Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN1210-NMO-307

A PHASE 3, EXTERNAL PLACEBO-CONTROLLED, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RAVULIZUMAB IN ADULT PATIENTS WITH NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

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1. APPROVAL SIGNATURES

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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 Acronym	Explanation
AD	Anxiety/Depression
ADA	Antidrug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
Anti-AQP4 Ab	Anti-aquaporin-4 Antibody
ARR	Annualized Relapse Rate
AZA	Azathioprine
BMI	Body Mass Index
BP (SF-36)	Bodily Pain (SF-36)
C5	Complement Component 5
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOPT	End of Primary Treatment Period
EOS	End of Study
EQ-5D	EuroQol 5 dimension health status
EuroQol	European quality of life
FAS	Full Analysis Set
FSS	Functional System Scores
GH	General Health (SF-36)
HAI	Hauser Ambulation Index
HR	Heart Rate
HRQoL	Health-related Quality of Life
HT	Reported Health Transition (SF-36)
ICF	Informed Consent Form
INT	Integer
IRT	Item Response Theory
IST	Immunosuppressive Therapy

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
IV	Intravenous
IVIg	Intravenous immunoglobulin
kg	Kilograms
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
mg	Milligrams
MH	Mental Health (SF-36)
MMF	Mycophenolate Mofetil
MO	Mobility
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NA	Not applicable
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
ON	Optic Neuritis
OSIS	Optic Spinal Impairment Score
PCS	Physical Component Summary
PD	Pharmacodynamics
PE	Plasmapheresis or Plasma Exchange
PF	Physical Function (SF-36)
PH	Proportional Hazards
PI	Principal Investigator
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Interval between the P wave and QRS complex
PT	Preferred Term (MedDRA)
PTAE	Pre-Treatment Adverse Events
PTSAE	Pre-Treatment Serious Adverse Event
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
QTc	corrected QT interval
QTcF	QT interval, Fridericia Correction
RAC	Relapse adjudication committee
RE	Role Emotional (SF-36)
RP	Role Physical (SF-36)
RR	Respiration rate
SAE	Serious Adverse Event

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software®
SC	Self-care
SBP	Systolic Blood Pressure
SF	Social Function (SF-36)
SF-36	Short Form Health Outcomes Survey (36 items)
sIPTW	Stabilized Inverse Probability of Treatment Weights
SoA	Schedule of Assessments
SOC	System Organ Class (MedDRA)
TAC	Tacrolimus
TEAE	Treatment-Emergent Adverse Event
TEAESI	Treatment-Emergent Adverse Events of Special Interest
TESAE	Treatment-Emergent Serious Adverse Event
TM	Transverse Myelitis
UA	Usual Activities
UMN	Upper Motor Neuron
VA	Visual Acuity
VAS	Visual Analogue Scale
VT	Vitality (SF-36)
WHO ATC	World Health Organization Anatomical Therapeutic Chemical
WHO-DD	World Health Organization Drug Dictionary

4. DESCRIPTION OF THE PROTOCOL

Study ALXN1210-NMO-307 is a Phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with neuromyelitis optica spectrum disorder (NMOSD). Approximately 55 eligible adult patients with NMOSD will be enrolled.

This study will employ a single-arm treatment design, utilizing the placebo group from Study ECU-NMO-301 (conducted 2014 to 2018) as a control. This will allow for a robust assessment of ravulizumab as a treatment option for NMOSD.

There are 4 periods in this study: Screening Period, Primary Treatment Period, Long-Term Extension Period, and Safety Follow-up Period. Patients will be screened for eligibility for up to 6 weeks during the Screening Period. The end of the Primary Treatment Period will be triggered when either (1) two patients have had an adjudicated On-Trial Relapse; or (2) all patients have completed, or discontinued prior to, the Week 26 Visit; whichever comes later. However, if 2 patients have not had an adjudicated On-Trial Relapse by the time all patients have completed, or discontinued prior to, the Week 50 Visit, the end of the Primary Treatment Period will be triggered at that time. Note that patients who complete the visits indicated above (Week 26 or Week 50) will remain on the study in the Primary Treatment Period until the Primary Treatment Period ends. Based on the estimated enrollment rate, the duration of the Primary Treatment Period for each patient is expected to be between 26 weeks and approximately 2.5 years. The Primary Treatment Period ends and the Long-Term Extension Period starts when all patients have completed their End of Primary Treatment (EOPT) Visit within the timeframe specified in Protocol Section 4.4. All patients will continue to receive ravulizumab during the Long-Term Extension Period for up to approximately 2 years, or until ravulizumab is approved and/or available (in accordance with country-specific regulations), whichever occurs first. The total treatment duration for each patient will be up to approximately 4.5 years. After the last dose of study drug or early discontinuation, patients will be followed for 8 weeks.

The study objectives and endpoints are as follows:

Objectives	Endpoints
Primary	
• To evaluate the effect of ravulizumab on adjudicated On-Trial[a] Relapses in adult patients with NMOSD	• Time to first adjudicated On-Trial Relapse and relapse risk reduction
Secondary[b]	
• To evaluate the safety of ravulizumab in adult patients with NMOSD	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
• To evaluate the effect of ravulizumab on adjudicated annualized relapse rate (ARR) in adult patients with NMOSD	• Adjudicated On-Trial ARR
• To evaluate the effect of ravulizumab on disease-related disability in adult patients with NMOSD	• Clinically important worsening from baseline in Expanded Disability Status Scale (EDSS)

