P						T/P
HAHA (serum)							X						X
PK and Free C5 (CSF) [3]	***Only to be collected in the event of a relapse***												
EuroQol (EQ-5D)							X						X
Short Form Health Survey (SF-36)							X						X
Columbia-Suicide Severity Scale (C-SSRS)[7]							X						X
Expanded Disability Status Scale (EDSS) [5]							X						X
Modified Rankin Scale (mRS)							X						X
Patient Education Card and NMO Symptom Evaluation [6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurologic Examination [6]							X						X
Optic Spinal Impairment Score (OSIS) [6]													
VA test (Snellen chart) [7]							X						X
Hauser Ambulation Index (HAI) [7]							X						X
Medically indicated tests [8]													
N meningitidis Revaccination [9]	**See Footnote**												
Patient Safety Identification Card [9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product (IP) Infusion [10]	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 7: Schedule of Assessments - Study Period (Beyond Visit 29/Week 52 to EOS/ET)

	Maintenance Phase			
Trial Visit	**In Clinic/Remote Short Visit**	**In Clinic Long Visit**	**In Clinic End of Study (EOS) / Early Termination (ET) Visit**	**In Clinic Unscheduled**
Trial Week from Year 2 Onwards	**Every 2nd week after Week 52 visit except Long Visits**	**Alternating every 14 or 12 Weeks from Week 52 visit (Weeks 66, 78, 92, 104, 118, 130, 144, 156, 170, 182, 196, 208, 222, 234, 248, 260, 274, 286)**		**Procedures, tests, and assessments will be performed at the discretion of the Investigator. Refer to Section 7.6.2.3 for further details.**
Physical Exam		**Only on annual basis (Week 104, 156, 208, 260, etc.)**	**X**	
Weight		**Only on annual basis (Week 104, 156, 208, 260, etc.)**	**X**	
Electrocardiogram (ECG)		**Only on annual basis (Week 104, 156, 208, 260, etc.)**	**X**	
Vital Signs	**X**	**X**	**X**	
Concomitant Medication	**X**	**X**	**X**	
Adverse Events (AEs)	**X**	**X**	**X**	
Clinical Laboratory Tests [1]		**X**	**X**	
Pregnancy serum test [2]		**X**	**X**	
NMO-IgG (serum)		**X**	**X**	
HAHA (serum)		**Only at Weeks 78, 130, 182, 234, 286)**		
NMO-IgG (CSF) [3]	***Only to be collected in the event of a relapse***			
PK/PD/Free C5 (serum) [4]	***Only to be collected in the event of a relapse***			
PK and Free C5 (CSF) [3]	***Only to be collected in the event of a relapse***			
EuroQol (EQ-5D)		**X**	**X**	
Short Form Health Survey (SF-36)		**X**	**X**	
Columbia-Suicide Severity Scale (C-SSRS)[7]		**X**	**X**	
Expanded Disability Status Scale (EDSS) [5]		**X**	**X**	
Modified Rankin Scale (mRS)		**X**	**X**	
Patient Education Card and NMO Symptom Evaluation [6]	**X**	**X**	**X**	
Neurologic Examination [6]		**X**	**X**	
VA Test (Snellen chart) [7]		**X**	**X**	
Hauser Ambulation Index (HAI) [7]		**X**	**X**	
Medically Indicated Tests [8]				

	Maintenance Phase			
Trial Visit	**In Clinic/Remote Short Visit**	**In Clinic Long Visit**	**In Clinic End of Study (EOS) / Early Termination (ET) Visit**	**In Clinic Unscheduled**
Trial Week from Year 2 Onwards	**Every 2nd week after Week 52 visit except Long Visits**	**Alternating every 14 or 12 Weeks from Week 52 visit (Weeks 66, 78, 92, 104, 118, 130, 144, 156, 170, 182, 196, 208, 222, 234, 248, 260, 274, 286)**		**Procedures, tests, and assessments will be performed at the discretion of the Investigator. Refer to Section**
N meningitidis Revaccination [9]	**See Footnote**			
Patient Safety Identification Card [9]	**X**	**X**	**X**	
Investigational Product (IP) Infusion [10]	**X**	**X**	**X**	

Table 8: Schedule of Assessments – Relapse Evaluation Period

Visit Location [Δ]	**In Clinic**				
Assessment	**Relapse Evaluation Visit**[11]	**Follow-up Relapse Evaluation Follow-up Visits**			
Trial Week	**Within 24-48 hours**	**+1 Week**	**+4 Weeks**	**+6 Weeks**	**Unscheduled**[12]
Vital Signs	**X**	**X**	**X**	**X**	**X**
Concomitant Medication	**X**	**X**	**X**	**X**	**X**
Adverse events (AEs)	**X**	**X**	**X**	**X**	**X**
Clinical Laboratory Tests [1]	**X**			**X**	**X**
NMO-IgG (serum)	**X**			**X**	**X**
NMO-IgG (CSF) [3]	**X**			**X**	**X**
PK/PD/Free C5 (serum) [4]	**T/P**	**T/P**	**T/P**	**T/P**	**T/P**
PK and Free C5 (CSF) [3]	**X**			**X**	**X**
EuroQol (EQ-5D)				**X**	**X**
Short Form Health Survey (SF-36)				**X**	**X**
Columbia-Suicide Severity Scale (C-SSRS)[7]				**X**	
Expanded Disability Status Scale (EDSS) [5]	**X**	**X**	**X**	**X**	**X**
Modified Rankin Scale (mRS)				**X**	
Patient Education Card and NMO Symptom Evaluation [6]	**X**	**X**	**X**	**X**	**X**
Neurologic Examination [6]	**X**	**X**	**X**	**X**	**X**
Optic Spinal Impairment Score (OSIS) [6]	**X**	**X**	**X**	**X**	**X**
VA test (Snellen chart) [7]	**X**	**X**	**X**	**X**	**X**
Hauser Ambulation Index (HAI) [7]	**X**	**X**	**X**	**X**	**X**
Medically indicated tests [8]	**X**	**X**	**X**	**X**	**X**
N meningitides Revaccination [9]	**See Footnote**				
Patient Safety Identification Card [9]	**X**	**X**	**X**	**X**	**X**
Investigational Product (IP) Infusion [10]	**Continue every 1 week ±2 days (blind induction phase) or** every 2 weeks ±2 days (open-label maintenance phase), as scheduled				

Table 9: Schedule of Assessments – Safety Follow-up Visit

Visit Location [Δ]	**In-Clinic**[13]
Trial Visit	**Safety Follow Up**
Trial Weeks	**+8 W**
Vital Signs	**X**
Concomitant Medication	**X**
Adverse events (AEs)	**X**
Columbia-Suicide Severity Scale (C-SSRS)[7]	**X**
Patient Education Card and NMO Symptom Evaluation [6]	**X**
Patient Safety Identification Card [9]	**X**

Table 10: Schedule of Assessments – Footnotes

Footnote	Description
1.	Clinical laboratory tests will be performed at a central laboratory. Reference Appendix 8 for a summary of the clinical laboratory test panels and tests.
2.	Serum samples for pregnancy test must be performed on all women of childbearing potential at a central laboratory at specified time points. Pregnancy test (urine or serum) may also be performed at any time during the trial at the Investigator's discretion.
3.	Patients may choose not to have CSF samples collected and will still be eligible for trial participation. CSF sampling will be collected at Day 1/Visit 1 only for patients who have provided consent and did not already provide a sample at the EOS Visit in Study ECU-NMO-301.
4.	Trough samples for PK/PD and free C5 level testing are to be taken approximately 5-90 minutes before the IP infusion. Peak samples are to be taken at least 60 minutes after completion of the IP infusion.
5.	The blinded EDSS Rater will perform the Kurtzke neurologic assessment and document the FSS and EDSS score. See Section 7.2.4 for more detail
6.	The Treating Physician will be responsible for assessment of the patient for any signs or symptoms indicative of relapse at every visit and perform a complete neurologic examination at the specified time points. The Treating Physician will document the Optic-Spinal Impairment Score (OSIS).
7.	The Treating Physician or appropriately trained designee will perform the VA test using Snellen chart, the Hauser Ambulatory Index (HAI) and the C-SSRS (Since Last Visit).
8.	Additional tests/procedures may be performed as medically indicated at the Investigator's discretion. If additional medically indicated tests/procedures are performed these procedures / tests must be recorded in source documents and on the electronic case report form (eCRF).
9.	Patients may be revaccinated for *N meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines. Patients will be given a Patient Safety Identification Card prior to the first dose of trial medication. At each visit throughout the trial, trial staff will ensure that the patient has the Patient Safety Identification Card.
10.	Patients will undergo a blind induction phase at Visits 1 – 4. All patients will receive open-label IP at Visits 5 and onward and throughout the trial. If a patient undergoes plasma exchange (PE) for On-Trial Relapse, a supplemental dose of IP must be administered after each PE session, preferably within 1-2 hours, according to the regimen described under Supplemental Dose in Section 9.1.
11.	Relapse Evaluation Visit: every effort should be made to evaluate potential relapses within 24 hours of notification of the Investigator of a possible relapse, and no later than 48 hours. All potential relapses must be evaluated by both the Treating Physician and the EDSS Rater.
12.	Additional unscheduled Follow-up Relapse Evaluation Visits are permitted at the discretion of the Investigator.
13.	If a patient is unable to attend the safety follow-up visit as deemed medically necessary by the Investigator, the Investigator may perform the follow-up visit by telephone. All visit assessments should be performed with exception of vital signs.
Δ	In Clinic visits must be conducted at the study sites; Remote visits may be conducted remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.
†	For patients who reach visit 29 (end of first year), the visit schedule and assessment scheme for the second year and beyond will restart from Visit 30 onward (Table 7) through the EOS Visit.
*	If a patient withdraws early from the trial an Early Termination (ET) visit will be performed.
Abbreviations: AEs = adverse events; C5 = complement factor 5; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Scale; ECG = electrocardiogram; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; EOS = End of Study; EQ-5D = EuroQol; ET = early termination visit; FSS = Functional Status Score; HAHA = human anti-human antibody; HAI = Hauser Ambulatory Index; IgG = immunoglobulin G; IP = investigational product; mRS = Modified Rankin Scale; *N meningitidis* = *Neisseria meningitidis*; NMO = neuromyelitis optica; OSIS = Optic-Spinal Impairment Score; P = peak sample; PD = pharmacodynamics; PE = plasma exchange; PK = pharmacokinetics; SF-36 = Short Form Health Survey; T = trough sample; V = visit; VA = visual acuity; W = week	

7.6. Trial Visit Procedures

7.6.1. Trial Period

Visit intervals during induction phase (Visits 1 to 5) are weekly (every 7 ±2 days). Visit intervals during the open-label maintenance phase (Visits 6 – 107) are every 2 weeks (every 14 days ±2 days). Patients who fail to return for a scheduled visit/dosing appointment must be contacted by the site's study staff to determine the reason for missing the appointment. Patients will be strongly encouraged to return to the study site for evaluation if a relapse or AE is suspected to have occurred. In the exceptional circumstance where a patient cannot or does not come to the study site for examination, then the patient will be instructed to see his or her local neurologist or physician. In this event, the study site will obtain relevant medical records as documentation from the local physician's examination and enter relevant data in the Relapse Evaluation Visit form or AE form, as appropriate.

As it is vital to obtain information on any patient's missing visit to ensure the missed appointment was not due to an AE or potential relapse, every effort must be made to undertake protocol-specified safety follow-up procedures. Follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the patient's last known address.

