

**A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial to Evaluate the Safety and Efficacy of Eculizumab in Patients With Relapsing Neuromyelitis Optica (NMO)**

<b>Unique Protocol ID:</b>	ECU-NMO-301
<b>NCT Number:</b>	NCT01892345
<b>EudraCT Number:</b>	2013-001150-10
<b>Date of Protocol:</b>	01 July 2016

# ECULIZUMAB

## ECU-NMO-301

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER TRIAL  
TO EVALUATE THE SAFETY AND EFFICACY OF ECULIZUMAB IN PATIENTS WITH  
RELAPSING NEUROMYELITIS OPTICA (NMO)

**IND 116,207**

**EudraCT Number: 2013-001150-10**

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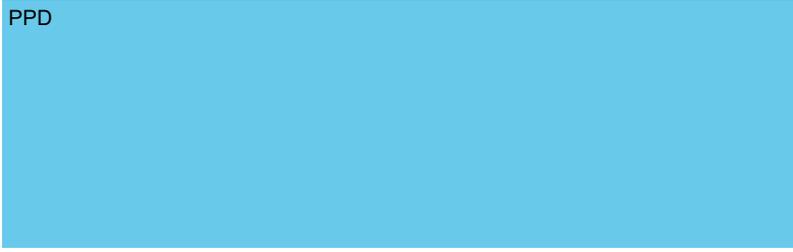
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## SPONSOR SIGNATURE PAGE

**PROTOCOL TITLE:** A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF ECULIZUMAB IN PATIENTS WITH RELAPSING NEUROMYELITIS OPTICA (NMO)

**PROTOCOL NUMBER:** ECU-NMO-301

PPD



11 July 2016

Date

Alexion Pharmaceuticals, Inc.

## INVESTIGATOR'S AGREEMENT

**PROTOCOL TITLE:** A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF ECULIZUMAB IN PATIENTS WITH RELAPSING NEUROMYELITIS OPTICA (NMO)

**PROTOCOL NUMBER:** ECU-NMO-301

I have received and read the Investigator's Brochure for Eculizumab. I have read the ECU-NMO-301 study protocol and agree to conduct the study 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 Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

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Printed Name of Investigator

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Signature of Investigator

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Date

## PROCEDURES IN CASE OF EMERGENCY

**Table 1: Emergency Contact Information**

<b>Role in Trial</b>	<b>Name</b>	<b>Address and Telephone number</b>
Clinical Trial Lead	PPD	Alexion Pharma GmbH Giesshübelstrasse 30, 8045 Zürich, Switzerland  Tel: PPD Mobile: PPD Fax: PPD E-Mail: PPD
Responsible Physician (Medical Monitor)	PPD	Alexion Pharmaceuticals, Inc. 33 Hayden Ave., Lexington, MA 02421, USA  Tel: PPD Mobile: PPD Fax: PPD E-Mail: PPD
Drug Safety Physician	PPD	Alexion Pharmaceuticals, Inc. 33 Hayden Ave, Lexington MA 02421, USA  Tel: PPD Mobile: PPD E-Mail: 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. 352 Knotter Drive Cheshire, CT. 06410  Email: PPD Fax Number: PPD

<b>Role in Trial</b>	<b>Name</b>	<b>Address and Telephone number</b>
Investigational Product Supply	Almac Clinical Services	USA: Almac Clinical Services 4204 Technology Drive Durham, NC 27704 Tel: PPD [REDACTED] Fax: PPD [REDACTED]  Europe: Almac Clinical Services 9 Charlestown Road Seagoe Industrial Estate Portadown BT63 5PW United Kingdom Tel: PPD [REDACTED]
Clinical Laboratory	ACM Medical Laboratory	North America and Latin America: ACM Medical Laboratory 160 Elmgrove Park Rochester, NY 14624 Phone: PPD [REDACTED] Fax: PPD [REDACTED]  Europe: ACM Global Central Laboratory Limited 23 Hospital Fields Road York, YO10 4DZ, UK Tel: PPD [REDACTED] Fax: PPD [REDACTED]  Asia-Pacific: Dorevitch Pathology 18 Banksia Street Heidelberg, VIC 3084, Australia Tel: PPD [REDACTED]

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> Alexion Pharmaceuticals, Inc.	
<b>Name of Investigational Product (IP):</b> Eculizumab or placebo	
<b>Name of Active Ingredient:</b> h5G1.1-mAb	
<p><b>Title of Trial:</b> A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial to Evaluate the Safety and Efficacy of Eculizumab in Patients with Relapsing Neuromyelitis Optica (NMO)</p> <p><b>Abbreviated Trial Name:</b> PREVENT</p> <p><b>Trial Rationale:</b> Neuromyelitis Optica (NMO) or NMO Spectrum Disorders (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. Throughout this protocol the term NMO refers to both NMO and NMOSD. Women are much more commonly affected than men, with a female to male ratio of at least 3:1. Currently there are no approved therapies for the treatment of NMO. Acute attacks are usually treated with high dose corticosteroids or plasma exchange (PE) or both. Supportive treatments for relapse prevention using immunosuppressive therapies (ISTs) are based on clinical experience and consensus; there have been no controlled trials. 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. In a recently reported investigator initiated trial, eculizumab reduced the annualized relapse rate (ARR) in a highly relapsing NMO patient population from a median of 3 relapses per year to zero relapses per year (<math>p &lt; 0.0001</math>). This phase 3 registrational trial is intended to confirm the safety and efficacy of eculizumab in the treatment of relapsing NMO.</p>	
<p><b>Trial Centers:</b> Approximately 120 – 150 centers in North America, South America, Europe, and Asia-Pacific; additional centers may be added as needed.</p>	
<p><b>Investigators:</b> A list containing all Investigators will be provided when site selection is completed.</p>	
<p><b>Studied period (years):</b> Estimated date first patient enrolled: 2014 Estimated date last patient completed: 2017 – since this is an event-driven trial, last patient last visit may vary depending on the accrued rate of primary endpoint events</p>	<p><b>Phase of development:</b> 3</p>
<p><b>Objectives:</b></p> <p><b>Primary:</b></p> <ul style="list-style-type: none"> <li>Assess the efficacy of eculizumab treatment as compared with placebo in relapsing NMO patients based on the time to first relapse and relapse risk reduction.</li> </ul> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>Characterize the overall safety and tolerability of eculizumab compared with placebo</li> </ul>	

in relapsing NMO patients.

- Evaluate the efficacy of eculizumab compared with placebo by additional efficacy measures including:
  - Disease related disability
  - Quality of life
  - Neurologic function
  - Annualized relapse rate
- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in relapsing NMO patients.

**Methodology:**

This is a randomized, double-blind, parallel-group, placebo-controlled, multi-center, time-to-event trial to evaluate the safety and efficacy of eculizumab in patients with relapsing NMO. Eligible patients will be randomized 2:1 to one of two parallel treatment arms: 1) eculizumab infusion or 2) placebo infusion. Patients may continue to receive stable maintenance dose of protocol permitted supportive ISTs for relapse prevention, as defined by their Treating Physician. Patients must remain on that dose for the duration of the study or until the patient experiences a relapse. Based on power calculations for this study, the study is designed to continue until 24 relapses (in 24 distinct subjects) occur, as adjudicated by a committee external to the Sponsor and blinded to treatment. Therefore, the enrollment will be closed when either 24 adjudicated events have occurred or when up to 132 patients are enrolled, whichever comes first. The trial duration is estimated to take approximately 3-4 years including enrollment. In this time-to-event trial, the trial duration for an individual patient will vary depending on when the patient enters the trial and on the patient's outcome. The course of the trial for an individual patient will consist of: Screening Period, Study Period, and Safety Follow-up Period (for patients who withdraw from this trial or for patients who do not enter the extension trial). The End of Study (EOS) Visit for an individual patient will take place when one of the following conditions is met, whichever comes first: (a) the patient experiences an On-Trial Relapse as defined by this protocol (see Standard Protocol Definitions, Section 7.4); or (b) the trial ends by meeting 24 adjudicated On-Trial Relapse events (in 24 distinct patients). Patients may be provided with the opportunity to participate in an extension trial (separate protocol ECU-NMO-302) to receive eculizumab after completion of the EOS Visit; patients who terminate the study early will not be eligible.

**Screening Period (1 – 6 weeks)**

At the Screening Visit, after informed consent is obtained from the patient, the patient will be screened for trial eligibility through medical history review, demographic data, and laboratory assessments. The medical history review will include confirmation of the diagnosis of NMO (as defined by Wingerchuk et. al., 2006; [Appendix 1](#)) or NMOSD (as defined by Wingerchuk et. al., 2007; [Appendix 2](#)). Relapses within the last 2 years prior to screening must be assessed by the Investigator to determine if they meet the criteria for the Historical Relapse Definition as specified by this protocol (see Standard Protocol Definitions Section 7.4). Detailed information related to relapses within the 2 years prior to the Screening Visit will be collected, if available. This includes date of onset, clinical presentation for each relapse (e.g., optic neuritis [ON], transverse myelitis [TM], longitudinally extensive transverse myelitis [LETM], or brainstem event), and Expanded Disability Status Scale (EDSS) score at the following time points: prior to relapse, at nadir and during recovery, for severity of relapse and recovery, if

available. Start/stop dates and dose regimen of all IST(s) including immunomodulatory agents and non-drug therapies taken for relapse prevention or for relapse treatment within the last 2 years will also be collected and recorded. If PE was administered, the number of sessions of PE for each relapse will also be collected. Information on all other previous historical relapses including relapse onset date and its clinical presentations, name /type of IST(s) or non-drug therapies received at the time of relapse and treatment received for the acute relapse or prevention of relapses will also be collected, if available. Only patients with a positive test for NMO-IgG (aquaporin-4 [AQP4] antibody) obtained prior to or during the screening will be included in the study. Only validated diagnostic tests performed by a qualified laboratory are acceptable.

Supportive ISTs for relapse prevention are allowed during the trial under certain restrictions (refer to Concomitant Medications, Section 9.2 for details). The ISTs are permitted either as mono-therapy or in combination, such as corticosteroids, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate, tacrolimus, cyclosporine and cyclophosphamide. If a patient enters the trial receiving IST(s) for relapse prevention, the patient must be on a stable maintenance dose of these IST(s), as defined by the Treating Physician, prior to the Screening Visit. No new IST(s) are permitted during the trial unless the patient experiences a relapse. Supportive ISTs for the purpose of relapse prevention or treatment of a relapse prior to the Screening Visit and all other medications taken within 30 days of screening will be reviewed and recorded on the electronic case report form (eCRF). Non-drug therapy for NMO relapse prevention or treatment within 24 months prior to the Screening Visit will also be collected and recorded on the eCRF. If PE was administered within the last 2 years, the number of cycles of PE for each relapse treatment or prevention of relapse will also be collected.

All patients must be vaccinated against *Neisseria meningitidis* at least 14 days prior to receiving the first dose of IP or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination.

Patients who experience a relapse during the Screening Period will be considered a screening failure. Following discussion with and approval by the Sponsor, such patients may be rescreened after receiving treatment for the relapse and when, in the opinion of the Investigator, the patient is medically stable.

### **Study Period**

#### **Randomization:**

All patients who are vaccinated and cleared for randomization by their Principal Investigator (PI) or the Sub-Investigator and by the Sponsor will be randomized on Day 1 on a 2:1 basis to the Eculizumab Arm or the Placebo Arm. The randomization will be across centers. The randomization stratification will include two variables: 1) EDSS score at randomization (Day 1) ( $\leq 2.0$ , vs.  $\geq 2.5$  to  $\leq 7$ ); and 2) patients' prior supportive (i.e., for relapse prevention) IST and IST status at the randomization (Day 1) (treatment naïve patients vs. patients continuing on the same IST(s) since last relapse vs. patients with changes in IST(s) since last relapse) (see Standard Protocol Definitions, Section 7.4).

Patients will receive either eculizumab or placebo according to the randomization assignment and the regimen described in the Investigational Product, Dosage and Mode of Administration

Section below.

The treatment duration for an individual patient varies in this time-to-event trial. All patients must remain on randomized treatment assignment until the EOS or Early Termination (ET) Visit. The end of trial is defined as completion of the EOS/ET Visit by all patients.

Relapse Evaluation:

a) Evaluation of Patient On-Trial Relapses by Investigators

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 in response of a possible relapse must be recorded.

As part of the Relapse Evaluation, a blinded EDSS Rater will perform the Kurtzke neurological assessment to determine the Functional System Scores (FSS) and 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 7.6.3). 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 7.4.2). If the event is confirmed as an On-Trial Relapse, the patient may be treated, according to the recommended Standardized On-Trial Relapse Treatment regimen (Section 9.2.1.3), and ISTs can be changed if deemed appropriate by the Treating Physician. The double-blinded IP administration visits will continue as scheduled every 1-2 weeks until the EOS.

Follow-up Relapse Evaluation Visits 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 are permitted at the discretion of the Investigator. As this trial is a time-to-event trial, patients who experience a relapse will be discontinued from this trial after completion of the Week 6 Relapse Evaluation Visit, which also serves as the EOS Visit.

Patients who complete this trial, either because of a relapse or because the trial is ended by meeting 24 adjudicated On-Trial Relapse events, may be provided with an opportunity to enter an extension trial (separate protocol ECU-NMO-302) to receive open-label eculizumab. The visit interval between this trial and the extension trial is 2 weeks from the last IP administration, therefore there will be no interruptions in IP dosing. Thus, patients who exit the trial due to a relapse will have their first extension visit once the Week 6 Relapse Evaluation Visit is completed and no later than 2 weeks (14 days  $\pm$  2 days) after the last IP dose; patients who exit this trial due to trial completion will have their first extension visit 2

weeks (14 days  $\pm$ 2 days) after the EOS Visit. All patients entering the extension trial will undergo a blinded eculizumab induction period similar to the induction in this trial in order to preserve the blind treatment assignment of this trial.

b) Independent Review of On-Trial Relapses by the Adjudication Committee

An independent Relapse Adjudication Committee will be established to 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 and are blinded to each patient's treatment assignment. 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. The Charter, which will be finalized prior to adjudication of the first relapse event, will describe the Adjudication Committee's purpose, process, relapse event definition, and specific data points for review and evaluation.

**Safety Follow-up Period (8 weeks)**

If a patient withdraws from the trial at any time after receiving any amount of IP or does not wish to enter the extension trial (ECU-NMO-302) after completion of this trial, the patient will be required to complete an ET or EOS Visit at the time of withdrawal and a Follow-Up Visit 8 weeks after the last dose of IP for safety measures.

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.

**Number of Patients (planned):** A minimum of 24 up to a maximum of 132 patients are planned to be enrolled in this trial. Based on power calculations for this trial, the trial is designed to continue until 24 adjudicated On-Trial Relapse events in 24 distinct subjects are observed. Therefore, the enrollment will be closed when either 24 adjudicated On-Trial Relapse events have occurred or up to 132 patients are enrolled, whichever comes first.

**Primary Efficacy Endpoint**

The primary efficacy endpoint is time to first adjudicated On-Trial Relapse. The trial will be considered to have met its primary efficacy objective if a statistically significant difference is observed between the eculizumab treatment group and placebo group. The comparison of the treatment groups for the primary endpoint will use a log-rank test including strata for the randomization stratification variables (1) EDSS score at randomization (Day 1) and (2) supportive IST status at randomization (Day 1).

**Secondary Efficacy Endpoints**

During the Study Period, Baseline is defined as the last available assessment prior to IP treatment for all patients regardless of their treatment group.

Hypothesis testing comparing eculizumab treatment with placebo treatment for the secondary efficacy analyses will be performed using a closed testing procedure with the following rank order:

1. Change from baseline in EDSS score at the EOS

2. Adjudicated annualized relapse rate
3. Change from baseline in EuroQoL (EQ-5D) at the EOS
4. Change from baseline in modified Rankin Scale (mRS) score at the EOS
5. Change from baseline in ambulatory function as measured by HAI at the EOS.

### **Sample Size**

The sample size and power calculation assumptions for this time-to-first event trial are as follows: Log-rank test for comparison of eculizumab to placebo, 2:1 randomization (eculizumab: placebo), 90% power, two-sided 5% level of significance, drop-out rate 10%, accrual period of approximately 21 months, relapse-free rate of 80% for the eculizumab arm at 12 months and 40% for the placebo arm. The total number of relapses to be observed for this trial is 24 adjudicated On-Trial Relapse events in 24 distinct patients. With these assumptions, a sample size of approximately 132 patients (88 eculizumab and 44 placebo) provides 90% power to detect a treatment difference in time-to-first adjudicated relapse.

### **Diagnosis and main criteria for inclusion:**

#### **Inclusion Criteria:**

1. Male or female patients  $\geq 18$  years old
2. Diagnosis of NMO as defined by 2006 Criteria by Wingerchuk et. al.(6) ([Appendix 1](#)), or NMOSD as defined by 2007 Criteria by Wingerchuk et al (18) ([Appendix 2](#))
3. NMO-IgG seropositive
4. Historical Relapse (as defined by this protocol) of at least 2 relapses in the last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to the screening
5. EDSS score  $\leq 7$
6. If a patient enters the trial receiving IST(s) for relapse prevention, the patient must be on a stable maintenance dose of IST(s), as defined by the Treating Physician, prior to screening and must remain on that dose for the duration of the study, unless the patient experiences a relapse.
7. Patients must give written informed consent
8. Patients must be willing and able to comply with the protocol requirements for the duration of the trial
9. Female patients of child-bearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]). 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. Use of rituximab within 3 months prior to screening

2. Use of mitoxantrone within 3 months prior to screening
3. Use of Intravenous Immunoglobulin (IVIg) within 3 weeks prior to screening
4. If a patient enters the trial receiving oral corticosteroid(s) with or without other IST(s), the daily corticosteroid dose must be no more than prednisone 20 mg/day (or equivalent) prior to screening and must remain on that dose for the duration of the study or until the patient experiences a relapse
5. Pregnant, breastfeeding, or intending to conceive during the course of the trial
6. Unresolved meningococcal infection
7. Any systemic bacterial or other infection which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics
8. Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days of screening
9. Has previously received treatment with eculizumab
10. Hypersensitivity to murine proteins or to one of the excipients of eculizumab
11. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the trial, poses any added risk for the patient, or confounds the assessment of the patients

**Investigational product, dosage and mode of administration:**

The IP will be given by intravenous (IV) administration over approximately 35 minutes according to the following regimen:

Induction Phase: 3 vials of IP (placebo or equivalent to 900 mg of eculizumab) weekly x 4 (every 7 days  $\pm$ 2 days) followed by 4 vials of IP (placebo or equivalent to 1200 mg of eculizumab) one week later for the fifth dose.