Objectives	Endpoints
• To evaluate the effect of ravulizumab on QoL in adult patients with NMOSD	• Change from baseline in EuroQol-5D (EQ-5D)
• To evaluate the effect of ravulizumab on neurologic function in adult patients with NMOSD	• Clinically important change from baseline in Hauser Ambulation Index (HAI)
• To characterize the PK of ravulizumab in adult patients with NMOSD	• Change in serum ravulizumab concentration over the study duration
• To characterize the pharmacodynamics (PD) of ravulizumab in adult patients with NMOSD	• Change in serum free C5 concentration over the study duration
• To characterize the immunogenicity of ravulizumab in adult patients with NMOSD	• Presence and titer of antidrug antibodies (ADAs) over the study duration
Exploratory	
• To evaluate the effect of ravulizumab on severity of adjudicated relapse in adult patients with NMOSD	• Change from baseline in Optic Spinal Impairment Score (OSIS)
• To evaluate the effect of ravulizumab on neurologic function in adult patients with NMOSD	• Characterize the change from baseline in visual acuity, color vision, and confrontational visual fields
• To evaluate the effect of ravulizumab on QoL in adult patients with NMOSD	• Change from baseline in Short Form Health Survey (SF-36)
• To evaluate the safety of ravulizumab in adult patients with NMOSD	• Change from baseline in vital signs, electrocardiogram (ECG) parameters, and clinical laboratory assessments • Shifts from baseline in Columbia Suicidal Severity Rating Scale (C-SSRS)
• To characterize biomarkers in adult patients with NMOSD	• Change from baseline in levels of biomarkers of complement dysregulation, neuroinflammation and neural injury • Blood and cerebrospinal fluid (CSF) AQP4 Ab concentration

[a] On-Trial Relapses refer to relapses as determined by the Treating Physician that occur during the Study Period. All relapses will be adjudicated by an independent Adjudication Committee.
[b] Secondary efficacy endpoints will be analyzed in the rank order provided in Section 5.1.2 in order to maintain study-level alpha.

This SAP describes the analyses of the Primary Treatment Period. Another SAP will be developed to describe the analyses that include the Long-Term Extension Period.

4.1. Changes from Analyses Specified in the Protocol

Applicable changes from Protocol Amendment 1.0 are as follows:

- The modified Full Analysis set (mFAS) had been identified as the analysis set for the primary analyses of the primary and secondary efficacy endpoints. However, per regulatory feedback, this analysis set is removed and the impact of participants having missed a dose or having delayed a dose by > 35 days due to the coronavirus disease 2019 (COVID-19) pandemic, is addressed using strategies described briefly in Section 4.2 and in later sections of this SAP.
- The protocol states “To account for potential differences in baseline characteristics between the ravulizumab group and the external placebo control, efficacy analyses will include covariate adjustment methodologies, as warranted. Details will be

provided in the SAP." In this SAP the covariate adjustment methodologies are described more specifically as propensity score methodologies.

- Sensitivity analyses have been added.

4.2. Changes from Analyses Specified in the Previous Version of the SAP

Changes from SAP version 2.0 described in bullets a, b, and c are in direct response to regulatory feedback concerning the mFAS:

a. The mFAS is removed, Section 6 Data Sets Analyzed (Study Populations).

b. The analysis set to be used for the primary analyses is the FAS; Section 7.2

c. The following updates were made to account for the impact of missing a dose or having delayed a dose by > 35 days due to the COVID-19 pandemic:

   i. The analysis of the primary endpoint (time to first adjudicated On-Trial Relapse) will be censored at the time of patients missing a dose or having delayed a dose by > 35 days due to COVID-19; Section 7.2.1, Appendix 9.5.1.

   ii. The analysis of the adjudicated On-Trial Annualized Relapse Rate (ARR) will exclude the time period from the first missed or delayed dose due to COVID-19 until the day before the next dose of study drug; Section 7.2.2, Appendix 9.5.2.

   iii. The EDSS, HAI, EQ5D index, and EQ5D VAS scores obtained prior to the first missed or delayed dose due to COVID-19 will be included in the analysis; Section 7.2.2, Appendix 9.5.2.

d. The analysis of the adjudicated On-Trial ARR had been described using a confidence interval (CI) approach, and has been reframed using a p-value approach, both approaches would result in the same outcome; Section 7.2.2, Appendix 9.5.10.2.1.

e. The randomization-based nonparametric ANCOVA approach described for analysis of the EQ-5D endpoints and SF-36 is replaced with an approach more suitable for a non-randomized trial. An ANCOVA on the ranks of the change from baseline will be performed with treatment as a factor and the ranks of the baseline values as a covariate.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint(s)

The primary efficacy endpoint is time to first adjudicated On-Trial Relapse.

Note, for the purposes of the protocol and this SAP, the terms “relapse” and “attack” are synonymous.

Relapses (ie, attacks) within 12 and within 24 months prior to the Screening Visit will be summarized and adjudicated On-Trial Relapses will be analyzed. For the definition of historical relapses, please refer to Protocol Section 8.2.3.1. For patients who have a relapse during any Screening Period and get rescreened and treated in the study, any relapses during the prior Screening Periods will be counted as historical relapses in the assessment of historical annualized relapse rate. The definitions of On-Trial Relapse and adjudicated On-Trial Relapse are as follows:

On-Trial Relapse:

On-Trial Relapses are acute attacks, as confirmed by the treating physician, that occur during the Study Treatment Period. 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 NMOSD, ie, 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.

Adjudicated On-Trial Relapse:

On-Trial Relapses will be independently reviewed by the Relapse Adjudication Committee (RAC), which consists of physicians who have particular expertise in NMOSD and will conduct independent reviews of all On-Trial Relapses. The committee will decide by majority vote whether each reported On-Trial Relapse meets the objective criteria for an On-Trial Relapse. A separate RAC Charter will document all adjudication criteria and procedures for this study. Throughout this SAP, adjudicated On-Trial Relapse refers to an On-Trial Relapse as confirmed by the treating physician that was positively adjudicated by the RAC. An adjudicated relapse refers to a relapse that was positively adjudicated by the RAC, regardless of whether it was confirmed as an On-Trial Relapse by the treating physician.

5.1.2. Secondary Endpoints

As described in the protocol, a closed testing procedure will be applied to control the type I error for the analyses of the primary and secondary endpoints. If the primary endpoint is statistically significant in favor of ravulizumab, the secondary endpoints will be evaluated according to the following rank order:

1. Adjudicated On-Trial Annualized Relapse Rate

2. Clinically important changes from baseline in ambulatory function as measured by HAI
3. Change from baseline in EuroQol (EQ-5D) index score
4. Change from baseline in EQ-5D visual analogue scale (VAS) score
5. Clinically important worsening from baseline in EDSS score

However, in support of submissions to the EMA, the secondary endpoints will be evaluated according to the following rank order:

1. Adjudicated On-Trial ARR
2. Clinically important worsening from baseline in EDSS score
3. Clinically important changes from baseline in ambulatory function as measured by HAI
4. Change from baseline in EQ-5D index score
5. Change from baseline in EQ-5D VAS score

5.1.2.1. Adjudicated On-Trial ARR

Based on adjudicated On-Trial Relapses and treatment duration in the study, an annualized relapse rate will be computed. Details of adjudicated On-Trial ARR can be found in Appendix 9.5.2.2.