7.6.1.1. Induction Phase (Visit 1 until Visit 5 [Week 4])

7.6.1.1.1. Visit 1

All patients who have completed the ECU-NMO-301 trial may be eligible to participate in this extension trial. Prior to initiating any extension trial procedures, an ICF must be signed and inclusion/exclusion criteria must be obtained, evaluated and met.

At Visit 1, patients must be registered in the interactive voice or web response system (IXRS) to be assigned IP. Patients maintain the identification number that they were assigned in ECU-NMO-301.

Patients who exit the ECU-NMO-301 trial due to relapse will have their first extension trial visit once the Week 6 Relapse Evaluation Visit is completed and no later than 2 weeks (14 days ±2 days) after the last IP dose in the ECU-NMO-301 trial; patients who exit the ECU-NMO-301 trial due to trial completion will have their first extension trial visit once the EOS Visit is completed and no later than 2 weeks (14 days ±2 days) after the last IP administration visit in the ECU-NMO-301 trial.

Once all of the Visit 1 procedures have been performed and the eligibility criteria have been confirmed by the PI, the patient will be assigned to a blinded induction treatment on Day 1 based on the treatment the patient received in the ECU-NMO-301 trial (please refer to Section 9.1 for treatment assignment). The following tests and procedures will be completed at Visit 1:

- Contact the IXRS to get IP kits assignation
- Questionnaires to evaluate QOL (EQ-5D and SF-36)
- The EDSS Rater will perform the Kurtzke neurologic assessment to determine the FSS and EDSS score.

- The Treating Physician will perform the following assessments:
  - Review Inclusion/Exclusion criteria
  - Review and assess the patient for any potential signs or symptoms indicative of relapse. Ensure the patient has the Patient Education Card and remind the patient to contact the study site at the first signs or symptoms of potential relapse.
  - Perform a complete neurologic examination
  - Document the OSIS
- The Treating Physician or appropriately trained designee will perform the following assessments:
  - Perform mRS
  - Perform VA test (Snellen chart)
  - Perform HAI
  - Perform C-SSRS (Since Last Visit)
  - Vital signs (VS) include assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and heart rate (HR)
  - Any new medications or changes to concomitant medications will be recorded
  - AEs since the previous visit will be evaluated and recorded
  - Clinical laboratory tests (chemistry, hematology and urinalysis)
  - Pregnancy test must be performed on all women of childbearing potential. Pregnancy test (urine or serum) may also be performed at any time during the trial at the Investigator's discretion
  - Collect blood samples for NMO-IgG
  - Collect baseline trough blood samples for PK, PD, free C5 and HAHA assays approximately 5-90 minutes before the IP infusion
  - Perform lumbar puncture to collect baseline CSF samples for NMO-IgG and PK, and free C5 assays before the IP infusion. Patients may choose not to have CSF samples collected and will still be eligible for trial participation. CSF sampling will be collected at Day 1/Visit 1 only for patients who have provided consent and did not already provide a sample at the EOS Visit in Study ECU-NMO-301.
  - Patients may be revaccinated for *N meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines
  - Instruct the patient on the signs and symptoms of *N. meningitidis*.
  - Provide the Patient Safety Identification Card describing the IP and emergency contact information to the patient prior to the first dose of IP.

- IP will be administered and patients will be observed for at least 1 hour following the end of the IP infusion.
- Collect peak blood samples for PK, PD and free C5 assays at least 60 minutes after completing the IP infusion

7.6.1.1.2. Visits 2-4 (Weeks 1-3)

Patients will return for weekly (7 ±2 days) IP infusions during the induction phase including Visit 2 (Week 1), Visit 3 (Week 2), and Visit 4 (Week 3). The following tests and procedures will be completed:

- The Treating Physician will review and assess the patient for any potential signs or symptoms indicative of relapse. Ensure the patient has the Patient Education Card and remind the patient to contact the study site at the first signs or symptoms of potential relapse.
- VS include assessments of systolic and diastolic BP, temperature, RR and HR
- Any new medications or changes to concomitant medications will be recorded
- Any new AEs or changes in AEs since the previous visit will be evaluated and recorded
- Patients may be revaccinated for *N meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines
- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information
- Contact the IXRS to get IP kits assignation
- IP will be administered and patients will be observed for at least 1 hour following the end of the IP infusion

7.6.1.1.3. Visit 5 (Week 4)

At Visit 5 (Week 4), patients will return for an IP infusion for the final visit in the induction phase. The following tests and procedures will be completed:

- Questionnaires to evaluate QOL (EQ-5D and SF-36)
- The EDSS Rater will perform the Kurtzke neurologic assessment to determine the FSS and EDSS score.
- The Treating Physician will perform the following assessments:
  - Review and assess the patient for any potential signs or symptoms indicative of relapse. Ensure the patient has the Patient Education Card and remind the patient to contact the study site at the first signs or symptoms of potential relapse.
  - A complete neurologic examination

- The Treating Physician or appropriately trained designee will perform the following assessments:
  - mRS
  - VA test (Snellen chart)
  - HAI
  - C-SSRS
  - VS include assessments of systolic and diastolic BP, temperature, RR and HR
  - Any new medications or changes to concomitant medications will be recorded
  - Any new AEs or changes in AEs since the previous visit will be evaluated and recorded
  - Clinical laboratory tests (chemistry, hematology and urinalysis)
  - Pregnancy test must be performed on all women of childbearing potential. Pregnancy test (urine or serum) may also be performed at any time during the trial at the Investigator's discretion.
  - Collect blood samples for NMO-IgG
  - Collect trough blood samples for PK, PD, free C5, and HAHA approximately 5-90 minutes before the IP infusion
  - Patients may be revaccinated for *N meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines
  - Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information
  - Contact the IXRS to get IP kits assignation. IP will be administered and patients will be observed for at least 1 hour following the end of the IP infusion.
  - Collect peak blood samples for PK, PD and free C5 assays at least 60 minutes after completing the IP infusion

7.6.1.2. Open-label Phase (Visit 6 [Week 6] until End of Study / Early Termination Visit)

Patients will receive IP infusions every two weeks (14 ±2 days) during the Open-label Phase.

All patients must be present at the trial site, as applicable, for visit-specific procedures/assessments including IP administration (see Schedule of Assessments in Section 7.5). Note that when a patient continues beyond Visit 29 (end of first year), the visit schedule and assessments scheme for the second year and beyond will restart from the equivalent of Visit 30 onward. These visits and assessments in the second year and beyond are included in the Schedule of Assessments in Table 7.

For other visits, patients may have an opportunity to receive IP administration remotely at a medical facility that is located near the patient's home or at the patient's home with the

permission of the PI in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

The maximum total trial duration is 5.5 years from the time the first patient was enrolled. Trial duration for an individual patient will vary depending on when the patient enters the trial; participation may continue until the product is registered and available to treat patients diagnosed with relapsing NMO (in accordance with country specific regulations) or until the trial ends, whichever occurs first.

The following tests and procedures will be completed at every visit beginning at Visit 6 (Week 6) and continuing until the ET or EOS:

- VS include assessments of systolic and diastolic BP, temperature, RR and HR
- Any new medications or changes to concomitant medications will be recorded
- Any new AEs or changes in AEs since the previous visit will be evaluated and recorded
- The Treating Physician will review and assess the patient for any potential signs or symptoms indicative of relapse. Ensure the patient has the Patient Education Card and remind the patient to contact the study site at the first signs or symptoms of potential relapse.
- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information
- Contact the IXRS to get IP kits assignation. IP will be administered and patients will be observed for at least 1 hour following the end of the IP infusion.

The following additional procedures will also be completed at certain visits (see Schedule of Assessments in Section 7.5):

- Questionnaires to evaluate QOL (EQ-5D and SF-36)
- The EDSS Rater will perform the Kurtzke neurologic assessment to determine the FSS and EDSS score.
- The Treating Physician will perform a complete neurologic examination
- The Treating Physician or appropriately trained designee will perform the following assessments:
  - mRS
  - VA test (Snellen chart)
  - HAI
  - C-SSRS
  - Physical exam
  - Body weight
  - ECG

  - Clinical laboratory tests (chemistry, hematology and urinalysis)
  - Pregnancy test must be performed on all women of childbearing potential. Pregnancy test (urine or serum) may also be performed at any time during the trial at the Investigator's discretion.
  - Collect blood samples for NMO-IgG
- Collect trough samples for PK, PD, free C5 and HAHA assays approximately 5-90 minutes before the IP infusion
  - Perform lumbar puncture to collect CSF for NMO-IgG and PK and free C5 assays before IP infusion at Visits 9 and 16 and in the event of a relapse only. Patients may choose not to have CSF samples collected and will still be eligible for trial participation.
  - Collect peak blood samples for PK, PD, and free C5 assays at least 60 minutes after completing the IP infusion
- Patients may be revaccinated for *N. meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.

7.6.2. Relapse Evaluation Period

Patients will be instructed to contact the study site at the first sign or symptom of a potential relapse. Patients should be evaluated within 24 hours of notification of the Investigator of a possible relapse, and no later than 48 hours. All potential relapses must be evaluated by both the Treating Physician and the EDSS Rater.

Follow-up Relapse Evaluation Visits will be performed at 1, 4 and 6 weeks after the onset of relapse. Additional (Unscheduled) Relapse Evaluation Visits are permitted at the discretion of the Investigator.

7.6.2.1. Relapse Evaluation Visit (Within 24-48 Hours)

- The EDSS Rater will perform the Kurtzke neurologic assessment to determine the FSS and EDSS score.
- The Treating Physician will perform the following assessments:
  - A complete neurologic examination
  - OSIS
- The Treating Physician or appropriately trained designee will perform the following assessments:
  - VA test (Snellen chart)
  - HAI
  - VS include assessments of systolic and diastolic BP, temperature, RR and HR
  - Any new medications or changes to concomitant medications will be recorded

  - Any new AEs or changes in AEs since the previous visit will be evaluated and recorded
  - Clinical laboratory tests (chemistry, hematology and urinalysis)
  - Collect blood samples for NMO-IgG
  - Perform lumbar puncture to collect CSF sample for NMO-IgG, PK and free C5 assays. Patients may choose not to have CSF samples collected and will still be eligible for trial participation.
- If medically indicated for evaluation of relapse, additional tests (eg, MRI, CT scan, laboratory tests, etc.) may be performed at the discretion of the Investigator. If additional medically indicated tests/procedures are performed, the results must be recorded in source documents and on the eCRFs, and copies of reports should be sent to the Sponsor.
- The Treating Physician determines if the clinical signs, symptoms and neurologic change (objective findings on the examination) meet the definition for On-Trial Relapse as outlined in this protocol (see Section 7.2.1).
- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information
- After all specified relapse procedures are complete; the recommended standardized treatment regimen for confirmed relapse outlined in this protocol can be initiated at the discretion of the Treating Physician (Section 9.2.1.3).
- IP administration:
  - Patients will continue IP administration in accordance with protocol-specified IP administration schedule, ie, every week (7days ±2 days) during the blind induction phase and every two weeks (14 days ±2 days) during the open-label phase.
  - If patients undergo PE, a supplemental dose must be administered after each PE session, preferably within 1-2 hours, according to the regimen described under Supplemental Dose in Section 9.1.
  - If IP will be administered at this visit, obtain IP kit assignation through the IXRS
- PK, PD and free C5 sampling – the number of samples to be collected at this visit will depend upon whether or not the patients receive IP infusion and/or PE at this visit.
  - Collect one blood sample for PK, PD and free C5 (if no IP and/or no PE administration at this visit)
  - If only IP is administered at this evaluation visit according to the IP administration schedule, collect two blood samples: a trough and a peak sample for PK, PD and free C5, approximately 5-90 minutes prior to IP infusion and at least 60 minutes after the completion of the IP infusion, respectively.
  - If the patient receives PE and IP infusion, three blood samples for PK, PD and free C5 collection should be collected [1] approximately 5-90 minutes prior to PE

[2] after PE and before IP infusion, and [3] at least 60 minutes after the completion of IP infusion.

