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

Unique Protocol ID:	ECU-NMO-302
NCT Number:	NCT02003144
EudraCT Number:	2013-001151-12
Date of SAP:	08 July 2021

Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ECU-NMO-302

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

Author: PPD

Date: **8 Jul 2021**

Version: **1.0**

1. APPROVAL SIGNATURES

PPD

09-Jul-2021 | 11:31:47 EDT

Date dd Mmm yyyy

09-Jul-2021 | 11:44:02 EDT

Date dd Mmm yyyy

09-Jul-2021 | 11:40:55 EDT

Date dd Mmm yyyy

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this statistical analysis plan (SAP).

Table 1: Abbreviations and acronyms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
ARR	annualized relapse rate
BP	blood pressure
C5	complement component 5
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
(e)CRF	(electronic) case report form
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
EOS	end of study
EQ-5D	EuroQol 5 dimension health status
EQ-VAS	EuroQol Visual Analog Scale
FAS	full analysis set
FSS	functional system scores
HAI	Hauser Ambulation Index
HR	heart rate
IP	investigational product
IST	immunosuppressant therapy
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
ON	optic neuritis
OSIS	optic spinal impairment score
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PR	Interval between the P wave and QRS complex
PT	preferred term
QoL	quality of life
QRS	a combination of the waves in ECG arbitrarily named Q, R, and S
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	corrected QT interval
QTcB	QT interval, the Bazett's formula
QTcF	QT interval, Fridericia Correction
RR	respiration rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure

Table 1: Abbreviations and acronyms

Abbreviation or Specialist Term	Explanation
SF-36	short form health survey (36 question version)
SOC	system organ class
TEAE	treatment-emergent adverse events
TESAE	treatment-emergent serious adverse event
TM	transverse myelitis
VA	visual acuity

4. DESCRIPTION OF THE PROTOCOL

Study ECU-NMO-302 is a Phase III, open-label, extension trial of Study ECU-NMO-301 to evaluate the safety and efficacy of eculizumab in the treatment of patients with relapsing Neuromyelitis Optica (NMO) or NMO Spectrum Disorder (NMOSD). NMO, or NMOSD, 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 disease course. Throughout this document, the term NMO refers to both NMO and NMOSD.

Study ECU-NMO-301 was a randomized, placebo-controlled study designed to establish the safety and efficacy of eculizumab in patients with relapsing NMO. The ECU-NMO-302 extension study was designed to provide patients that complete Study ECU-NMO-301 with the opportunity to receive eculizumab for up to 5.5 years and to inform on the long-term safety and efficacy of eculizumab in patients with relapsing NMO. In Russia, Malaysia, Thailand, and Argentina, the maximum total trial duration is 6.5 years from the time the first patient was enrolled.

In order to enroll into Study ECU-NMO-302, patients must have completed an End of Study (EOS) Visit in Study ECU-NMO-301. Study ECU-NMO-301 is an event-driven study in which the EOS Visit for an individual patient occurs when one of the following conditions is met, whichever comes first: (a) the patient experiences an On-Trial Relapse; or (b) the study ends by meeting the target number of relapses (24 adjudicated On-Trial relapses in 24 distinct patients). Patients who complete Study ECU-NMO-301 due to relapse will have their first Study ECU-NMO-302 extension study visit once the ECU-NMO-301 Week 6 Follow-up Relapse Evaluation Visit is completed and no later than 2 weeks (14 days ± 2 days) after the last investigational product (IP) dose; patients who complete Study ECU-NMO-301 due to the study milestone of 24 adjudicated On-Trial relapses in 24 patients will have their first Study ECU-NMO-302 extension study visit once the ECU-NMO-301 EOS Visit is completed and no later than 2 weeks (14 days ± 2 days) after the last IP administration in Study ECU-NMO-301. Patients who prematurely discontinue the Study ECU-NMO-301 or whose treatment assignment was unblinded in Study ECU-NMO-301 may not enroll in Study ECU-NMO-302.

The primary objective of Study ECU-NMO-302 is to evaluate the long-term safety of eculizumab in patients with relapsing NMO. The secondary objectives of Study ECU-NMO-302 are to:

- Evaluate the long-term efficacy of eculizumab in patients with relapsing NMO as measured by annualized relapse rate (ARR)
- Evaluate the long-term efficacy of eculizumab by additional efficacy measures including:
  - Disability
  - Quality of life (QoL)
  - Neurologic functions

- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in relapsing NMO patients

The objective of this SAP is to describe the final analyses of data from Study ECU-NMO-302.

4.1. Changes from Analyses Specified in the Protocol

Changes from analyses specified in the protocol include:

1. The Extension Full Analysis Set (FAS) will be defined as patients who have received at least 1 dose of eculizumab in this extension study. The Extension FAS will not exclude patients who have not had at least one post-infusion efficacy assessment, because a relapse may be reported and assessed at any time on or after the first dose.
2. In this SAP, the primary, secondary, and tertiary endpoints (see Sections 5.1.1, 5.1.2, and 5.1.3 for the details) will be summarized for the Extension FAS. The Extension Per-Protocol (PP) Set will not be defined or analyzed.
3. The Study ECU-NMO-302 protocol states that the baseline value for the summaries of the changes in Expanded Disability Status Scale (EDSS) score will be the Study ECU-NMO-302 baseline (ie, the value prior to first dose in Study ECU-NMO-302), and that covariates in the model would include baseline and visit. Additionally, data will also be summarized by ECU-NMO-301 treatment group and will include summaries of changes from the ECU-NMO-301 baseline. These elements were added to reveal any potential impact of ECU-NMO-301 treatment assignment on the ECU-NMO-302 study results (ie, a carry-over or a cross-over effect). These changes were also applied to summaries of Hauser Ambulation Index (HAI), modified Rankin Scale (mRS), European Quality of Life Health 5-item questionnaire (EQ-5D), and Kurtzke Visual Functional System Scores (FSS).
4. The ECU-NMO-302 protocol states that a Combined FAS and a Combined PP Set would be defined; however, a combined summary of efficacy will not be performed for the ECU-NMO-301 and ECU-NMO-302 studies. Instead, for patients who enroll in Study ECU-NMO-302, selected results from Study ECU-NMO-301 will be presented with data from Study ECU-NMO-302 to show the treatment effect over time.
5. The ECU-NMO-302 protocol states that a Combined Safety Population would be defined; however, the analysis of combined summary of safety for the ECU-NMO-301 and ECU-NMO-302 studies will not be described in the current document and will be described in a separate SAP.
6. The Study ECU-NMO-302 protocol states that the analysis of the ARR will be based on the change from baseline ARR. The protocol-defined baseline ARR was to include events in the 1 year prior to Study ECU-NMO-301, and in a sensitivity analysis the baseline ARR would also include events observed in Study ECU-NMO-301 for patients randomized to placebo. Instead, the baseline ARR will be defined from prior to enrollment in the ECU-NMO-301 study by strictly using events in the 24-months prior to Study ECU-NMO-301 Screening for all patients in Study ECU-NMO-302 and will be referred to as the historical ARR. By using this historical ARR, no unintended bias is

introduced by calculating the endpoints differently for each Study ECU-NMO-301 treatment assignment.

7. The Study ECU-NMO-302 protocol states that shift tables from baseline in the mRS score will be produced by visit. Since the mRS score is a continuous score, summary statistics for the changes from baseline in the mRS score will be produced by visit instead of the shift tables.
8. The Study ECU-NMO-302 protocol states that changes from the last assessment prior to the relapse to all trial collected time points after a relapse (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and visual acuity (VA). The Study ECU-NMO-302 protocol also states that changes from the assessment 1 week after the relapse to all trial collected time points after that time point (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and VA. These summaries will not be produced. Changes from baseline to all of the trial collected time points after a relapse (and before the next relapse if the patient happens to have more than one relapse) will be summarized for EDSS, HAI, and Kurtzke Visual FSS.
9. The Study ECU-NMO-302 protocol states that treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) will be summarized by gender, by race, and by-region. These summaries will not be produced.