5.1.2.2. Hauser Ambulation Index (HAI)

The HAI evaluates mobility. This index is used to assess the time and degree of assistance required for the patient to walk 25 feet (8 meters). The scale ranges from 0 to 9; 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst (restricted to wheelchair; unable to transfer self independently). This HAI score will be presented as clinically important change (clinical improvement, stable, clinical worsening). For details, please refer to Appendix 9.5.4.

5.1.2.3. EQ-5D Index Score and VAS Score

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, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 3 levels (some, moderate, or 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-5D Visual Analogue Scale (EQ-5D VAS), which captures the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.

For details please refer to Appendix 9.5.5.

5.1.2.4. Extended Disability Status Scale (EDSS)

The EDSS is an ordinal clinical rating scale which 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 (Functional System Scores, 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.

The EDSS Rater will perform the neurological assessment to determine if the relapse is associated with changes in any of the FSS or total EDSS score.

This EDSS score will be presented as clinically important worsening (yes/no). For details, please refer to Appendix 9.5.6.

5.1.3. Exploratory Endpoints

The exploratory efficacy endpoints for the study are:

1. Optic Spinal Impairment Score (OSIS)
2. Change from baseline in visual acuity, color vision, and confrontational visual fields
3. Change from baseline in the SF-36 domain scales and summary scores
4. Change from baseline in the EQ-5D 5 dimensions of health
5. Medical resource utilization

5.1.3.1. OSIS

Severity of relapse (major or minor) will be measured by the OSIS. Visual Acuity (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.

See Appendix 9.5.7 for details.

5.1.3.2. Visual Acuity

Visual acuity is usually affected by ON, progressing over a period of hours to days. The Landolt C ring chart will be used to assess VA in Study ALXN1210-NMO-307; in Study ECU-NMO-301, the Snellen chart was used.

The Landolt C ring chart and the Snellen chart measure visual acuities using different characters. The Landolt C ring chart is performed at 4 meters or 13 feet in this study while the Snellen chart has been developed to be performed at multiple distances, including 6 meters or 20 feet. Both are typically recorded as acuity ratio distance (6 meters or 20 feet, 4 meters or 13 feet); so, for normal VA they would be recorded as 20/20 or 6/6, or 13/13 or 4/4. Sometimes this is entered as the denominator of the Landolt or Snellen fraction (in the US) or as a decimal (outside the US). Differences in methodologies have been reported as resulting in small differences in visual acuity ratios, which are not statistically significant.

Summaries and analyses will be performed using the results from the EDSS Rater assessments.

5.1.3.3. Color Vision

Color vision will be assessed using Ishihara plates [Ishihara, 2020]. Patients with 14 or more correctly identified plates will be considered as having normal color vision, and patients with 13 or less correctly identified will be considered as having abnormal color vision.

5.1.3.4. Confrontational Visual Fields

Confrontational Visual Fields will be measured for each quadrant of each seeing eye as whether a deficit was identified (yes/no) to obtain the number of quadrants with a deficit.

5.1.3.5. SF-36 Quality of Life

The SF-36 is a patient self-administered questionnaire designed to assess generic health related quality of life (QoL) in healthy and ill adult populations. The SF-36 consists of 36 items organized into the 8 scales shown below as well as the reported health transition item. The SF-36 also yields 2 summary measures of physical health (the Physical Component Summary[PCS] measure) and mental health (the Mental Component Summary [MCS] measure) 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 form 1 year prior based on SF-36 item 2

Version 2 of the SF-36 questionnaire will be used in this study. See the protocol appendix 8 for SF-36 questionnaire.

5.1.3.6. EQ-5 Dimensions

The EQ-5D is described in Section 5.1.2.3 and comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 3 levels (some, moderate, or extreme problems).

See the protocol appendix 7 for the EQ-5D.

5.1.3.7. Medical Resource Utilization

Medical resource utilization, associated with medical encounters, will be collected for all patients throughout the study. The data will include:

- Duration of hospitalization
- Number and type of diagnostic and therapeutic tests and procedures
- Number of surgeries, and other selected procedures (inpatient or outpatient)

5.2. Safety

The safety of ravulizumab will be assessed based on adverse events (AEs), serious adverse events (SAEs), and changes from baseline through study completion in vital signs, routine clinical laboratory tests (eg, clinical chemistry, hematology), physical examination, electrocardiogram results, Columbia-Suicide Severity Rating Scale, and pregnancy tests for female patients of childbearing potential.

5.2.1. Adverse Events (AEs)

Adverse events are defined in Protocol Section 10.3.

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the last visit at the time points specified in the Schedule of Assessments (SoA) (Protocol Section 1.3).

For the purposes of this SAP, four types of AEs will be noted:

- Pre-treatment adverse events and serious adverse events (PTAEs and PTSAEs, respectively)
- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (TESAEs)

PTAEs are the AEs that occur between the signing of informed consent and first dose of study drug (ie, ravulizumab or placebo). PTSAEs are the serious AEs that occur between the signing of informed consent and first study drug dose (ie, ravulizumab or placebo). TEAEs are AEs with onset on or after the first study drug dose in the study. Likewise, TESAEs are SAEs with onset on or after the first study drug dose in the study.

5.2.2. Vital Signs

Temperature (°C or °F), pulse rate, respiratory rate, and systolic and diastolic blood pressure (SBP and DBP, respectively) (mmHg) will be assessed.

Body weight will be measured in pounds or kilograms. Height will be measured in inches or centimeters.

5.2.3. Laboratory Assessments

Chemistry panel, complete blood count and differential, urinalysis, and serum pregnancy test will be collected as outlined in the SoA (See Protocol Section 1.3).

Immunogenicity: blood samples will be collected for evaluation for antidrug antibody at specified time points to describe the presence or absence of an immune response to ravulizumab.