Maintenance Phase: 4 vials of IP (placebo or equivalent to 1200 mg of eculizumab) every two weeks (every 14 days  $\pm$ 2 days) from the time of the last dose of the induction phase.

Supplemental Doses: If a patient undergoes PE for On-Trial Relapse during the Study Period, a supplemental dose of 2 vials of IP (placebo or equivalent to 600 mg of eculizumab) must be administered after each PE, preferably within 1-2 hours. If the PE is on the day of a scheduled IP infusion the scheduled dose of IP should be administered after each PE, preferably within 1-2 hours. Per-protocol scheduled IP administration will be continued according to the specified dose administration schedule for the patient through the end of study.

**Duration of treatment (Study Period):**

The duration of treatment for an individual patient in this time-to-event trial will vary. The actual duration will be determined by time of relapse for that patient or the completion of the trial if the patient does not have a relapse. The maximum projected duration of treatment for an individual patient is approximately 3-4 years.

**Reference therapy, dosage and mode of administration:**

Placebo with the same buffer components as eculizumab and without the active ingredient, administered IV as described in the section above on Investigational Product, Dosage and

Mode of Administration.

**Criteria for evaluation:**

**Efficacy:**

Duration of treatment commences with the first IP infusion. The Study Period defines the time period for assessment of the trial endpoints. A total of 24 adjudicated On-Trial Relapse events in 24 distinct individual patients are to be observed. Patients must be discontinued from this trial after completion of the 6-week Follow-Up Relapse Evaluation Visit and may be offered enrollment in the extension trial in which all patients will receive eculizumab.

The trial will continue until the 24th adjudicated On-Trial Relapse has been observed (24 adjudicated events in 24 distinct patients). When the trial is stopped, all data from all patients will be collected, and the database cleaned, locked, and analyzed. Data from the Study Period will be used for efficacy analysis.

- On-Trial Relapses will be monitored closely throughout the trial and evaluated as described in the above section “Study Period, Relapse Evaluation”.
- Disability will be assessed by the EDSS and mRS scores comparing the change from baseline. The blinded EDSS Rater will perform the Kurtzke neurological assessment and document the FSS and the EDSS score throughout the trial at the protocol specified time points as well as at the On-Trial Relapse Evaluation Visit. 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 FSS. Ambulatory function will be assessed by HAI and visual function will be measured by VA using the Snellen chart. In addition, the 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.
- Quality of life (QOL) will be assessed by the patients’ self-assessment questionnaires EQ-5D and the Short Form Health Survey (SF-36) at the protocol specified time points.

**Safety:**

- The safety of eculizumab will be assessed based on the treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and the changes from baseline through trial completion in vital signs, electrocardiogram (ECG), 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 to analyze 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.
- An independent Data Monitoring Committee (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 unblinded safety data. The DMC may make recommendations to the Sponsor regarding safety issues, trial conduct, and modification, extension or stopping of 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 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.

### **Pharmacokinetics (PK) and Pharmacodynamics (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 for the double-blind Study Period in order to compare the eculizumab group with the placebo group. The analyses will include efficacy, safety, and PK/PD analyses.

### **Efficacy:**

Efficacy analyses will be performed on the Full Analysis Set (FAS) population as well as on the Per-Protocol (PP) population.

**FAS Population:** The population on which primary, secondary, tertiary and other efficacy analyses will be performed. This set consists of all patients who are randomized to treatment and who have received at least 1 dose of IP. Patients will be compared for efficacy according to the treatment they were randomized to receive, irrespective of the treatment they actually received.

**PP Population:** The per-protocol population is a subset of the full analysis set population, excluding patients with major protocol deviations. The 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 treatment doses while they were in the Study Period

The PP population will be determined prior to database lock and unblinding.

**Primary Efficacy Analysis for the Study Period:**

Note: During the Study Period, Baseline is defined as the last available assessment prior to IP treatment for all patients regardless of treatment group.

The primary efficacy endpoint is time to first adjudicated On-Trial Relapse as defined in the protocol. The trial will be considered to have met its primary efficacy objective if a statistically significant difference is observed between the eculizumab treatment group and the placebo group. The comparison of the treatment groups for the primary endpoint will use a log-rank test including strata for the randomization stratification variables: 1) patients' EDSS score at Randomization (Day 1), and 2) patients' IST status at the Randomization (Day 1). Confidence intervals and p-values will be presented. Kaplan-Meier curves for both treatment groups will be produced. Hazard ratio and risk reduction will be summarized. A sensitivity analysis will be performed on time to first On-Trial Relapse (as identified by the Investigator) using a log-rank test including strata for the randomization stratification variables. In addition, a sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator, and randomization stratification variables as the only covariates in the model. A second sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator, randomization stratification variables, and region as the only covariates in the model. Region will be defined based on the sites for the study and will include North America, South America, Europe, Asia-Pacific (including but not limited to Australia and Japan), and Other as applicable. In the event that the number of patients in some regions is too small to permit modeling, the smaller regions will be pooled together.

An additional sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator and randomization stratification variables as covariates and will also include withdrawals due to AEs as outcomes events (i.e., relapses).

An additional sensitivity comparison of the treatment groups for the primary endpoint will use a log-rank test including strata for the randomization stratification variables for the FAS patients with a follow-up assessment (i.e., FAS patients without a follow-up assessment will be excluded from the analysis).

**Secondary Efficacy Analysis for the Study Period:**

Unless otherwise specified, the secondary efficacy analyses will use the available data from the Study Period. Hypothesis testing comparing eculizumab treatment with placebo treatment for the secondary efficacy analyses will be performed using a closed testing procedure with the following rank order:

1. Change from baseline in EDSS score at the EOS

2. Adjudicated annualized relapse rate
3. Change from baseline in EQ-5D at the EOS
4. Change from baseline in mRS score at the EOS
5. Change from baseline in HAI at the EOS

The hypothesis testing will proceed from highest rank (#1) change from baseline in EDSS to the lowest rank (#5) change from baseline in HAI, and if statistical significance is not achieved at an endpoint ( $p \leq 0.05$ ), then endpoints of lower rank will not be considered to be statistically significant. Confidence intervals and p-values will be presented for all secondary efficacy endpoints for descriptive purposes, regardless of the outcome of the closed testing procedure. The EQ-5D has two endpoints, the index score and EQ-5D VAS. For the purposes of this closed testing procedure, the EQ-5D index score will be analyzed first and the EQ-5D VAS score will be analyzed second for the EQ-5D analyses.

The primary analysis for the change from baseline in EDSS score to the end of Study Period (i.e., 6 week post-relapse for the patients who have relapses or end of treatment period visit for patients who do not have relapses) will be a ranked ANCOVA with treatment group, baseline EDSS, and IST status at randomization as covariates. If a patient experiences a second relapse during the 6 week recovery phase after the initial relapse the last EDSS score prior to the second attack will be used for the analysis. If a patient has no follow-up assessments, a change from baseline of 0 (i.e., baseline value carried forward) will be used. A sensitivity analysis for the change from baseline in EDSS score to the end of Study Period (i.e., 6 week post-relapse for the patients who have relapses or EOS for patients who do not have relapses) will be a ranked ANCOVA with treatment group, Baseline EDSS, and IST status at randomization as covariates in the subset of the FAS population who do have a follow-up assessment (i.e., FAS patients without a follow-up assessment will be excluded from the analysis). If a patient experiences a second relapse during the 6 week recovery phase after the initial relapse, the last EDSS score prior to the second attack will be used for the analysis. In addition, sensitivity analyses for the change from Baseline in EDSS will be analyzed using a mixed model for repeated measures with baseline EDSS score, IST status at randomization, treatment group indicator, trial visit and trial visit by treatment group interaction as covariates. All post-baseline EDSS scores will be included in the models; patients without any post-baseline scores will not be included. In addition, other sensitivity analyses will include imputations for missing visit assessments. Patients who discontinue the trial early without a relapse will have subsequent missing EDSS assessments imputed using the LOCF approach. Patients who discontinue the trial early with a relapse will have subsequent missing EDSS assessments imputed by using the EDSS assessment conducted 6 weeks after the first relapse attack. If the EDSS assessment 6 weeks after the first relapse is missing, then the last available EDSS score after the relapse at trial discontinuation for the patient will be imputed using the LOCF approach. If the patient does not have an EDSS score after the relapse then the 6 week recovery EDSS score will be imputed using the patient's last EDSS before the relapse adjusted according to the average % change in EDSS at week 6 after a relapse observed in all other patients who did have relapses in the same treatment group.

The comparison of the two treatment groups for secondary endpoint, adjudicated ARR, will use Poisson regression analysis. Treatment group, the stratification variables, and baseline

ARR will be covariates in the model, and the log of time in the trial will be used as the offset variable. A sensitivity analysis will be performed for ARR using all On-Trial Relapses (as identified by the Investigator) in a Poisson regression analysis with treatment group, the stratification variables, and baseline ARR as covariates in the model, and the log of time in the trial will be used as the offset variable.

Changes from baseline in the HAI, EQ-5D index score and EQ-5D VAS will be analyzed in a similar manner as changes in EDSS score. Baseline value and the stratification variables will be covariates in the modeling for these endpoints.

The primary analysis for the change from baseline in mRS score to the EOS (i.e., 6 week post-relapse for the patients who have relapses or EOS for patients who do not have relapses) will be a ranked ANCOVA with treatment group, baseline mRS, EDSS strata at randomization, and IST status at randomization as covariates. If a patient experiences a second relapse during the 6 week recovery phase after the initial relapse, the last mRS score prior to the second attack will be used for the analysis. If a patient has no follow-up assessments, a change from baseline of 0 (i.e., baseline value carried forward) will be used. A sensitivity analysis for the change from baseline in mRS score to the end of the Study Period will be a ranked ANCOVA with treatment group, baseline mRS, EDSS strata at randomization, and IST status at randomization as covariates in the subset of the FAS population who do have a follow-up assessment (i.e., FAS patients without a follow-up assessment will be excluded from the analysis). An additional sensitivity comparison of the two treatment groups for the mRS score will use generalized estimating equations (GEE) methods at the EOS (i.e., 6 week post-relapse for the patients who have relapses or end of treatment period visit for patients who do not have relapses). PROC GENMOD in SAS will be used to fit a GEE model of the mRS score at the end of the study (i.e., 6 week post-relapse for the patients who have relapses or end of treatment period visit for patients who do not have relapses). The GEE model will include covariates for treatment group, randomization stratification variables, baseline mRS score, visit, and the treatment group by visit interaction term. A multinomial distribution will be used in the model along with a cumulative logit link function and an independent working correlation matrix. If the treatment group by visit interaction term is not significant ( $p \leq 0.10$ ), it will be removed from the GEE model and the model will be refit and used as the final model in the analyses. In addition, summary statistics for the changes from baseline in the mRS score will be produced by visit and treatment group. Likewise, shift tables from baseline in the mRS score will be produced by visit and treatment group.

#### **Tertiary Efficacy Analysis for the Study Period:**

1. Change from baseline in HAI at EOS in patients with abnormal baseline ambulatory function
2. Change from baseline in VA at EOS in all patients and in patients with abnormal baseline visual function
3. Change from baseline in the SF-36 at EOS
4. Change from baseline in the EDSS FSS at EOS

Changes from baseline in the VA will be analyzed in a similar manner as changes in the EDSS score. Baseline value and the stratification variables will be covariates in the modeling for

these endpoints. Changes from baseline in the HAI and in the VA for patients who were abnormal at baseline will be analyzed in a similar manner to the analyses described for the HAI and the VA in all patients.

Change from baseline in QOL will be summarized as appropriate to the quality of life instrument, and treatment group comparisons 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.

**Safety:**

Safety analyses will be performed on the Safety Population. The Safety Population includes all patients who receive at least 1 dose of IP. Patients will be compared for safety according to the treatment they actually received. All AEs and other safety information including untreated patients collected after the signing of informed consent will be reported in listings, as applicable.

**Safety for the Study Period:**

Note: During the Study Period, Baseline is defined as the last available assessment prior to treatment for all patients regardless of their treatment group.

For the Study Period, AEs will be summarized by incidence, system organ class (SOC), preferred term (PT), seriousness, severity, relationship to treatment, and by treatment group. Concomitant medications will be summarized by treatment group.

Changes from Baseline in vital signs, laboratory assessments (chemistry and hematology,) and C-SSRS will be summarized by treatment group. Likewise, shift tables (L [low], N [normal], H [high]) by treatment group will be produced for clinical laboratory tests and pregnancy tests will be summarized in patient listings. Shift tables for the C-SSRS will be produced by treatment group and visit.

Immunogenicity as measured by HAHA will be summarized in tabular form by treatment group and in-patient listing.

**PK/ PD:**

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.

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#### 4. LIST OF ABBREVIATIONS

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
aHUS	Atypical hemolytic uremic syndrome
AQP4	Aquaporin-4
ARR	Annualized Relapse Rate
AZA	Azathioprine
BP	Blood Pressure
C5	Complement protein 5
C <sub>max</sub>	Maximal concentration
C <sub>min</sub>	Minimal concentration
CNS	Central Nervous System
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EIU	Exposure in-utero
EOS	End of Study
EQ-5D	EuroQoL
ET	Early Termination
EU	European Union
FAS	Full Analysis Set
FS	Functional System
FSS	Functional System Scores
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HAHA	Human Anti-human Antibody
HAI	Hauser Ambulation Index
HCG	Human Chorionic gGonadotropin
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
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
LETM	Longitudinally Extensive Transverse Myelitis
mAb	Monoclonal Antibody
MMF	Mycophenolate Mofetil

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
mRS	Modified Rankin Scale
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NMO	Neuromyelitis Optica
NMO-IgG	Aquaporin-4 antibody
NMOSD	Neuromyelitis Optica Spectrum Disorders
OAE	Other Adverse Event
ON	Optic Neuritis
OSIS	Optic Spinal Impairment Score
PD	Pharmacodynamics
PE	Plasmapheresis Or Plasma Exchange
PI	Principal Investigator
PK	Pharmacokinetics
PNH	Paroxysmal Nocturnal Hemoglobinuria
PP	Per-Protocol
PT	Preferred Term
QOL	Quality Of Life
RR	Respiration Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	Short Form Health Survey
SIADH	Syndrome of Inappropriate Anti-Diuretic Hormone
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
VA	Visual Acuity
US	United States

## **5. INTRODUCTION**

### **5.1. Neuromyelitis Optica (NMO)**

NMO, also known as Devic's Disease or Devic's Syndrome, 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. Women are much more commonly affected than men, with a female to male ratio of at least 3:1 (1). Median age of onset is generally in the late 30s early 40s, with a very wide range (1-3). Currently, there is no therapy approved for the treatment of NMO. Eculizumab (h5G1.1-mAb) is a terminal complement inhibitor that blocks conversion of C5 to C5a and C5b thus blocking terminal complement activation which leads to demyelinating lesions in NMO attacks. In a recent investigator-initiated trial, eculizumab reduced the annualized relapse rate (ARR) in highly relapsing NMO patient population from a median of 3 relapses per year to zero relapse per year (4). This phase 3 registrational trial is intended to confirm the safety and efficacy of eculizumab in the treatment of relapsing NMO.

### **5.2. Clinical presentation of NMO**

The clinical hallmarks of NMO are acute optic neuritis and transverse myelitis that frequently involves greater than 3 vertebral levels, described as longitudinally extensive transverse myelitis (LETM) (3). These clinical events can occur either simultaneously or in isolation (5). Signs and symptoms attributable to lesions beyond the optic nerves and spinal cord can also occur in patients with NMO, and are reported in about 15% of patients (6-9). The clinical presentation of NMO can be quite variable and may elude diagnosis at the time of the first attack or even the second attack.

The clinical features of the optic neuritis include central visual loss accompanied by ocular pain and occasionally by dyschromatopsia. In more than half of the patient's optic neuritis, unilateral or bilateral, is the initial event of relapsing NMO (9;10). Clinical manifestations of myelitis may include severe symmetric paraplegia, sensory loss below the lesion, bladder dysfunction, Lhermitte's sign, paroxysmal tonic spasms, and radicular pain. Myelitis may extend up into the brainstem causing respiratory failure and death. Brainstem involvement may manifest with nausea, vomiting, hiccups, vertigo, hearing loss, facial weakness, trigeminal neuralgia, diplopia, ptosis or nystagmus. In addition several studies have documented signs and symptoms due to hypothalamic involvement, including syndrome of inappropriate anti-diuretic hormone (SIADH), hypersomnolence and hypothermia (11;12).

The clinical course of NMO can be either monophasic or relapsing. Recent studies have shown that in more than 90% of cases, NMO is a relapsing disease (13). Once a relapsing course has been established, recurrent optic neuritis and myelitis attacks result in stepwise accumulation of neurologic disability. Within 5 years, more than 50% of such patients are functionally blind (visual acuity [VA] worse than 20/200) or have lost the ability to ambulate without assistance (9). NMO is unlike multiple sclerosis (MS), where a secondary and progressive phase is common and is a major predictor of disability. In NMO patients, the disability accumulation is

associated with relapse (5). Therefore, relapse prevention is paramount for successful treatment of relapsing NMO (5).

In 1999, Wingerchuk et al, proposed diagnostic criteria for NMO which were based on clinical and radiographic features (9). The discovery of antibodies directed at the aquaporin-4 (AQP4) channel (AQP4-IgG or NMO-IgG) by Lennon et. al. (14), has clearly defined this disorder as an inflammatory autoimmune disease. The AQP4-IgG, hereafter referred to as NMO-IgG, is the first biomarker for demyelinating disorders. Clinical and pathologic studies have clearly demonstrated the role of NMO-IgG in the pathophysiology of NMO and the role of complement in lesion formation (15-17). In a high percentage of patients, the disease is associated with NMO-IgG in the peripheral circulation. With the discovery of NMO-IgG, the diagnostic criteria for NMO were revised in 2006 to include the testing of this disease-specific antibody.

The identification of the sensitive and specific biomarker has led to the recognition that this distinct disease, NMO, in fact encompasses a number of closely related clinical presentations that have been defined as both definite NMO and NMO spectrum disorders (NMOSD) (13;18). The characteristics of NMO/NMOSD are unified by the clinical course of disease and the presence of the NMO-IgG in the vast majority of patients. At present, these proposed diagnostic criteria for definite NMO and NMOSD are widely accepted and in practice. The criteria for the diagnosis of NMO have been independently validated in different patient populations (19). Throughout this document, the term NMO refers to both NMO and NMOSD.