The analyses as specified in this SAP over-ride those specified in the Study ECU-NMO-302 protocol.

5. DEFINITIONS

5.1. Efficacy

NMO relapses are key to the assessment of efficacy in Study ECU-NMO-302. The definitions of On-Trial Relapse, Adjudicated On-Trial Relapse, and Historical Relapse are as follows:

On-Trial Relapse:

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

Adjudicated On-Trial Relapse:

An adjudicated On-Trial Relapse is defined as an On-Trial Relapse that was positively adjudicated by the relapse adjudication committee. A separate charter documents the adjudication criteria and procedures of the committee.

Historical Relapse:

Historical relapses are the relapses that occurred prior to the Study ECU-NMO-301 Screening Visit, including the first NMO attack. See Section 9.4.1 for the definition of historical relapses and the calculation of historical ARR.

Note, for the purposes of the Study ECU-NMO-302 protocol and this SAP, relapses and attacks are synonymous.

5.1.1. Primary Efficacy Endpoint(s)

The primary efficacy endpoint in Study ECU-NMO-302 is the ARR based on all On-Trial Relapses identified by the treating physician and time in the study period; the change from historical ARR will be calculated.

Patient-level On-Trial ARR will be computed for each patient based on all On-Trial Relapse(s). Patient-level adjudicated On-Trial ARR will also be computed for a sensitivity analysis, based on all adjudicated On-Trial Relapse(s) for each patient. A historical ARR will be computed for each patient based on historical relapses in the 24 months prior to the Study ECU-NMO-301 Screening Visit.

See Sections 9.4.1 and 9.4.2 for the formulas for calculating ARR and time at risk.

5.1.2. Secondary Efficacy Endpoint(s)

The following secondary endpoints in Study ECU-NMO-302 will be summarized:

1. Change from baseline in EDSS score
2. Change from baseline in mRS score

3. Change from baseline in HAI in patients with abnormal baseline ambulatory function
4. Change from baseline in EQ-5D
5. Change from baseline in Kurtzke Visual Functional System Scores (FSS) in patients with abnormal baseline visual function

5.1.2.1. EDSS Score

The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. Briefly, the assessing neurologist rates functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral) and ambulation in the context of a standard neurological examination and then uses these ratings (FSS) in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score. EDSS steps 1.0 to 4.5 refer to people who are fully ambulatory, while EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.

See Protocol ECU-NMO-302 Appendix 3 for the EDSS rating scale.

5.1.2.2. Modified Rankin Scale (mRS)

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. The treating physician will administer the mRS.

The scale ranges from 0 (no disability) to 6 (death).

See Protocol ECU-NMO-302 Appendix 9 for the mRS.

5.1.2.3. Hauser Ambulatory Index (HAI)

The HAI evaluates mobility based on the time and degree of assistance required for the patient to walk 25 feet (8 meters). The scale ranges from 0 (asymptomatic; fully active) to 9 (restricted to wheelchair; unable to transfer self independently). Patients with abnormal ambulatory function have a baseline HAI value of 1 to 9 (ie, a baseline value of 0 is considered normal). The treating physician or a designee is to administer the HAI.

See Protocol ECU-NMO-302 Appendix 5 for the HAI.

5.1.2.4. European Quality of Life Health 5-item Questionnaire (EQ-5D)

The EQ-5D is a generic, standardized patient self-administered instrument that provides a simple, descriptive profile and a single index value for health status. The EQ-5D comprises 5 dimensions of health: mobility, self care, pain/discomfort, anxiety/depression, and overall health. Each dimension consists of 3 levels (some, moderate, extreme problems), generating a total of 243 theoretically possible health states. The response period is the day of assessment only. Assessments will also be made using the EQ Visual Analog Scale (EQ-VAS), which captures the self-rating of current health status using a visual "thermometer" with the endpoints of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.

See Protocol ECU-NMO-302 Appendix 7 for the EQ-5D.

5.1.2.5. Visual Acuity (VA)

The Kurtzke Visual FSS will be used for statistical analysis of changes from baseline in VA. The Kurtzke Visual FSS is scored as follows:

- 0 = Normal
- 1 = disc pallor and/or mild scotoma and/or VA (corrected) of worse eye less than 20/20 but better than 20/30
- 2 = worse eye with large scotoma and/or maximal VA (corrected) of 20/30 to 20/59
- 3 = worse eye with large scotoma or moderate decrease in fields and/or maximal VA (corrected) of 20/60 to 20/99
- 4 = worse eye with marked decrease of fields and/or maximal VA (corrected) of 20/100 to 20/200; Grade 3 plus maximal acuity of better eye of 20/60 or less
- 5 = worse eye with maximal VA (corrected) less than 20/200; Grade 4 plus maximal acuity of better eye of 20/60 or less
- 6 = Grade 5 plus maximal VA of better eye of 20/60 or less

Patients with abnormal VA at baseline are patients with a Kurtzke Visual FSS for VA of 1 to 6 at baseline (ie, a baseline value of 0 is considered normal).

5.1.3. Tertiary Efficacy Endpoints

The following tertiary endpoints in Study ECU-NMO-302 will be summarized:

1. Change from baseline in HAI score
2. Change from baseline in Kurtzke Visual FSS
3. Change from baseline in the Short Form Health Survey (36 question version) (SF-36)
4. Change from baseline in each EDSS FSS

5.1.3.1. SF-36

The SF-36 is a patient self-administered questionnaire designed to assess generic health-related QoL in healthy and ill adult populations. The SF-36 consists of 36 items organized into the 8 scales shown below. The SF-36 also yields 2 summary measures of physical health (the Physical Component Summary measure [PCS]) and mental health (the Mental Component Summary measure [MCS]) derived from scale aggregates. Higher global scores are associated with better QoL.

Table 2: Components of the SF-36

Scale	Number of Items	Definition of Scale
Physical Functioning (PF)	10	Limitations in physical activity because of health problems
Social Functioning (SF)	2	Limitations in social activities because of physical or emotional problems
Role Limitations Physical (RP)	4	Limitations in usual role activities because of physical health problem
Bodily Pain (BP)	2	Presence of pain and limitations due to pain
General Medical Health (GH)	5	Self-evaluation of personal health
Mental Health (MH)	5	Psychological distress and well-being
Role Limitations Emotional (RE)	3	Limitations in usual role activities because of emotional problems
Vitality (VT)	4	Energy and fatigue
Reported Health Transition (HT)	1	Health transition from 1 year prior based on SF-36 item 2

Version 2 of the SF-36 will be used in this study. See Protocol ECU-NMO-302 Appendix 6 for the SF-36 questionnaire.

5.1.3.2. Kurtzke Functional System Score (FSS)

The Kurtzke instrument has 7 functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral) evaluated in the context of a standard neurologic examination. The score ranges from 0 to 6. A score of 0 in the functional systems implies the patient is normal. Higher scores represent worse disability. These ratings are then used together with observations and information about gait and use of assistive devices to rate the EDSS.

5.1.4. Other Efficacy Endpoints

5.1.4.1. Severity of a Relapse

Severity of relapse (major or minor) will be measured by the Optic Spinal Impairment Score (OSIS). VA Subscale Scores will be used to categorize the severity of Optic Neuritis (ON) relapses. Motor Subscale Scores and Sensory Subscale Scores will be used to categorize the severity of Transverse Myelitis (TM) relapses. Severity will be assessed at the time of the relapse.

In the event a patient has a relapse that includes more than one type of relapse, the worst grade will be used for the severity of the relapse. For example, if the relapse is both ON (minor) and TM (major), then the relapse will be considered a major relapse.