5.2.4. Other Safety Assessments

5.2.4.1. Physical Examination

A complete physical examination will include, at a minimum, assessments of the following organs/body systems: general appearance, skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and musculoskeletal.

A brief physical examination will include, at a minimum, a body-system relevant examination based upon Investigator judgment and patient symptoms.

5.2.4.2. Electrocardiogram (ECG)

Single 12-lead ECG will be obtained as outlined in the SoA (see Protocol Section 1.3) using an ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, and QT intervals. Whether the ECG is within normal limits and the clinical significance of abnormal results will be documented.

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

The C-SSRS is a measure of suicidal ideation and behavior.

As the study drug is being evaluated for a neurologic indication, patients being treated with the study drug should be monitored appropriately and observed closely for suicidal ideation or behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study drug, or at the time of dose changes.

Baseline assessment of suicidal ideation and behavior as well as intervention-emergent suicidal ideation and behavior will be monitored during this study using C-SSRS.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

This study will employ a single-arm treatment design, utilizing the placebo group from Study ECU-NMO-301 (conducted from 2014 to 2018) as an external placebo control. This will allow for a robust assessment of ravulizumab as a treatment option for NMOSD.

6.1. Full Analysis Set (FAS)

The FAS consists of all patients who have received at least 1 dose of study drug (ravulizumab or placebo).

6.2. Per Protocol Set (PPS)

The Per Protocol Set (PPS) is a subset of the FAS population, excluding patients with major (ie, important) protocol deviations. The PPS will include all patients who:

- Have no important 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 Treatment Period.

Important protocol deviations and key inclusion/exclusion criteria that will result in excluding patients from the PPS are discussed in Section 7.1.2.

For FAS patients in the study who have an On-Trial Relapse, the calculation for being at least 80% compliant with the required treatment doses for the PPS will include the time period from the first study dose of study drug to the day of the first On-Trial Relapse. Time on study after the date of the first On-Trial Relapse is not counted in the determination of treatment compliance for this PPS requirement, as the PPS will be used in the analysis of time to first relapse.

The PPS for the ravulizumab group will be determined prior to database lock and will be used in a sensitivity analysis of the time to adjudicated On-Trial Relapse. The PPS for the Study ECU-NMO-301 placebo group was determined prior to the database lock for that study (details of patients excluded from that PPS are given in Appendix 9.6).

6.3. Safety Set

The Safety Set includes all patients who receive at least 1 dose of study drug (ravulizumab or placebo).

Patients who have signed informed consent but are not treated in the study are not included in the Safety Set. However, if these patients report SAEs, after the signing of informed consent, these events will be summarized separately in listings, as appropriate.

6.4. Other Sets

6.4.1. PK/PD

Pharmacokinetics/pharmacodynamics (PK/PD) analyses will be performed on the PK/PD Analysis Set. This population includes patients who receive at least 1 dose of study drug and who have at least one evaluable PK or PD result.

7. STATISTICAL ANALYSIS

This is an open-label, external placebo-controlled study to evaluate ravulizumab in NMOSD patients with the primary endpoint of time to first adjudicated On-Trial Relapse. The placebo treatment arm in Study ECU-NMO-301 will serve as the external control.

The primary analysis will be conducted when all patients have completed the Primary Treatment Period. This analysis will include all efficacy, safety, and PK/PD study data for regulatory submission purposes and will be the final analysis of the Primary Treatment Period.

Summary statistics will be computed and displayed by treatment group and by visit, where applicable (eg, summaries related to the COVID-19 pandemic are only relevant to the ravulizumab arm). Descriptive statistics for continuous variables will minimally include the number of patients, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate. All statistical analyses will be performed based on a 2-sided type I error of 5% unless noted otherwise.

Analyses will be performed using the SAS® software Version 9.4 or higher.

7.1. Study Patients

7.1.1. Disposition of Patients

A table summarizing the number of screened patients, number and percentage of screen failures, reasons for screen failure (including COVID-19 related reasons overall and by reason), and number and percentage of treated patients among all screened patients will be provided. A summary and by-patient listing of the reasons for screen failure will also be produced.

Summaries of patient disposition will include all patients treated in the current study. The following summaries will be generated:

- Patients who were treated
  - In the current study (ie, with ravulizumab)
  - By region (America, Europe, and Asia-Pacific)
  - By site
- Patients who discontinued the study with reason for discontinuation (including COVID-19 related reasons)
- Patients in analysis datasets and reason for exclusion from specific datasets
- Patients with inclusion/exclusion criteria violations

The disposition of patients at study visits will also be summarized to show the number and percentage of patients who completed at least one study visit that was altered to accommodate COVID-19 restrictions, reasons for these modified study visits, and a summary showing descriptive statistics of the proportion of modified study visits per patient. 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 the listings.

7.1.2. Protocol Deviations

The protocol deviations will be summarized in a table and a listing. Summaries will be presented overall and for COVID-19 related deviations, by important and not important deviations.

For the purposes of defining the PPS, important protocol deviations are:

- Not meeting all of the key inclusion or meeting any of key exclusion criteria.

  Key inclusion criteria are:

  – Anti-aquaporin-4 antibody (anti-AQP4 Ab)-positive and a diagnosis of NMOSD as defined by the 2015 international consensus diagnostic criteria (Wingerchuk, 2015). A historically positive anti-AQP4 Ab test may be acceptable if the test was performed using an acceptable, validated cell-based assay from an accredited laboratory

  – At least 1 attack or relapse in the last 12 months prior to the Screening Period

    NOTE: Patients with a single lifetime attack will be considered to satisfy this inclusion criterion if the attack occurred in the last 12 months

  – Expanded Disability Status Scale (EDSS) score ≤ 7

  – Patients who enter the study receiving supportive immunosuppressive therapy (IST) (eg, corticosteroids; azathioprine [AZA]; mycophenolate mofetil [MMF]; methotrexate [MTX]; and tacrolimus [TAC]) for the prevention of relapse, either in combination or monotherapy, must be on a stable dosing regimen of adequate duration prior to Screening with no plan to change the dose during the Study Period as follows:

    a) If patients who enter the study are receiving AZA, they must have been on AZA for ≥ 6 months and have been on a stable dose for ≥ 2 months prior to Screening.

    b) If patients who enter the study are receiving other ISTs (eg, MMF, MTX, or TAC), they must have been on the IST for ≥ 3 months and have been on a stable dose for ≥ 4 weeks prior to Screening.

    c) If patients who enter the study are receiving oral corticosteroids, they must have been on a stable dose for ≥ 4 weeks prior to Screening.

    d) If a patient enters the study 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.