7.6.2.2. Follow-up Relapse Evaluation Visits (Week 1, 4 and 6)

The following tests and procedures will be completed at the Follow-up Relapse Evaluation visit:

- The EDSS Rater will perform the Kurtzke neurologic assessment to determine the FSS and EDSS score.
- The Treating Physician will perform the following assessments:
  - A complete neurologic examination
  - OSIS
- Ensure the patient has the Patient Education Card and remind the patient to contact the study site at the first signs or symptoms of potential relapse.
- The Treating Physician or appropriately trained designee will perform the following assessments:
  - mRS (Week 6 only)
  - VA test (Snellen chart)
  - HAI
  - C-SSRS (Week 6 only)
  - VS include assessments of systolic and diastolic BP, temperature, RR and HR
  - Any new medications or changes to concomitant medications will be recorded
  - Any new AEs or changes in AEs since the previous visit will be evaluated and recorded
- If medically indicated for evaluation of relapse, additional tests (eg, MRI, CT scan, laboratory tests, etc.) may be performed at the discretion of the Investigator. If additional medically indicated tests/procedures are performed, the results must be recorded in the source documents and in the eCRFs, and copies of reports should be sent to the Sponsor.
- IP administration during the relapse evaluation period:
  - Patients will continue IP administration in accordance with protocol-specified IP administration schedule, i.e. every week (7 days ±2 days) during the blind induction phase and every two weeks (14 days ±2 days) during the open-label phase.
  - If patients undergo PE, a supplemental dose must be administered after each PE session, preferably within 1-2 hours, according to the regimen described under Supplemental Dose in Section 9.1.
  - If IP will be administered at this visit, obtain IP kit assignation through the IXRS

- For patients who undergo PE, blood samples for PK, PD and free C5 assays will be collected immediately before and after each session of PE. A peak sample, ie, one hour after completion of IP infusion, will also be collected.
- Questionnaires to evaluate QOL (EQ-5D and SF-36) at Week 6 only
- Clinical laboratory tests (chemistry, hematology and urinalysis) at Week 6 only
- Collect blood samples for NMO-IgG at Week 6 only
- PK, PD, and free C5 sampling at Week 6 only– the number of samples to be collected at this visit will depend up whether or not the patients receive IP infusion and/or PE at this visit.
  - Collect one blood sample for PK, PD and free C5 (if no IP and/or no PE administration at this visit).
  - If only IP is administered at this evaluation visit, according to the IP administration schedule, collect two blood samples: a trough and a peak blood sample for PK, PD, and free C5, approximately 5-90 minutes prior to IP infusion and at least 60 minutes after the completion of the IP infusion, respectively.
  - If the patient receives PE and IP infusion, three blood samples for PK, PD and free C5 collection should be collected: [1] approximately 5-90 minutes prior to PE [2] after PE and before IP infusion, and [3] at least 60 minutes after the completion of IP infusion.

  Note: Trough and peak blood samples for PK, PD and free C5 will be collected at the IP administration visits, if per protocol scheduled IP administration does not coincide with the relapse evaluation visit. Vitals signs, information on concomitant medication and AE will be collected at the IP administration visit.
- Perform lumbar puncture to collect CSF for NMO-IgG and PK and free C5 assays before IP infusion at Week 6 only. Patients may choose not to have CSF samples collected and will still be eligible for trial participation.
- If IP will be administered, patients will be observed for 1 hour following the end of the IP infusion.
- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information

7.6.2.3. Unscheduled Visit

Additional (unscheduled) Follow-up Relapse Evaluation Visits outside the specified visits are permitted at the discretion of the Investigator. Procedures, tests and assessments listed under the Relapse Evaluation Visit may be performed at the discretion of the Investigator. Any procedures, tests or assessments performed at the unscheduled visit must be recorded on the eCRF.

7.6.2.4. Adjudication of On-Trial Relapse Events

An independent Relapse Adjudication Committee will confirm all On-Trial Relapse events using objective and consistent clinical criteria described in a Relapse Adjudication Charter. The

Adjudication Committee will consist of three independent medical experts in neurology/neuroophthalmology who are each experienced in the management of patients with NMO. The Adjudication Committee will decide by majority vote whether each relapse meets the pre-defined objective criteria for an adjudicated On-Trial Relapse, as described in the Relapse Adjudication Charter.

7.6.3. Safety Follow-up Period (post-treatment)

If a patient withdraws from the trial or discontinues eculizumab treatment at any time during the trial after receiving any amount of IP (eculizumab or placebo), a follow-up visit for safety assessments is required at 8 weeks after the last dose of IP. Patients who withdraw from the extension trial and transition to treatment with the commercially available eculizumab will not be required to complete a Follow-up Visit. The following tests and procedures will be completed at the follow-up visit:

- VS include assessments of systolic and diastolic BP, temperature, RR and HR
- Any new medications or changes to concomitant medications will be recorded
- Any new AEs or changes in AEs since the previous visit will be evaluated and recorded
- Perform C-SSRS
- The Treating Physician will assess the patient for any signs or symptoms indicative of relapse
- Ensure that the patient has the Patient Safety Identification Card

If a patient is discontinued due to an AE, the event will be followed until it is resolved or, in the opinion of the Investigator, is determined medically stable.

If a patient is unable to attend the safety follow-up visit as deemed medically necessary by the Investigator, the follow-up visit may be performed by telephone. All visit assessments should be performed with exception of vital signs.

7.6.4. Post-Treatment Follow-up (a Maximum of 2 years)

The Sponsor may seek to collect follow-up information concerning NMO status in patients who have prematurely discontinued from the trial for a maximum of 2 years from the last dose of eculizumab (refer to Appendix 11).

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

1. Patient completed the ECU-NMO-301 trial (ie, patients completed Week 6 Follow-up Relapse Evaluation Visit or EOS Visit)
2. Patient has given written informed consent
3. Patient is willing and able to comply with the protocol requirements for the duration of the trial
4. Female patients of child-bearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]). All patients must practice an effective, reliable, and medically approved contraceptive regimen during the trial and for up to 5 months following discontinuation of treatment.

8.2. Patient Exclusion Criteria

1. Patient withdrew from the ECU-NMO-301 trial as a result of an AE related to IP
2. Female patients who are pregnant, breastfeeding, or intend to conceive during the course of the trial
3. Any medical condition or circumstances that, in the opinion of the Investigator, might interfere with the patient's participation in the trial, pose any added risk for the patient, or confound the assessment of the patients

8.3. Patient Withdrawal Criteria

8.3.1. Withdrawal of Patients From the Trial

Patients are allowed to withdraw consent at any time. All efforts should be made to ensure patients are willing to comply with trial participation prior to conducting the screening procedures. The trial staff should notify the Sponsor and their site monitor of all trial withdrawals as soon as possible. The reason for patient discontinuation must be recorded in the source documents and eCRF.

Reproduction and development studies with eculizumab have not been performed; therefore eculizumab should not be administered to pregnant women. At the time of the last follow-up visit, all patients of childbearing potential must continue to use adequate contraception for up to 5 months following discontinuation of eculizumab treatment. If a patient becomes pregnant, the IP must be immediately discontinued and the Sponsor must be notified as per Section 12.2.1.10 . Each pregnancy will be followed to term and the Sponsor notified regarding the outcome.

8.3.2. Handling of Withdrawals

When a patient withdraws or is withdrawn from the trial, the Investigator shall record the withdrawal reason(s) in the source documents and eCRF. At the time of withdrawal, all patients

who prematurely withdraw from the trial will undergo all assessments at the ET visit for safety as per the Schedule of Assessments.

An additional follow-up visit for safety assessment is required 8 weeks after the last dose of IP administration.

If a patient is discontinued due to an AE, the event will be followed until it is resolved or in the opinion of the PI the patient is determined to be medically stable. Every effort will be made to undertake protocol-specified safety follow-up procedures.

Patients who fail to return for final assessments will be contacted by the site's trial staff in an attempt to have them comply with the protocol. As it is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE, follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the patient's last known address. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures.

8.3.3. Sponsor's Termination of Trial

The Sponsor or a regulatory authority may discontinue the trial at any time for any reason including, for example, clinical or administrative reasons.

9. TREATMENT OF PATIENTS

9.1. Investigational Product Dosage and Administration

IP, eculizumab or placebo (during the blind-induction phase), will be administered intravenously over approximately 35 minutes.

Blind-Induction Phase

To maintain the blind of ECU-NMO-301 trial, all patients will undergo a blind-induction phase. IP (eculizumab or placebo) will be administered weekly during the induction phase according to the following schedule:

Table 11: Investigational Product Dosage and Administration

ECU-NMO-301 (PREVENT) Cohort	Dose	Visit #
Eculizumab arm	4 vials IP (eculizumab 1200 mg)	1, 3
	4 vials IP (placebo)	2, 4
Placebo arm	4 vials IP (3 vials eculizumab 900 mg + 1 vial placebo)	1, 2, 3, 4

Open-label Maintenance Phase

All patients will receive 4 vials eculizumab (1200 mg) every 2 weeks from Visit 5 and onward throughout the trial.

Supplemental Dose

If a patient undergoes PE for an On-Trial Relapse during the Study Period, the patient must be administered IP after each PE session, preferably within 1-2 hours, as outlined below:

- If the relapse occurs during the blinded induction phase, and the PE coincides with the day of a regularly scheduled IP infusion,
  - For Visit 1 (Day1) and Visit 3 (Week 2), administer the 4 vials of blinded IP indicated in Table 11 above;
  - For Visit 2 (Week 1) and Visit 4 (Week 3) administer only a supplemental IP dose, ie, 2 vials eculizumab (600 mg)
- If the relapse occurs during the maintenance phase, and the PE coincides with the day of a regularly scheduled IP infusion,
  - administer the scheduled IP dose (4 vials/1200 mg eculizumab)
- In all other cases, administer only a supplemental IP dose, ie, 2 vials eculizumab (600 mg)

After receiving the supplemental dose, patients are to continue eculizumab infusion according to the protocol-specified dosing regimen.

9.2. Concomitant Medications

9.2.1. Allowed Medications

9.2.1.1. Palliative and Supportive Care

Palliative and supportive care is permitted during the course of the trial for underlying conditions.

9.2.1.2. Immunosuppressive Agents

- Immunosuppressive agents, eg, corticosteroid, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate, tacrolimus, or cyclophosphamide either in combination or mono-therapy are allowed at the discretion of the Investigator.
- Change in IST or its dose/schedule will be allowed if due to relapse, intolerance, or medically indicated at the discretion of the Treating Physician. Any changes in immunosuppressive therapy will be recorded in the eCRF page for concomitant medication.

9.2.1.3. Recommended Standardized Relapse Treatment

For this protocol, the treatment of relapse is at the discretion of the Treating Physician. The following standardized treatment regimen for a confirmed On-Trial Relapse is recommended, in accordance with expert opinion (1):

- One gram intravenous methylprednisolone (IVMP) administered daily for 3-5 days followed by an oral prednisone tapering. If the patient improves, then continue the trial assessments as per schedule of this protocol.
- If there is no or minimal response to IVMP, PE will be allowed at the discretion of the treating neurologist. Five cycles of PE, each removing 1.0-1.5 volumes of circulating plasma, are recommended for treatment of attacks that do not respond to IVMP.