See Protocol ECU-NMO-302 Appendix 4 for details of the scores.

5.2. Safety

The safety of eculizumab in Study ECU-NMO-302 will be assessed based on TEAEs, TESAEs, and changes from baseline through study completion in vital signs, electrocardiogram (ECG), routine clinical laboratory tests (chemistry, hematology), physical examination, Columbia-Suicide Severity Rating Scale (C-SSRS), and pregnancy tests for female patients of childbearing potential.

5.2.1. Adverse Events

Adverse event (AEs), including serious adverse events (SAEs), are defined in Protocol ECU-NMO-302 Section 12.2. Adverse events of special interest (AESIs) are defined in SAP Section 7.5.2.6.

5.2.2. Vital Signs

Vital signs include assessments of systolic and diastolic blood pressure (SBP and DBP), temperature, respiration rate (RR) and heart rate (HR) that will be performed as specified by the protocol. SBPs and DBPs will be documented in mmHg. Temperature will be obtained in degrees Celsius or degrees Fahrenheit. HR will be documented in beats per minute.

Body weight will be measured in pounds or kilograms.

5.2.3. Laboratory Assessments

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

Chemistry panel, routine hematology laboratory assessments, including complete blood count (CBC) and serum pregnancy test, urinalysis, hemolytic markers, and renal function measures will be performed as specified by the protocol

Immunogenicity: blood samples will be collected for evaluation of antidrug antibody as specified by the protocol to describe the presence or absence of an immune response to eculizumab.

See Protocol ECU-NMO-302 Appendix 8 for the clinical laboratory tests.

5.2.4. Other Safety

5.2.4.1. Physical Examination

A complete physical examination will be performed at study visits specified in the protocol Schedule of Assessments (Protocol ECU-NMO-302, Tables 5 - 10). 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.

5.2.4.2. Electrocardiogram (ECG)

A 12-lead ECG will be conducted as specified in the protocol and at study visits specified in the protocol Schedule of Assessments (Protocol ECU-NMO-302, Tables 5 - 10). Additional ECG assessments are permitted at the investigator's discretion.

5.2.4.3. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a validated questionnaire and is extensively used across primary care, clinical practice, surveillance, research, and institutional settings to assess suicidal ideation and behavior. The C-SSRS will be performed by the treating physician or an appropriately trained designee at

visits specified in the protocol Schedule of Assessments (Protocol ECU-NMO-302, Tables 5 - 10). Additional C-SSRS assessments are permitted as needed.

See Protocol ECU-NMO-302 Appendix 10 for the C-SSRS.

5.2.4.4. Vaccination and Revaccination for Meningococcal Infection

All vaccinations and revaccinations for meningococcal infection will be recorded.

5.3. Assessment of Biomarker

5.3.1. NMO Disease Biomarker

Only patients with a documented positive test for the AQP4 autoantibody (also called NMO-IgG) obtained prior to or during the Screening were included in Study ECU-NMO-301. Blood samples for measuring serum NMO-IgG antibody levels will be collected at study visits as outlined in the protocol Schedule of Assessments (Protocol ECU-NMO-302, Tables 5 - 10). Sample analysis will be conducted at the Mayo Clinic laboratory. Cerebrospinal fluid (CSF) samples for measuring NMO-IgG antibody level will also be collected at specified time points for patients who consent to having these assessments.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

6.1. Extension Full Analysis Set (FAS)

The efficacy endpoint analyses will be based on the Extension FAS. The Extension FAS consists of all patients who have received at least 1 dose of eculizumab in Study ECU-NMO-302. Tables will be presented according to the treatment to which the patient was randomized to in Study ECU-NMO-301.

6.2. Extension Per-Protocol (PP) Set

Not applicable; no summaries for a PP set are planned.

6.3. Extension Safety Set

Safety analyses will be performed on the Extension Safety Set. The Extension Safety Set consists of all patients who have received at least 1 dose of eculizumab in Study ECU-NMO-302. Tables will be presented according to the treatment the patient received in Study ECU-NMO-301.

6.4. PK/PD Analysis Set

PK/PD analyses will be performed on the PK/PD Analysis Set. This analysis set includes patients with at least one PK or PD result during the ECU-NMO-302 study. Details for the PK/PD Analysis Set can be found in a separate PK/PD analysis plan.

7. STATISTICAL ANALYSIS

Alexion will be responsible for data collection and editing, reviewing and validating all the information in the electronic case report forms (eCRFs), statistical analysis, and generation of the interim clinical report(s). The analyses will be performed using the SAS® statistical software system Version 9.4 or higher.

Treatment groups will constitute both Study ECU-NMO-301 and Study ECU-NMO-302 treatments: eculizumab/eculizumab for the patients in the eculizumab arm in Study ECU-NMO-301 and placebo/eculizumab for the patients in the placebo arm in Study ECU-NMO-301. Summaries will be presented by treatment group and overall.

For continuous variables, summary statistics will include the sample size, mean, standard deviation, median, minimum, and maximum. Frequencies and percentages will be calculated for categorical variables. Graphical displays will be produced, as appropriate. By-patient data listings will also be presented.

7.1. Study Patients

7.1.1. Disposition of Patients

The number and percentage of patients enrolled in the study, treated, completed the study, discontinued from the study, along with the reasons for discontinuation (including Coronavirus Disease 2019 [COVID-19] related reasons), will be tabulated. A by-site and by-region summary will include the number and percentage of patients treated, completed the study, and discontinued from the study.

7.1.2. Protocol Deviations

The number of major and minor protocol deviations and the number of each type of major or minor protocol deviations will be presented. Summaries will be presented overall and for COVID-19 related deviations.

A listing of protocol deviations will be provided.

7.1.3. Demographics and Disease Characteristics

All demographic and baseline characteristics, including baseline disease characteristics will be summarized using the Extension Safety Set. Summary statistics will be presented by treatment group and overall. No formal hypothesis testing will be performed.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (years) at Day 1 (First Dose Date) in Study ECU-NMO-302 (continuous, < 45 years/≥ 45 years, and 18-65 years)
- Sex
- Race and ethnicity
- Japanese patient

- Region
  - Americas (Argentina, Colombia, USA),
  - Europe (Czech Republic, Germany, Denmark, Spain, United Kingdom, Croatia, Italy, Russian Federation, Turkey), and
  - Asia-Pacific (Australia, Hong Kong, Japan, South Korea, Malaysia, Thailand, Taiwan)

  Countries reflect those in which patients are treated in Study ECU-NMO-301. The countries in which patients are treated in Study ECU-NMO-302 will be a subset of those countries.

7.1.3.2. Disease Characteristics

The following NMO disease characteristics, including NMO history, will be summarized:

- Age at NMO Initial Clinical Presentation (years)
- Age at NMO/NMOSD Diagnosis (years)
- NMO Initial Clinical Presentation
- NMO Diagnosis
- Time from Initial Clinical Presentation to First IP Dose Date in Study ECU-NMO-301 and Study ECU-NMO-302 (years)
- Time from NMO Diagnosis to First IP Dose Date in Study ECU-NMO-301 and Study ECU-NMO-302 (years)
- Time from Initial Clinical Presentation to NMO Diagnosis (months)
- Study ECU-NMO-301 Baseline values of EDSS, HAI, and mRS

7.1.4. Medical/Surgical History

Baseline medical/surgical history by system organ class (SOC) and preferred term (PT), ie, number (%) of patients, will be summarized for the Extension Safety Set.