  Key exclusion criteria are:

  – Previously or currently treated with a complement inhibitor

  – Use of rituximab within 3 months prior to Screening

  – Use of mitoxantrone within 3 months prior to Screening

  – Use of intravenous immunoglobulin (IVIg) within 3 weeks prior to Screening

- Patients who took less than 80% of the required treatment doses
- Taking a prohibited medication. The following medications are prohibited during the study and will result in the patient being excluded from the PPS:
  - Mitoxantrone
  - Rituximab or other biologics that may affect immune system functioning (eg, tocilizumab, ocrelizumab, satralizumab, or inebilizumab)
  - Immunomodulatory therapies, including interferon beta-1b; interferon beta-1a, glatiramer acetate, natalizumab, alemtuzumab, dimethyl fumarate, teriflunomide, siponimod, and fingolimod
  - IVIg or subcutaneous Ig used as maintenance therapy

    Note: IVIg used acutely for relapse treatment is allowed
  - PE for relapse prevention
  - Bruton tyrosine kinase (BTK) inhibitors
- Change in dosing or addition of an IST during the Primary Treatment Period if the patient did not relapse in that period, or prior to the first relapse, if the patient relapsed during the Primary Treatment Period. A single dose steroid injection due to safety related event will not be considered a protocol deviation. More than single dose steroid injection up to 3 days of injection of high-dose steroids will be considered a minor (not important) protocol deviation. High-dose steroids of greater than 3 days will be considered a major (important) protocol deviation.

Patients in the placebo treatment group excluded from the PPS in Study ECU-NMO-301 will be excluded from the PPS in this study; reasons for exclusion were similar to those described for excluding patients in the ravulizumab treatment group, but include also excluding patients who were unblinded to study treatment. Appendix 9.6 identifies the patients in the placebo treatment group who are excluded from the PPS.

7.1.3. Demographics, Disease Characteristics, and History

Patient demographic and baseline characteristics will be summarized by treatment group, using the Safety Set and the PPS. Summary statistics will be presented. No formal hypothesis testing will be performed.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (at first dose date)
- Sex
- Race and ethnicity
- Japanese patient

- Region

- Baseline weight
- Baseline height
- Baseline body mass index (BMI)

7.1.3.2. Disease Characteristics

The following NMOSD disease characteristics will be summarized:

- Age at NMOSD initial clinical presentation (years)
- Age at NMOSD diagnosis (years)
- NMOSD initial clinical presentation
- Time from initial clinical presentation to first dose date (years)
- Time from NMOSD diagnosis to first dose date (years)
- Time from initial clinical presentation to NMOSD diagnosis (months)
- EDSS, EQ-5D index, EQ-5D VAS, HAI, and OSIS scores at baseline

7.1.3.3. Medical/Surgical History, Baseline Physical Examination

Baseline medical history information, ie, number and percentage of patients who have a medical or surgical history will be summarized by treatment group for the Safety Set. Likewise, baseline physical examination information will be summarized for the Safety Set. The medical and surgical history will be summarized by the Medical Dictionary for Regulatory (MedDRA) Activities, Version 21.0, or later by SOC and Preferred Terms. By-patient listings will be created for medical/surgical history and physical examinations.

History of prior NMOSD relapses including a summary of the type of relapses and the number of prior relapses and the annualized relapse rate in the 24 months prior to the Screening Visit and the 12 months prior to Screening Visit will be summarized by treatment group for patients in the Safety Set and PPS.

7.1.4. Prior and Concomitant Medications/Therapies

Prior medications are defined as medications taken or therapies received by patients prior to the first study treatment. Concomitant medications are defined as medications taken or therapies received by patients during the study after first dose of study drug. Medications will be coded using the World Health Organization Drug Dictionary (WHO DD 2021MAR or higher). Summaries will be performed on the Safety Set.

Prior and concomitant medications will be summarized for patients in the ravulizumab arm, unless otherwise specified. The number and percentage of patients using prior and concomitant medications will be summarized based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Level 4 Class Code and generic name. Listings of prior and concomitant medications will be produced. For those patients diagnosed with COVID-19, a summary table of concomitant medications with a start date on or after as well as, on or within 6 months after the first COVID-related AE will also be presented.

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

The following medications are allowed under certain circumstances and restrictions.

Immunosuppressive therapy agents:

- The choice of IST agents is at the discretion of the Treating Physician with the exception of the disallowed medications. Immunosuppressive agents, such as corticosteroid, AZA, MMF, methotrexate, tacrolimus, cyclosporine or cyclophosphamide either in combination or as monotherapy are permitted.
- If a patient enters the study receiving IST(s) for relapse prevention, the patient must have been on a stable maintenance dose of these IST(s), as defined by the protocol, prior to the Screening Visit. No adjustment in IST dosage, including discontinuation, and no new ISTs will be permitted for the first 106 weeks, unless the patient experiences a relapse or a safety event, and a change in IST dose or regimen is deemed necessary by the Investigator to guarantee the patient's safety.
- If a patient enters the trial receiving steroids either as monotherapy or in combination with another IST, the daily steroid dose cannot be more than prednisone 20 mg daily (or equivalent).

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). Supportive IST treatment for relapse prevention used prior to study treatment and at baseline will be summarized by treatment group. The subgroups of supportive IST at baseline will be summarized by treatment group. Listings of supportive ISTs will be produced. Changes in ISTs during the study will be summarized.

If prohibited medications are used by patients in this study, then a listing of those patients and the respective prohibited medication(s) will be produced.

7.2. Efficacy Analyses

The primary analysis of efficacy will be performed on the FAS. The primary efficacy analysis of time to first adjudicated On-Trial Relapse and some sensitivity analyses will also be performed on the PPS as described in Section 7.2.1. Baseline is defined as the last available assessment prior to treatment for all patients regardless of treatment group.