If a patient undergoes PE for an On-Trial Relapse during the Treatment Period, a supplemental dose of IP should be administered after each PE, preferably within 1-2 hours, as described under Supplemental Dose in Section 9.1 above. After receiving the supplemental dose, patients are to continue protocol-specified dosing until the Week 6 Follow-up Visit.

9.2.2. Disallowed Medications

The following medications are prohibited during the trial:

- Concomitant use of rituximab with eculizumab is contraindicated
- Use of mitoxantrone
- Use of immunomodulatory therapies including: interferon beta-1b; interferon beta-1a, and glatiramer acetate
- Other biologic agents such as tocilizumab

- Intravenous immunoglobulin (IVIg) for relapse prevention.
- PE for relapse prevention

9.3. Treatment Compliance

Patients will be infused with IP under the supervision of the Treating Physician or designee to ensure that the patient receives the appropriate dose at the appropriate time-points during the trial.

Patients who fail to return for a scheduled visit must be contacted by the site's study staff to determine the reason for missing the appointment. Patients will be strongly encouraged to return to the study site for evaluation if a relapse or AE is suspected to have occurred. In the exceptional circumstance where a patient cannot or does not come to the study site for examination, then the patient will be instructed to see his or her local neurologist or physician. In this event, the study site will obtain relevant medical records as documentation from the local physician's examination, and enter relevant data in the Relapse Evaluation Visit form or AE form as appropriate. As it is vital to obtain any patient's missing visit to assure the missed appointment was not due to an AE or potential relapse, every effort must be made to undertake protocol-specified safety follow-up procedures. Follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the patient's last known address.

9.4. Randomization and Blinding

9.4.1. Randomization

This is a long-term, open-label extension of the ECU-NMO-301 trial. Patients who enter this trial are required to complete the ECU-NMO-301 trial. No randomization of patients will be performed. The patient identification number and IP kits assignation will be provided by the IXRS.

9.4.2. Blinding and Unblinding

This is an open-label trial; therefore, unblinding is not applicable. All subjects will receive eculizumab during the trial, including during the 4-week blind induction phase and during the open-label maintenance phase.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

Each vial of IP contains eculizumab 300 mg or matching placebo for IV administration.

Table 12: Investigational Product

	Investigational Product	
Product Name:	Eculizumab	Placebo
Dosage Form:	Concentrate solution for infusion	Solution for infusion
Unit Dose:	300 mg	0 mg
Route of Administration:	Intravenous Infusion	Intravenous Infusion
Physical Description:	30 mL vial	30 mL vial
Manufacturer:	Alexion Pharmaceuticals, Inc. or selected contract manufacturing organization	Alexion Pharmaceuticals, Inc. or selected contract manufacturing organization

10.2. Investigational Product Packaging and Labeling

The active IP, eculizumab, is manufactured and supplied by Alexion Pharmaceuticals, Inc., or selected contract manufacturing organization in single 30 mL vials as a solution concentration of 10 mg/mL. The comparator product is manufactured by Alexion Pharmaceuticals, Inc., or selected contract manufacturing organization as a matching sterile, clear, colorless solution with the same buffer components but without active ingredient, in an identical 30 mL vial.

IP vials will be individually packaged into kits. Both vials and kits will be labeled according to the protocol and local regulatory requirements. IP will be shipped and released to each participating trial center upon receipt of all required essential documents based upon federal, state, and local regulations. Each IP kit will have a unique kit number and have a booklet label describing the contents and a place for the pharmacist to record the patient number, patient initials and Investigator name.

10.3. Investigational Product Storage

IP will be released to the site upon receipt of all required essential documents based upon federal, state, and local regulations.

Upon arrival at the center, the IP should be promptly removed from the shipping cooler and stored in refrigerated conditions at 2°C to 8°C with minimal light exposure. The pharmacist should immediately record the receipt of the IP in the IXRS and notify the distributor and the Sponsor if vials are damaged and/or if temperature excursions have occurred during transportation. IP must be stored in a secure, limited-access storage area, and temperature should be monitored daily.

Diluted solutions of IP are stable for 24 hours at 2 to 8°C (36-46°F) and at room temperature.

10.4. Investigational Product Preparation

Infusions of IP should be prepared using aseptic technique and the dose regimen described in Section 9.1. Each vial of IP contains 300 mg of active ingredient in 30 mL of product solution or matching placebo.

Withdraw the required amount of IP from the vials. Transfer the recommended dose to an infusion bag. Dilute IP to a final concentration of 5 mg/mL by addition to the infusion bag of the appropriate amount (equal volume) of one of the following diluents: 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP. The final volume of a 5 mg/mL diluted IP solution is 120 mL for 600 mg doses (2 vials), 180 mL for 900 mg doses (3 vials) and 240 mL for 1200 mg doses (4 vials) as shown in Table 13.

Table 13: Investigational Product Preparation and Reconstitution

Investigational Product	Volume of IP	Volume of Diluent[a]	Total Volume of Administration
600 mg (2 vials)	60 mL	60 mL	120 mL
900 mg (3 vials)	90 mL	90 mL	180 mL
1200 mg (4 vials)	120 mL	120 mL	240 mL

[a] Choose one of the following diluents: a. 0.9% sodium chloride; b. 0.45% sodium chloride; c. 5% dextrose in water; d. Ringer's injection

Gently invert the infusion bag containing the diluted IP solution to ensure thorough mixing of the product and diluents. Discard any unused portion left in a vial, as the product contains no preservatives.

The 24-hour expiration period includes preparation, storage at room temperature and under refrigeration, warming and infusion.

10.5. Investigational Product Administration

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

IP should only be administered **via IV infusion** via gravity feed, a syringe-type pump, or an infusion pump, and must be diluted to a final concentration of 5 mg/mL prior to administration. Prior to administration, if the diluted solution is refrigerated, it should be allowed to warm to room temperature by exposure to ambient air. The diluted solution must not be heated in a microwave or with any heat source other than ambient air temperature. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

The diluted IP should be intravenously administered over approximately 35 minutes.Diluted IP is stable for 24 hours at 2-8°C (36-46°F) and at room temperature. It is not necessary to protect the infusion bags from light while IP is being administered to the patient. The patients will be monitored for at least 1 hour following the infusion for signs or symptoms of an infusion reaction.

If an AE occurs during the administration of the IP, the infusion may be slowed or stopped at the discretion of the Investigator, depending upon the nature and severity of the event. The AE must be captured in the patient's source document and eCRF.

10.6. Investigational Product Accountability

When an IP shipment is received at the site, the pharmacist should verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the trial monitor. A signed copy should be faxed to the contact provided on the packing list and the duplicate copy kept in the pharmacy binder.

Additionally, reception of IP (as well as reception conditions) must be reported to the IXRS to allow IP resupply, estimations and expiration control.

Accountability logs and Inventory logs will be provided to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the IP. During the trial, the following information must be noted in the accountability log: the patient number(s), initials of patient(s) to whom IP is dispensed, kit number, the date(s) and time that the IP is prepared, and the initials of the pharmacist or designee who prepared the IP. Sites should keep a running total of their IP supply. Empty vials and vials with residual materials should be kept for inspection and accountability by the CRA prior to their destruction and handled per local site pharmacy standard operating procedures for clinical IPs. Destruction of used and unused vials, either locally or centrally, must be properly documented. Refer to the Pharmacy Manual for detailed instructions on general receipt, storage, preparation, administration, destruction and return of IP.

Each kit label will have a place for the pharmacist to record the patient number and initials.

The CRA will examine the inventory during the trial. Additionally, the inventory records must be readily available and may be subject to regulatory authorities, the local regulatory agency, or an independent auditor's inspection at any time.

10.7. Investigational Product Handling and Disposal

At the completion of the trial, in order to satisfy regulatory requirements regarding drug accountability, all remaining IP inventory will be reconciled and retained or destroyed according to applicable provincial and federal regulations.

11. ASSESSMENT OF EFFICACY

This extension trial is designed to provide the patients who have participated in the ECU-NMO-301 trial with an opportunity to receive eculizumab and to collect clinical data that will provide long term safety and tolerability information on eculizumab in patients with relapsing NMO. Efficacy is a secondary objective of this trial. The long-term efficacy of eculizumab in patients with relapsing NMO will be measured by determining the ARR.

Duration of treatment commences with the first IP infusion (eculizumab).

11.1. Efficacy Parameters

Primary Efficacy Endpoint:

Annualized Relapse Rate (ARR) including all relapses as identified by the Investigator.

Secondary Efficacy Endpoints:

1. Change from baseline in EDSS score
2. Change from baseline in EQ-5D
3. Change from baseline in mRS score
4. Change from baseline in HAI in patients with abnormal baseline ambulatory function
5. Change from baseline in VA in patients with abnormal baseline visual function

Tertiary Efficacy Endpoints:

1. Change from baseline in HAI score
2. Change from baseline in VA
3. Change from baseline in the SF-36
4. Change from baseline in the EDSS FSS

11.1.1. Relapses

On-Trial Relapses will be monitored throughout the trial. Patients will be educated on the potential signs and symptoms of NMO relapse. The Investigator or his/her designee will review, in detail, the signs and symptoms of a potential relapse with the patient at each visit. The patients will be instructed to contact the study site at the first sign or symptom of a potential relapse. Patients should be evaluated within 24 hours of notification of the Investigator or the appropriate designee for any signs or symptoms suggestive of a potential relapse, and no later than 48 hours. All potential relapses must be evaluated by both the Treating Physician and the EDSS Rater. The Treating Physician will make the decision as to whether the clinical signs, symptoms, and neurologic change (objective findings on neurological examination) meet the definition for On-Trial Relapse and may treat the patient's relapse according to the recommended Standardized On-Trial Relapse Treatment Plan (Section 9.2.1.3). The relapse treatment is at the Treating

Physician's discretion. All investigations/tests related to the relapse evaluation (eg, MRIs, CTs, lumbar punctures, etc) should be recorded in the source documents and in the eCRF; copies of all reports should be sent to the Sponsor.

Follow-up Relapse Evaluation Visits, to monitor the course of the relapse until stabilization, will be performed at 1, 4, and 6 weeks after the onset of the relapse. Additional (unscheduled) Follow-up Relapse Evaluation Visits will be made at the Treating Physician's discretion. All reports of possible relapses and actions taken must be documented in the patient's source documents and recorded in the eCRF; copies of reports should be sent to the Sponsor.

Relapses that do not meet the criteria for SAE (see Section 12.2.1.3) should be reported as part of the relapse evaluation visits, and not as AEs.

All PI-determined relapses will be reviewed by the Adjudication Committee; if confirmed by the Committee, these events qualify as adjudicated On-Trial Relapses. Adjudicated events will be used in the ARR assessment.

11.1.2. Disability

Disability will be assessed by the EDSS and mRS scores comparing the change from baseline. The EDSS Rater, who is blinded to all other trial data as well as all other patient clinical data, will be responsible for performing the EDSS assessments throughout the trial at the protocol-specified time points as well as at visits during the Relapse Evaluation Period. The Treating Physician or designee will perform the mRS throughout the trial at the protocol-specified time points.

11.1.3. Neurologic Functions

Neurologic function will be assessed based on the EDSS FSS. Ambulatory function will be assessed by HAI scale and visual function will be measured by VA test using the Snellen chart. In addition, the EDSS visual (optic) FSS will be used for statistical analysis of changes in VA.