In light of the fact that NMO is a disorder that has the potential to cause significant disability, the ability to recognize and differentiate NMO and related disorders from other demyelinating disorders is important from a clinical perspective. The prognosis of relapsing NMO is poor. Before universal recognition of NMO as a disease distinct from MS and thus requiring a very different treatment paradigm, the 5-year mortality of NMO was reported to be 30%; 50% sustain permanent severe disability, visual (blind in one or both eyes) or ambulatory (requiring a wheelchair). Most deaths result from neurogenic respiratory failure secondary to a high cervical cord or brainstem lesion (9). Frequent early relapses predict a poor prognosis.

### **5.3. Unmet Medical Need**

Currently, there is no therapy approved for the treatment of NMO. Additionally, there have been no randomized placebo-controlled trials examining therapeutic approaches for treatment of NMO. Standard treatment options including steroids and other immunosuppressive agents as supportive treatments are used based on clinical experience and consensus (13). Acute NMO relapses are generally treated with high-dose intravenous (IV) steroids with plasma exchange (PE) often used as a rescue therapy for those who do not respond. Supportive treatments against relapse currently use broad spectrum or selective B-lymphocyte immunosuppressants. Of the immunosuppressive agents, corticosteroid, azathioprine (AZA), mycophenolate mofetile (MMF) and rituximab are probably most commonly used for long-term prophylaxis. Depending on regional medical options, the supportive medications option for NMO may vary. In the United States (US), options include corticosteroids, AZA, MMF, rituximab, and mitoxantrone (3;20), whereas corticosteroids including oral prednisone or pulse-high dose steroids (IV) are common treatments in Japan. A significant number of patients (>50%) will continue to have attacks resulting in additional and permanent neurologic deficits and disability (21-25). Given the seriousness of the disease, limitations of currently available therapies, and the limited options for

treatment, there remains a significant unmet medical need for an effective and safe treatment for NMO.

#### **5.4. Role of Complement in NMO**

In a high percentage of patients, NMO is associated with a disease specific antibody to the aquaporin-4 water channel (AQP4), NMO-IgG antibody. AQP4 is an integral homotetrameric protein complex and is expressed primarily on the abluminal surface of astrocyte foot process and can also be found on ependymocytes and endothelial cells (26). AQP4 is one of the main water channels in the CNS but it is also found outside of the CNS in many solid organs including kidney distal collecting tubes and in a proportion of gastric parietal cells. An increasing body of literature implicates that NMO-IgG induces complement activation as a major pathogenic mechanism in the course of the disease (27). Once bound to AQP4, NMO-IgG can impair sodium-dependent glutamate transport in vitro and activate complement cascade leading to membrane lesioning. The activation of complement cascade contributes to both the increase of blood-brain barrier permeability and to the recruitment of inflammatory cells to the lesion sites observed in pathological studies (28).

Furthermore, in vitro observations predict that availability of complement components at sites of IgG interaction with AQP4 (e.g., before downregulation of surface AQP4 expression) could trigger an explosive inflammatory cascade (29). The initiation of complement activation is thus described as a critical factor of an individual patient's clinical presentation and disease course. These pathological findings support the notion that complement activation and subsequent astrocyte injury may represent the pathologic molecular outcome of NMO-IgG interactions with AQP4 in NMO attacks.

#### **5.5. Eculizumab as the First Terminal Complement Inhibitor Therapeutic**

Eculizumab (h5G1.1-mAb) is a humanized monoclonal antibody (mAb) that was derived from the murine anti-human C5 antibody m5G1.1. Eculizumab specifically binds the terminal complement protein C5, thereby inhibiting its cleavage to C5a and C5b during complement activation. This strategic blockade of the complement cascade at C5 prevents the release of proinflammatory mediators and the formation of the cytolytic pore, while preserving the early components of complement activation that are essential for the opsonization of microorganisms and clearance of immune complexes.

Eculizumab was approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) under the trade name Soliris<sup>®</sup> on 16 March 2007 in the US and on 20 June 2007 in the European Union (EU). Extension of the indication of eculizumab to include a second rare disease indication, atypical hemolytic uremic syndrome (aHUS), was granted under Accelerated Approval in the US on 23 September 2011 and was approved in the EU on 24 November 2011. Eculizumab is not approved for treatment of NMO.(30)

##### **5.5.1. Eculizumab in NMO Patients**

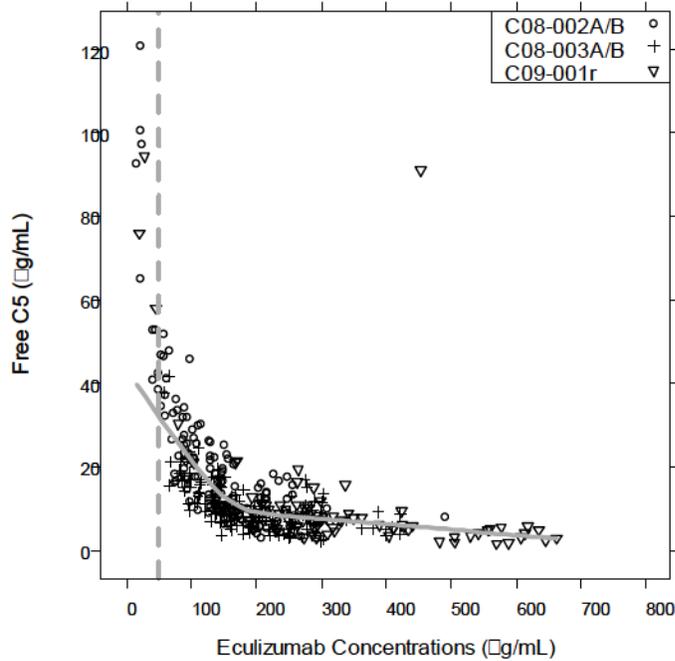
A recently reported investigator-initiated trial designed to evaluate the safety and efficacy of eculizumab in NMO-IgG seropositive NMO patients, demonstrated preliminary safety and efficacy in relapsing NMO (4). After 12 months of treatment, 12/14 (86%) patients were attack-

free, two had possible attacks. The median annualized attack rate declined from 3 (pre-eculizumab, range 2-4) to zero (post-eculizumab, range 0-1;  $p < 0.0001$ ). During treatment two patients had single attacks, one back pain only (without objective clinical or radiological evidence) treated with steroid as a “possible” attack; the other received Intravenous Immunoglobulin (IVIg) for a presumed optic neuritis. At 12 months, no patient had worsened disability by any outcome measure. The pretreatment baseline median Expanded Disability Status Scale (EDSS) score was 4.3, and at follow-up examination the median EDSS score was 3.5 ( $p = 0.0078$ ). One patient developed meningococcal septicemia and sterile meningitis and recovered with antibiotic therapy. There were no other serious adverse events (SAEs) and treatment was otherwise well tolerated. Eight attacks in 5 patients were reported within 12 months of eculizumab withdrawal.

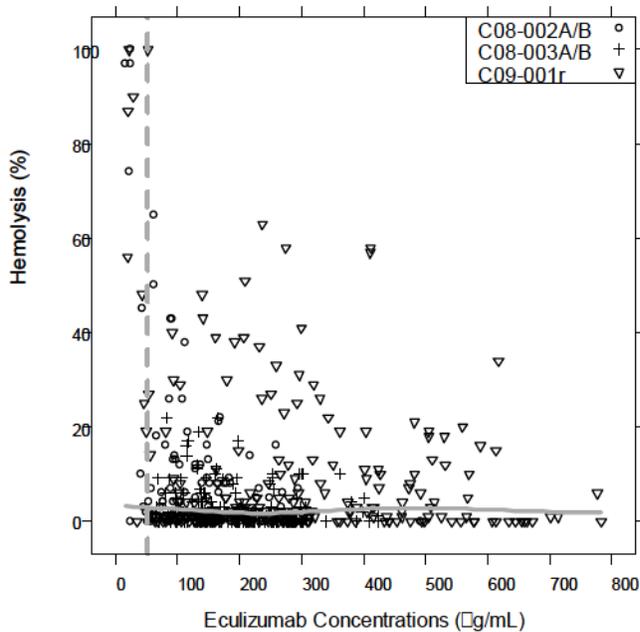
## 5.6. Eculizumab Dose for NMO

Empirical data from aHUS clinical trials using the now approved aHUS dose regimen of 900/1200 mg indicate that serum eculizumab concentrations greater than 50  $\mu\text{g/mL}$  and closer to at least 100  $\mu\text{g/mL}$  (Figure 1) were required to significantly reduce free C5 concentrations. Specifically, free C5 concentration was reduced significantly with increasing concentrations of eculizumab beginning at  $>50 \mu\text{g/mL}$  and was at near zero levels with eculizumab concentrations above 100  $\mu\text{g/mL}$ . Based on the free C5 pharmacokinetics (PK)/pharmacodynamics (PD) model, mean  $C_{\text{max}}$  and  $C_{\text{min}}$  values of eculizumab during the Induction Phase (900 mg dose weekly) would result in 92.9% and 91.8% inhibition of free C5, respectively. Similarly, mean  $C_{\text{max}}$  and  $C_{\text{min}}$  values of eculizumab during the Maintenance Phase (1200 mg every 14 days) would result in 93.4% and 92.8% inhibition of free C5, respectively.

**Figure 1: Relationship between Serum Concentration of Eculizumab and Free C5 Inhibition**



**Figure 2: Relationship between Serum Concentration of Eculizumab and Percent Hemolysis (Induction and Maintenance Periods)**



Overall, significant and sustained terminal complement inhibition as measured by the validated PD assay measuring hemolytic activity was demonstrated in all patients who had achieved a serum concentration of eculizumab  $>100 \mu\text{g/mL}$  (Figure 2).

Potential breakthrough, loss of complement inhibition, in the setting of NMO is deemed unacceptable because of the potential clinically serious consequences including functional blindness or paralysis that may result from a single attack. The approved eculizumab dosing regimen for patients with aHUS (900/1200 mg) should result in a complete and sustained terminal complement blockade. Therefore the aHUS approved dose, Induction Phase of 900 mg weekly for 4 weeks and Maintenance Phase of 1200 mg every 14 days will be used in this trial.

For additional information on dosing of eculizumab, refer to the Eculizumab Investigator's Brochure.

## **6. TRIAL OBJECTIVES AND PURPOSE**

### **6.1. Primary Objective**

The primary objective of this trial is to assess the efficacy of eculizumab treatment as compared with placebo in relapsing NMO patients based on time to first relapse and relapse risk reduction.

### **6.2. Secondary Objectives**

- Characterize the overall safety and tolerability of eculizumab compared with placebo in relapsing NMO patients.
- Evaluate the efficacy of eculizumab compared with placebo by additional efficacy measures including:
  - Disease related disability
  - Quality of life (QOL)
  - Neurologic function
  - Annualized relapse rate
- Describe the PK and PD of eculizumab in relapsing NMO patients

### **6.3. Primary and Secondary Efficacy Endpoints**

#### **6.3.1. Primary Efficacy Endpoint**

Time to first adjudicated On-Trial Relapse for eculizumab compared with placebo.

#### **6.3.2. Secondary Efficacy Endpoints (eculizumab outcomes as compared with placebo outcomes):**

1. Change from baseline in EDSS score at the end of study (EOS)
2. Adjudicated annualized relapse rate
3. Change from baseline in EuroQoL (EQ-5D) at the EOS
4. Change from baseline in modified Rankin Scale (mRS) score at the EOS
5. Change from baseline in Hauser Ambulatory Index (HAI) score at the EOS

## 7. OVERALL TRIAL DESIGN AND PLAN

This is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, time-to-event trial to evaluate the safety and efficacy of eculizumab in patients with relapsing NMO.

There are three periods in the trial including: Screening Period, Study Period and Safety Follow-Up Period (only for patients who withdraw from this trial or patients who do not enter the extension trial).

Patients who complete the Study Period may have the opportunity to enter an extension trial (separate protocol ECU-NMO-302) to receive open-label eculizumab. Patients entering the extension trial will undergo a blinded Induction Phase similar to the induction in this trial in order to preserve the blinded nature of this trial.

### 7.1. Screening Period

At the Screening Visit, after informed consent is obtained from the patient, the patient will be screened for trial eligibility through medical history review, demographic data, electrocardiogram (ECG) and laboratory assessments. The medical history review will include confirmation of the diagnosis of NMO (as defined by Wingerchuk et. al. 2006; [Appendix 1](#)) or NMOSD (as defined by Wingerchuk et. al. 2007; [Appendix 2](#)). Detailed information on relapses within the last 2 years prior to screening must be assessed by the Investigator to determine if they meet the definition for Historical Relapse as specified by this protocol (see Section 7.4, Standard Protocol Definitions). Detailed information related to relapses within the last 2 years will be collected and recorded in the electronic case report form (eCRF), if available. This includes date of onset and its clinical presentation for each relapse (e.g., optic neuritis [ON], transverse myelitis [TM], LETM, or brainstem event); and EDSS score at the following time points: prior to relapse, at nadir and during recovery, for severity of relapse and recovery. Start/stop dates and dose regimen of all immunosuppressant therapy(ies) (IST[s]) including immunomodulatory agents and non-drug therapies taken for relapse prevention or treatment of a relapse will also be collected and recorded. If PE was administered for treatment of a relapse, the number of cycles of PE will also be collected. Information on all other previous historical relapses including relapse onset date and its clinical presentations, name /type of IST(s) at the time of relapse, and treatment received for the acute relapse and/or to prevent relapse will also be collected, if available. Only patients with documented positive test for the AQP4 autoantibody (also called NMO-IgG) obtained prior to or during the screening will be included in the study. Only validated diagnostic tests performed by a qualified laboratory are acceptable.

Supportive ISTs for relapse prevention are allowed during the trial under certain restrictions (refer to Section 9.2, Concomitant Medications, for details). The following ISTs are allowed either as mono-therapy or in combination such as corticosteroids, AZA, MMF, methotrexate, tacrolimus, cyclosporine and cyclophosphamide. If a patient enters the trial receiving IST(s), the patient must be on a stable maintenance dose of IST(s), as defined by their Treating Physician, prior to the Screening Visit. **No new IST(s) are permitted during the trial unless a patient experiences a relapse.** IST and/or therapies for NMO relapses (either acute treatment or prevention) prior to screening and all other medications taken within 30 days of the Screening

Visit will be reviewed and recorded on the eCRF. Non-drug therapy for NMO relapse prevention or treatment within 24 months prior to screening will also be collected and recorded on the eCRF. If PE was administered for treatment of a relapse, the number of cycles of PE will also be collected and recorded on the eCRF.

All patients must be vaccinated against *N. meningitidis* (if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer). Patients must be vaccinated at least 14 days prior to receiving the first dose of Investigational Product (IP) or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination.

Patients who experience a relapse during the Screening Period will be considered a screening failure. Such patients may be rescreened for enrollment into the trial after receiving treatment for the relapse and when, in the opinion of the Investigator, the patient is medically stable. The patient must meet the enrollment criteria in order to enter the trial.

## 7.2. Study Period

All patients who are vaccinated and cleared for randomization by their Principal Investigator (PI) and by the Sponsor will be randomized on Day 1 on a 2:1 basis to the Eculizumab Arm or the Placebo Arm. A randomization worksheet will be provided and the Sponsor's approval is required to ensure proper randomization. The randomization will be across centers. The randomization stratification will include two variables: 1) EDSS score at randomization (Day 1); and 2) patients' prior supportive (i.e., for relapse prevention) IST and IST status at the randomization (Day 1) (see Standard Protocol Definitions, Section 7.4).

1. Patients' EDSS score at randomization (Day 1)
  - a. EDSS scores are  $\leq 2.0$
  - b. EDSS scores are  $\geq 2.5 - \leq 7.0$
2. Patients' prior IST and IST status at randomization (Day 1)
  - a. Treatment naïve patients (i.e., patients with no prior or current ISTs, except steroids alone)
  - b. Patients continuing on the same IST(s) since the last relapse (i.e., including patients with dose adjustments since the last relapse)
  - c. Patients with changes in IST(s) since last relapse (i.e., switched IST(s) [e.g., AZA to MMF], added IST [e.g., corticosteroid], or withdrew any IST treatment)

Patients will receive either eculizumab or placebo according to the randomization assignment and the regimen described in the Investigational Product, Dosage and Mode of Administration (Section 9.1). The treatment duration for an individual patient varies in this time-to-event trial. All patients must remain on randomized treatment assignment until the EOS Visit. The end of trial is defined as completion of the EOS or Early Termination (ET) Visit by all patients.

Identification of potential relapse is critical for patient safety and for 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. Any potential relapse will be evaluated according to the information in the Relapse Evaluation Section 7.2.1 below.

Follow-up 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 are permitted and will be made at the discretion of the Treating Physician. During this time, the double-blind IP administration will continue to be administered as scheduled every 1-2 weeks ( $\pm 2$  days) until EOS. All reports of possible relapses and actions taken for the possible relapse must be documented in the patient's medical chart or source documents and recorded in the eCRF.

As this is a time-to-event trial, patients who experience a relapse will be discontinued from this trial after completion of the Week 6 Relapse Evaluation Visit. Thus, the Week 6 Relapse Evaluation Visit also serves as the EOS Visit for these patients.

For patients who do not have relapses, the EOS Visit will be completed when the trial ends by meeting 24 adjudicated On-Trial Relapses (in 24 distinct patients). The EOS Visit for these patients should be completed as soon as possible, preferably within 1 month of the end of trial notification.

Patients who complete the trial either because of a relapse or because of the trial is ended may be provided with an opportunity to enter an extension trial (separate protocol ECU-NMO-302) to receive open-label eculizumab. The visit interval between this trial and the extension trial is 2 weeks from the last IP administration, therefore there will be no interruptions in IP dosing. Thus, patients who exit this trial due to a relapse will have their first extension visit once the Week 6 Relapse Evaluation Visit is completed and no later than 2 weeks (14 days  $\pm 2$  days) after the last IP dose; patients who exit this trial due to trial completion will have their first extension visit 2 weeks (14 days  $\pm 2$  days) after the EOS Visit. All patients entering the extension trial will undergo a blinded eculizumab induction period similar to the induction in this trial in order to preserve the blind treatment assignment of this trial.

Patients who do not continue in the open label extension trial will enter the 8-week Safety Follow-Up Period.

### **7.2.1. Relapse Evaluation**

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 EDSS Rater. 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.