7.2.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is time to first adjudicated On-Trial Relapse. The time to first adjudicated On-Trial Relapse will be evaluated using the log-rank test; the null hypothesis will be that there is no difference in the survival curves of the ravulizumab and the placebo treatment groups. The alternative hypothesis will be that there is a difference between the two survival curves, and ravulizumab is superior to placebo.

The study will be considered to have met its primary efficacy objective if a statistically significant difference (ie, 2-sided p-value ≤ 0.05) is observed between the ravulizumab treatment group and the placebo group for the primary endpoint of the time to first adjudicated On-Trial Relapse. The comparison of the treatment groups for the primary endpoint will use a log-rank

test. Hazard ratio and risk reduction will be summarized from a Cox proportional hazards model including treatment group as a factor. If there is no observed event in a treatment arm then Firth's Penalized Likelihood (Heinze, 2001) will be used to estimate the hazard ratio, risk reduction, and the profile likelihood 95% CIs (see Appendix 9.5.10.1 for more details). The Kaplan-Meier estimates of proportion of patients with no adjudicated On-Trial Relapse will be presented for various time points (eg, Week 24, Week 48) with a 95% CI based on the complementary log-log transformation. A figure showing the Kaplan-Meier curves of the time to first adjudicated On-Trial Relapse for each treatment group will be produced.

Definitions of the time to first event and the censoring times are provided in Appendix 9.5.1. A censoring indicator will be equal to 1 if the patient did not experience a relapse (was censored) during this time, and 0 if the patient experienced a relapse. In addition, those patients who, for COVID-19-related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether will be censored at the time of the missed dose, if the missed or delayed dose occurred before the EOPT Visit or the 6-week Post-relapse Visit. To balance the evaluation period, patients in the placebo treatment group who were followed longer than patients in the ravulizumab treatment group will be censored at the maximum time observed in the ravulizumab treatment group. Any relapses that had been observed among patients in the placebo group after that time will not be included in the primary analysis.

Sensitivity Analyses of the Primary Endpoint

The following sensitivity analyses will be performed:

- A sensitivity analysis of the primary analysis described above for the FAS will also be performed using the PPS.
- A sensitivity analysis of the primary analysis described above for the FAS will be performed in which patients who were diagnosed with COVID-19 and had not relapsed prior to COVID-19 infection are censored on the start date of the first COVID-19 related AE.
- A sensitivity analysis of the primary analysis will also be performed in which patients who, for COVID-19 related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether are not censored at the time of the missed dose.
- A sensitivity analysis for the comparison of the treatment groups for the primary endpoint will be performed as described above but stratified using propensity score strata. The propensity score is the probability of being assigned to the placebo arm vs the ravulizumab arm and is estimated from a logistic regression that includes observed baseline characteristics as predictors of the treatment assignment. In lieu of having a randomized study, the propensity score serves to balance treatment groups on the baseline characteristics. (Austin, 2011). A propensity score will be estimated for each patient and categorized into two strata, such that each patient is identified has having a low (≤ median) or high (> median) probability of being in the placebo treatment group. The analysis will be performed using a log-rank test, stratified on

propensity score strata. Hazard ratio and risk reduction will be summarized from a Cox proportional hazards model, also stratified using propensity score strata. This will be performed for the FAS and the PPS. Further details of the propensity score are provided in Appendix 9.5.3.

- A sensitivity analysis of the comparison of the treatment groups for the primary endpoint will be performed as described above, but weighted using the stabilized inverse probability of treatment weights (sIPTW), which are calculated using the propensity score and described in more details in Appendix 9.5.3. The analysis will be performed using a weighted log-rank test and Kaplan-Meier curves will be presented using weighted Kaplan-Meier estimates (Xie, 2005); the hazard ratio and risk reduction will be summarized from a weighted Cox proportional hazards model. Estimates of the hazard ratios from the weighted Cox proportional hazards model represent the average treatment effect. This will be performed using the FAS, and the PPS.
- A tipping point analysis using the E-value approach proposed by Vanderweele, 2017 will be conducted. The E-value, constructed as a risk ratio, quantifies the level of confounding which could compensate the estimated treatment effect; the smallest E-value of 1 represents no confounding. The E-value will be calculated using the hazard ratio from the Cox proportional hazards model using both the unstratified model described for the primary analysis and the model stratified using propensity score strata. This value will be calculated for both the estimate and the upper 95% confidence limit using the FAS, and the PPS. See Appendix 9.5.11 for details.
- A sensitivity analysis of the primary analysis will be performed, using the randomization stratification variable from Study ECU-NMO-301: four strata based on the EDSS score and IST status (1) low EDSS stratum at randomization (≤ 2.0), (2) high EDSS stratum (≥ 2.5 to ≤ 7) and treatment naïve patients at randomization, (3) high EDSS stratum (≥ 2.5 to ≤ 7) and patients continuing on the same IST(s) since last relapse at randomization, and (4) high EDSS stratum (≥ 2.5 to ≤ 7) and patients with changes in IST(s) since last relapse at randomization. These analyses will be performed using the observed strata based on the EDSS and IST strata observed at baseline.
- A sensitivity analysis of the primary analysis will be performed using a Cox proportional hazards model including treatment group as a factor and adjusting for the time since the most recent relapse relative to Day 1.
- An analysis of adjudicated relapses in which the primary endpoint includes adjudicated On-Trial Relapses as well as any positively adjudicated relapses that were not determined by the treating physician to be an On-Trial Relapse (ie, case of interest) will be performed for the FAS and the PPS.

A summary of adjudicated On-Trial Relapses by region, age group (≥ 45 vs < 45 years), gender, and race, propensity score strata, and the randomization stratification variable from Study ECU-NMO-301 will be produced. In addition, the following subgroups will be used for data summary purposes based on anticipated IST and steroid usage as standard of care.

  - No IST usage (monotherapy)

- Use of steroids alone
- Use of azathioprine*
- Use of mycophenolate mofetil*
- Any Other IST usage
- Any IST usage
- Use of rituximab in the year prior to Screening

Note: * indicates aggregate subgroup including the IST alone or in combination with steroids.