Additionally, the following will be summarized for the Extension Safety Set:

- History of NMO relapses prior to the ECU-NMO-301 Screening Visit,
- The number of historical relapses within the 24 months prior to Screening in Study ECU-NMO-301,
- Whether the patient was receiving immunosuppressant therapy (IST) at the time of the Historical Relapse,
- Immunomodulators or nondrug therapy at the time of the Historical Relapse,
- Acute treatment for each relapse within 24 months prior to Screening in Study ECU-NMO-301 (high dose oral steroids, intravenous [IV] methylprednisolone, plasma exchange, intravenous immunoglobulin [IVIg], other), and

- The total number of rounds of plasma exchange within 24 months prior to Screening in ECU-NMO-301.

A summary of the type of relapses and the ARR in the 24 months prior to the ECU-NMO-301 Screening Visit will also be provided.

7.1.5. Prior and Concomitant Medications/Therapies

Medications will be coded using the World Health Organization Drug Dictionary (WHODrug B3 092020 or higher).

Concomitant medications in Study ECU-NMO-302 are defined as medications taken or therapies received by patients during the study after the first dose of eculizumab on Day 1 in the ECU-NMO-302 study. Prior medications, therapies, and nondrug procedures are defined as medications or therapies initiated prior to the first dose of IP in the ECU-NMO-301 study.

All prior and concomitant medications, therapies, and nondrug therapies and procedures will be summarized for the Extension Safety Set, with prior and concomitant medications including any vaccination for meningococcal infection. The number and percentage of patients taking prior and concomitant medication will be summarized based on the Anatomic Therapeutic Chemical Class 4 level code of the WHODrug Dictionary and the generic name. A similar summary will be presented for supportive ISTs used for NMO preventative treatment prior to ECU-NMO-301 study treatment.

Concomitant supportive IST treatment will be summarized. In addition, the number and percentage of patients with changes in concomitant supportive ISTs will be presented overall and for each type of change. This summary will be presented for the Extension Safety Set.

For patients who experience an On-Trial Relapse in Study ECU-NMO-302, the use of ISTs, plasmapheresis, and plasma exchange will be summarized.

Listings of prior and concomitant medications, concomitant supportive ISTs, nondrug procedures, and prohibited medications will be produced. Additionally, listings of ISTs, plasmapheresis, plasma exchange, investigational procedures for On-Trial Relapses, will also be produced for patients with On-Trial Relapses.

7.1.6. Summary of Study Visit Impacted by COVID-19

The number and percentage of patients who completed at least one study visit that was altered for COVID-19 related reasons or restrictions, reasons for these modified study visits, and the number of modified study visits per patient will be summarized. Similar summaries will be presented for patients who missed at least one study visit. The method of data ascertainment, if the visit was modified, will be presented in listings.

7.2. Efficacy Analyses

Efficacy analyses will be presented by treatment group and overall, using the Extension FAS.

7.2.1. Primary Efficacy Analysis

The primary efficacy endpoint in Study ECU-NMO-302 is ARR including all relapses identified by the treating physician. The number of On-Trial Relapses, number of patient-years in the study

period, and the study-level ARR (and 95% CI) in Study ECU-NMO-301 and Study ECU-NMO-302 will be summarized descriptively. The patient-level ARR will also be summarized using mean, standard deviation, minimum, median, and maximum. This summary will be produced for all On-Trial Relapses, as well as for all adjudicated On-Trial Relapses.

The primary analysis will be the change from historical patient-level ARR (calculated based on 24-months prior to enrollment in Study ECU-NMO-301) to the ECU-NMO-302 ARR of On-Trial Relapses for all patients in Study ECU-NMO-302; the change in ARR will be evaluated using the Wilcoxon signed-rank test. Descriptive statistics of the change in the ARR and the results of the Wilcoxon signed-rank test will be presented for the change from historical patient-level ARR, as well as, for the change by treatment group from Study ECU-NMO-301 ARR. A sensitivity analysis of the change in ARR from historical patient-level ARR to adjudicated On-Trial ARR will also be performed.

Graphical displays of ARRs will be presented for the Extension FAS by treatment group and overall. In addition, by-patient line plots for ARRs will be presented.

For patients who missed 2 or more infusions consecutively due to COVID-19-related reasons, the time period for the calculation of On-Trial ARR will exclude the time period when the patient missed eculizumab infusion, to account for the impact of the pandemic. Any relapse occurring during this period will not be included in the calculation of On-Trial ARR and will be presented in listings. Please refer to Section 9.4.2 for the definition of ARR and time in study period. A sensitivity analysis will be performed in which all On-Trial relapses are included in the calculation of On-Trial ARR irrespective of the impact of the pandemic.

7.2.1.1. Handling of Dropouts or Missing Data

The primary endpoint is ARR, which is based on the duration of patients in the study period. The end of study period is the last dose date plus 16 days (or last dose date plus 9 days if in induction period) or the last date observed in the study, whichever comes first. Relapses after the end of the study period will not be counted. Please refer to Appendix 9.4.2 for the definition of ARR and study period.

No imputation of missing or partially missing data will be applied, regardless of efficacy endpoint.

7.2.1.2. Multicenter Studies

Study ECU-NMO-301 was randomized across centers and not within centers, because a small number of patients were anticipated at each site. For this reason, center will not be used in the efficacy analyses.

7.2.1.3. Hypothesis Testing and Significance Level

The Wilcoxon signed-rank test will be presented for the change in ARR; for some variables, 95% confidence intervals (CIs) will be presented.

The Wilcoxon signed-rank test evaluates whether the median change in ARR is zero. This will be a two-sided test at the 0.05 α level. If the median change from historical ARR to Study ECU-NMO-302 On-Trial ARR is negative (ie, the On-Trial ARR is lower than the historical ARR), it will mean that there is an improvement.

7.2.1.4. Time to First On-Trial Relapse

The number and proportion of patients with On-Trial and adjudicated On-Trial Relapses will be summarized, as well as the number and proportion of patients experiencing each number of relapses (0, 1, 2, etc.).

The time to first On-Trial Relapse and the percentage of patients who are relapse-free while on eculizumab treatment along with 95% CIs based on complementary log–log transformation will be computed using the Kaplan-Meier method by treatment group. Definitions of the time to first event and the censoring times are provided in Appendix 9.4.3. A sensitivity analysis of the time to first adjudicated On-Trial Relapse will be performed in a similar manner.

For the analysis of time to first On-Trial Relapse, patients who miss 2 or more doses consecutively due to COVID-19-related reasons will be censored to account for the impact of the pandemic. The study period will be truncated to the Last Pre-COVID-19 Dose Period Date, which is the last dose date prior to missing 2 or more infusions consecutively due to COVID-19-related reasons + 16 days (or +9 days if in induction phase), and patients without an On-Trial Relapse prior to this date will be censored at this date. See Appendix 9.4.3 for more details on the study period. Any relapse after the Last Pre-COVID-19 Dose Period Date will be presented in listings. A sensitivity analysis will be performed in which all On-Trial relapses will be included in the analysis of time to first On-Trial Relapse irrespective of the impact of the pandemic.

7.2.2. Secondary Efficacy Endpoint Analysis

The secondary efficacy endpoints are the following:

1. Change from baseline in EDSS score
2. Change from baseline in mRS score
3. Change from baseline in HAI in patients with abnormal baseline ambulatory function
4. Change from baseline in EQ-5D VAS and Index
5. Change from baseline in Kurtzke Visual FSS in patients with abnormal baseline visual function

The Study ECU-NMO-301 and the Study ECU-NMO-302 baselines are defined in Section 9.3. The primary analysis for the change from ECU-NMO-302 baseline in EDSS score at a particular visit in the study period will be based on the repeated measures model for each treatment group. The model will include a continuous fixed covariate for baseline EDSS score and study visit. All postbaseline EDSS scores at the scheduled visits will be included in the models; patients without any postbaseline scores will not be included. An unstructured covariance structure will be used to model the within patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion (AIC): first-order autoregressive, compound symmetry, and Toeplitz. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The estimated change from ECU-NMO-302 baseline in EDSS score at each scheduled visit along with 95% CIs and p-values will be provided. A figure showing the estimated change from ECU-NMO-302 baseline to scheduled visits will be presented with 95% CIs. Change from ECU-NMO-302 baseline in mRS score, HAI in patients with abnormal baseline ambulatory function, EQ-5D VAS and Index, and

Kurtzke Visual FSS in patients with abnormal baseline visual function will be analyzed in a similar manner as change in EDSS score.