At each Relapse Evaluation Visit, the blinded EDSS Rater will perform the Kurtzke neurologic assessment and document the Functional System Scores (FSS) and the 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 VA test (Snellen chart) and HAI.

The Treating Physician determines if the clinical signs, symptoms and neurologic change (objective findings on examination) meet the definition for On-Trial Relapse as outlined in this protocol (Section 7.4.2). The blinded EDSS Rater completes the Kurtzke neurological exam to determine if the relapse is associated with changes in any of the Functional System Scores (FSS)

or total EDSS score. After all specified relapse evaluation procedures are complete and the On-Trial Relapse is confirmed, the Treating Physician may initiate the recommended relapse treatment outlined in this protocol (Section 9.2.1.3) and change the supportive ISTs if needed.

All relapses should be reported in source documents and the eCRF at the Relapse Evaluation Visit. Relapses that meet the criteria of a SAE should also be reported as a SAE. See Section 12.2.1.3 for more details on SAE criteria.

To monitor the course of the relapse, Follow-Up Relapse Evaluation Visits will be performed at 1, 4 and 6 weeks after the onset of relapse. Additional unscheduled Follow-Up Relapse Evaluation Visits are permitted at the discretion of the Treating Physician and must be documented in the patient's source documents and recorded in the eCRF. During the Relapse Evaluation Period, the double-blind IP administration visits will continue as scheduled every 1-2 weeks until the EOS/ET; therefore depending on when the relapse occurs, IP administration visits may or may not overlap with the Relapse Evaluation Visit and/or Follow-Up Relapse Evaluation Visits.

An independent Relapse Adjudication Committee will be established to confirm all On-Trial Relapse events using objective and consistent clinical criteria described in a Relapse Adjudication Charter. The Charter, which will be finalized prior to adjudication of the first relapse event, will describe the Adjudication Committee's purpose, process, relapse event definition, and specific data points for review and evaluation. The Adjudication Committee will consist of three independent medical experts in neurology or neuroophthalmology who are each experienced in the management of patients with NMO and are blinded to each patient's treatment assignment. The Adjudication Committee will decide by majority vote whether each relapse meets the pre-defined objective criteria for an adjudicated On-Trial Relapse.

### **7.3. Safety Follow-Up Period (Post-Treatment)**

If patients withdraw from this trial after receiving any amount of IP or do not enter the extension trial after completing this trial, a follow-up visit for safety assessments is required at 8 weeks after the last dose of IP. 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 PI, is determined medically stable.

### **7.4. Standard Protocol Definitions**

#### **7.4.1. Historical Relapse**

Historical relapses are the relapses that occurred prior to the Screening Visit, including the first NMO attack. For this protocol, historical relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or magnetic resonance imaging [MRI] findings or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of existing neurologic symptoms that required treatment. Treatment is defined as use of high-dose IV steroids, PE or IVIg. Events that occur within a 30-day interval are considered as one relapse.

#### **7.4.2. 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, i.e., not caused by an identifiable cause such as infection, excessive exercise, or excessively high ambient temperature. Isolated changes on 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. Treating Physician is not required to wait 24 hours prior to initiating treatment for the relapse.

### 7.4.3. Severity of Relapse

Severity of an On-Trial Relapse will be measured by the OSIS (Appendix 4). The OSIS VA Subscale Scores will be used to categorize the severity of ON. The OSIS Motor Subscale Scores and Sensory Subscale Scores will be used to categorize the severity of Transverse Myelitis (TM). OSIS score will be assessed by the Treating Physician at the time of the relapse.

**Table 3: Relapse Severity as Measured by OSIS**

Optic Neuritis (ON)		
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 $\geq 2$ points	Major
Transverse Myelitis (TM)		
Motor Subscale Score		Relapse Descriptor
Pre-Relapse	Post-Relapse	
0-1	0-2	Minor
0-1	3+	Major
2-6	Increase by 1 point	Minor
2-6	Increase by $\geq 2$ points	Major
Sensory Subscale Score		Relapse Descriptor
Based on proprioceptive loss only	If severe loss in one or more limbs with prior normal function or with mild proprioceptive loss	Major

### 7.4.4. Patient Population / Immunosuppressant Therapy Status

There are 3 patient populations based on their prior supportive IST(s) (i.e., used for relapse prevention) and IST status at the time of randomization.

- a. Treatment naïve patients (i.e., patients with no prior or current ISTs, except steroids alone)
- b. Patients continuing on the same IST(s) since the last relapse (i.e., including patients with dose adjustments since the last relapse)

- c. Patients with changes in IST(s) since the last relapse (i.e., switched IST(s) [e.g., AZA to MMF], added IST [e.g., corticosteroid], or withdrew any IST treatment)

#### **7.4.4.1. Treatment Naïve Patients**

Treatment naïve patients are defined as those who have received or are receiving either no ISTs or have received only corticosteroids following treatment of acute relapses prior to the screening.

#### **7.4.4.2. Patients Continuing on the Same IST at the Time of Randomization**

Patients continuing on the same IST(s) used for relapse prevention since the last relapse are defined as those who previously received IST(s) other than only corticosteroids alone and are continuing on the same IST(s) on which they had the most recent relapse at the time of randomization. Patients who had dose adjustment with the same IST(s) following a relapse are included in this group, e.g., AZA 1.5 mg/kg/day prior to relapse to AZA 2.0 mg/kg/day after relapse.

#### **7.4.4.3. Patients with Changes in IST(s) at the Time of Randomization**

Patients with changes in IST(s) used for relapse prevention since the last relapse are defined as those who at the time of randomization had switched IST (e.g., AZA to MMF), added another IST (e.g., added a corticosteroid), or withdrew any IST(s) following the treatment of the last relapse.

#### **7.4.5. The Treating Physician**

The Treating Physician is the PI or the Sub-Investigator for the study, and will be responsible for the overall patient management including patient eligibility evaluation, supervision of the blinded IP administration, recording and treating of AEs and monitoring of safety assessment. 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 and may treat the patient's relapse according to the recommended On-Trial Relapse Treatment regimen in Section 7.4.2. Treatment for On-Trial Relapse and any changes in the ISTs following an On-Trial Relapse is at the discretion of the Treating Physician. The Treating Physician is blinded to patient's treatment assignment.

#### **7.4.6. The EDSS Rater (Blinded)**

The blinded EDSS Rater will be responsible for performing the EDSS assessments throughout the trial including at the time of a relapse. The EDSS Rater will perform a complete Kurtzke neurologic exam (32) and document the FSS and the EDSS score. The EDSS Rater shall not be the PI or the Sub-Investigator, 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 (e.g. specialized nurses) will be used, the rater must be approved by the Sponsor prior to initiation of the study. For specific requirements for EDSS rater qualification, refer to the training materials.

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

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

<b>Treating Physician</b>	<b>EDSS Rater</b>
<p><b>Blinded to the patient’s treatment assignment:</b></p> <ul style="list-style-type: none"> <li>• Determine patient eligibility for the trial</li> <li>• Overall patient management during the trial, including IP administration and safety assessments.</li> <li>• Perform mRS*</li> <li>• Perform Columbia-Suicide Severity Rating Scale (C-SSRS)*</li> </ul> <p><b>At the time of relapse:</b></p> <ul style="list-style-type: none"> <li>• Initial patient assessment</li> <li>• Have the EDSS Rater record FSS and EDSS score*</li> <li>• Perform a complete neurologic examination</li> <li>• Determine if the patient has experienced an On-Trial Relapse</li> <li>• Determine relapse severity by OSIS</li> <li>• Assess VA, Snellen Chart*</li> <li>• Assess ambulation by HAI*</li> <li>• Have the patient complete the EQ-5D and Short Form Health Survey (SF-36)*</li> <li>• Treat relapse</li> </ul>	<p><b>Blinded to all other trial data as well as all other patient clinical chart data:</b></p> <p>At protocol specified time points:</p> <ul style="list-style-type: none"> <li>• Kurtzke neurological assessment</li> <li>• Document FSS</li> <li>• Record EDSS score</li> </ul> <p><b>At the time of relapse:</b></p> <ul style="list-style-type: none"> <li>• Perform the Kurtzke neurologic assessment</li> <li>• Document FSS</li> <li>• Record EDSS score</li> </ul>

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

**7.4.7. Adjudication of On-Trial Relapses**

To obtain an independent assessment of all On-Trial Relapse events using objective and consistent clinical criteria, all relapses will be independently reviewed by an Adjudication Committee. The Committee, consisting of medical experts in neurology and/or neuroophthalmology, will conduct independent reviews for all relapse events identified by the Investigators. The Committee will decide by majority vote whether each Investigator-identified On-Trial Relapse meets the objective criteria for an adjudicated On-Trial Relapse. A separate Charter will document all adjudication criteria and procedures for this trial.

## 7.5. Schedule of Assessments

**Table 5: Schedule of Assessments – Screening Period<sup>1</sup>**

Trial Visit	V1
Screening Period Duration	1-6 Weeks
Informed Consent <sup>2</sup>	X
Medical History and Demography	X
NMO History <sup>3</sup>	X
Physical Examination <sup>4</sup>	X
Weight and Height	X
Vital Signs <sup>5</sup>	X
Electrocardiogram (ECG) <sup>6</sup>	X
Concomitant Medications <sup>7</sup>	X
Adverse Events (AEs) <sup>8</sup>	
Clinical Laboratory Tests <sup>9</sup>	X
Pregnancy test (serum) <sup>10</sup>	X
NMO-IgG (serum) <sup>11</sup>	X
NMO-IgG (CSF) <sup>12</sup>	
PK/PD/Free C5 (serum) <sup>11</sup>	
PK/C5 (CSF) <sup>12</sup>	
EuroQol (EQ-5D) <sup>13</sup>	
Short Form Health Survey (SF-36) <sup>13</sup>	
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>15</sup>	
Expanded Disability Status Scale (EDSS) <sup>14</sup>	X
Modified Rankin Scale (mRS) <sup>15</sup>	
Patient Education Card and NMO Symptom Evaluation <sup>15</sup>	X
Neurologic Examination <sup>14, 15</sup>	X
Optic Spinal Impairment Score (OSIS) <sup>15</sup>	
Snellen chart <sup>15</sup>	X
Hauser Ambulation Index (HAI) <sup>15</sup>	X
Medically indicated tests <sup>16</sup>	
Review Inclusion / Exclusion criteria <sup>15</sup>	X
Randomization <sup>17</sup>	
<i>N. meningitidis</i> vaccination <sup>18</sup>	X
Patient Safety Identification Card <sup>18</sup>	
Investigational Product (IP) Infusion <sup>19</sup>	

**Table 6: Schedule of Assessments – Study Period (Visit 2 – Visit 17)**

Trial Visit	Induction Phase					Maintenance Phase										
	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Trial Week	Day1	W1	W2	W3	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26
Informed Consent <sup>2</sup>																
Medical History and Demography																
NMO History <sup>3</sup>																
Physical Examination <sup>4</sup>																
Weight and Height																
Vital Signs <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) <sup>6</sup>																
Concomitant Medications <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs) <sup>8</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests <sup>9</sup>	X				X		X		X						X	
Pregnancy test (serum) <sup>10</sup>	X				X		X		X						X	
NMO-IgG (serum) <sup>11</sup>	X				X		X		X						X	
NMO-IgG (CSF) <sup>12</sup>	X								X						X	
PK/PD/Free C5 (serum) <sup>11</sup>	B/P				T/P		T/P		T/P						T/P	
HAHA (serum) <sup>11</sup>	X				X				X						X	
PK/Free C5 (CSF) <sup>12</sup>	X								X						X	
EuroQol (EQ-5D) <sup>13</sup>	X				X		X		X						X	
Short Form Health Survey (SF-36) <sup>13</sup>	X				X		X		X						X	
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>15</sup>	X				X		X		X						X	
Expanded Disability Status Scale (EDSS) <sup>14</sup>	X				X		X		X						X	
Modified Rankin Scale (mRS) <sup>15</sup>	X				X		X		X						X	
Patient Education Card and NMO Symptom Evaluation <sup>15</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurologic Examination <sup>14,15</sup>	X				X		X		X						X	
Optic Spinal Impairment Score (OSIS) <sup>15</sup>	X															
Snellen chart <sup>15</sup>	X				X		X		X						X	
Hauser Ambulation Index (HAI) <sup>15</sup>	X				X		X		X						X	
Medically indicated tests <sup>16</sup>																
Review Inclusion / Exclusion criteria <sup>15</sup>	X															
Randomization <sup>17</sup>	X															
<i>N. meningitidis</i> vaccination <sup>18</sup>																
Patient Safety Identification Card <sup>18</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product (IP) Infusion <sup>19</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

**Table 7: Schedule of Assessments – Study Period (Visit 18 – Visit 30)**

Trial Visit	Maintenance Phase												
	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29	V30
Trial Week	W28	W30	W32	W34	W36	W38	W40	W42	W44	W46	W48	W50	W52
Informed Consent <sup>2</sup>													
Medical History and Demography													
NMO History <sup>3</sup>													
Physical Examination <sup>4</sup>													
Weight													X
Vital Signs <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) <sup>6</sup>													X
Concomitant Medications <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs) <sup>8</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests <sup>9</sup>					X						X		
Pregnancy test (serum) <sup>10</sup>					X						X		
NMO-IgG (serum) <sup>11</sup>					X						X		
NMO-IgG (CSF) <sup>12</sup>											X		
PK/PD/Free C5 (serum) <sup>11</sup>					T/P						T/P		
HAHA (serum) <sup>11</sup>					X						X		
PK/Free C5 (CSF) <sup>12</sup>											X		
EuroQol (EQ-5D) <sup>13</sup>					X						X		
Short Form Health Survey (SF-36) <sup>13</sup>					X						X		
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>15</sup>					X						X		
Expanded Disability Status Scale (EDSS) <sup>14</sup>					X						X		
Modified Rankin Scale (mRS) <sup>15</sup>					X						X		
Patient Education Card /NMO Symptom Evaluation <sup>15</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurologic Examination <sup>14, 15</sup>					X						X		
Optic Spinal Impairment Score (OSIS) <sup>15</sup>													
Snellen chart <sup>15</sup>					X						X		
Hauser Ambulation Index (HAI) <sup>15</sup>					X						X		
Medically indicated tests <sup>16</sup>													
Review Inclusion / Exclusion criteria													
Randomization <sup>17</sup>													
<i>N. meningitidis</i> vaccination <sup>18</sup>													
Patient Safety Identification Card <sup>18</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product (IP) Infusion <sup>19</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X

**Table 8: Schedule of Assessments – Study Period (Visit 31 – Visit 43)**

Trial Visit	Maintenance Phase												
	V31	V32	V33	V34	V35	V36	V37	V38	V39	V40	V41	V42	V43
Trial Week	W54	W56	W58	W60	W62	W64	W66	W68	W70	W72	W74	W76	W78
Informed Consent <sup>2</sup>													
Medical History and Demography													
NMO History <sup>3</sup>													
Physical Examination <sup>4</sup>													
Weight and Height													
Vital Signs <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) <sup>6</sup>													
Concomitant Medications <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs) <sup>8</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests <sup>9</sup>				X						X			
Pregnancy test (serum) <sup>10</sup>				X						X			
NMO-IgG (serum) <sup>11</sup>				X						X			
NMO-IgG (CSF) <sup>12</sup>										X			
PK/PD/Free C5 (serum) <sup>11</sup>				T/P						T/P			
HAHA (serum) <sup>11</sup>				X						X			
PK/Free C5 (CSF) <sup>12</sup>										X			
EuroQol (EQ-5D) <sup>13</sup>				X						X			
Short Form Health Survey (SF-36) <sup>13</sup>				X						X			
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>15</sup>				X						X			
Expanded Disability Status Scale (EDSS) <sup>14</sup>				X						X			
Modified Rankin Scale (mRS) <sup>15</sup>				X						X			
Patient Education Card / NMO Symptom Evaluation <sup>15</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurologic Examination <sup>14, 15</sup>				X						X			
Optic Spinal Impairment Score (OSIS) <sup>15</sup>													
Snellen chart <sup>15</sup>				X						X			
Hauser Ambulation Index (HAI) <sup>15</sup>				X						X			
Medically indicated tests <sup>16</sup>													
Review Inclusion / Exclusion criteria <sup>15</sup>													
Randomization <sup>17</sup>													
<i>N. meningitidis</i> vaccination <sup>18</sup>													
Patient Safety Identification Card <sup>18</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product (IP) Infusion <sup>19</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X

**Table 9: Schedule of Assessments – Study Period (Visit 44 – Visit 52 )**

Trial Visit	Maintenance Phase								
	V44	V45	V46	V47	V48	V49	V50	V51	V52
Trial Week	W80	W82	W84	W86	W88	W90	W92	W94	W96
Informed Consent <sup>2</sup>									
Medical History and Demography									
NMO History <sup>3</sup>									
Physical Examination <sup>4</sup>									X
Weight									X
Vital Signs <sup>5</sup>	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) <sup>6</sup>									X
Concomitant Medication <sup>7</sup>	X	X	X	X	X	X	X	X	X
Adverse Events <sup>8</sup>	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests <sup>9</sup>			X						X
Pregnancy test (serum) <sup>10</sup>			X						X
NMO-IgG (serum) <sup>11</sup>			X						X
NMO-IgG (CSF) <sup>12</sup>									X
PK/PD/Free C5 (serum) <sup>11</sup>			T/P						T/P
HAHA (serum) <sup>11</sup>			X						X
PK/Free C5 (CSF) <sup>12</sup>									X
EuroQol (EQ-5D) <sup>13</sup>			X						X
Short Form Health Survey (SF-36) <sup>13</sup>			X						X
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>15</sup>			X						X
Expanded Disability Status Scale (EDSS) <sup>14</sup>			X						X
Modified Rankin Scale (mRS) <sup>15</sup>			X						X
Patient Education Card and NMO Symptom Evaluation <sup>15</sup>	X	X	X	X	X	X	X	X	X
Neurologic Examination <sup>14, 15</sup>			X						X
Optic Spinal Impairment Score (OSIS) <sup>15</sup>									
Snellen chart <sup>15</sup>			X						X
Hauser Ambulation Index (HAI) <sup>15</sup>			X						X
Medically indicated tests <sup>16</sup>									
Review Inclusion / Exclusion criteria <sup>15</sup>									
<i>N. meningitidis</i> vaccination <sup>18</sup>									
Patient Safety Identification Card <sup>18</sup>	X	X	X	X	X	X	X	X	X
Investigational Product (IP) Infusion <sup>19</sup>	X	X	X	X	X	X	X	X	X