For each subgroup, the following descriptive summaries of adjudicated On-Trial Relapses and graphical information will be produced by treatment group:

1. Summary of the number of patients
2. Summary of the number and percentage of patients with adjudicated On-Trial Relapses
3. Estimated proportion of subjects experiencing no adjudicated On-Trial Relapse at various time points (Kaplan-Meier estimate)
4. Summary of the total number of adjudicated On-Trial Relapses
5. Summary of the total patient-years in Study Period
6. Summary of the adjudicated On-Trial ARR
7. Kaplan-Meier curves for the time to first adjudicated On-Trial Relapse, with p-values generated for the IST and steroid use subgroups listed above, prior rituximab use, and propensity score strata subgroups, of the treatment group comparison using the log-rank test. Figures will include estimates and 95% CI of the proportion of patients relapse free.
8. Forest plots showing the treatment group hazard ratio for each subgroup will be provided, with p-values of treatment group comparisons within subgroups from a log-rank test and interactions of subgroup and treatment group from a Cox proportional hazards model presented for each subgroup listed above.

   P-values of planned statistical tests of these subgroups will be considered nominal.

Adjudicated On-Trial Relapses will also be evaluated summarizing the number and rate of relapses requiring hospitalization and the number and rate of acute treatments for relapses (ie, IV methylprednisolone, plasma exchange, and high-dose oral steroids) by treatment group. Rates will be compared across treatment groups using Poisson regression, with treatment group as a factor and the log of time as an offset variable. For those patients who, for COVID-19 related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether, the time interval from the missed dose until the start of the next dose and any relapse requiring hospitalization or acute treatment that occurred in this interval will be excluded from these summaries and analyses. Use of IVIg will be summarized but not analyzed.

7.2.1.1. Handling of Dropouts or Missing Data

In this study, all FAS, and PPS patients would either have experienced an adjudicated On-Trial Relapse or would have ended participation in the Primary Treatment Period without an adjudicated On-Trial relapse. The patients who do not have adjudicated On-Trial Relapses will be censored and will have a censor time that is based on the patient's time from first dose of study drug to the end of the Primary Treatment Period date (or end of study for the placebo treatment group). In addition, those patients who, for COVID-19 related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether will be censored at the time of the missed dose, if the missed or delayed dose occurred before the EOPT Visit or the 6-week Post-relapse Visit. A censoring indicator will be equal to 1 if the patient did not experience an adjudicated On-Trial Relapse (was censored), and 0 if the patient experienced an adjudicated On-Trial Relapse. Reasons for censoring will be summarized by treatment group. Censoring times are described in more detail in Appendix 9.5.1.

Missing data for the primary analysis of EDSS, EQ-5D (index and VAS), and HAI, at the EOPT will be handled as follows which is consistent with the approach used in Study ECU-NMO-301: If the assessment 6 weeks after the first On-Trial Relapse is missing or if a non-relapse patient is missing the EOPT score (for the ravulizumab treatment group) or the EOS score (for the placebo treatment group), the last observed score from a protocol scheduled visit will be used. If a patient has no post-baseline assessments, the baseline value will be used. If a patient experiences a second On-Trial Relapse during the 6-week recovery phase after the initial relapse, the last score prior to the second attack will be used for the analysis.

Missing data for SF-36 QoL will be handled as specified in this SAP in Appendix 9.5.8.7.

7.2.1.2. Subgroup Analysis

Some efficacy analyses will involve subgroups of the FAS:

1. The assessment of the severity and type of relapses will be conducted by treatment group in the subgroup of patients who had adjudicated On-Trial Relapses.
2. The assessment of visual acuity, color vision, and confrontational visual fields will be conducted in the subgroup of patients with vision at baseline in at least one eye.

7.2.1.3. Multicenter Studies

Since a small number of patients are anticipated at each center, center will not be used as a covariate in the efficacy analyses.

7.2.1.4. Hypothesis Testing and Significance Level

The ravulizumab 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.

7.2.1.5. Sensitivity Analyses

Sensitivity analyses for the primary endpoint are described above. In addition, sensitivity analyses of the secondary endpoints will be performed adjusting for propensity score strata and also adjusting for Study ECU-NMO-301 observed randomization strata, with details provided in Section 7.2.2.

7.2.2. Secondary Efficacy Endpoint Analyses

The primary analysis of secondary efficacy endpoints will be performed on the FAS.

A closed testing procedure will be applied to control the type I error for the analyses of the primary and secondary endpoints. If the primary endpoint is statistically significant in favor of ravulizumab, the secondary endpoints will be evaluated according to the following rank order:

1. Adjudicated On-Trial ARR
2. Clinically important changes from baseline in ambulatory function as measured by HAI
3. Change from baseline in EQ-5D index score
4. Change from baseline in EQ-5D VAS score
5. Clinically important worsening from baseline in EDSS score

The hypothesis testing will proceed from highest rank (#1) the adjudicated On-Trial ARR to the lowest rank (#5) EDSS score, and if statistical significance is not achieved at an endpoint ($p > 0.05$), 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.

However, in support of submissions to the EMA, the rank order of analyses of these endpoints will be as follows:

1. Adjudicated On-Trial ARR
2. Clinically important worsening from baseline in EDSS score
3. Clinically important changes from baseline in ambulatory function as measured by HAI
4. Change from baseline in EQ-5D index score
5. Change from baseline in EQ-5D VAS score

The hypothesis testing will proceed as described above, however, beginning with the highest rank (#1) the adjudicated On-Trial ARR to the lowest rank (#5) change from baseline in EQ-5D VAS score.

Baseline is defined as the last available assessment prior to treatment for all patients regardless of their treatment group. The HAI, EQ-5D index score, EQ-5D VAS score, and the EDSS will be evaluated as the change from baseline to the 6-week post-relapse/EOPT time point (ie, for the placebo arm: 6 weeks post-relapse for the patients who have an On-Trial Relapse, or Study ECU-NMO-301 end of study (EOS) for patients who did not have a relapse; for the ravulizumab arm: the 6-week Post-relapse Visit for the first observed On-Trial Relapse for the

patients who have an On-Trial Relapse or the EOPT Visit for patients who did not have a relapse). For those patients who, for COVID-19 related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether, the change from baseline to the last value before the missed dose, if the missed or delayed dose occurred before the EOPT Visit or the 6-week Post-relapse Visit, will be summarized and analyzed. Sensitivity analyses will be performed for these secondary endpoints, in which the change from baseline does not account for having a missed or delayed dose due to COVID-19.