In addition, for each secondary efficacy endpoint, summaries will be presented using both the ECU-NMO-302 baseline and the ECU-NMO-301 baseline. Changes from baseline in EDSS score, including 95% CIs, at each scheduled study visit will be summarized. A figure showing the mean change from ECU-NMO-302 baseline to scheduled ECU-NMO-302 visits will be presented with 95% CIs. In addition, a figure showing the mean change from ECU-NMO-301 baseline to ECU-NMO-301 EOS and to scheduled ECU-NMO-302 visits will be presented with 95% CIs. Similar summaries will be presented for change from baseline in mRS, HAI, EQ-5D, and Kurtzke Visual FSS.

By-patient listings of the secondary endpoint assessments and changes from ECU-NMO-302 baseline in the secondary endpoints will be produced.

For the secondary endpoints, some summaries by subgroups will be produced. Patients will belong to one of four possible subgroups based on their treatment assignment and On-Trial Relapse status as determined by the treating physician in Study ECU-NMO-301:

a. patients randomized to eculizumab who did not have On-trial relapses as determined by the treating physician in the ECU-NMO-301 study,
b. patients randomized to eculizumab who did have On-trial relapses as determined by the treating physician in the ECU-NMO-301 study,
c. patients randomized to placebo who did not have On-trial relapses as determined by the treating physician in the ECU-NMO-301 study, and
d. patients randomized to placebo who did have On-trial relapses as determined by the treating physician in the ECU-NMO-301 study.

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

Missing secondary endpoint assessments will not be imputed. Any secondary endpoints assessments after the end of the study period will be presented in listings.

7.2.3. Tertiary Efficacy Endpoint Analyses

The tertiary efficacy endpoints are the following:

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

Changes from baseline in the HAI score, Kurtzke Visual FSS, and the EDSS FSS will be analyzed in a similar manner to the secondary endpoint analyses described for the EDSS score using the repeated measures model for each treatment group. In addition, summaries of changes from baseline will be presented using both the Study ECU-NMO-302 baseline andStudy ECU-NMO-301 baseline. Changes from baseline in the HAI score, Kurtzke Visual FSS, and the EDSS FSS, including 95% CIs, at each scheduled study visit will be summarized.

Changes from baseline in the SF-36 will be summarized using descriptive statistics in a similar manner, using both the Study ECU-NMO-302 baseline and the Study ECU-NMO-301 baseline.

By-patient listings of the tertiary endpoint assessments and changes from Study ECU-NMO-302 baseline in the tertiary endpoints will be produced.

In addition, analysis of changes from baseline like those for the secondary efficacy endpoints will also be conducted for the tertiary efficacy endpoints for the four subgroups of patients defined in Section 7.2.2.

Missing tertiary endpoint assessments will not be imputed. Any tertiary endpoints assessments after the end of the study period will be presented in listings.

7.2.4. Other Efficacy Analyses

7.2.4.1. Summary of Types and Severity of On-Trial Relapse(s)

For patients with an On-Trial Relapse(s) in Study ECU-NMO-302, summaries of the types and severity of relapses in the study period will be produced. Summary tables will also be produced only for those patients with adjudicated On-Trial Relapse(s). A by-patient listing of the On-Trial Relapses will be produced. The severity of a relapse will be determined using the OSIS scale and will only be summarized for ON and TM relapses based on the OSIS VA, Motor, and Sensory Scales. The worst severity observed over all relapse visits will be used for a relapse event of more than one type.

Summaries of the types and severity of relapses will be presented both including and excluding the relapses occurring during the time period when a patient missed eculizumab infusion for patients who missed 2 or more infusions consecutively due to COVID-19-related reasons.

See Appendix 9.4.5 for details of determining the severity of a relapse.

7.2.4.2. Summary of Hospitalization and Treatment of Relapses

Summaries of the number and the rate of relapses that require hospitalization in the study period and the treatments for these relapses will be presented.

7.2.4.3. Summary of Changes in EDSS, HAI and VA Scores in Patients with On-Trial Relapse(s)

For patients with an On-Trial Relapse(s), changes from baseline with 95% CIs to all of the trial collected time points after a relapse will be summarized for EDSS, HAI, and Kurtzke Visual FSS. These summaries will also be produced for patients with adjudicated On-Trial Relapse(s).

Patient listings for the EDSS, HAI, and Kurtzke Visual FSS assessments before and after a relapse will be created for each patient who experiences an On-Trial Relapse.

7.3. Pharmacokinetic (PK) and Pharmacodynamic (PD) Analyses

PK/PD summaries in the study period will be presented for patients treated with eculizumab in the Study ECU-NMO-302 PK/PD Analysis Set. The summary statistics will include the number of patients, mean, standard deviation, median, minimum, and maximum. Any PK/PD assessments after the end of the study period will be presented in listings.

7.3.1. PK Analyses

Blood samples will be collected at specified time points to study 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.

CSF samples for PK/PD analyses will also be collected at specified time points for patients who consent to these assessments. Summaries by visit may be presented if enough patients provided consent.

The trough and peak plasma concentration of eculizumab for patients who were treated with eculizumab in the study period will be summarized by visit. Likewise, the CSF concentration of eculizumab for patients who were treated by eculizumab in the study period will also be summarized by visit.

Patient listings of the PK/PD parameters will be produced.

7.3.2. PD Analyses

The PD parameters including serum hemolytic activity and free complement component (C5) concentration for patients who were treated by eculizumab in the study period will be summarized by visit and by time point (trough or peak). Likewise, the CSF free C5 concentrations for patients who were treated with eculizumab in the study period will be summarized by visit.

Details for PK/PD analyses and potential exposure response analyses may be described in a separate PK/PD analysis plan.

7.4. Biomarker Analyses

Shifts from baseline in serum and CSF NMO-IgG antibody titer levels in the study period will be summarized by visit and by treatment group for the Extension Safety Set. By-patient listings of serum and CSF NMO-IgG antibody titer levels will also be produced for the Extension Safety Set.

7.5. Safety Analyses

All safety analyses will be conducted on the Extension Safety Set and presented by treatment group and overall. No formal hypothesis testing is planned. Safety data will also be provided in patient listings.

7.5.1. Study Duration, Treatment Duration, Treatment Compliance, and Exposure

Study duration, treatment duration, treatment compliance, and exposure will be summarized by treatment group.

Study duration will be calculated as the time in days from first eculizumab dose date in the ECU-NMO-302 study until the date of completion of the study or discontinuation (or death) from the study (ie. Study duration [days] = Date of study completion/discontinuation (or death) – Date of First IP Dose + 1).

Treatment duration will be calculated as the time in days from the first IP dose date of eculizumab in the ECU-NMO-302 study until the last IP dose date of eculizumab (ie, Treatment duration [days] = Last IP Dose Date – First IP Dose Date + 1).

The number of patients with any missed infusions per schedule of assessment due to COVID-19 related reasons will be presented; the total number of missed infusions per patient due to COVID-19 related reasons will be summarized. These summaries will be produced by date of study completion or discontinuation before 01 March 2020 or after 01 March 2020, and overall.

Treatment compliance will be calculated as a ratio between the actual doses taken and the doses required per protocol during the study. Patients who took at least 80% of the required doses are considered to be compliant with treatment. The number and percentage of patients with at least an 80% compliance rate will be summarized.