**Table 10: Schedule of Assessments - Study Period (Beyond Visit 52 to EOS / ET)**

Trial Visit	Maintenance Phase		
	Short Visit	Long Visit	End of Study (EOS) / Early Termination (ET) Visit
Trial Week	Every 2 <sup>nd</sup> week after Visit 52 until EOS Visit except Long Visits (e.g., Weeks 98, 100, 102, 104, 106, 110, etc...)	Every 12 <sup>th</sup> week after Visit 52 until EOS Visit (e.g., Weeks 108, 120, 132, 144, etc...)	
Physical Examination <sup>4</sup>			X
Weight			X
Vital Signs <sup>5</sup>	X	X	X
Electrocardiogram (ECG) <sup>6</sup>			X
Concomitant Medication <sup>7</sup>	X	X	X
Adverse Events <sup>8</sup>	X	X	X
Clinical Laboratory Tests <sup>9</sup>		X	X
Pregnancy test (serum) <sup>10</sup>		X	X
NMO-IgG (serum) <sup>11</sup>		X	X
NMO-IgG (CSF) <sup>12</sup>		X (every 24 <sup>th</sup> week)	X
PK/PD/Free C5 (serum) <sup>11</sup>		T/P	T/P
HAHA (serum) <sup>11</sup>		X	X
PK/Free C5 (CSF) <sup>12</sup>		X (every 24 <sup>th</sup> week)	X
EuroQol (EQ-5D) <sup>13</sup>		X	X
Short Form Health Survey (SF-36) <sup>13</sup>		X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>15</sup>		X	X
Expanded Disability Status Scale (EDSS) <sup>14</sup>		X	X
Modified Rankin Scale (mRS) <sup>15</sup>		X	X
Patient Education Card and NMO Symptom Evaluation <sup>15</sup>	X	X	X
Neurologic Examination <sup>14, 15</sup>		X	X
Optic Spinal Impairment Score (OSIS) <sup>15</sup>			
Snellen chart <sup>15</sup>		X	X
Hauser Ambulation Index (HAI) <sup>15</sup>		X	X
Medically indicated tests <sup>16</sup>			
Patient Safety Identification Card <sup>18</sup>	X	X	X
Investigational Product (IP) Infusion <sup>19</sup>	X	X	X

**Table 11: Schedule of Assessments – Relapse Evaluation Period**

Assessment	Relapse Evaluation Visit	Follow- Up Relapse Evaluation Visits <sup>20</sup>			
		Within 24-48 hours	+W1	+W4	+W6/EOS
Informed Consent <sup>2</sup>					
Medical History and Demography					
NMO History <sup>3</sup>					
Physical Examination <sup>4</sup>				X	
Weight				X	
Vital Signs <sup>5</sup>	X	X	X	X	X
Electrocardiogram (ECG) <sup>6</sup>				X	
Concomitant Medication <sup>7</sup>	X	X	X	X	X
Adverse Events (AEs) <sup>8</sup>	X	X	X	X	X
Clinical Laboratory Tests <sup>9</sup>	X			X	X
Pregnancy test (serum) <sup>10</sup>				X	X
NMO-IgG (serum) <sup>11</sup>	X			X	X
NMO-IgG (CSF) <sup>12</sup>	X			X	X
HAHA (serum)				X	
PK/PD/Free C5 (serum) <sup>11</sup>	T/P	T/P	T/P	T/P	T/P
PK/Free C5 (CSF) <sup>12</sup>	X			X	X
EuroQol (EQ-5D) <sup>13</sup>				X	X
Short Form Health Survey (SF-36) <sup>13</sup>				X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>15</sup>				X	X
Expanded Disability Status Scale (EDSS) <sup>14</sup>	X	X	X	X	X
Modified Rankin Scale (mRS) <sup>15</sup>				X	
Patient Education Card and NMO Symptom Evaluation <sup>15</sup>	X	X	X	X	X
Neurologic Examination <sup>14, 15</sup>	X	X	X	X	X
Optic Spinal Impairment Score (OSIS) <sup>15</sup>	X	X	X	X	X
Snellen chart <sup>15</sup>	X	X	X	X	X
Hauser Ambulation Index (HAI) <sup>15</sup>	X	X	X	X	X
Medically indicated tests <sup>16</sup>	X	X	X	X	X
Review Inclusion / Exclusion criteria <sup>15</sup>					
Randomization <sup>17</sup>					
<i>N. meningitidis</i> vaccination <sup>18</sup>					
Patient Safety Identification Card <sup>18</sup>	X	X	X	X	X
Investigational Product (IP) Infusion <sup>19</sup>	Continue every 1-2 weeks (± 2 days) as scheduled				

**Table 12: Schedule of Assessments – Safety Follow-Up Period (Post-Treatment)**

Assessment	Follow-Up Visit
<b>Trial Week</b>	<b>+8 W</b>
Informed Consent <sup>2</sup>	
Medical History and Demography	
NMO History <sup>3</sup>	
Physical Examination <sup>4</sup>	
Weight and Height	
Vital Signs <sup>5</sup>	<b>X</b>
Electrocardiogram (ECG) <sup>6</sup>	
Concomitant Medication <sup>7</sup>	<b>X</b>
Adverse Events (AEs) <sup>8</sup>	<b>X</b>
Clinical Laboratory Tests <sup>9</sup>	
Pregnancy test (serum) <sup>10</sup>	
NMO-IgG (serum) <sup>11</sup>	
NMO-IgG (CSF) <sup>12</sup>	
PK/PD/Free C5 (serum) <sup>11</sup>	
PK/Free C5 (CSF) <sup>12</sup>	
EuroQol (EQ-5D) <sup>13</sup>	
Short Form Health Survey (SF-36) <sup>13</sup>	
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>15</sup>	<b>X</b>
Expanded Disability Status Scale (EDSS) <sup>14</sup>	
Modified Rankin Scale (mRS) <sup>15</sup>	
Patient Education Card and NMO Symptom Evaluation <sup>15</sup>	<b>X</b>
Neurologic Examination <sup>14, 15</sup>	
Optic Spinal Impairment Score (OSIS) <sup>15</sup>	
Snellen chart <sup>15</sup>	
Hauser Ambulation Index (HAI) <sup>15</sup>	
Medically indicated tests <sup>16</sup>	
Review Inclusion / Exclusion criteria <sup>15</sup>	
Randomization <sup>17</sup>	
<i>N. meningitidis</i> vaccination <sup>18</sup>	
Patient Safety Identification Card <sup>18</sup>	<b>X</b>
Investigational Product (IP) Infusion <sup>19</sup>	

**Table 13: Schedule of Assessments – Footnotes**

Footnote	Description
1.	All screening procedures must be completed within 1-6 weeks prior to the randomization at Baseline (Visit 2 [Day 1]). Patients who experience a relapse during the Screening Period will be considered a screening failure. Such patients may be rescreened for enrollment into the trial. See Sections 7.1 and 7.6.1 for additional information.
2.	The patient’s signed and dated informed consent form (ICF) must be obtained before conducting any trial procedures. The trial duration for an individual patient in this time-to-event trial will vary, i.e., the trial duration for an individual patient will be determined by the time of relapse or, for those patients who do not have a relapse, by the time of trial closure.
3.	The Treating Physician will review the patient’s history and diagnosis and document the following at the Screening Visit: NMO or NMOSD diagnosis date (Wingerchuk et.al., 2006 and 2007; refer to Appendix 1 and Appendix 2); and the number of relapses (onset dates) and the clinical presentation of each relapse (e.g., ON, TM, LETM, brainstem or other). See Sections 7.1 and 7.6.1 for additional information.
4.	Additional Physical Examinations can be performed as medically indicated during the trial at the Investigator’s discretion.
5.	Vital signs include assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and heart rate (HR). Vital signs 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.
6.	ECG will be performed at the protocol specified time points. In addition, ECG may be performed if the Investigator feels it is clinically warranted.
7.	Concomitant medications will be recorded at the Screening Visit as described in Section 7.1. Use of concomitant medication will be evaluated during the trial and all new medications or changes to concomitant medications will be recorded.
8.	AEs will be evaluated by the Investigator and recorded at every visit in accordance with the trial protocol as described in Section 12.2.
9.	Clinical laboratory tests (chemistry, hematology and urinalysis) will be performed by a central laboratory. Refer to Appendix 8 for a summary of the clinical laboratory tests to be measured.
10.	Pregnancy test must be performed on all women of childbearing potential at specified time points. Pregnancy test (urine or serum) may also be performed at any time during the trial at the Investigator’s discretion. Patients must practice an effective, reliable and medically approved contraceptive regimen during the trial and for up to 5 months following discontinuation of treatment. If a patient or a patient’s partner becomes or is found pregnant while in the trial, the Sponsor will be notified in accordance with the trial protocol.
11.	Serum samples for NMO-IgG and trough PK/PD/Free C5/HAHA are to be taken approximately 5-90 minutes before the IP infusion. Peak serum samples for PK, PD and free C5 are to be taken at least 60 minutes after completion of the IP infusion.
12.	Cerebrospinal fluid (CSF) samples for NMO-IgG and PK /Free C5 analyses may be collected from consented patients. Patients may choose not to have CSF samples collected and will still be eligible for trial participation.
13.	The QOL self- assessments (EQ-5D and SF-36) will be performed by the patients before any other trial procedures at all trial visits.
14.	The blinded EDSS Rater will perform the Kurtzke neurological assessment and document the FSS and EDSS score. See Section 7.4.6 for more detail.
15.	The Treating Physician will be responsible for overall patient management including patient eligibility evaluation, the supervision of the blinded IP administration, the recording and treating of AEs and the monitoring of safety assessments. The Treating Physician will determine if a patient experiences an On-Trial Relapse and treat the patient’s relapse as needed (see recommended On-Trial Relapse Treatment regimen in Section 9.2.1.3). The Treating Physician will assess the patient for any signs or symptoms indicative of relapse at every visit, perform a complete neurologic examination at the specified time points during the trial, and document the OSIS. The Treating Physician or appropriately trained designee will perform the mRS, the visual acuity (VA) test (Snellen chart), the HAI and the C-SSRS.
16.	If medically indicated for evaluation of relapse, additional tests (e.g., 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 eCRF.
17.	Both the Principal Investigator and the Sponsor must approve patient eligibility prior to randomization. Randomization will be done by using an interactive voice or web-response system (IXRS) on Day 1.

Footnote	Description
18.	All patients must be vaccinated against <i>N. meningitidis</i> (if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer). Patients must be vaccinated at least 14 days prior to receiving the first IP dose or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination. The <i>N. meningitidis</i> vaccination and any antibiotics must be recorded in the eCRF. Patients will be given a Patient Safety Identification Card prior to the first dose of IP. At each visit throughout the trial, trial staff will ensure that the patient has the Patient Safety Identification Card.
19.	<p>During the Study Period, IP (eculizumab [600 mg, 900 mg or 1200 mg] or matching placebo) will be administered IV over approximately 35 minutes according to the following regimen:</p> <p><b>Induction Phase</b> 3 vials of IP (equivalent to 900 mg of eculizumab) weekly x 4 (every 7 days ±2 days) followed by 4 vials of IP (equivalent to 1200 mg of eculizumab) one week later for the fifth dose (Visit 6).</p> <p><b>Maintenance Phase</b> 4 vials of IP (equivalent to 1200 mg of eculizumab) every two weeks (14 days ±2 days)</p> <p><b>*Supplemental Doses</b> If patient undergoes PE for On-Trial Relapse on a day that IP administration is not routinely scheduled during the Study Period, a supplemental dose (2 vials IP; equivalent to 600 mg of eculizumab) must be administered after each PE, preferably within 1-2 hours. Patients will continue in accordance with the protocol specified IP administration schedule (i.e., if PE is administered on the day of regularly scheduled IP administration, patients will receive the regularly scheduled number of vials [3 vials on Visits 2-5, 4 vials on all other Visits] after each PE, preferably within 1-2 hours).</p>
20.	Patient should be evaluated within 24-48 hours of notification of the Investigator of a potential relapse, and no later than 48 hours. All potential relapses must be evaluated by both the Treating Physician and the blinded EDSS Rater. Follow-Up Relapse Evaluation Visits will be performed at 1, 4 and 6 weeks after the onset of relapse. Additional Relapse Evaluation Visits (Unscheduled Visits) are permitted at the discretion of the Treating Physician. Tests, procedures and assessments listed under the Unscheduled Visits are to be performed at the discretion of the Investigator. All investigations/tests related to the relapse evaluation (e.g., 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.
Abbreviations	B = Baseline sample; CSF = Cerebrospinal Fluid; EOS = End of Study; ET = Early Termination; HAHA = Human anti-human antibody; T = Trough sample; P = Peak sample; V = Visit; W = Week

## **7.6. Trial Visit Procedures**

### **7.6.1. Screening Period (Screening Visit [Visit 1]) Occurs 1-6 weeks Prior to Baseline (Visit 2 [Day 1])**

After obtaining written informed consent, the following tests and evaluations will be performed within 1-6 weeks prior to randomization at Baseline /Visit 2 (Day 1) to determine patient eligibility for participation in this trial:

- Upon ICF signature, register the patient in the interactive voice or web response (IXRS) system to get the patient identification number in the study and trigger IP shipment
- Medical History and Demography
- NMO History
- NMO-IgG test history (if any), including information on type of test and the laboratory where the test was performed
- The EDSS Rater will perform the Kurtzke neurological assessment to determine the FSS and EDSS score
- The Treating Physician will perform the following:
  - Review the signs and symptoms of potential NMO relapse with the patient and instruct the patient to contact the study site at the first signs or symptoms of potential relapse. Provide the Patient Education Card describing the potential signs and symptoms of NMO relapse and the contact information of the study site
  - A complete neurologic examination
- The Treating Physician or appropriately trained designee will perform the following:
  - VA test (Snellen chart)
  - HAI
  - Complete Physical Examination including 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
  - Body weight and height
  - Vital signs include assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and heart rate (HR)
  - ECG
  - Concomitant medications will be recorded at the Screening Visit including any known IST(s) and/or non-drug therapy for the purpose of relapse prevention or treatment prior to screening and all other concomitant medications within 30 days prior to the Screening Visit. If PE was administered within 2 years prior to screening visit, the number of PE cycles for each relapse will also be collected

- Clinical laboratory tests (chemistry, hematology and urinalysis)
- Pregnancy test (serum) must be performed on all women of childbearing potential. Note: if the patient is taking/using contraceptive medication/device, please be sure to record the medication or device in the eCRF (concomitant medication or procedure)
- Blood sample for NMO-IgG will be obtained
- All patients must be vaccinated against *N. meningitidis* (if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer). Patients must be vaccinated at least 14 days prior to receiving the first IP dose or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination

## **7.6.2. Study Period**

### **7.6.2.1. Visit Schedule and Frequency**

Visit intervals during Induction Phase (Visits 2, 3, 4, 5 and 6) are weekly (every  $7 \pm 2$  days ). Visit intervals during the Maintenance Phase (Visits 7 – EOS/ET) are every two weeks (every 14 days  $\pm 2$  days).

### **7.6.2.2. Missed Visits**

Patients who fail to return for a scheduled visit must be contacted by the site study staff to determine the reason for missing the appointment, and this information must be recorded in the source documents. 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, if possible, the Treating Physician or designee will contact the local neurologist or physician to obtain as much information as possible about the patient's medical and neurological condition, and provide clinical guidance, if needed. 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 in the AE form as appropriate.

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

If the recommended acceptable visit windows cannot be observed, or if the patient misses an IP dose, the Investigator will discuss the patient's status and future treatment plan with the Sponsor.

### 7.6.2.3. Induction Phase (Baseline [Visit 2/Day 1] Through Visit 6 [Week 4])

#### 7.6.2.3.1. Baseline (Visit 2/Day 1)

Once all of the Baseline visit procedures have been performed and the eligibility criteria have been confirmed by the Treating Physician and by the Sponsor, the patient will be randomized on Day 1. Randomization will be done by using an interactive voice or web response system (IXRS; please refer to the IXRS Quick Reference document for randomization procedures). The following tests and procedures will be completed at the Baseline visit (Visit 2/Day 1):

- The patient will complete the self-assessment questionnaires to evaluate quality of life (EQ-5D and SF-36)
- The EDSS Rater will perform the Kurtzke neurological assessment to determine the FSS and EDSS
- The Treating Physician will perform the following assessments:
  - Review and assess the patient for 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
  - Document the OSIS
- The Treating Physician or appropriately trained designee will perform the following:
  - mRS
  - VA test (Snellen chart)
  - HAI
  - C-SSRS Screening / Baseline
  - Vital signs including assessments of systolic and diastolic BP, temperature, RR and HR
  - Any new medications or changes to concomitant medications will be recorded
  - AEs will be evaluated and recorded
  - Clinical laboratory tests (chemistry, hematology and urinalysis)
  - Pregnancy test (serum) must be performed on all women of childbearing potential
  - Collect blood samples for NMO-IgG
  - Collect baseline blood samples for PK, PD, free C5 and HAHA assays before the IP infusion
- For those patients who have consented, perform lumbar puncture to collect baseline CSF samples for NMO-IgG, PK and free C5 assays before the IP infusion
- 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

- Randomize the patient using IXRS. Reminder: EDSS Day 1 score is used for randomization stratification.
- IP (3 vials) 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

#### **7.6.2.3.2. Visits 3-5 (Weeks 1-3)**

The following tests and procedures will be completed:

- The Treating Physician or appropriately trained designee 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
- Vital signs including 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
- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information
- Obtain IP kit assignment through IXRS
- IP (3 vials) will be administered and patients will be observed for at least 1 hour following the end of the IP infusion

#### **7.6.2.3.3. Visit 6 (Week 4)**

The following tests and procedures will be completed at this visit:

- Questionnaires to evaluate quality of life (EQ-5D and SF-36)
- The EDSS Rater will the Kurtzke neurological 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 Investigator at the first signs or symptoms of potential relapse
  - A complete neurologic examination
- The Treating Physician or appropriately trained designee will perform the following:
  - mRS
  - VA test (Snellen chart)

- HAI
- C-SSRS Since Last Visit
- Vital signs 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
- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information
- Clinical laboratory tests (chemistry, hematology and urinalysis)
- Pregnancy test must be performed on all women of childbearing potential
- Collect blood samples for NMO-IgG
- Collect trough blood samples for PK, PD, free C5 and HAHA assays before the IP infusion
- Obtain IP kit assignment through IXRS
- IP (4 vials) 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

**7.6.2.4. Maintenance Phase (Visit 7 [Week 6] Through End of Study Visit or Early Termination Visit)**

Patients will return for IP infusions every two weeks ( $14 \pm 2$  days; short visits) during the Maintenance Phase. The following tests and procedures will be completed at every visit beginning at Visit 7 (Week 6) and continuing until the EOS or ET:

- The Treating Physician or appropriately trained designee 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.
- Vital signs 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
- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information
- Obtain IP kit assignment through IXRS

- IP (4 vials) 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 be completed at long visits, i.e, Visit 8 (Week 8), Visit 10 (Week 12), and every 12<sup>th</sup>-week thereafter, i.e., Visit 16 (Week 24), Visit 22 (Week 36), Visit 28 (Week 48), Visit 34 (Week 60), Visit 40 (Week 72), Visit 46 (Week 84), Visit 52 (Week 96), etc. through the EOS or ET Visit:

- The patient will complete the self-assessment questionnaires to evaluate their quality of life (EQ-5D and SF-36)
- The EDSS Rater will perform the Kurtzke neurological 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 Investigator at the first signs or symptoms of potential relapse
  - A complete neurologic examination
- The Treating Physician or appropriately trained designee will perform the following:
  - mRS
  - VA test (Snellen chart)
  - HAI
  - C-SSRS Since Last Visit
  - Body weight will be measured at Visits 30 and 52 or EOS/ET Visit
  - ECG will be performed at Visits 30 and 52 or EOS/ET Visit
  - Complete Physical Examination including 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 at Visit 52 or EOS/ET Visit
  - Clinical laboratory tests (chemistry, hematology and urinalysis)
  - Pregnancy test must be performed on all women of childbearing potential
  - 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. Note: HAHA will not be collected at Visit 8
  - For those patients who have consented, perform lumbar puncture to collect CSF for NMO-IgG, PK and free C5 assays before IP infusion at Visits 2, 10, 16, 28, 40, 52, and every 24<sup>th</sup>-week visit thereafter through the EOS or ET Visit
  - Collect peak blood samples for PK, PD, and free C5 assays at least 60 minutes after completing the IP infusion

Patients will be required to re-consent to continue in the trial on the same treatment assignment.