The Snellen chart should be positioned at 6 meters (20 feet) distance, in a well-illuminated area, and the best available visual correction should be used (eg, the patient should use their latest eyeglasses or eye lenses). The patient can miss one letter per row to score that row. If the patient is unable to read the chart, then test the patients' ability to count fingers (at approximately 1 meter distance), distinguish hand motion or perceive light (by shining bright light in the eye).

Neurologic function evaluation will be assessed at the protocol-specified time points as well as at visits during the Relapse Evaluation Period.

11.1.4. Quality of Life

QOL will be assessed by the patient self-assessment using both the EQ-5D and SF-36 instruments at the protocol-specified time points.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

The safety of eculizumab will be assessed based on treatment-emergent AEs (TEAEs), SAEs, and changes from baseline through trial completion in VS, routine clinical laboratory tests (chemistry, hematology, and urinalysis), C-SSRS, and pregnancy tests for female patients of childbearing potential.

Blood samples will be collected for evaluation for HAHA at specified time points to describe the presence or absence of an immune response to eculizumab and to evaluate, if antibodies are detected, whether the antibodies neutralize the activity of eculizumab.

The same independent DMC that will conduct the monitoring of safety data for the ECU-NMO-301 trial will be used in this extension trial. Since its primary function will be to ensure patient safety, the DMC will have access to all safety data. The DMC may make recommendations to the Sponsor regarding safety issues, trial conduct, and modifying, extending or stopping the trial. A separate DMC Charter will document all DMC procedures and processes for the trial. Data and analysis for the DMC will be prepared by an independent statistical group.

12.1.1. Demographic/Medical History

At Visit 1, patients' initials, date of birth, race or ethnic origin and sex will be collected. Medical history, including relevant medical/surgical history and NMO history, will be reviewed and recorded in the ECU-NMO-302 trial.

12.1.2. Vital Signs

VS will be measured at every visit and will include assessments of systolic and diastolic blood pressure (BP), temperature, RR and heart rate (HR). VS will be obtained after the patient has been supine or seated for at least 5 minutes. Ideally, each patient's BP should be measured using the same arm. Systolic and diastolic BPs will be documented in mmHg. Temperature will be obtained in degrees Celsius or Fahrenheit. HR will be documented in beats per minute.

12.1.3. Weight

Body weight will be measured in pounds or kilograms. Body weight will be measured at visits specified in the Schedule of Assessments in Section 7.5.

12.1.4. Physical Examination

A complete physical examination will be performed at visits specified in the Schedule of Assessments in Section 7.5. The complete physical examination will include assessments of the following organ/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, pulse, chest, heart, abdomen, extremities, musculoskeletal, and general neurologic examination. For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff at these visits.

12.1.5. Electrocardiogram

A 12-lead ECG will be conducted at visits specified in the Schedule of Assessments in Section 7.5. Additional ECG assessments are permitted at the Investigator's discretion. The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and to determine the clinical significance of the results. These assessments will be indicated on the eCRF. For any clinically significant abnormal ECG results, the Investigator must contact the Sponsor to discuss the patient's continued eligibility to participate in this protocol.

12.1.6. Laboratory Assessments

Patients will have biologic samples collected for analysis of various parameters. The central laboratory will supply established or generally acknowledged methods, normal reference ranges, and shipping instructions.

Chemistry panel, complete blood count and urinalysis, hemolytic markers, renal function measures, and serum pregnancy test (See Appendix 8 for details) will be prepared and shipped according to the instructions in the laboratory manual to the central laboratory. Samples will be analyzed at the central laboratory. Leukopenia has been reported in about 10% of patients with aHUS treated with eculizumab. In the NMO patient population, who may also be treated with immunosuppressive agents that are known to affect WBC counts, close monitoring of cell counts is imperative. Routine hematology laboratory assessment including CBC will be performed at various time points as specified by the protocol and should be reviewed as soon as the lab result is available. Additional assessments to monitor WBC counts can be performed at the discretion of the Treating Physician as medically indicated. Treatment of leukopenia is at the discretion of the Treating Physician and consultation with hematologist is encouraged as medically indicated.

Blood samples for PK, PD, free C5 and HAHA and CSF samples for PK and free C5 analysis will be prepared and shipped according to the instructions in the laboratory manual to the central laboratory. Sample analysis will be conducted at Alexion Pharmaceuticals, Inc. or a contracted organization. Patients may choose not to have CSF samples collected and will still be eligible for trial participation.

Samples for NMO-IgG will be prepared and shipped according to the instructions in the central laboratory manual. Sample analysis will be conducted at a central laboratory.

AEs and events related to the patients' underlying disease that have occurred during the trial will be collected at every visit (see Section 12.2 Adverse and Serious Adverse Events Section).

Any clinically significant, abnormal laboratory result is to be reported as an AE.

12.1.7. Columbia-Suicidal Severity Rating Scale (C-SSRS)

The C-SSRS- Since Last Visit will be performed by the Treating Physician or an appropriately trained designee at visits specified in the Schedule of Assessments in Section 7.5. Additional C-SSRS assessments are permitted as needed. This is to ensure that patients who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed or referred for further evaluation.

12.2. Adverse Events and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

All observed or volunteered AEs regardless of causal relationship will be reported as described in the sections below.

For all AEs the Investigator must obtain adequate information for the following: 1) determine the outcome of the AE; 2) determine if the event meets criteria for an SAE; 3) assess the severity of the AE, and 4) determine the causality of the AE. For AEs with a causal relationship to the IP, the Investigator must follow-up on the outcome of the event until the event or sequelae either resolve or stabilize.

As this is an extension to the ECU-NMO-301 trial, patients may sign the informed consent for the extension trial while still enrolled in the ECU-NMO-301 trial. AEs with an onset date before Study Day 1 of the extension trial (ECU-NMO-302) will be recorded in eCRF of ECU-NMO-301 regardless of when the patient signed the ICF for the extension trial. Any ongoing AEs at the time of Study Day 1 of the extension trial will be transferred to the extensions trial eCRF. AEs with an end date before Study Day 1 of ECU-NMO-301 will be recorded only on the ECU-NMO-301 eCRF.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedite Reporting E2A. Step 4 version, dated 27 October, 1994). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered. AEs can be classified into non-serious AEs or SAEs.

For this trial, information about relapses that do not meet the SAE criteria below (Section 12.2.1.3) should be recorded in source documents and in the eCRF as part of the relapse evaluation visits and not reported as AEs.

12.2.1.2. Abnormal Test Finding

Abnormal test findings may be considered AEs or SAEs at the Investigator's discretion; however, Investigators are strongly encouraged to report the diagnosis, sign or symptom instead of just the abnormal result. The criteria for an abnormal test finding being classified as an AE or SAE are as follows:

- Test result is associated with a sign or symptom;
- Test result requires additional diagnostic testing;
- Test result requires a medical or surgical intervention;
- Test result leads to a change in trial dosing outside of the protocol defined dosing or discontinuation from the trial;

- Test result requires significant additional treatment

12.2.1.3. Serious Adverse Events

Any AE that fulfills one or more of the criteria listed below must be recorded as a SAE. A SAE (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.2.1.4. Lack of Efficacy

Since eculizumab treatment in relapsing NMO patients is not an approved indication, lack of efficacy need not be reported as an AE.

12.2.1.5. Hospitalization

AEs that are associated with hospitalization or prolongation of hospitalization are considered SAEs. All admissions to a health care facility meet this criteria, even if less than 24 hours. Criteria for seriousness are also met if transfer within the hospital is done to receive more intense medical / surgical care (eg, medical floor to the intensive care unit [ICU]).

Hospitalization does not include the following:

- Rehabilitation facility
- Hospice facility
- Nursing facility
- Emergency Room
- Same day surgery

Hospitalization or prolongation of hospitalization not associated with an AE is not an SAE; examples include:

- Admission for a pre-existing condition not associated with either a new AE or with worsening of a pre-existing AE
- Protocol-specified admission
- Pre-planned admission

12.2.1.6. Procedures

Diagnostic and therapeutic procedures (invasive and non-invasive) such as surgery or angiography should not be reported as an AE or SAE. However, the medical condition or the diagnosis that was responsible for the procedure should be recorded. The procedure should be recorded in the narrative as treatment for the AE or SAE; for example: "Laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder".

12.2.1.7. Other Adverse Events

Other AEs (OAEs) will be identified by the Drug Safety Physician and if applicable also by the Clinical Trial Team Physician during the evaluation of safety data for the Clinical Study Report. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient/subject from the trial, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

12.2.1.8. Severity Assessment

AE severity will be rated by the Investigator as mild, moderate, or severe using the following criteria:

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concerns with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Change in severity of an AE should be documented based on specific guidelines in the eCRF Completion Guidelines.

Severity and seriousness must be differentiated. Severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE.

12.2.1.9. Causality Assessment

An Investigator causality assessment (Unrelated, Unlikely, Possible, Probable, or Definite) must be provided for all AEs (both serious and non-serious). This assessment must be recorded in the source documents and eCRF and any additional SAE forms as appropriate. The definitions for the causality assessments appear below.

- Not related (unrelated): This relationship suggests that there is no association between the IP and the reported event.
- Unlikely related: This relationship suggests that the clinical picture is highly consistent with a cause other than the IP but attribution cannot be made it absolute certainty and a relationship between the IP and AE cannot be excluded with complete confidence.
- Possibly related: This relationship suggests that treatment with the IP may have caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of IP administration and/or follows a known response pattern to the IP, but could also have been produced by other factors.
- Probably related: This relationship suggests that a reasonable temporal sequence of the event with the IP administration exists and the likely association of the event with the IP. This will be based upon the known pharmacological action of the IP, known or previously reported adverse reactions to the IP or class of drugs, or judgment based on the PI's clinical experience.
- Definitely related: Temporal relationship to the IP, other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain event, corresponds with the known pharmaceutical profile, improvement on discontinuation, re-appearance on re-challenge.

12.2.1.10. Exposure during Pregnancy and Lactation

Pregnancy data will be collected during this trial extension for all patients.

Investigational product exposure during pregnancy must be recorded and followed. Exposure during pregnancy, also called exposure in-utero (EIU), can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

If a patient or a patient's partner becomes or is found pregnant while treated or exposed to eculizumab, the Investigator must submit a pregnancy form to the Sponsor via the same method as SAE reporting. The Sponsor will supply the Investigator with a copy of a "Pregnancy Reporting and Outcome Form / Breast Feeding". The Sponsor must be notified via the same method as SAE reporting.

Exposure of an infant to IP during breastfeeding needs to be reported in the "Pregnancy Reporting and Outcome Form / Breast Feeding", and any AE an infant may experience following breastfeeding needs to be reported to the Sponsor.

The patient or patient's partner should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), even if the patient discontinued IP or discontinues from the trial. When the outcome of the pregnancy becomes known the form should be completed and returned to the Sponsor. If additional follow-up is required, the Investigator will be requested to provide the information.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that IP may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet criteria for a SAE.

Complications of pregnancy and abnormal outcomes of pregnancy such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death or congenital anomaly would meet criteria of an SAE and thus, should be reported as an SAE. Elective abortions without complications should not be handled as AEs.

12.2.1.11. Withdraw due to an Adverse Event

Withdrawal due to an AE or SAE event must be clearly differentiated from withdrawal due to other reasons.

12.2.1.12. Obtaining Adverse Event

The Investigator must collect all AEs observed, obtained by direct questioning or volunteered from the trial patient.