7.5.2. Adverse Events (AEs)

AEs are defined in Protocol ECU-NMO-302 Section 12.2. All AEs will be coded by primary SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 23.1 or higher).

Two types of AEs will be noted:

- TEAEs
- TESAEs

TEAEs are AEs that onset on or after the first IP dose in the ECU-NMO-302 study. Likewise, TESAEs are SAEs that onset on or after the first IP dose in the ECU-NMO-302 study.

7.5.2.1. Overall Summary of Adverse Events

The number of TEAEs, the number and percentage of patients with TEAEs, and event rates per 100 patient-years will be presented. In addition, the number of TEAEs and the number and percentage of patients with TEAEs will be presented for the following event subcategories: relationship to study drug (related TEAEs, not related TEAEs), intensity/severity (mild TEAEs, moderate TEAEs, severe TEAEs), and TEAEs leading to withdrawal from study drug. These statistics will also be prepared for non-serious TEAEs and TESAEs (except in the case of intensity/severity).

Additional overall TEAE summary tables will be presented, which exclude TEAEs that occurred during the time period of missing infusions for the patients who missed 2 or more infusions consecutively due to COVID-19-related reasons.

Additionally, the number of patients who died on study will be presented. See SAP Section 9.3 for the definition of related TEAEs.

7.5.2.2. AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number of TEAEs/TESAEs, the number and percentage of patients with TEAEs/TESAEs, and event rates per 100 patient-years will be presented by SOC and PT. At the patient level, patients are counted once in each SOC and PT. Percentages will be based on the total number of patients in the treatment group in the Extension Safety Set. SOCs will be listed in alphabetical order and PTs within each SOC will be presented in descending order of total frequency.

A similar summary of TEAEs/TESAEs will be presented by PT. PTs will be listed in order of overall frequency of occurrence.

Additional summary tables will be presented which exclude TEAEs that occurred during the time period of missing infusions for the patients who missed 2 or more infusions consecutively due to COVID-19-related reasons.

7.5.2.3. AEs and SAEs by SOC, PT, and Relationship

The number of TEAEs/TESAEs and the number and percentage of patients with TEAEs/TESAEs will be summarized by SOC, PT, and grouped relationship (related, unrelated).

7.5.2.4. AEs by SOC, PT, and Severity

The number of TEAEs and the number and percentage of patients with TEAEs will be summarized by SOC, PT, and severity (mild, moderate, severe).

7.5.2.5. AEs and SAEs Over Time

The incidence of AEs and SAEs by time intervals, SOC, and PT will be presented for the Extension Safety Set. The denominator per time interval will be the patients with study duration that includes all or part of the interval.

7.5.2.6. Deaths, Other SAEs, and Other Significant Adverse Events

The number and percentage of patients with TEAEs resulting in death will be presented overall and by PT for each treatment group and overall. The number and percentage of patients with TEAEs leading to withdrawal from study drug will be presented overall and by PT for each treatment group and overall; these summaries will also be presented for TEAEs leading to withdrawal from the study. Listings of patients with TEAEs leading to withdrawal from the study and of patients with AEs resulting in death will be produced, if applicable.

AESIs include infections (meningococcal infections, aspergillus infections, and other serious infections), sepsis, infusion reactions, serious cutaneous adverse reactions, cardiac disorders, and angioedema. The number and percentage of patients with each AESI and event rates per 100 patient-years will be presented by SOC and PT. In addition to a summary of all AESI, summaries of AESI by relationship, and time interval will be presented. Other events of interest may be identified during the conduct of this study.

7.5.3. Other Safety

7.5.3.1. Analyses for Laboratory Tests

Two baselines, the ECU-NMO-301 study baseline and the ECU-NMO-302 study baseline are described in Section 9.3. Tables described in this section will be presented once for each baseline.

Descriptive statistics of observed values and changes from baseline will be presented by treatment group and visit for each quantitative laboratory test (hematology, serum chemistry). Postbaseline visits will include results from Study ECU-NMO-301 if the baseline is the Study ECU-NMO-301 baseline; visits will be limited to postbaseline Study ECU-NMO-302 visits if the baseline is the Study ECU-NMO-302 baseline. The observed value and the change from Study ECU-NMO-302 baseline to each post-relapse assessment will also be presented. Shift tables for changes in status (low, normal, high) from the Study ECU-NMO-301 baseline and the Study ECU-NMO-302 baseline will also be presented by visit for each laboratory parameter. Shift tables for the changes in status from the Study ECU-NMO-302 baseline to each post-relapse visit will also be presented. All laboratory values will be classified as normal, below normal (low), or above normal (high) based on normal ranges supplied by the central laboratory.

Figures showing the mean and standard deviation of observed laboratory values over time for each quantitative laboratory test (hematology, serum chemistry) will be presented by treatment group for the Extension Safety Set. Reference ranges will also be presented.

7.5.3.2. Vital Signs

Descriptive statistics will be presented by visit (including post-relapse visits) for the actual values and the changes from baseline for each vital sign (SBP and DBP), temperature, RR, and seated or supine HR) and for body weight.

Vital signs outliers for SBP and DBP, HR, RR, temperature, and weight will be presented by treatment group. The number and percentage of patients having observed any vital signs that satisfy any of the following conditions will be presented by time point:

- SBP < 90 mmHg; SBP > 140 mmHg; SBP > 160 mmHg
- DBP < 50 mmHg; DBP > 90 mmHg; DBP > 100 mmHg
- HR < 60 beats per minute; HR > 100 beats per minute
- RR < 12 breaths per minute; RR > 20 breaths per minute
- Temperature < 36 degrees Celsius; Temperature > 38 degrees Celsius
- Weight ≥ 7% decrease from baseline; Weight ≥7% increase from baseline

7.5.3.3. Physical Examination

A by-patient listing of the physical examination data will be produced.

7.5.3.4. Other Safety Parameters of Special Interest

7.5.3.4.1. Electrocardiograms (ECG)

The number and percentage of patients with ECG results (normal; abnormal, not clinically significant; abnormal, clinically significant) will be summarized by visit. Descriptive statistics will be presented by visit for each ECG parameter (ventricular rate, PR duration, QRS duration, QT duration, and RR duration).

The number and percentages of patients will be presented by visit for each treatment group for QTc, QTcF, and QTcB for the following categories:

- < 450 msec,
- 450 to ≤ 480 msec,
- > 480 to ≤ 500 msec, and
- > 500 msec.

The number and percentages of patients will also be presented by visit for each treatment group for the change from baseline in QTc, QTcF, and QTcB for the following categories:

- ≤ 0 msec,
- > 0 to ≤ 30 msec,
- > 30 to ≤ 60 msec, and
- > 60 msec.

7.5.3.4.2. Columbia-Suicide Severity Rating Scale (C-SSRS)

The number and percentage of patients with treatment-emergent Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent based on the C-SSRS during the treatment period will be summarized by treatment group. The number and percentage of patients who experience the particular event at least once during the treatment period will be summarized. The particular events are:

- Suicidal Ideation (1-5)

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent

- Suicidal Behavior (6-10)

6. Preparatory acts or behavior
7. Aborted attempt
8. Interrupted attempt
9. Non-fatal suicide attempt

10. Completed suicide

- Self-injurious behavior without suicidal intent

For the composite endpoint of suicidal ideation (Categories 1-5), the number and percentage of patients who experience any one of the five suicidal ideation events at least once during the treatment period will be summarized. For the composite endpoint of suicidal behavior (Categories 6-10), the number and percentage of patients who experience any one of the five suicidal behavior events at least once during the treatment period will be summarized by treatment group. For the composite endpoint of suicidal ideation or behavior (Categories 1-10), the number and percentage of patients who experience any one of the ten suicidal ideation or behavior events at least once during the treatment period will be summarized by treatment group.