### 7.6.3. 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 EDSS Rater.

Follow-Up Relapse Evaluation Visits will be performed at 1, 4 and 6 weeks after the onset of the On-Trial Relapse. Additional (unscheduled) Relapse Evaluation Visits are permitted at the discretion of the Investigator.

#### 7.6.3.1. Relapse Evaluation Visit (Within 24-48 Hours)

The following tests and procedures will be performed at the Relapse Evaluation Visit:

- The EDSS Rater will perform the Kurtzke neurological 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
- The Treating Physician or appropriately trained designee will perform the following:
  - VA test (Snellen chart)
  - HAI
  - Vital signs 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
- If medically indicated for evaluation of relapse, additional tests (e.g., 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 on the eCRFs
- 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 (Section 7.6.3.1)

- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information
- After all specified relapse evaluation procedures are complete, the Treating Physician may initiate the recommended treatment regimen for confirmed On-Trial Relapse outlined in this protocol (Section 9.2.1.3) and any changes in the supportive IST(s) for relapse prevention, as needed.
- IP administration:
  - Patients will continue IP administration in accordance with protocol specified IP administration schedule, i.e., every week (7days  $\pm$  2 days) during Induction Phase and every two weeks (14 days  $\pm$  2 days) during Maintenance Phase
  - Extra dose (supplemental dose) must be administered if patients undergo PE. A supplemental dose (2 vials IP) must be administered after each PE session, preferably within 1-2 hours. If PE is administered on the day of regularly scheduled IP administration visit, patients will receive the regular scheduled number of vials (3 vials on Visits 2-5, 4 vials on all other Visits) after each PE session, preferably after 1-2 hours.
  - If IP will be administered at this visit, obtain IP kit assignment through the IXRS
- PK, PD sampling:
  - Collect one blood sample for PK, PD and free C5 (if no IP administration at the Relapse Evaluation Visit)
  - If IP is administered at the Relapse Evaluation Visit according to the regular IP administration schedule, two blood samples, trough and peak, for PK, PD and free C5 will be collected at: [1] approximately 5-90 minutes before the IP infusion and [2] peak sample at least 60 minutes after the completion of the IP infusion
  - If the patient receives PE and IP infusion at the Relapse Evaluation Visit, three blood samples for PK, PD and free C5 collection should occur: [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

#### **7.6.3.2. Follow-Up Relapse Evaluation Visits (Weeks 1, 4 and 6)**

Follow-Up Relapse Evaluation Visits will be performed at 1, 4 and 6 weeks after the onset of the On-Trial Relapse. Patients must be discontinued from this trial and may enter the extension trial (separate protocol ECU-NMO-302) after completion of the Week 6 Follow-Up Relapse Evaluation Visit. Week 6 Follow-Up Relapse Evaluation Visit will serve as the EOS Visit, all procedures listed under the EOS Visit will be performed. Patients may enter the extension trial (separate protocol ECU-NMO-302) once the Week 6 Follow-Up Relapse Evaluation Visit has been completed and no later than 2 weeks ( $\pm$  2 days) after the last IP administration. This is to ensure no interruption in IP dosing.

The following tests and procedures will be completed at these Relapse Evaluation Period visits:

- The EDSS Rater will perform the Kurtzke neurological assessment to determine the FSS and EDSS Score

- The Treating Physician will perform the following:
  - A complete neurologic examination
  - OSIS
  - Ensure the patient has the Patient Education Card
- The Treating Physician or appropriately trained designee will perform the following:
  - VA test (Snellen chart)
  - HAI
  - mRS – Week 6 only
  - C-SSRS Since Last Visit – Week 6 only
  - Vital signs 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
  - Patient self-assessments questionnaires to evaluate quality of life (EQ-5D and SF-36) – Week 6 only
  - Complete Physical Examination including 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 – Week 6 only
  - Body weight – Week 6 only
  - ECG – Week 6 only
  - Clinical laboratory tests (chemistry, hematology and urinalysis) – Week 6 only
  - Collect blood sample for HAHA analysis – Week 6 only
  - Pregnancy test must be performed on all women of childbearing potential – Week 6 only
  - Collect blood samples for NMO-IgG – Week 6 only
  - For those patients who have consented, perform lumbar puncture to collect CSF for NMO-IgG, PK and free C5 assays – Week 6 only
- If medically indicated for evaluation of relapse, additional tests (e.g., MRI, CT scan, laboratory tests, etc.) may be performed at the discretion of the Investigator. All test results should be recorded in the source documents and in the eCRF, and copies of reports should be sent to the Sponsor.
- Ensure that the patient has the Patient Safety Identification Card describing the IP and emergency contact information.
- IP administration during the relapse evaluation period:

- Patients will continue IP administration in accordance with protocol specified IP administration schedule, i.e., every week (7days  $\pm$  2 days) during Induction Phase and every two weeks (14 days  $\pm$  2 days) during Maintenance Phase
- Extra doses (supplemental doses) must be administered if patients undergo PE. A supplemental dose (2 vials IP) must be administered after each PE session, preferably within 1-2 hours. If PE is administered on day of regular scheduled IP administration per protocol schedule, patients will receive the regular scheduled number of vials IP (3 vials on Visits 2 - 5, 4 vials on all other Visits) each PE session, preferably within 1-2 hours
- If IP will be administered at this visit, obtain IP kit assignment through IXRS
- PK, PD sampling during relapse evaluation follow-up period:
  - Collect one blood sample for PK, PD and free C5 (if no IP administration at the Follow-Up Relapse Evaluation Visits)
  - If IP is administered at any Follow-Up Relapse Evaluation Visit according to the regular IP administration schedule, two blood samples, trough and peak, for PK, PD and free C5 will be collected at: [1] approximately 5-90 minutes before the IP infusion and [2] at least 60 minutes after the completion of the IP infusion
  - If the patient receives PE and IP infusion at any Follow-Up Relapse Evaluation Visit, three blood samples for PK, PD and free C5 will be collected at: [1] 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.

#### **7.6.3.3. Unscheduled Follow-Up Relapse Evaluation Visits**

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 will be performed at the discretion of the Investigator. Any tests, procedures or assessments performed at the unscheduled visit must be recorded in the eCRFs.

#### **7.6.3.4. Adjudication of On-Trial Relapses**

Following the occurrence of an On-Trial Relapse (as determined by the Investigator), relevant clinical information will be provided to the Adjudication Committee for independent review (Section 7.4.7) as outlined in the Adjudication Committee Charter.

#### **7.6.4. Safety Follow-up Period (Post-Treatment)**

If a patient withdraws from the trial at any time during the Study Period after receiving any amount of IP, or if the patient does not wish to enter the extension trial after completion of the ET or EOS Visit, a follow-up visit for safety assessments is required at 8 weeks after the last dose of IP. The following tests and procedures will be completed at the Safety Follow-Up Visit:

- Vital signs 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 Since Last Visit
- The Treating Physician or appropriately trained designee will assess the patient for any signs or symptoms indicative of relapse
- Ensure the patient has the Patient Education Card and 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 PI, is determined medically stable.

### **7.7. Number of Patients**

A maximum of 132 NMO patients will be randomized in a 2:1 (eculizumab: placebo) ratio at approximately 120 – 150 centers. Patients will be randomized to 1 of 2 treatment groups in a 2:1 ratio (eculizumab or placebo). Randomization will be across centers and will be stratified by two variables: 1) EDSS score at randomization (Day 1); and 2) patients' prior supportive IST (i.e., for relapse prevention) and IST status at randomization (Day 1). All patients will remain on assigned double-blind treatment and background treatment regimen until EOS/ET visit.

### **7.8. Treatment Assignment**

If all 132 patients are enrolled, approximately 88 patients will be randomized to eculizumab and 44 patients will be randomized to placebo. Randomized patients who discontinue after initiation of study treatment will not be replaced. All patients will remain on their assigned double-blind treatment until EOS/ET Visit. IP assignment will be performed through the IXRS at each visit.

### **7.9. Criteria for Trial Termination**

#### **7.9.1. End of Trial for an Individual Patient**

The trial will be ended for a patient when one of the following conditions is met, whichever comes first:

- a. The patient experiences an On-Trial Relapse; or
- b. The trial ends when 24 adjudicated On-Trial Relapse events (in 24 distinct patients) have occurred.

#### **7.9.2. End of Trial for All Patients**

The trial will end when 24 adjudicated On-Trial Relapse events (in 24 distinct patients) are reached. The end of trial is defined as completion of the EOS/ET Visit by all patients. The EOS/ET Visit is to be completed as soon as possible, preferably within 1 month of the end of the trial notification, with the exception of patients who experience an On-Trial Relapse who will continue until completion of the Relapse Evaluation Period. Following the EOS Visit, patients

may enroll in the extension trial (ECU-NMO-302). Patients who do not enroll in the extension trial will enter the 8-week Safety Follow-Up Period.

## **8. SELECTION AND WITHDRAWAL OF PATIENTS**

### **8.1. Patient Inclusion Criteria**

1. Male or female patients  $\geq 18$  years old.
2. Diagnosis of NMO as defined by 2006 Criteria by Wingerchuk et al, ([Appendix 1](#)), or NMOSD as defined by 2007 Criteria by Wingerchuk et al ([Appendix 2](#)).
3. NMO-IgG seropositive.
4. Historical Relapse (as defined by this protocol) of at least 2 relapses in last 12 months or 3 relapses in the last 24 months with at least 1 relapse in the 12 months prior to screening.
5. EDSS score  $\leq 7$ .
6. If a patient enters the trial receiving IST(s) for relapse prevention, the patient must be on a stable maintenance dose of IST(s), as defined by the Treating Physician, prior to screening and must remain on that dose for the duration of the study, unless the patient experiences a relapse.
7. Patients must give written informed consent.
8. Patients must be willing and able to comply with the protocol requirements for the duration of the trial.
9. Female patients of child-bearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]). 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. Use of rituximab 3 months prior to screening.
2. Use of mitoxantrone 3 months prior to screening.
3. Use of IVIg within 3 weeks prior to screening.
4. If a patient enters the trial receiving oral corticosteroid(s) with or without other IST(s), the daily corticosteroid dose must be no more than prednisone 20 mg/day (or equivalent) prior to the screening, and must remain on that dose for the duration of the study or until the patient experiences a relapse.
5. Pregnant, breastfeeding, or intending to conceive during the course of the trial.
6. Unresolved meningococcal disease.
7. Any systemic bacterial or other infection which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics.
8. Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days of screening.
9. Has previously received treatment with eculizumab.
10. Hypersensitivity to murine proteins or to one of the excipients of eculizumab.

11. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the trial, poses any added risk for the patient, or confounds 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. Every effort should be made to ensure patients are willing to comply with trial participation prior to conducting the screening procedures and the patients should be fully informed of the restrictions related to the change of concomitant medications during the trial. Investigators may choose to discontinue a patient's treatment because of AEs, as well as conditions or illnesses that preclude compliance with the protocol from the standpoint of the patient's safety or well-being. The study 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. Whenever possible, all patients who prematurely withdraw from the trial will undergo all assessments at the ET visit as per the Schedule of Assessments.

A follow-up visit for safety assessment is required at 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 study staff to be reminded of the necessary follow-up. 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

Eculizumab (600 mg, 900 mg or 1200 mg) or matching placebo will be administered IV over approximately 35 minutes according to the regimen in [Table 14](#):

**Table 14: Investigational Product Dosage and Administration**

Dose Period	Frequency of Investigational Product (IP) Administration	Visit #	# of Vials	Equivalent Eculizumab Dose
Induction Phase	Weekly (every 7 ± 2 days)	2-5	3	900 mg
		6	4	1200 mg
Maintenance Phase	Every 2 weeks (14 ± 2 days) from the fifth dose onward	7 – EOS/ET	4	1200 mg
Supplement Doses*	If PE is given for On-Trial Relapse, administer after each PE as described below*.		2	600 mg

#### **Induction Phase**

3 vials of IP (equivalent to 900 mg of eculizumab) weekly x 4 (every 7 days ±2 days, Visits 2-5 [Day 1 – Week 3]) followed by 4 vials of IP (equivalent to 1200 mg of eculizumab) one week later (7 days ±2 days) for the 5th dose (Visit 6 [Week 4]).

#### **Maintenance Phase**

4 vials of IP (equivalent to 1200 mg of eculizumab) every two weeks (14 days ±2 days)

#### **\*Supplemental Doses**

If the patient undergoes PE for On-Trial Relapse on a day that IP administration is not routinely scheduled during the Study Period, a supplemental dose (2 vials IP; equivalent to 600 mg of eculizumab) must be administered after each PE, preferably within 1-2 hours. If PE is administered on a day of regularly scheduled IP administration, patients must receive the regularly scheduled number of vials (3 vials on Visits 2 - 5; 4 vials on all other Visits) after each PE, preferably within 1-2 hours. In addition patients are to continue protocol-specified dosing until EOS.

## 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 Therapy Agents

- The choice of IST agents is at the discretion of the Treating Physician with the exception of the disallowed medications. Standard recommended dosing should be used for the chosen IST. Use of corticosteroids is permitted, however to assure balance between treatment groups with respect to steroid dosing, the total daily dose should not exceed prednisone 20 mg per day or equivalent.
- Immunosuppressive agents, such as corticosteroid, AZA, MMF, methotrexate, tacrolimus, cyclosporine or cyclophosphamide either in combination or mono-therapy are permitted.
- If a patient enters the trial receiving supportive IST(s), the patient must have been on a stable maintenance dose of IST(s), as defined by their Treating Physician, prior to the Screening Visit and must remain on that dose for the duration of the study. No new IST(s) or switch to another IST is permitted during the trial unless the patient experiences a relapse. After a relapse there are no restrictions on IST adjustments or changes.
- If a patient enters the trial receiving steroids either as mono-therapy or in combination with another IST, the daily steroid dose cannot be more than prednisone 20 mg daily (or equivalent). The patient must remain on that dose for the duration of the trial unless the patient experiences a relapse.
- The IST(s) and its dosing regimen for a particular patient must remain stable during the trial. If changes in the dose or dosing regimen are considered, due to a known toxicity or side effects associated with the given immunosuppressive agent, the Sponsor should be notified of the change.

### 9.2.1.3. Recommended Standardized Relapse Treatment

For this protocol, the treatment for 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 published Expert Opinion (31).

1. One gram IV 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 the schedule of this protocol.
2. If there is no or minimal response to methylprednisolone, PE will be allowed at the discretion of the Treating Physician. Five cycles of PE that each removes 1.0-1.5 volumes of circulating plasma is 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, 2 vials (equivalent to 600 mg of eculizumab) should be administered after each PE, preferably within 1-2 hours. If PE is administered on a day of regularly scheduled IP administration, patients will receive the regularly scheduled number of vials (3 vials at Visits 2-5, 4 vials at all other Visits) after each PE, preferably within 1-2 hours. In addition patients are to continue protocol-specified dosing until EOS.

### **9.2.2. Disallowed Medications**

The following medications are prohibited during the trial:

- Concomitant use of rituximab with eculizumab is contraindicated
- Mitoxantrone
- Immunomodulatory therapies including: interferon beta-1b; interferon beta-1a and glatiramer acetate
- Other biologic agents such as tocilizumab
- IVIg for relapse prevention
- PE for relapse prevention

### **9.3. Treatment Compliance**

Patients will be infused IV 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.

### **9.4. Randomization and Blinding**

#### **9.4.1. Randomization**

Patients will be randomized on Day 1 after the PI or Sub-Investigator and the Sponsor have verified that they are eligible. A randomization worksheet will be provided and the Sponsor's approval is required to ensure that patients are randomized properly. Patients will be randomized on a 2:1 basis to the Eculizumab Arm or the Placebo Arm. The randomization and stratification will be across centers. The randomization stratification will include two variables: 1) EDSS score at randomization (Day 1); and 2) patients' prior supportive (i.e., for relapse prevention) IST and IST status at the time of randomization (Day 1) (see Standard Protocol Definition, Section 7.4).

1. EDSS score at randomization (Day 1)
  - a. EDSS scores are  $\leq 2.0$
  - b. EDSS scores are  $\geq 2.5$  to  $\leq 7$
2. Patients' IST status at randomization (Day 1)
  - a. Treatment naïve patients (i.e., patients with no prior or current ISTs, except steroids alone)
  - b. Patients continuing on the same supportive IST(s) for relapse prevention since the last relapse (i.e., including patients with dose adjustment with the same IST(s) since the last relapse)
  - c. Patients with changes in IST(s) since last relapse (i.e., switched IST(s) [e.g., AZA to MMF], added IST [e.g., corticosteroid], or withdrew any IST treatment)

Patients will be centrally randomized using IXRS. All patients will be assigned to double-blind treatment by the secure IXRS randomization application.