12.2.1.13. Reporting Period

For SAEs the reporting period to the Sponsor begins following the patient's signing of the ICF (providing consent to participate in the trial) and continues through 8 weeks after the last dose of IP. No time limit exists on reporting SAEs that are thought to be possibly or probably or definitely related to the IP.

For non-serious AE the reporting period starts following first dose of IP (Day 1) and continues through the last visit, including the safety Follow-up Visit. AEs, particularly causally related, are to be followed until the event or sequalae resolve or are determined to be medically stable.

12.2.1.14. Reporting Requirements for Adverse Events

All AEs must be assessed by the Investigator to determine if they meet criteria for an SAE. If criteria are met for an SAE the event must be reported to the Sponsor as per SAE reporting requirements in Section 12.2.1.14.2 , Serious Adverse Events.

12.2.1.14.1. Reporting Requirements for Non-serious Adverse Events

All non-serious AEs must be recorded in the eCRF system upon awareness or prior to the next patient visit.

12.2.1.14.2. Reporting Requirements for Serious Adverse Events

For SAEs, the Sponsor must be notified immediately or within 24 hours of the Investigator site becoming aware of the event, regardless of the presumed relationship to the IP. If the event meets the fatal or life threatening SAE criteria, the Investigator should notify the Sponsor immediately. The SAE report should be submitted electronically via the Safety Gateway. These reporting timelines need to be followed for all initial SAE cases and follow-up versions to the initial case.

In the event that either the electronic data capture (EDC) or the Safety Gateway is unavailable at the site(s), the SAE must be reported on paper. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via Email or fax to contact information provided below:

Email: PPD

Fax: PPD

Additional follow-up information, if required or available, should be sent via the Safety Gateway to the Sponsor or Sponsor's designee within 24 hours of the Investigator becoming aware of this additional information. Follow-up information should be recorded on the SAE eCRF and placed with the original SAE information and kept with the appropriate section of the original subject records and/or trial file. For all SAEs the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed above
- Causality of the serious event(s)
- Outcome of the serious event(s)
- Medical records and laboratory / diagnostic information

12.2.1.15. Sponsor Reporting Requirements

The Sponsor or legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria as per regional and local regulations.

12.2.1.16. Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for trial Investigators. It is the PI's responsibility to notify the IRB or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. These additional SAEs are required to be reported to the IRB or IEC according to local regulations.

12.2.1.17. Reference Safety Document

This protocol will use the current IB as the Reference Safety Document. The expectedness of a SAE is determined by the Sponsor from the Reference Safety Information section of the IB.

12.2.1.18. Data Monitoring Committee

An independent DMC will conduct interim monitoring of unblinded data as described in Section 16.4.

13. ASSESSMENT OF BIOMARKER

13.1. NMO Biomarker

Blood samples (from all patients) and CSF samples (from patients who have consented to CSF testing) will be measured for NMO-IgG (AQP4-Ab) at protocol-specified time points, including during the Relapse Evaluation Period (see Section 7.5 for details) for all consented patients.

14. ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

The population PK analysis of eculizumab in NMO patients will be performed to assess the concentration of eculizumab versus time. PK parameters such as maximum concentration as well as trough and peak eculizumab concentration during the induction and maintenance treatment phases will be reported. Clearance and terminal half-life will be estimated. PD analysis will be performed to assess pre- and post-treatment serum hemolytic activity and therefore C5 complement activity inhibition. Free C5 concentration also may be measured.

CSF samples for PK and free C5 will be measured at the protocol-specified time points, including during the Relapse Evaluation Period, for all consented patients.

15. STATISTICS

Analyses will be produced using the data from this trial alone as well as combined analyses that will include data from the ECU-NMO-301 trial. The analyses will include safety, efficacy, and PK/PD analyses. The statistical analysis plan will cover both the standalone trial analyses and the combined ECU-NMO-301 and extension trial (ECU-NMO-302) analyses.

15.1. General Considerations

ECU-NMO-302 is an extension of the Phase 3 Trial ECU-NMO-301. At the completion of the trial, the Sponsor will analyze the trial data. Analyses will be produced using the data from this trial alone as well combined analyses that will include data from the ECU-NMO-301 trial. The analyses will include safety, efficacy, and PK/PD analyses. The statistical analysis plan will cover both the standalone trial analyses and the combined ECU-NMO-301 and ECU-NMO-302 trial analyses.

The Sponsor will be responsible for data collection and editing, reviewing and validating all the information in the eCRFs, statistical analysis, and generation of the clinical report.

Prior to locking the database, all data editing will be completed and decisions regarding the evaluability of all patient data for inclusion in the statistical analysis for the extension trial and Combined Per-Protocol (Combined PP) Sets will be made. The rationale for excluding any data from the statistical analyses will be prospectively defined, and classification of all or part of a patient's data as non-evaluable will be completed before the statistical analysis is begun. The statistical analysis will not begin until the entire database is locked and signed-off.

The Alexion Biostatistics Department will perform the statistical analysis of the data derived from this trial. The analysis will be performed using the SAS® statistical software system Version 9.2 or higher.

A DMC will conduct periodic safety reviews.

All summary statistics will be computed and displayed by scheduled assessment time. Summary statistics for continuous variables will minimally include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

15.2. Determination of Sample Size

This is an extension trial to ECU-NMO-301 trial. A maximum of 132 patients will be enrolled in the ECU-NMO-301 trial. Patients who complete the ECU-NMO-301 trial may participate in this extension trial.

15.3. Analysis Sets

Efficacy analyses will be performed on the Extension Trial Full Analysis Set (Extension FAS) population as well as the Extension Trial Per-Protocol (Extension PP) population. In addition, efficacy analyses will be performed on the Combined Full Analysis Set (Combined FAS)

population as well as the Combined PP population from the combined ECU-NMO-301 trial and the extension trial.

15.3.1. Extension Trial Full Analysis Set Population

The Extension FAS population, on which primary, secondary, and tertiary efficacy analyses and other efficacy analyses will be performed, consists of all patients who have received at least 1 dose of eculizumab in this extension trial and have a post-IP-infusion efficacy assessment.

15.3.2. Extension Trial Per-Protocol Set Population

The Extension PP population is a subset of the Extension FAS population, excluding patients with major extension trial protocol deviations. The Extension PP population will include all patients who:

- Have no major protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy
- Took at least 80% of the required treatment doses during participation in the extension trial

15.3.3. Combined Full Analysis Set Population

The Combined FAS population, on which primary, secondary, and tertiary efficacy analyses will be performed, consists of all patients who have received at least 1 dose of eculizumab in either ECU-NMO-301 or this trial and have a post-IP-infusion efficacy assessment.

15.3.4. Combined Per-Protocol Set Population

The Combined PP population is a subset of the Combined FAS population, excluding patients with major protocol deviations from either the ECU-NMO-301 or extension trial. The Combined PP population will include all patients who:

- Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy
- Took at least 80% of the required eculizumab doses during participation in ECU-NMO-301 and/or this trial

The Extension PP population as well as the Combined PP population will be determined prior to database lock.

15.3.5. Extension Safety Set Population

Safety analyses will be performed on the Extension Safety Set Population and the Combined Safety Population from both studies. The Extension Safety Set Population includes all patients who receive at least 1 dose of eculizumab in this trial. The Combined Safety Population includes all patients who receive at least 1 dose of eculizumab in trial ECU-NMO-301 or this trial.

15.3.6. Other Set(s)

PK/PD analyses will be performed on the PK/PD Analysis Set. The PK/PD Analysis Set includes all NMO patients who have PK/PD data assessments during the trial.

15.4. Demographics and Baseline Characteristics

All demographic and baseline characteristics information will be summarized using the following sets: Extension FAS, Extension PP, Combined FAS, Combined PP, Extension Safety Set, and Combined Safety Set. No formal hypothesis testing will be performed. Summary statistics will be presented.

15.5. Patient Disposition and Treatment Compliance

The number of patients, treated, completing the trial, and included in the safety and efficacy analysis sets will be tabulated by counts and percentage of patients combined. Reasons for any patient withdrawals will be provided.

Treatment compliance with IP will be summarized using descriptive statistics. The extra usage of IP for patients who are treated with PE during the trial will be summarized and listings will be produced.

15.6. Prior and Concomitant Medications

Prior and concomitant medications will be summarized. Listings of prior and concomitant medications will be produced.

Supportive ISTs are allowed during the trial. Thus, supportive IST treatment will be summarized. Listings of supportive ISTs will be produced. Changes in ISTs during the trial will be summarized.

For patients with On-Trial Relapses, the use of methylprednisolone and PE will be summarized by treatment group. Listings of methylprednisolone, plasmapheresis, and plasma exchange usage by patients with On-Trial Relapses will be produced.

Medications will be coded using the World Health Organization Drug Dictionary (WHODrug).

15.7. Efficacy Analyses

Efficacy analyses will be performed on the Extension FAS population as well as the Extension PP population. In addition, Efficacy analyses will be performed on the Combined FAS population as well as the Combined PP population from the combined ECU-NMO-301 trial and the Extension trial.

15.7.1. Primary Efficacy Analysis

The primary efficacy endpoint is ARR including all relapses as identified by the Investigator. Baseline ARR for all patients will be calculated starting 1 year prior to enrollment in the ECU-NMO-301 trial. Baseline ARR will be compared to rates calculated for the time period that patients are on eculizumab in ECU-NMO-302. The trial will be considered to have met its primary efficacy endpoint if a statistically significant p-value (< 0.05) is observed for the change in ARR between the baseline ARR and the On-Trial ARR when on eculizumab treatment in ECU-NMO-302 using a Wilcoxon signed rank test. Confidence intervals (95%) for the change and percentage change in the ARR will be presented. The percentage of patients who are relapse-free based on On-Trial Relapse events while on eculizumab treatment in ECU-NMO-302 along with 95% confidence intervals will be computed using the Kaplan-Meier method. A sensitivity analysis will be performed for the change in ARR between the baseline ARR and the adjudicated

On-Trial ARR when on eculizumab treatment in ECU-NMO-302 using a Wilcoxon signed rank test. The percentage of patients who are relapse-free while on eculizumab treatment in ECU-NMO-302 along with 95% confidence intervals will also be computed using the Kaplan-Meier method for the adjudicated On-Trial relapses.

Additional analyses will be performed on the combined data from ECU-NMO-301and ECU-NMO-302 trials. Baseline ARR for all patients will be calculated starting 1 year prior to enrollment in the ECU-NMO-301 trial and will include all On-Trial attacks (as identified by the Investigator) that occur in the ECU-NMO-301 trial for patients randomized to placebo. Baseline ARR for patients who were randomized to eculizumab in the ECU-NMO-301 trial will be calculated starting one year prior to enrollment in the ECU-NMO-301 trial. Baseline ARR will be compared to rates calculated for the time period that patients are on eculizumab. For patients who are treated in the placebo arm of the ECU-NMO-301 trial, the ARR for comparison with baseline will be calculated once the patient transitions to eculizumab treatment. A Wilcoxon signed rank test will be used to assess the change in ARR between the baseline ARR and the On-Trial ARR when on eculizumab treatment. Confidence intervals (95%) for the change and percentage change in the ARR will be presented. The percentage of patients who are relapse-free based on On-Trial Relapse events while on eculizumab treatment along with 95% confidence intervals will be computed using the Kaplan-Meier method. A sensitivity analysis will be performed for the change in ARR between the baseline ARR and the adjudicated On-Trial ARR when on eculizumab treatment using a Wilcoxon signed rank test. The percentage of patients who are relapse-free while on eculizumab treatment along with 95% confidence intervals will also be computed using the Kaplan-Meier method for the adjudicated On-Trial relapses.