A shift table to demonstrate changes in C-SSRS groupings from baseline will be presented. The three groupings for the shift table are: (a) No suicidal ideation or behavior, (b) Suicidal Ideation, and (c) Suicidal Behavior. Suicidal Ideation includes any one of the five suicidal ideation events (Categories 1-5). Suicidal behavior includes any one of the five suicidal behavior categories (Categories 6-10). Each patient will be counted in one cell only for the table. Patients with both Suicidal Ideation and Suicidal Behavior will be included in the Suicidal Behavior category.

Patient listings for the C-SSRS will also be produced.

7.5.3.4.3. Immunogenicity

Immunogenicity as measured by antidrug antibody will be summarized to indicate the number and percentage of patients positive and negative for antidrug antibody at baseline and each postbaseline time point, including each post-relapse assessment. Antidrug antibody data will also be presented in a by-patient listing.

8. REFERENCES

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52.

Hauser SL, Dawson DM, Lehrich JR, et al. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. N Engl J Med. 1983;308(4):173-80.

Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J. 1957;2(5):200-15.

Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke. 1988;19(12):1497-500.

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19(5):604-7.

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

9. APPENDICES

9.1. Protocol Schedule of Events

Refer to the protocol for a schedule of events (Protocol ECU-NMO-302, Tables 5 - 10).

9.2. Sample Size, Power, and Randomization

Study ECU-NMO-302 is an open-label extension study of Study ECU-NMO-301. No randomization was performed. No sample size or power calculations were performed for this study.

9.3. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

Age

Age will be presented as the number of years between date of birth and the reference date (ie, (Reference Date – Date of Birth + 1)/365.25). The following ages will be computed, with reference dates indicated:

Table 3: Age and Reference Date

AGE	REFERENCE DATE
• Age at First IP Infusion	• Date of First IP Infusion
• Age at Onset of NMO	• Date of Initial Clinical Presentation

For all dates, in cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing months will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as June 15.

Definition of Baseline Values

The Study ECU-NMO-302 baseline is defined as the last available assessment prior to treatment for all patients, regardless of ECU-NMO-301 treatment group. In general, these data will be from Study ECU-NMO-302 Day 1; if missing then the last available assessment in the ECU-NMO-301 study will be used. The ECU-NMO-301 baseline is defined as the last available assessment prior to first eculizumab dose in Study ECU-NMO-301.

Change from Baseline

Change from baseline will be calculated as

Change from Baseline = Assessment Value – Baseline Assessment Value.

QTcB and QTcF Calculations

The Bazett's formula, QTcB, is as follows:

QTcB = QT interval/sqrt(RR)

The Fridericia formula, QTcF, is as follows:

QTcF = QT interval/(RR)^(1/3)

Adverse Events

The analysis of AEs is described in detail in Section 7.5.2.

TEAEs are events with start dates on or after the date of the first eculizumab dose in Study ECU-NMO-302. If the start date of an AE is partially or completely missing and the end (stop) date of the AE does not indicate that it occurred prior to the first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first eculizumab dose, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first eculizumab dose and
  - the start month is missing, then the AE is treatment-emergent; else if
  - the start month is present and is the same or after the month of the first study drug dose, then the AE is treatment-emergent; else,
- If the start date is completely missing, then the AE is treatment-emergent.
- If the start date and end date are completely missing, then the AE is treatment-emergent.

All other AEs are considered to be AEs prior to the start of the ECU-NMO-302 study.

Patient percentages are based on the total number of patients in the particular treatment group or overall.

In general, for the related AE tables, related AEs are defined as AEs that are possibly, probably, or definitely related to study treatment. Unrelated AEs are defined as AEs that are unlikely or not related to study treatment. AEs with missing relationship to study treatment will be assumed as related to study treatment.

Adverse Event Rates

Patient-years of follow-up is defined as:

Patient-years of follow-up = (Last study date – First Dose date + 1)/365.25

where the Last study date is the last date observed in the ECU-NMO-302 study as collected on the CRF. Total patient-years of follow-up for a particular treatment group based on the Extension Safety Set is the sum of the patient-years of follow-up for all the patients in the particular treatment group.

AE rates based on 100 patient-years of follow-up for a particular PT and treatment group will be calculated as the number of events for the particular AE in the particular treatment group times 100 (years) divided by the total patient-years of follow-up for that particular treatment group.

9.4. Additional Details on Statistical Methods

9.4.1. Historical Annualized Relapse Rate (ARR [historical])

Detailed information on relapses within the last 24 months prior to Study ECU-NMO-301 Screening must be assessed by the treating physician to determine if they meet the criteria for the Historical Relapse Definition.

Historical Relapses are the relapses that occurred prior to the Study ECU-NMO-301 Screening Visit (ie, the last Screening Visit for the patient). The Historical Relapse is defined as new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or MRI findings or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of an existing neurologic symptom that required treatment.

The ARR(historical) will include relapses that started 24 months prior to Study ECU-NMO-301 Screening. To allow for the 30-day window of counting distinct relapses, the historical ARR will be calculated for each patient as:

$ARR_{(historical)}$ = Number of relapses in 25 months prior to Screening / (Historical relapse time)

Historical relapse time will be based on data 25 months prior to the date of the Study ECU-NMO-301 Screening Visit. Historical relapse time will be 25 months for NMO patients with disease greater than 25 months from the date of that Screening Visit and Historical Relapse time will be based on the difference in time from date of initial presentation to date of Screening Visit + 1 day for patients with an initial presentation within 25 months of the Screening date.

9.4.2. On-Trial Relapse and Relapse Rate

The definition of an On-Trial Relapse is a relapse as determined by the treating physician that occurs during the study period. Time in study period is defined below.

The patient-level On-Trial ARR will be calculated as:

$$ARR_{(On-Trial)} = \frac{Number\ of\ On-Trial\ relapses\ in\ the\ study\ period}{Time\ in\ study\ period}$$

and the adjudicated On-Trial annualized relapse rate will be calculated as:

$$ARR_{(Adjudicated)} = \frac{Number\ of\ adjudicated\ On-Trial\ relapses\ in\ the\ study\ period}{Time\ in\ study\ period}$$

The number of On-Trial relapses in the study period is the number of relapses from the start of study treatment (first dose date) to the end of the study period for the patient.

The end of study period date (EOS Date) will be determined by the last date in Study ECU-NMO-302, or the last dose date + 16 days (or + 9 days if in induction phase), whichever occurs first. The time in study period (in years) for the purposes of calculating ARR is as follows:

$$Time\ in\ Study\ Period = (EOS\ Date - First\ Dose\ Date + 1)/365.25.$$

For patients who miss 2 or more doses consecutively due to COVID-19-related reasons, the study period for the calculation of ARR will exclude that time when the patient miss eculizumab infusion, to account for the impact of the pandemic. The Last Pre-COVID-19 Dose Period Date is defined in Section 7.2.1.4. The First Post-COVID-19 Dose Date will be the date of first dose that the patient receives post the COVID-19 disruption of study drug treatment. The time in study period (in years) will be calculated as follows:

$$Time\ in\ Study\ Period = (Last\ Pre-COVID-19\ Dose\ Period\ Date - First\ Dose\ Date + EOS\ Date - First\ Post-COVID-19\ Dose\ Date + 2)/365.25.$$

If patients have a second COVID-19 disruption of study drug treatment and miss 2 or more doses consecutively due to COVID-19-related reasons, the study period for the calculation of ARR will exclude all the time when the patient miss eculizumab infusion, to account for the impact of the pandemic. The Last Pre-COVID-19 Dose Period Date 2 will be the last dose date prior to the second time of missing 2 or more infusions consecutively due to COVID-19-related reasons + 16 days (or +9 days if in induction phase). The First Post-COVID-19 Dose Date 2 will be the date of first dose that the patient receives post the second COVID-19 disruption of study drug treatment. The time in study period (in years) will be calculated as follows:

$$Time\ in\ Study\ Period = (Last\ Pre-COVID-19\ Dose\ Period\ Date - First\ Dose\ Date + Last\ Pre-COVID-19\ Dose\ Period\ Date\ 2 - First\ Post-COVID-19\ Dose\ Date + EOS\ Date - First\ Post-COVID-19\ Dose\ Date\ 2 + 3)/365.25.$$

If patients miss 2 or more doses consecutively due to COVID-19-related reasons and did not restart study drug treatment before study discontinuation, the time in study (in years) for the purposes of calculating ARR is as follows:

$$Time\ in\ Study\ Period = (EOS\ Date - First\ Dose\ Date + 1)/365.25.$$

For the sensitivity analyses, the study period will not be adjusted and all On-Trial relapses or adjudicated On-Trial relapses will be included in the calculation of ARR.