#### **9.4.2. Blinding and Unblinding**

All trial patients, study site personnel, Sponsor staff, Sponsor designees and all staff directly associated with the conduct of the trial will be blinded to the patient treatment assignments. The doubleblind will be maintained by using identical IP kits and labels for eculizumab and placebo. The placebo will have an identical appearance to that of eculizumab. The randomization code will be maintained by IXRS.

There is no antidote to reverse the effects of eculizumab. Therefore unblinding would not be helpful in the planning of patient treatment for a given event. Unblinding should only be considered for the safety of the subject. If unblinding is deemed necessary by the Investigator, the Investigator can unblind the patient's treatment allocation using the IXRS. The Investigator must note the date, time and reason for unblinding. The Investigator should inform the Sponsor that the patient was unblinded, however they are not required to reveal to the Sponsor the patients' treatment allocation.

When an AE is an unexpected related serious AE, the blind will be broken by the Sponsor only for that specific subject. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigators, etc.) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Ethics Committees/Institutional Review Boards (IRBs) and Data Monitoring Committee (DMC) or persons performing ongoing safety evaluations during the trial.

Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

## **10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT**

### **10.1. Investigational Product**

Each vial of investigational product (IP) contains eculizumab 300 mg or matching placebo for IV administration.

### **10.2. Investigational Product Packaging and Labeling**

The active IP, eculizumab, is manufactured and supplied by Alexion Pharmaceuticals, Inc. or selected contracted manufacturing organizations in single 30 mL vials as a solution concentration of 10 mg/mL. The comparator product is manufactured by Alexion Pharmaceuticals, Inc. or selected contracted manufacturing organizations 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.

**Table 15: Investigational Product**

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

### 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. Each IP kit will have a booklet label describing the contents and a place for the pharmacist to record the patient number, patient initials and Investigator name.

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 16](#).

**Table 16: Investigational Product Preparation and Reconstitution**

	Volume of IP	Volume of Diluent <sup>a</sup>	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

<sup>a</sup> 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 includes preparation time, storage time at room temperature and under refrigeration, and warming time.

### 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 study 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 system to allow IP assignment, 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. Refer to the Pharmacy Manual for detailed instructions on general receipt, storage, preparation, administration, destruction and return of IP.

Each kit will have a label and a place for the pharmacist to record the patient number and initials. The CRA will examine the inventory during the study. 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**

### **11.1. Efficacy Parameters**

Duration of treatment commences with the first IP infusion. The Study Period i.e., double-blind treatment period, defines the time period for assessment of the trial endpoints. A total of 24 adjudicated On-Trial Relapse events in 24 distinct patients are to be observed. The trial will continue until the time that the 24th adjudicated event has been observed during the Study Period. At the point when the trial is stopped, all data from all patients will be collected, database cleaned, locked, and analyzed. Data from the Study Period will be used for efficacy analysis.

#### **11.1.1. Relapses**

Accurate identification and evaluation of On-Trial Relapses is critical for the integrity of this study. The primary efficacy endpoint is time-to-first adjudicated On-Trial Relapse; the secondary efficacy endpoints include analysis of the adjudicated ARR.

Pre-treatment historical relapses will be reviewed by the Investigator to determine if they meet criteria for Historical Relapse as defined by this protocol. On-Trial Relapses will be monitored throughout the trial. Patients will be educated on the potential signs and symptoms of NMO relapse. Patients will be also given a Patient Education Card that details the signs and symptoms of a potential relapse and instructions to contact the study site at the first sign or symptoms of a potential 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. Patients will be instructed to contact the study site at the first sign or symptom of a relapse. Patients should be evaluated within 24 hours of notification of the Investigator or the appropriate designee of a possible attack, and no later than 48 hours.

All potential relapses must be evaluated by both the Treating Physician and EDSS Rater. The Treating Physician will make the decision as to whether the clinical signs, symptoms and neurological change (objective findings on exam) meet the protocol definition of On-Trial Relapse (based on On-Trial Relapse Definition, 7.4.2) and may treat the patient's relapse according to the recommended Standardized 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 (e.g. 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 made according at the Treating Physician's discretion (see Section 7.2.1). All reports of possible relapses and actions taken must be documented in the patient's source documents and recorded in the eCRF.

Relapses that do not meet the criteria for SAE (see Section 12.2.1 below) should be reported as part of the Relapse Evaluation visits, and not as AEs.

### **11.1.2. Disability**

Disability will be assessed based on the EDSS scores comparing the change from baseline at the EOS in the two treatment groups. An EDSS Rater who is blinded to all other trial and 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.

In addition, disability will also be assessed based on the mRS score comparing the change from baseline in the two treatment groups. MRS score will be assessed by The Treating Physician or a designee at the protocol specified time points.

### **11.1.3. Neurologic Functions**

Neurologic function will be assessed based on EDSS FSS. Ambulatory function will be assessed by HAI scale, and visual function will be measured by VA using the Snellen chart and the Visual FSS of the Kurtzke neurological assessment. The Visual 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 (e.g., 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 and VA 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 questionnaires EQ-5D and SF-36 at the protocol specified time points.

## **12. ASSESSMENT OF SAFETY**

### **12.1. Safety Parameters**

#### **12.1.1. Demographic/Medical History**

At Visit 1 (Screening), patients' initials, date of birth, race or ethnic origin and sex will be collected, medical history will be reviewed, and data will be recorded. Medical history including relevant medical/surgical history and NMO history will be reviewed and recorded.

#### **12.1.2. Vital Signs**

Vital signs will be measured at every visit and will include assessments of systolic and diastolic BP, temperature, RR and HR. Vital signs 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 and Height**

Body weight will be measured in pounds or kilograms. Height will be measured in inches or centimeters. Body weight will be measured at the Screening Visit, Visit 30 (Week 52), Visit 52 (Week 96) and EOS/ET Visit. Height will be measured at the Screening Visit.

#### **12.1.4. Physical Examination**

A complete physical examination will be performed at Visit 1 (Screening), Visit 52 (Week 96), and at the EOS/ET Visit. 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 (ECG)**

A 12-lead ECG will be conducted at Visits 1, 30, 52 and EOS/ET. 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 (CBC) and urinalysis, hemolytic markers, renal function measures, and serum pregnancy test (See [Appendix 1](#) 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 that may also be treated with ISTs 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 and CSF samples for PK, free C5 and blood samples for HAHA 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 the 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 will be performed by the Treating Physician or an appropriately trained designee. The Baseline/Screening C-SSRS ([Appendix 10](#)) will be performed at Baseline (Visit 2). The Since Last Visit C-SSRS ([Appendix 11](#)) will be performed at Visit 6 (Week 4), Visit 8 (Week 8), Visit 10 (Week 12), and every 12<sup>th</sup>-week visit thereafter through the EOS/ET Visit. The Since Last Visit C-SSRS also needs to be performed at the Week 6 Follow-Up Relapse Evaluation Visit and the safety Follow-Up Visit (8 weeks after the EOS/ET Visit). Additional C-SSRS assessments are permitted, as needed. This is to ensure that patients who are experiencing suicidal ideation or behavior are properly recognized and adequately managed or referred for further evaluation.

### **12.2. Adverse and Serious Adverse Events**

#### **12.2.1. Definition of Adverse Events**

##### **12.2.1.1. Adverse Event**

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline, even if no IP has been administered. AEs can be classified into non-serious AEs or SAEs.

All observed or volunteered AEs regardless of Treatment Group or 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 a 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.

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 (reference ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. Step 4 version, dated 27 October 1994).

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 study dosing outside of the protocol defined dosing or discontinuation from the trial
- Test result requires significant additional treatment

#### **12.2.1.3. Serious Adverse Event (SAE)**

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

- Is an 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; 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 for less than 24h. Criteria for seriousness are also met if transfer within the hospital is done to receive more intense medical/surgical care (e.g., from the medical floor to the Intensive Care Unit).

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 Event (OAE)**

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

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode if the severity of the intermittent event changes.

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 a 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 with absolute certainty and a relationship between the IP and the 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, i.e., the event follows a reasonable temporal sequence from the time of drug 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 Investigator'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 for all patients.

IP 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 the one for 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 the 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 the IP may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and many 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 a SAE and thus, should be reported as a SAE. Elective abortions without complications should not be handled as AEs.

#### **12.2.1.11. Withdrawal due to an Adverse Event**

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

#### **12.2.1.12. Obtaining the 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 IP dose. 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 the first dose of IP (Day 1, Visit 2) and continues through the last study visit including the safety Follow-Up Visit. AEs, particularly causally related, are to be followed until the event or sequelae resolve or are determined to be medically stable. All non-serious medical events that occur during the Screening Period or prior to first IP dose administration should be reported as Medical History (pre-existing conditions).

### **12.2.1.14. Reporting Requirements for Adverse Events**

All AEs must be assessed by the Investigator to determine if they meet criteria for a SAE. If criteria are met for a SAE the event must be reported to the Sponsor as per SAE reporting requirements in Section 12.2.1.16.

### **12.2.1.15. Reporting Requirements for Non-serious Adverse Events**

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

### **12.2.1.16. 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 presumed relationship to the IP. If the event meets criteria for a fatal or life threatening SAE, the Investigator should notify the Sponsor immediately. These reporting timelines need to be followed for all initial SAE cases and follow-up versions to the initial case.

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 [REDACTED]

Fax: PPD [REDACTED]

Additional follow-up information, if required or available, should be emailed or faxed 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

#### **12.2.1.17. 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.

#### **12.2.1.18. Investigator Reporting Requirements**

The investigator must fulfill all local regulatory obligations required for study 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.

#### **12.2.1.19. Reference Safety Document**

This protocol will use the current Investigators Brochure (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.

#### **12.2.1.20. Data Monitoring Committee**

An independent Data Monitoring Committee (DMC) will conduct interim monitoring of unblinded data as described in Section [15.4](#).

## **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 at protocol specified time points (Section 7.5) and at the On-Trial Relapse Evaluation Visit.

## **14. STATISTICAL METHOD AND PLANNED ANALYSES**

### **14.1. General considerations**

ECU-NMO-301 is a Phase 3, randomized, double-blinded, two-arm, time-to-event trial comparing eculizumab and placebo in patients with NMO. At completion of the trial, the Sponsor will analyze the trial data. Further elaboration of statistical issues is provided in the Statistical Analysis Plan (SAP).

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 complete and decisions regarding the evaluability of all patient data for inclusion in the statistical analysis for the Per-Protocol (PP) Set 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 and documented before the database is locked and 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 treatment group and 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.

### **14.2. Determination of Sample Size**

This is a randomized double-blind placebo controlled trial to evaluate eculizumab in NMO patients with a primary endpoint of time to first adjudicated On-Trial Relapse. As such, the trial is based on observing relapse events.

The sample size and power calculation assumptions for this time to first event trial are as follows:

- Log-rank test for comparison of eculizumab to placebo
- 2:1 randomization (eculizumab:placebo)
- Power 90%
- Two-sided 5% level of significance
- Drop-out rate 10%
- Accrual period of approximately 21 months
- Relapse-free rate of 80% for the eculizumab arm at 12 months

- Hazard ratio of 0.24 (-log hazard ratio = 1.41) which corresponds to a relapse-free rate of 40% for the placebo arm at 12 months

The total number of relapse events to be observed for this trial is 24 adjudicated On-Trial Relapse events in 24 distinct patients. With these assumptions, a maximum sample size of approximately 132 patients (88 eculizumab and 44 placebo) provides 90% power to detect a treatment difference in time to first relapse.

### **14.3. Analyses Sets**

#### **14.3.1. Full Analysis Set (FAS)**

The population on which primary, secondary, tertiary, and other efficacy analyses will be performed consists of all patients who are randomized to treatment and who have received at least 1 dose of IP. Patients will be compared for efficacy according to the treatment they were randomized to receive, irrespective of the treatment they actually received.

#### **14.3.2. Per-Protocol (PP) Set**

The PP Set is a subset of the FAS, excluding patients with major protocol deviations. The 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 treatment doses while they were in the double-blind Study Period (for patients who have relapses any dosing after the relapse will not be included in this calculation)

The PP population will be fully described in the statistical analysis plan, and patients identified prior to database lock.

#### **14.3.3. Safety Set**

Safety analyses will be performed on the Safety Set Population. The Safety Population includes all patients who receive at least 1 dose of IP. Patients will be compared for safety according to the treatment they actually received.

Patients who have signed informed consent but are not treated in the trial are not in the Safety Population. However, if these patients report AEs or SAEs, these events will be summarized separately in tables and listings as appropriate.

#### **14.3.4. 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.

### **14.4. Demographics and Baseline Characteristics**

All demographic and baseline characteristics information will be summarized using the following sets: Full Analysis, PP, and Safety Sets. No formal hypothesis testing will be performed. Summary statistics will be presented by treatment group and overall.

Medical history and medical history related to NMO will be summarized by treatment group. Listings related to medical history will also be produced.

#### **14.5. Subject Disposition and Treatment Compliance**

The number of patients screened, randomized, treated, completing the trial, and included in the safety and efficacy analysis sets will be tabulated by counts and percentage of patients by treatment group and overall. 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.

#### **14.6. Prior and Concomitant Medications**

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

Supportive ISTs are allowed during the trial under certain restrictions (refer to Section 9.2 Concomitant Treatment, for details). The following ISTs are allowed either as mono-therapy or in combination: corticosteroids, AZA, MMF, methotrexate, tacrolimus, cyclosporine and cyclophosphamide. Thus, supportive IST will be summarized by treatment group. 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 PE usage by patients with On-Trial Relapses will be produced.

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

Analyses will be produced for the double-blind Study Period in order to compare the eculizumab group with placebo group. The analyses will include efficacy, safety, and PK/PD analyses.

#### **14.7. Efficacy Analyses**

Analyses will be produced for the double-blind Study Period in order to compare the eculizumab group with placebo group. The analyses will include efficacy, safety, and PK/PD analyses.

Efficacy analyses will be performed on the FAS population as well as the PP population.

##### **14.7.1. Primary Efficacy Endpoint**

The primary efficacy endpoint is time to first adjudicated On-Trial Relapse. The trial will be considered to have met its primary efficacy objective if a statistically significant difference is observed between the eculizumab treatment group and the placebo group. The comparison of the treatment groups for the primary endpoint will use a log-rank test including strata for the randomization stratification variables (1) EDSS score at randomization (Day 1) ( $\leq 2$  vs.  $\geq 2.5$  to  $\leq 7$ ), and (2) patients' prior supportive (i.e., for relapse prevention) IST and IST status at the randomization (Day 1) (treatment naïve patients vs. patients continuing on the same IST(s) since last relapse vs. patients with changes in IST(s) since last relapse). Confidence intervals and p-values will be presented. Hazard ratio and risk reduction will be summarized. A sensitivity analysis will be performed on time to first On-Trial Relapse (as identified by the Investigator)

using a log-rank test including strata for the randomization stratification variables. In addition, a sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator, and randomization stratification variables as the only covariates in the model. A second sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator, randomization stratification variables, and region as the only covariates in the model. Region will be defined based on the sites for the trial and will include North America, South America, Europe, Asia-Pacific, and Other as applicable. In the event that the number of patients in some regions is too small to permit modeling, the smaller regions will be pooled together.

An additional sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator and randomization stratification variables as covariates and will also include withdrawals due to AEs as outcomes events (i.e., relapses).

An additional sensitivity of the treatment groups for the primary endpoint will use a log-rank test including strata for the randomization stratification variables for the FAS patients with a follow-up assessment (i.e., FAS patients without a follow-up assessment will be excluded from the analysis).

An additional sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator and randomization stratification variables as covariates only including the relapses assessed within 48 hours. Confirmed relapses assessed after 48 hours will be censoring events based on the patient's last date in the study.

In order to account for relapses that are not evaluated according to the protocol (i.e., within 48 hours of the onset of relapse sign and symptoms), a Cochran-Mantel-Haenszel (CMH) test will be used assessing eculizumab and placebo treatment and patient evaluated within 48 hrs (yes, no) for patients with confirmed relapses. Summaries of the severity of the confirmed relapses versus patient evaluated within 48 hours (yes, no) by treatment group will also be produced.

Kaplan-Meier curves for both treatment groups will be produced. Likewise, Kaplan-Meier curves for the strata within each treatment group will be produced.

#### **14.7.2. Secondary Efficacy Analysis**

During the Study Period, Baseline is defined as the last available assessment prior to treatment for all patients regardless of their treatment group.

Unless otherwise specified, the secondary efficacy analyses will use the available data from the Study Period. Hypothesis testing comparing eculizumab treatment with placebo treatment for the secondary efficacy analyses will be performed using a closed testing procedure with the following rank order:

1. Change from baseline in EDSS score at the EOS
2. Adjudicated annualized relapse rate
3. Change from baseline in EQ-5D at the EOS
4. Change from baseline in mRS score at the EOS
5. Change from baseline in ambulatory function as measured by HAI at EOS

The hypothesis testing will proceed from highest rank (#1) change from baseline in EDSS to the lowest rank (#5) change from baseline in HAI, and if statistical significance is not achieved at an endpoint ( $p \leq 0.05$ ), then endpoints of lower rank will not be considered to be statistically significant. Confidence intervals and p-values will be presented for all secondary efficacy endpoints for descriptive purposes, regardless of the outcome of the closed testing procedure. The EQ-5D has two endpoints, the index score and EQ-5D VAS. For the purposes of this closed testing procedure, the EQ-5D index score will be analyzed first and the EQ-5D VAS score will be analyzed second for the EQ-5D analyses.

The primary analysis for the change from baseline in EDSS score to the end of Study Period (i.e., 6 week post-relapse for the patients who have relapses or end of treatment period visit for patients who do not have relapses) will be a ranked ANCOVA with treatment group, baseline EDSS, and IST status at randomization as covariates. If a patient experiences a second relapse during the 6 week recovery phase after the initial relapse the last EDSS score prior to the second attack will be used for the analysis. If a patient has no follow-up assessments, a change from baseline of 0 (i.e., baseline value carried forward) will be used.