15.7.2. Secondary Efficacy Analysis for the Trial Period

Note: Baseline for the extension trial alone is defined as the last available assessment prior to starting treatment with eculizumab in the extension trial. Baseline for the combined trial efficacy analyses is defined as the last available assessment prior to starting treatment with eculizumab in ECU-NMO-301 or this trial for all patients.

Changes from baseline for the various secondary efficacy endpoints will be summarized over the applicable visits.

- Change from baseline in EDSS score
- Change from baseline in EQ-5D
- Change from baseline in mRS score
- Change from baseline in HAI in patients with abnormal baseline ambulatory function
- Change from baseline in VA in patients with abnormal baseline visual function

The primary analysis for the change from baseline in EDSS score at a particular visit for will be based on the repeated measures model with effects for baseline EDSS and visit. Changes from baseline in the HAI, VA, EQ-5D index score, EQ-5D visual analog scale, and mRS score will be analyzed in a similar manner as changes in EDSS score using the baseline and visit as covariates in the modeling. In addition, summary statistics for the changes from baseline in the mRS score will be produced by visit. Likewise, shift tables from baseline in the mRS score will be produced

by visit. By-patient listings of the secondary endpoints assessments and changes from baseline in the secondary endpoints will be produced.

For the secondary endpoints, some summaries by subgroups will be produced. Patients will belong to one of four possible subgroups:

(a) patients randomized to eculizumab who did not have relapses in the ECU-NMO-301 trial,

(b) patients randomized to eculizumab who did have relapses in the ECU-NMO-301 trial,

(c) patients randomized to placebo who did not have relapses in the ECU-NMO-301 trial, and

(d) patients randomized to placebo who did have relapses in the ECU-NMO-301 trial.

For the patients in sub-group (a), baseline is defined as the baseline assessment (last available assessment) prior to dosing in the ECU-NMO-301 trial. For the patients in sub-group (c), baseline is defined as the last available assessment prior to dosing with eculizumab in this trial. For the patients in subgroups (b) and (d), baseline for these subgroup analyses is defined as the last available assessment prior to eculizumab dosing in this extension trial in consideration of neurologic changes and recoveries as a result of relapse in the ECU-NMO-301 trial. Changes from baseline for the various secondary efficacy endpoints will be summarized separately for the 4 subgroups of patients over the applicable visits.

Missing secondary endpoint assessments will not be imputed.

15.7.3. Tertiary Efficacy Analysis for the Trial Period

Like the secondary efficacy endpoint, the tertiary endpoint analyses will be based on changes from baseline.

- Change from baseline in HAI score
- Change from baseline in VA
- Change from baseline in the SF-36
- Change from baseline in the EDSS FSS

Changes from baseline in the HAI score and VA will be analyzed in a similar manner to the secondary endpoint analyses described for HAI with abnormal baseline ambulatory function and VA with abnormal baseline visual function using repeated measures models.

Change from baseline in QOL will be summarized as appropriate to the QOL instrument and analyses will be performed as specified in the statistical analysis plan (SAP).

Changes from baseline in the EDSS FSS will be analyzed in a similar manner to the secondary endpoint analyses described for the EDSS score using repeated measures model.

In addition, summaries of changes from baseline like those for the secondary efficacy endpoints will also be created for the tertiary efficacy endpoints for the 4 subgroups of patients from the ECU-NMO-301 trial who are treated in the extension trial.

15.7.4. Other Efficacy Analyses: On-Trial Relapses

For patients with a PI-determined On-Trial relapse(s), summary tables of the types of relapses and the severity of the relapses will be produced. Summary tables will also be produced only for those patients with adjudicated On-Trial relapse(s). A by-patient listing of the On-Trial relapses, including the adjudication outcome will be produced. The severity of a relapse will be determined using the OSIS scale. Severity will be assessed at the time of the relapse.

Changes from baseline to all of the trial collected time-points after a relapse (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and VA. Changes from the last assessment prior to the relapse to all trial collected time-points after a relapse (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and VA. Likewise, changes from the assessment 1 week after the relapse to all trial collected time points after that time point (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and VA. These summaries will be produced for patients with a PI-determined On-Trial relapse(s) as well as for only those patients with adjudicated On-Trial relapse(s). Patient listings for the EDSS, HAI, and VA assessments before and after a relapse will be created for the patients with all On-Trial relapses as determined by the PI(s), including the subsequent adjudication outcome.

15.8. Safety Analyses

Safety analyses will be performed on the Extension Safety Population and the Combined Safety Population from both studies. The Extension Safety Population includes all patients who receive at least 1 dose of eculizumab in this trial. The Combined Safety Population includes all patients who receive at least 1 dose of eculizumab in trial ECU-NMO-301 or this trial.

For the extension trial alone, AEs onset on or after the first dose date for eculizumab in the extension trial will be summarized by incidence, system organ class (SOC), preferred term, seriousness, severity, and relationship to treatment. Concomitant medications taken during the extension trial will be summarized. Changes in IST usage (i.e. increases, decreases, switching ISTs, etc) will be summarized.

For the Combined Safety Population, AEs that occurred on or after the first dose of eculizumab whether in the ECU-NMO-301or this extension trial will be summarized by incidence, preferred term, SOC, seriousness, severity, and relationship to treatment. Concomitant medications taken during eculizumab treatment will be summarized.

Changes from baseline in laboratory assessments (chemistry and hematology,) will be summarized for the extension trial alone as well as for the two studies combined. Likewise, shift tables (L [low], N [normal], H [high]) will be produced for clinical laboratory tests for the extension trial alone as well as for the two studies combined. Pregnancy tests will be summarized in patient listings. ECG data will be summarized for the extension trial. Shift tables for the C-SSRS will be produced for the extension trial.

15.8.1. Physical Examinations and Vital Signs

Physical examinations will be summarized for the extension trial. VS (systolic and diastolic BP, temperature, and sitting or lying HR, and weight and changes from baseline in VS (including

weight) will be summarized for the extension trial. Listings of physical exams and VS will be produced.

15.8.2. Laboratory Assessments

Changes from baseline in laboratory assessments (chemistry, hematology, and urinalysis) will be summarized for the extension trial alone as well as for the two trials combined. Likewise, shift tables (L [low], N [normal], H [high]) for the extension trial alone as well as for the two trials combined will be produced for clinical laboratory tests. Listings of laboratory data will be produced.

15.8.3. Adverse Events

Treatment emergent AEs (TEAEs) are AEs that onset after the start of treatment in the trial. TEAEs will be summarized by incidence, SOC, preferred term, seriousness, severity, and relationship to treatment for the extension trial alone as well as for the two trials combined. Serious AEs will be summarized for the extension trial alone as well as for the two trials combined. TEAEs and SAEs will be summarized by gender, by race, and by region (of the world) for the extension trial alone as well as for the two trials combined.

AEs and general medical/surgical histories will be coded by primary SOC and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (version 13.0 or higher).

15.8.3.1. Columbia-Suicide Severity Rating Scale

The C-SSRS will be summarized by visit. Shift tables for the C-SSRS will be produced by visit. Patient listings for the C-SSRS will also be produced.

15.8.4. Other Safety Endpoints

The ECG parameters will be summarized by visit including QT and QTc level categories. ECG results will be summarized in patient listings.

Pregnancy tests will be summarized in patient listings.

Immunogenicity as measured by HAHA will be summarized in tabular form as well as a patient listing for the extension trial alone as well as for the two trials combined.

15.9. Pharmacokinetic/Pharmacodynamic Analyses

The population PK analysis of eculizumab in NMO patients will be performed to assess the concentration of eculizumab versus time. PK parameters such as maximum concentration as well as trough and peak eculizumab concentrations during the induction and maintenance treatment phases will be reported. Clearance and terminal half-life will be estimated. PD analysis will be performed to assess pre- and post-treatment serum hemolytic activity and therefore C5 complement activity inhibition. Free C5 concentration also may be measured.

15.10. Biomarker Analysis

Changes from baseline for NMO-IgG assessments will be summarized and patient listings for the NMO biomarker data will be created.

15.11. Other Statistical Issues

15.11.1. Significance Levels

For all analyses, hypothesis testing will be two-sided and performed at the 0.05 level of significance, unless otherwise specified. Estimates of treatment effect on efficacy parameters will be accompanied by two-sided 95% confidence intervals.

15.11.2. Missing or Invalid Data

For secondary and tertiary efficacy analyses, missing post-baseline efficacy and safety data will not be imputed unless indicated in the described analysis in the SAP.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Trial Monitoring

Before a study site can enter a patient into the trial, a representative of the Sponsor or its designee will visit the investigational trial site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or the Sponsor's designee or its representatives. This will be documented in a Clinical Trial Agreement between the Sponsor or the Sponsor's designee and the Investigator.

During the trial, a monitor from the Sponsor or the Sponsor's designee or representative will have regular contacts with the study site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the trial. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor or the Sponsor's designee.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor or the Sponsor's designee and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

16.2. Audits and Inspections

Authorized representatives of the Sponsor or the Sponsor's designee or its representative, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor or the Sponsor's designee immediately if contacted by a regulatory agency about an inspection.

16.3. Institutional Review Board/Independent Ethics Committee

The PI, or Sponsor or Sponsor's designee, depending on country requirements, must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials that have been submitted and approved by the IRB/IEC for this trial, including the patient ICF form and recruitment materials, must be maintained by the Investigator and made available for inspection.

16.4. Data Monitoring Committee

An independent DMC will conduct interim monitoring of unblinded safety data. Since its primary function will be to ensure patient safety, the DMC will have access to all safety data. The DMC may make recommendations to the Sponsor regarding safety issues, trial conduct, and modifying, extending or stopping the trial. A separate DMC Charter will document all DMC procedures and processes for the trial.

17. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices (GCPs) and all applicable regulatory requirements, the Sponsor or the Sponsor's designee or its representative may conduct a quality assurance audit. Please see Section 16.2 for more details regarding the audit process.

18. ETHICS

18.1. Ethics Review

The final trial protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit a copy of the written approval to the Sponsor or the Sponsor's designee before he or she can enroll any patient/subject into the trial.

The PI, or Sponsor or Sponsor's designee, depending on country requirements, is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the trial. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, per local regulations.

The PI is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other trial conducted with the IP. The Sponsor or the Sponsor's designee will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

18.2. Ethical Conduct of the Trial

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

18.3. Written Informed Consent

The PI(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the trial. Patients must also be notified that they are free to discontinue from the trial at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated ICF must be obtained before conducting any trial procedures.

The PI(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

Local regulations should be followed for blind or other disabled patients. If there are not clear requirements, it is strongly recommended that at the very minimum an impartial witness or, if applicable, a Legal Guardian, is present during the consent process and signs the consent., Additionally, the PI should discuss with the Local EC/IRB the recommended consent process for these patients and adhere to it.

19. DATA HANDLING AND RECORDKEEPING

19.1. Inspection of Records

The Sponsor or the Sponsor's designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the trial. The Investigator agrees to allow the monitor to inspect the IP storage area, IP stocks, IP accountability records, patient charts and trial source documents, and other records relative to trial conduct.

19.2. Retention of Records

The PI must maintain all documentation relating to the trial according to the local regulations or a minimum period of 2 years after the last marketing application approval worldwide, or if not approved 2 years following the discontinuance of the test article for investigation. The PI must also maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents. If it becomes necessary for the Sponsor or the Sponsor's designee or the Regulatory Authority to review any documentation relating to the trial, the Investigator must permit access to such records.