The $ARR_{(On-Trial)}$ will be 0 for patients with no relapse during the study period. The $ARR_{(Adjudicated)}$ will be 0 for patients with no adjudicated On-Trial Relapses during the study period.

The study-level ARR will be calculated as

$$ARR_{(On-Trial)} = \frac{Total\ Number\ of\ On\ Trial\ relapses\ in\ the\ study\ period\ across\ patients}{Sum\ of\ the\ Time\ in\ study\ period\ across\ patients}$$

The study-level ARR will also be calculated for adjudicated On-Trial relapses.

$$ARR_{(Adjudicated)} = \frac{Total\ Number\ of\ \text{Adjudicated On} - \text{Trial}\ relapses\ in\ the\ study\ period\ across\ patients}{Sum\ of\ the\ Time\ in\ study\ period\ across\ patients}$$

The 95% CI of the ARR will be calculated using a Poisson regression model of the number of relapses and the offset parameter will be the log of the time in study period; a treatment covariate will be included to calculate the 95% CI for each treatment group, and no covariates will be included in the model calculating the overall 95% CI.

9.4.3. Time to First Event, Censoring Time, and Calculations

A censoring indicator will be equal to 1 if the patient did not experience an On-Trial Relapse (was censored) during the study period, and 0 if the patient experienced an On-Trial Relapse during the study period.

For patients with an On-Trial Relapse during the study period, the time to first event (in days) is defined as:

$$Time\ to\ First\ Relapse = (Date\ of\ 1st\ On\ Trial\ Relapse - First\ Dose\ Date + 1)$$

For patients without an On-Trial Relapse during the study period, the censoring time (in days) is defined as:

$$Censoring\ Time = (EOS\ Date - First\ Dose\ Date + 1)$$

where EOS Date is defined as in the ARR calculation.

For patients with an adjudicated On-Trial Relapse during the study period, the time to first event (in days) is defined as:

$$Time\ to\ First\ Relapse = (Date\ of\ 1st\ adjudciated\ On\ Trial\ Relapse - First\ Dose\ Date + 1)$$

For patients without an adjudicated On-Trial Relapse during the study period, the censoring time (in days) is defined as:

$$Censoring\ Time = (EOS\ Date - First\ Dose\ Date + 1)$$

where EOS Date is defined as in the ARR calculation.

For patients who miss 2 or more doses consecutively due to COVID-19-related reasons, in the primary analysis, the patients will be censored to account for the impact of the pandemic. The time period for the analysis of time to first On-Trial Relapse and time to first adjudicated On-Trial Relapse will be truncated to the Last Pre-COVID-19 Dose Period Date. For patients without an On-Trial Relapse prior to COVID-19 disruption of study drug treatment, the censoring time (in days) is defined as:

$$Censoring\ Time = (Last\ Pre - COVID - 19\ Dose\ Period\ Date - First\ Dose\ Date + 1)$$

For patients without an adjudicated On-Trial Relapse, the censoring time is defined in a similar manner. In sensitivity analysis, no adjustment will be made to the censoring time and all On-Trial Relapse or adjudicated On-Trial Relapse will be included in the analysis.

9.4.4. EQ-5D Calculations

The 3-level version of EQ-5D (EQ-5D-3L) was used in this study. EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (ie, state 11111). EQ-5D index scores for this study will be obtained using the US time trade-off (TTO) method.

The calculation is illustrated in the table below:

US TTO value set		Example: the value for health state 21232	
Full health (11111)	1.0	Full health =	1
Mobility = 2	-0.146	Minus MO level 2	-0.146
Mobility = 3	-0.558		
Self care = 2	-0.175	Minus SC level 1	-0.000
Self care = 3	-0.471		
Usual activities = 2	-0.140	Minus UA level 2	-0.140
Usual activities = 3	-0.374		
Pain/discomfort = 2	-0.173	Minus PD level 3	-0.537
Pain discomfort = 3	-0.537		
Anxiety/depression = 2	-0.156	Minus AD level 2	-0.156
Anxiety / depression = 3	-0.450		
D1	+0.140	Plus D1	+3*0.140
I2-square	-0.011	Minus I2-square	-4*0.011
I3	+0.122	Plus I3	+0*0.122
I3-square	+0.015	Plus I3-square	+0*0.015
		State 21232 = 0.397	

Where:

D1 = (Number of States ≠ 1) – 1

I2 = (Number of States = 2) – 1

I3 = (Number of States = 3) – 1

9.4.5. Severity of a Relapse

Severity of relapse (major or minor) will be measured by the OSIS scale. VA Subscale Scores will be used to categorize the severity of ON relapses. Motor Subscale Scores and Sensory Subscale Scores will be used to categorize the severity of TM relapses. Severity will be assessed at the time of the relapse.

If a patient has a relapse that includes more than one type of relapse, the worst grade will be used for the severity of the relapse. For example, a relapse that is both ON (minor) and TM (major) will be considered a major relapse.

ON Relapses:

The OSIS VA Scale is as follows:

- 0 = Normal
- 1 = Scotoma but corrected VA better than 20/30
- 2 = VA 20/30 – 20/59
- 3 = VA 20/60 – 20/100
- 4 = VA 20/101 – 20/200
- 5 = VA 20/201 – 20/800
- 6 = Count fingers only
- 7 = Light perception only
- 8 = No light perception

Severity of ON:

Visual Acuity Subscale Score		Relapse Descriptor
Pre-Relapse	Post-Relapse	
0-1	0-2	Minor
0-1	3+	Major
2-7	Increase by 1 point	Minor
2-7	Increase by ≥ 2 points	Major
0-8	No change or decrease	Minor

TM Relapses:

The OSIS Motor Function Scale is as follows:

- 0 = Normal
- 1 = Abnormal signs (hyperreflexia, Babinski sign) without weakness
- 2 = Mild weakness (Medical Research Council [MRC], Grade 5- or 4+) in affected limb(s)
- 3 = Moderate weakness (Grade 3 or 4) in 1 or 2 upper motor neuron (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

Severity of 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 ≥ 2 points	Major
0-7	No change or decrease	Minor

The OSIS Sensory Function Scale is as follows:

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

Severity of TM:

Sensory Subscale Score: any change in sensory function accompanied by a change of ≥ 1 point in any of the treating physician assessments below will be classified as a major relapse. If the sensory function is not unknown, the relapse will be classified as a minor severity. An unknown sensory function will be classified as an unknown severity.

Extremity	Assessment
Position sense upper extremity – Right	0-Normal 1-Mild 2-Moderate 3-Marked
Position sense upper extremity – Left	0-Normal 1-Mild 2-Moderate 3-Marked
Position sense lower extremity – Right	0-Normal 1-Mild 2-Moderate 3-Marked
Position sense lower extremity – Left	0-Normal 1-Mild 2-Moderate 3-Marked