A sensitivity analysis for the change from baseline in EDSS score to the end of Study Period (i.e., 6 week post-relapse for the patients who have relapses or EOS for patients who do not have relapses) will be a ranked ANCOVA with treatment group, baseline EDSS, and IST status at randomization as covariates in the subset of the FAS population who do have a follow-up assessment (i.e., FAS patients without a follow-up assessment will be excluded from the analysis). If a patient experiences a second relapse during the 6 week recovery phase after the initial relapse the last EDSS score prior to the second relapse will be used for the analysis.

In addition, sensitivity analyses for the change from Baseline in EDSS will be analyzed using a mixed model for repeated measures with baseline EDSS score, IST status at randomization, treatment group indicator, trial visit and trial visit by treatment group interaction as covariates. All post-baseline EDSS scores will be included in the models; patients without any post-baseline scores will not be included. In addition, other sensitivity analyses will include imputations for missing visit assessments. Patients who discontinue the trial early without a relapse will have subsequent missing EDSS assessments imputed using the LOCF approach. Patients who discontinue the trial early with a relapse will have subsequent missing EDSS assessments imputed by using the EDSS assessment conducted 6 weeks after the first relapse. If the EDSS assessment 6 weeks after the first relapse is missing, then the last available EDSS score after the relapse at trial discontinuation for the patient will be imputed using the LOCF approach. If the patient does not have an EDSS score after the relapse then the 6 week recovery EDSS score will be imputed using the patient's last EDSS before the relapse adjusted according to the average % change in EDSS at Week 6 after a relapse observed in all other patients who did have relapses in the same treatment group.

The comparison of the two treatment groups for the secondary endpoint, adjudicated ARR, will use Poisson regression analysis. Treatment group, the stratification variables, and baseline ARR will be covariates in the model, and the log of time in the trial will be used as the offset variable. A sensitivity analysis will be performed for ARR using all On-Trial Relapses (as identified by the Investigator) in a Poisson regression analysis with treatment group, the stratification variables, and baseline ARR as covariates in the model, and the log of time in the trial will be used as the offset variable.

Changes from baseline in the HAI, EQ-5D index score, and EQ-5D VAS will be analyzed in a similar manner as changes in EDSS score. Baseline value and the stratification variables will be covariates in the modeling for these endpoints.

The primary analysis for the change from baseline in mRS score to the end of the Study Period (i.e., 6 week post-relapse for the patients who have relapses or EOS for patients who do not have relapses) will be a ranked ANCOVA with treatment group, baseline mRS, EDSS strata at randomization, and IST status at randomization as covariates. If a patient experiences a second relapse during the 6 week recovery phase after the initial relapse the last mRS score prior to the second attack will be used for the analysis. If a patient has no follow-up assessments, a change from baseline of 0 (i.e., baseline value carried forward) will be used. A sensitivity analysis for the change from baseline in mRS score to the end of the Study Period will be a ranked ANCOVA with treatment group, baseline mRS, EDSS strata at randomization, and IST status at randomization as covariates in the subset of the FAS population who do have a follow-up assessment (i.e., FAS patients without a follow-up assessment will be excluded from the analysis). An additional sensitivity comparison of the two treatment groups for the mRS score will use generalized estimating equations (GEE) methods at the end of the Study Period (i.e., 6 week post-relapse for the patients who have relapses or end of treatment period for patients who do not have relapses). PROC GENMOD in SAS will be used to fit a GEE model of the modified Rankin score at the end of the study (i.e., 6 week post-relapse for the patients who have relapses or end of treatment period visit for patients who do not have relapses). The GEE model will include covariates for treatment group, randomization stratification variables, baseline mRS score, visit, and the treatment group by visit interaction term. A multinomial distribution will be used in the model along with a cumulative logit link function and an independent working correlation matrix. If the treatment group by visit interaction term is not significant ( $p \leq 0.10$ ), it will be removed from the GEE model and the model will be refit and used as the final model in the analyses. In addition, summary statistics for the changes from baseline in the mRS score will be produced by visit and treatment group. Likewise, shift tables from baseline in the mRS score will be produced by visit and treatment groups.

### **14.7.3. Tertiary Efficacy Endpoints**

Unless otherwise specified, the tertiary efficacy analyses will use the available data from the Study Period. The tertiary efficacy endpoints include:

1. Change from baseline in ambulatory function as measured by HAI at EOS in patients with abnormal baseline ambulatory function.
2. Change from baseline in visual function as measured by VA at EOS in all patients and in patients with abnormal baseline visual function.
3. Change from baseline in the SF-36 at EOS.
4. Change from baseline in the EDSS FSS at EOS.

Changes from baseline in VA will be analyzed in a similar manner as changes in EDSS score. Baseline value and the stratification variables will be covariates in the modeling for these endpoints. Changes from baseline in the HAI and VA for patients who were abnormal at baseline will be analyzed in a similar manner to the analyses described for HAI and VA in all patients.

Change from baseline in quality of life will be summarized as appropriate to the quality of life instrument and treatment group comparisons will be performed as specified in the 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.

#### **14.7.4. Other Efficacy Endpoints**

Severity of an individual relapse as assessed by OSIS (as noted in Section 7.4.3) and recovery will be assessed by changes in EDSS score.

### **14.8. Safety Analyses:**

Safety analyses will be performed on the Safety Population. The Safety Population includes all patients who receive at least 1 dose of IP. Patients will be compared for safety according to the treatment they actually received.

During the Study Period, Baseline is defined as the last available assessment prior to treatment for all patients regardless of their treatment group.

All AEs and other safety information including untreated patients collected after the signing of informed consent will be reported in listings, as applicable.

AEs will be summarized by incidence, SOC, preferred term (PT), seriousness, severity, relationship to treatment, and by treatment group. Concomitant medications will be summarized by treatment group.

Changes from Baseline in vital signs, laboratory assessments (chemistry and hematology,) and C-SSRS will be summarized by treatment group. Likewise, shift tables (L [low], N [normal], H [high]) by treatment group will be produced for clinical laboratory tests and pregnancy tests will be summarized in patient listings. Shift tables for the C-SSRS will be produced by treatment group and visit.

#### **14.8.1. Physical Examinations and Vital Signs**

Physical examinations will be summarized by visit and treatment group. Vital signs (systolic and diastolic BP, temperature, and sitting or supine HR), height, and weight and changes from baseline in vital signs (including height and weight) will be summarized by visit and by treatment group. Listings of physical exams and vital signs will be produced.

#### **14.8.2. Laboratory Assessments**

Changes from Baseline in laboratory assessments (chemistry and hematology,) will be summarized by visit and treatment group. Likewise, shift tables (L [low], N [normal], H [high]) by visit and treatment group will be produced for clinical laboratory tests. Listings of laboratory data will be produced.

#### **14.8.3. Adverse Events**

SAEs occurring from the signing of informed consent and prior to the initiation of IP treatment (pre-treatment SAEs) will be summarized by treatment group.

Treatment-emergent AEs (TEAEs) are AEs that onset after the start of treatment in the trial. TEAEs will be summarized by incidence, preferred term, SOC, seriousness, severity, relationship to treatment, and by treatment group. SAEs will be summarized by treatment group. TEAEs and SAEs will be summarized by gender and treatment group, by race and treatment group, and by region (of the world) and treatment group.

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

#### **14.8.3.1. Columbia-Suicide Severity Rating Scale**

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

#### **14.8.4. Other Safety Endpoints**

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 patient listing.

#### **14.9. PK/PD 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 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.

#### **14.10. Biomarker Analysis**

NMO-IgG antibody titer level will be summarized by treatment group and visit.

#### **14.11. Other Statistical Issues**

##### **14.11.1. Significance Levels**

For all analyses, the eculizumab treated group will be compared to the placebo group and all 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 for the effect size.

##### **14.11.2. 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.

## **15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **15.1. 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 case report forms 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

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

### **15.2. Audits and Inspections**

Authorized representatives of the Sponsor or the Sponsor's designee, a regulatory authority, an IEC or 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, Good Clinical Practice (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.

### **15.3. Institutional Review Board / International Ethics Committee**

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

### **15.4. Data Monitoring Committee (DMC)**

An independent Data Monitoring Committee (DMC) will conduct interim monitoring of unblinded safety data.

The DMC will have access to all unblinded safety data, since its primary function is to ensure patient safety. The DMC may make recommendations to the Sponsor regarding safety issues, trial conduct, and modifying, extending or stopping the trial.

In addition, the DMC will receive reports concerning patients who have dropped out and any patients with missing primary and secondary efficacy data. Notification of the drop out and reason for the drop out will be sent to the DMC according to the schedule defined in the charter. Any missing data regarding the primary and secondary endpoints will be noted in the regularly scheduled meeting of the DMC. The DMC will also review summaries of all patient reported relapses to assure no bias has occurred in relapse assessments by the Treating Physician.

A separate DMC Charter will document all DMC procedures for this trial.

## **16. QUALITY CONTROL AND QUALITY ASSURANCE**

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or Sponsor's designee may conduct a quality assurance audit. Please see Section [15.2](#) for more details regarding the audit process.

## **17. ETHICS**

### **17.1. Ethics Review**

The final trial protocol, including the final version of the ICF, 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 designees before he or she can enroll any subject into the trial.

The PI, or Sponsor or Sponsor 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, or per local regulations.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other trial conducted with the IP. The Sponsor or the Sponsor's designees 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.

### **17.2. 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/GCP, applicable regulatory requirements.

### **17.3. Written Informed Consent**

The PI(s) at each trial site 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 informed consent 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.

## **18. DATA HANDLING AND RECORDKEEPING**

### **18.1. 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.

### **18.2. Retention of Records**

The PI must maintain all documentation relating to the trial according to 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.

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## **APPENDICES**

- Appendix 1: Diagnostic Criteria for NMO (2006) (6)
- Appendix 2: Diagnostic Criteria for NMO spectrum disorder (2007) (18)
- Appendix 3: Kurtzke Expanded Disability Status Scale (EDSS) (32)
- Appendix 4: Optic-Spinal Impairment Scale (OSIS)
- Appendix 5: Hauser Ambulation Index (HAI) (33)
- Appendix 6: Short Form Health Survey (SF-36)
- Appendix 7: EuroQoL (EQ-5D)
- Appendix 8: Clinical Laboratory Tests
- Appendix 9: Modified Rankin Scale (mRS)
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- Appendix 11: Columbia-Suicide Severity Rating Scale (C-SSRS) -Since Last Visit (35)

## **APPENDIX 1. 2006 DIAGNOSTIC CRITERIA FOR NMO(6)**

### 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 (18)**

Neuromyelitis optica

Limited forms of neuromyelitis optica:

- Idiopathic single or recurrent events of longitudinally extensive myelitis ( $\geq 3$  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) 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.

<b>Kurtzke Expanded Disability Status Scale</b>	
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 - 20/1200
- 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 plegic (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 (33)**

- 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)

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# Your Health and Well-Being

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**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
▼	▼	▼	▼	▼
<input type="checkbox"/>				

**2. Compared to one year ago, how would you rate your health in general now?**

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
▼	▼	▼	▼	▼
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

Yes, limited a lot	Yes, limited a little	No, not limited at all
--------------------------	-----------------------------	------------------------------

- Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports .....  .....  .....
- Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf .....  .....  .....
- Lifting or carrying groceries .....  .....  .....
- Climbing several flights of stairs .....  .....  .....
- Climbing one flight of stairs .....  .....  .....
- Bending, kneeling, or stooping .....  .....  .....
- Walking more than a mile .....  .....  .....
- Walking several hundred yards .....  .....  .....
- Walking one hundred yards .....  .....  .....
- Bathing or dressing yourself .....  .....  .....

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**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 <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/>				
b. <u>Accomplished less</u> than you would like.....	<input type="checkbox"/>				
c. Were limited in the <u>kind</u> of work or other activities.....	<input type="checkbox"/>				
d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort).....	<input type="checkbox"/>				

**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 <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/>				
b. <u>Accomplished less</u> than you would like.....	<input type="checkbox"/>				
c. Did work or other activities <u>less carefully than usual</u> .....	<input type="checkbox"/>				

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

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/>				

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/>					

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/>				

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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? .....	<input type="checkbox"/>				
b. Have you been very nervous? .....	<input type="checkbox"/>				
c. Have you felt so down in the dumps that nothing could cheer you up? .....	<input type="checkbox"/>				
d. Have you felt calm and peaceful? .....	<input type="checkbox"/>				
e. Did you have a lot of energy? .....	<input type="checkbox"/>				
f. Have you felt downhearted and depressed? .....	<input type="checkbox"/>				
g. Did you feel worn out? .....	<input type="checkbox"/>				
h. Have you been happy? .....	<input type="checkbox"/>				
i. Did you feel tired? .....	<input type="checkbox"/>				

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
▼	▼	▼	▼	▼
<input type="checkbox"/>				

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11. How TRUE or FALSE is each 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.....	<input type="checkbox"/>				
b. I am as healthy as anybody I know.....	<input type="checkbox"/>				
c. I expect my health to get worse.....	<input type="checkbox"/>				
d. My health is excellent.....	<input type="checkbox"/>				

***THANK YOU FOR COMPLETING THESE QUESTIONS!***

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## **APPENDIX 7. EUROQOL (EQ-5D)**



**Health Questionnaire**  
**(English version for the US)**

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

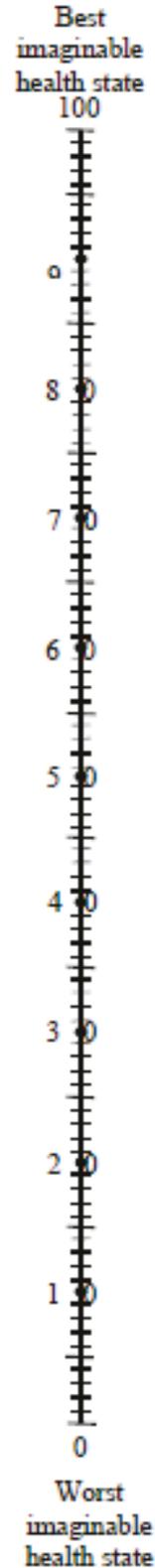
**Anxiety/Depression**

- 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

<p><b>Chemistry Panel</b></p> <ul style="list-style-type: none"><li>Sodium</li><li>Potassium</li><li>Chloride</li><li>Bicarbonate</li><li>Blood urea nitrogen</li><li>Creatinine</li><li>Glucose</li><li>Alkaline phosphatase</li><li>Alanine amino transferase (ALT)</li><li>Aspartate amino transferase (AST)</li><li>Total bilirubin</li><li>Albumin</li><li>Total protein</li><li>Uric acid</li></ul> <p><b>Complete Blood Count (CBC) &amp; Differential</b></p> <ul style="list-style-type: none"><li>White blood cell count (WBC)</li><li>White blood cell differential</li><li>Red blood cell count (RBC)</li><li>RBC mean corpuscular volume (MCV)</li><li>RBC distribution width</li><li>Hemoglobin</li><li>Hematocrit</li><li>Platelet count</li></ul> <p><b>Urinalysis</b></p> <ul style="list-style-type: none"><li>Appearance</li><li>Specific gravity</li><li>PH</li><li>Protein</li><li>Blood</li><li>Glucose</li><li>Ketone</li><li>Bilirubin</li><li>Urobilinogen</li><li>Nitrite</li></ul>	<p><b>Human Chorionic Gonadotropin (<math>\beta</math>-HCG)</b></p> <p><b>Auto Aquaporin 4 antibody (AQP4 Ab or NMO-IgG)</b></p> <p><b>Pharmacokinetics (PK) and Pharmacodynamics (PD)</b></p> <p><b>Complement factor 5 (C5)</b></p> <p><b>Human Anti-human Antibody (HAHA)</b></p>
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## APPENDIX 9. MODIFIED RANKIN SCALE (MRS)

### MODIFIED

Patient Name: \_\_\_\_\_

### RANKIN

Rater Name: \_\_\_\_\_

### SCALE (mRS)

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):** \_\_\_\_\_

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<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>	Since Last Visit
<p><b>Actual Attempt:</b> A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <i>There does not have to be any injury or harm</i>, 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 (e.g., 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. <i>Have you made a suicide attempt?</i> <i>Have you done anything to harm yourself?</i> <i>Have you done anything dangerous where you could have died?</i> <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Did you want to die (even a little) when you _____?</i> <i>Were you trying to end your life when you _____?</i> <i>Or did you think it was possible you could have died from _____?</i> <i>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)</i> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts _____</p> <p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p>	<p><input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Interrupted Attempt:</b> When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an 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. <i>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?</i> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted _____</p>
<p><b>Aborted Attempt:</b> 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. <i>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?</i> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted _____</p>
<p><b>Preparatory Acts or Behavior:</b> Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). <i>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)?</i> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicide:</b></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Answer for Actual Attempts Only</b></p>	<p>Most Lethal Attempt Date: _____</p>
<p><b>Actual Lethality/Medical Damage:</b> 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death</p>	<p>Enter Code _____</p>
<p><b>Potential Lethality: Only Answer if Actual Lethality=0</b> 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</p>	<p>Enter Code _____</p>



<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>	Since Last Visit
<p><b>Actual Attempt:</b> A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <i>There does not have to be any injury or harm</i>, 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.  <b>Inferring Intent:</b> 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 (e.g., 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.  <i>Have you made a suicide attempt?</i>  <i>Have you done anything to harm yourself?</i>  <i>Have you done anything dangerous where you could have died?</i>  <i>What did you do?</i>  <i>Did you _____ as a way to end your life?</i>  <i>Did you want to die (even a little) when you _____?</i>  <i>Were you trying to end your life when you _____?</i>  <i>Or did you think it was possible you could have died from _____?</i>  <i>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)</i>                      If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts</p> <p>_____</p> <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p> <p><b>Interrupted Attempt:</b> When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>).                      Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an 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.  <i>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?</i>                      If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted</p> <p>_____</p>
<p><b>Aborted Attempt:</b> 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.  <i>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?</i>                      If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted</p> <p>_____</p>
<p><b>Preparatory Acts or Behavior:</b> Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).  <i>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)?</i>                      If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicide:</b></p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Answer for Actual Attempts Only</b></p>	<p>Most Lethal Attempt Date:</p>
<p><b>Actual Lethality/Medical Damage:</b>                      0. No physical damage or very minor physical damage (e.g., surface scratches).                      1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).                      2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).                      3. Moderately severe physical damage, <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).                      4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).                      5. Death</p>	<p>Enter Code</p> <p>_____</p>
<p><b>Potential Lethality; Only Answer if Actual Lethality=0</b>                      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</p>	<p>Enter Code</p> <p>_____</p>