20. LIST OF REFERENCES

(1) Kimbrough D, Fujihara K, Jacob A, et al. Treatment of neuromyelitis optica: Review and recommendations. Multiple Sclerosis and Related Disorders 2012;1:180-7.

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(3) Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006 May 23;66(10):1485-9.

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(7) Rankin J. Cerebral vascular accidents in patients over the age of 60. SCOTT MED J 1957;2:200-15.

(8) Bonita R, Beaglehole R. Modified Rankin Scale; Recovery of Motor function After Stroke. Stroke 1988 Dec;19(12):1497-500.

(9) Van Swieten J, Koudstaal P, Visser M, Schouten H. Interobserver Agreement for the Assessment of Handicap in Stroke Patients. Stroke 1988;19(5):604-7.

(10) Posner K, Brent D, Lucas C, Gould M, Stanley B, Brown G, et al. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) Since Last Visit. 2009.

Ref Type: Online Source

21. APPENDICES

Appendix 1: Diagnostic Criteria for NMO (2006) (3)

Appendix 2: Diagnostic Criteria for NMO spectrum disorder (2007) (4)

Appendix 3: Kurtzke Expanded Disability Status Scale (EDSS) (5)

Appendix 4: Optic-Spinal Impairment Scale (OSIS)

Appendix 5: Hauser Ambulation Index (HAI) (6)

Appendix 6: Short Form Health Survey (SF-36)

Appendix 7: EuroQoL (EQ-5D)

Appendix 8: Clinical Laboratory Tests

Appendix 9: Modified Rankin Scale (mRS) (7-9)

Appendix 10: Columbia-Suicide Severity Rating Scale (C-SSRS)-Since Last Visit (10)

Appendix 11: Collection of Follow-Up Information From Patients Who Withdraw From the Study

APPENDIX 1: 2006 DIAGNOSTIC CRITERIA FOR NMO

Definite NMO

Optic neuritis

Acute myelitis

At least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over 3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

APPENDIX 2: 2007 DIAGNOSTIC CRITERIA FOR NMO SPECTRUM DISORDER

Neuromyelitis optica

Limited forms of neuromyelitis optica

- Idiopathic single or recurrent events of longitudinally extensive myelitis (≥ 3 vertebral segment spinal cord lesion seen on MRI
- Optic neuritis: recurrent or simultaneous bilateral

Asian optic-spinal multiple sclerosis

Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease

Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica

(hypothalamic, corpus callosal, periventricular, or brainstem)

APPENDIX 3: KURTZKE EXPANDED DISABILITY STATUS SCALE (EDSS)

The Kurtzke Expanded Disability Status Scale (EDSS) (5) is a method of quantifying disability in multiple sclerosis. The EDSS replaced the previous Disability Status Scales used in Multiple Sclerosis (MS).

The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The Functional Systems are:

pyramidal

cerebellar

brainstem

sensory

bowel and bladder

visual

cerebral

other

EDSS steps 1.0 to 4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.

Kurtzke Expanded Disability Status Scale	
0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

APPENDIX 4: OPTIC-SPINAL IMPAIRMENT SCORE (OSIS)

Visual Acuity (VA)
0 Normal
1 Scotoma but VA (corrected) better than 20/30
2 VA 20/30 - 20/59
3 VA 20/60-20/100
4 VA 20/ I 0 I - 201200
5 VA 20/20 I - 20/800
6 Count fingers only
7 Light perception only
8 No light perception

Motor Function
0 Normal
1 Abnormal signs (hyperreflexia, Babinski sign) without weakness
2 Mild weakness (MRC grade 5- or 4+) in affected limb(s)
3 Moderate weakness (grade 3 or 4) in 1 or 2 UMN muscles in affected limb(s)
4 Moderate weakness (grade 3 or 4) in 3 UMN muscles in affected limb(s)
5 Severe weakness (grade 2) in 1 or more muscles in affected limb(s)
6 Some plcgic (grade 0 or 1) muscles in 1 or more limbs
7 Plegia (grade 0 or 1) of all muscles in 1 or more limbs

Sensory Function
0 Normal
1 Mild decrease in vibration
2 Mild decrease in pinprick/temperature/proprioception or moderate decrease in vibration
3 Moderate decrease in touch/pin/proprioception or essentially lost vibration sense
4 Loss of all sensory modalities
5 Unknown

Sphincter Function
0 Normal
1 Mild urinary urgency or hesitancy; constipation
2 Moderate urinary urgency, hesitancy, or retention of bladder or bowel, infrequent urinary incontinence (less than once/week)
3 Frequent incontinence or retention requiring intermittent bladder catheterization or aggressive (manual) bowel assistance
4 Indwelling urinary catheter or absence of sphincter control
5 Unknown

APPENDIX 5: HAUSER AMBULATION INDEX

☐ 0 = Asymptomatic; fully active.

☐ 1 = Walks normally, but reports fatigue that interferes with athletic or other demanding activities.

☐ 2 = Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 feet (8 meters) in 10 seconds or less.

☐ 3 = Walks independently; able to walk 25 feet in 20 seconds or less.

☐ 4 = Requires unilateral support (cane or single crutch) to walk; walks 25 feet in 20 seconds or less.

☐ 5 = Requires bilateral support (canes, crutches, or walker) and walks 25 feet in 20 seconds or less; *or* requires unilateral support but needs more than 20 seconds to walk 25 feet.

☐ 6 = Requires bilateral support and more than 20 seconds to walk 25 feet; may use wheelchair* on occasion.

☐ 7 = Walking limited to several steps with bilateral support; unable to walk 25 feet; may use wheelchair* for most activities.

☐ 8 = Restricted to wheelchair; able to transfer self independently.

☐ 9 = Restricted to wheelchair; unable to transfer self independently.

*The use of a wheelchair may be determined by lifestyle and motivation. It is expected that patients in Grade 7 will use a wheelchair more frequently than those in Grades 5 or 6. Assignment of a grade in the range of 5 to 7, however, is determined by the patient's ability to walk a given distance, and not by the extent to which the patient uses a wheelchair.

APPENDIX 6: SHORT FORM HEALTH SURVEY (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

APPENDIX 7: EUROQOL (EQ-5D)

Health Questionnaire

(English version for the United States)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

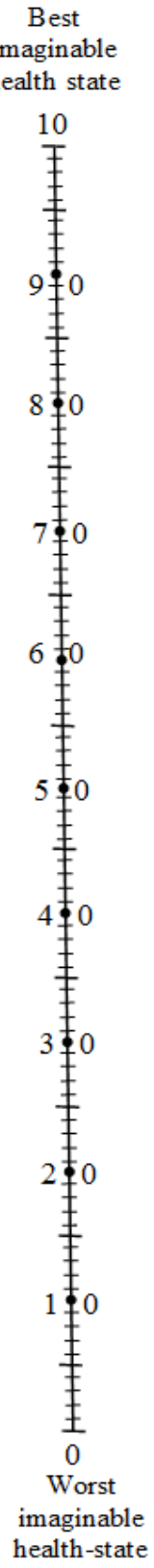
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion.

Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX 8: CLINICAL LABORATORY TESTS

Chemistry Panel Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Glucose Alkaline phosphatase Alanine amino transferase (ALT) Aspartate amino transferase (AST) Total bilirubin Albumin Total protein Uric acid **Complete Blood Count (CBC) & Differential** White blood cell count (WBC) White blood cell differential Red blood cell count (RBC) RBC mean corpuscular volume (MCV) RBC distribution width Hemoglobin Hematocrit Platelet count **Urinalysis** Appearance Specific gravity PH Protein Blood Glucose Ketone Bilirubin Urobilinogen Nitrite	**Human Chorionic Gonadotropin (β-HCG)** **Auto Aquaporin 4 antibody (AQP4-Ab or NMO-IgG)** **Pharmacokinetics (PK) and Pharmacodynamics (PD)** **Complement factor 5 (C5)** **Human Anti-human Antibody (HAHA)**

APPENDIX 9: MODIFIED RANKIN SCALE

MODIFIED RANKIN SCALE (mRS)

Patient Name: _____

Rater Name: _____

Date: _____

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

TOTAL (0–6): _____

APPENDIX 10: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – SINCE LAST VISIT

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** □ **No** □
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (eg, *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** □ **No** □
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (eg, thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** □ **No** □
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** □ **No** □
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** □ **No** □
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (ie, 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	

SUICIDAL IDEATION	
Duration ***When you have the thoughts, how long do they last?*** Fleeting - few seconds or minutes (4) 4-8 hours/most of day Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous 1-4 hours/a lot of time	
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** Easily able to control thoughts (4) Can control thoughts with a lot of difficulty Can control thoughts with little difficulty (5) Unable to control thoughts Can control thoughts with some difficulty (0) Does not attempt to control thoughts	
Deterrents ***Are there things - anyone or anything (eg, family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you Deterrents probably stopped you (5) Deterrents definitely did not stop you Uncertain that deterrents stopped you (0) Does not apply	
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on Mostly to get attention, revenge or a reaction from others living with the pain or how you were feeling) Equally to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on and to end/stop the pain living with the pain or how you were feeling) (0) Does not apply	
SUICIDAL BEHAVIOR **(Check all that apply, so long as these are separate events; must ask about all types)**	Since Last Visit

SUICIDAL IDEATION	
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (eg, gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you___?*** ***Or did you think it was possible you could have died from____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes No □ □ Total # of Attempts ____ Yes No □ □
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes and attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang – is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No □ □ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No □ □ Total # of aborted

SUICIDAL IDEATION	
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (eg, buying pills, purchasing a gun) or preparing for one's death by suicide (eg, giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes □ No □
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes □ No □
Suicide:	Yes □ No □
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (eg, surface scratches). Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains). Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel). Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).	Enter Code _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code _____

APPENDIX 11: COLLECTION OF FOLLOW-UP INFORMATION FROM PATIENTS WHO WITHDRAW FROM THE STUDY

To gain understanding of the patient's post-treatment disease status, the Sponsor may request additional follow-up information from patients who discontinue prematurely. An updated ICF (and/or an ICF Addendum) will be provided to all patients describing the following: the reason for collecting follow-up information from patients who discontinue prematurely, the information that will be collected, that the information will be collected for up to 2 years after the last dose of eculizumab, and how the information will be used. The updated ICF (and/or ICF Addendum) will clearly state that the patient has the option to accept or reject, and that either decision will have no impact on their medical benefits. Prior to collecting any follow-up information, the updated ICF (and/or ICF Addendum) must be signed by the patient.

The Sponsor may obtain patient post-treatment data by querying the patient's medical records, through the study physician, or through the patient's current treating physician. The follow-up data to be collected from the physician may include the following:

- Immunosuppressive medications (eg, azathioprine, mycophenolate mofetil, corticosteroids) and their dose regimen that the patient has received since Study ECU-NMO-302 for the prevention of relapses of NMOSD
- Any NMOSD relapses the patient has experienced since discontinuing Study ECU-NMO-302 including:
    - Date of relapse(s)
    - Type of relapse(s)
    - Outcome of the relapse(s)
    - Whether the patient was hospitalized and/or admitted to the ICU for the relapse(s)
    - Acute treatment for the relapse(s)
    - Has the patient required acute relapse treatment with IV corticosteroids, plasma exchange, IVIg, or other therapies?
- Since leaving Study ECU-NMO-302, has the patient experienced any NMOSD related hospitalizations? If yes, how many times?

This information will not be entered into the trial Electronic Data Capture systems and will not be part of any safety or efficacy analysis that will be included in the ECU-NMO-302 clinical study report.