The adjudicated On-Trial ARR will be presented with a 95% CI to provide an estimate of the adjudicated On-Trial ARR for patients treated with ravulizumab. The null hypothesis will be that the mean adjudicated On-Trial ARR is equal to 0.25 relapse/patient-year. The alternative hypothesis will be that the mean adjudicated On-Trial ARR is not equal to 0.25. The study will be considered to have met this endpoint if the adjudicated On-Trial ARR < 0.25 (ie, in favor of ravulizumab) and a 2-sided p-value ≤ 0.05.

The adjudicated On-Trial ARR will be presented showing the ravulizumab treatment group estimate and 95% CI from a Poisson regression model in which the log of time in the Study Period will be used as the offset variable and historical annualized relapse rate for the 24 months prior to Screening will be a covariate in the model. This endpoint will be considered statistically significant if the 2-sided p-value is ≤ 0.05 (as described in Appendix 9.5.10.2.1), or if 0 relapses are observed. Summaries of the total number of adjudicated On-Trial Relapses in the ravulizumab arm, the total number of patient-years in the study period, as defined in Appendix 9.5.2, the estimate of the adjudicated On-Trial ARR in the ravulizumab arm, and the p-value will be presented. For those patients who, for COVID-19 related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether, the time interval from the missed dose until the start of the next dose any relapse that occurred in this interval will be excluded from the ARR calculations and summaries. A sensitivity analysis will be performed that includes the time of the missed dose due to COVID-19 related reasons. A sensitivity analysis will also be performed in which the time interval of COVID-19 infection will be excluded from the ARR.

A sensitivity analysis comparing the ARR in the ravulizumab arm with the ARR of the placebo arm will be performed using Poisson regression, with treatment group as a factor, the log of time will be used as an offset variable and adjusting for historical annualized relapse rate for the 24 months prior to Screening. The ARR will be determined, as described above, but using a time period for patients in the ravulizumab arm that more closely matches the time period for patients in the placebo arm; details of this time period are provided in Appendix 9.5.2.3. Additional sensitivity analyses will be performed adjusting for propensity score strata, adjusting for observed randomization strata described in Section 7.2.1, in which the time interval of COVID-19 infection is excluded from the ARR, and in which the ARR includes the time of the missed dose due to COVID-19 related reasons.

For clinically important change in HAI the null hypothesis will be that the odds of a better outcome are the same between the ravulizumab arm and the placebo arm. The alternative hypothesis will be that there is a difference in the odds of a better outcome between the treatment arms and that ravulizumab has higher odds of a better outcome.

The change from baseline in HAI will be categorized into clinically important changes (clinical improvement, stable, clinical worsening), as described in more detail in Appendix 9.5.4. This 3-level endpoint will be analyzed using a partial proportional odds model including treatment group with baseline HAI as a covariate. The proportional odds of each term will be evaluated using a score test for proportional odds. Should baseline HAI be non-proportional, it will be treated as non-proportional in the model resulting in separate estimates of baseline HAI on each of the 2 odds (clinical improvement and stable vs clinical worsening, and clinical improvement vs stable and clinical worsening). Should the treatment group be non-proportional, logistic regression to evaluate the effect of ravulizumab on reduction in clinical worsening will be fit in which the clinical improvement category will be combined with the patients identified as stable; this endpoint will be analyzed using a logistic regression model including treatment group with baseline HAI as a covariate. The primary analysis will be the analysis of clinically important change from baseline, unless the proportional odds is not met for the treatment effect in that model; in which case, the primary analysis will be the analysis of clinically worsening from baseline.

A sensitivity analysis of the clinically important change in HAI will be performed, adjusting for propensity score strata. The partial proportional odds model will include treatment group with baseline HAI and propensity score strata as covariates. The proportional odds of baseline HAI and propensity score strata will be evaluated using a score test for proportional odds and if the score test is significant, the covariate will be treated as non-proportional. Should the treatment group be non-proportional, logistic regression of the clinical worsening endpoint will include treatment group with baseline HAI as a covariate and stratified according to propensity score strata. This analysis will also be performed adjusting for the Study ECU-NMO-301 observed randomization strata described in Section 7.2.1.

Table summaries and by-patient listings of the HAI clinically important change in HAI will be produced. Tables of the change from baseline to the 6-week post-relapse/EOPT time point will be presented by treatment group, showing the number and percentage of patients with clinical improvement, stable, clinical worsening. Results of the proportional odds model will also be presented showing the treatment effect, 95% CI, and p-value on the odds of a better outcome, with covariate estimates and p-value of the baseline covariate as well. The distribution of HAI scores and the clinically important change at each scheduled visit will also be summarized for the ravulizumab arm.

For the EQ-5D index and the EQ-5D VAS, the null hypothesis will be that there is no difference between the distribution of the ravulizumab arm and the placebo arm. The alternative hypothesis will be that there is a difference between the distribution of the treatment arms and that ravulizumab is superior to placebo.

The change from baseline in the EQ-5D index score will be analyzed using ANCOVA, in which the ranks of the change from baseline will be the dependent variable with treatment as a factor and the ranks of the baseline values as a covariate.

Sensitivity analyses of the EQ-5D index score and the EQ-5D VAS will be performed adjusting for propensity score strata in which the ANCOVA will include the ranks of the baseline values and propensity score strata as covariates. This analysis will also be performed adjusting for the Study ECU-NMO-301 observed randomization strata described in Section 7.2.1.

Table summaries and by-patient listings of the EQ-5D index score and the EQ-5D VAS will be produced. Tables of the change from baseline to the 6-week post-relapse/EOPT time point will be presented by treatment group, showing descriptive statistics of the observed results and the change from baseline as well as the p-value from the ANCOVA of the ranks of the change from baseline. The distribution of the EQ-5D index score and the EQ-5D VAS including the observed results and the changes from baseline at each scheduled visit will also be summarized for the ravulizumab arm.

For the EDSS the null hypothesis will be that the odds of a worse outcome are the same between the ravulizumab arm and the placebo arm. The alternative hypothesis will be that there is a difference in the odds of a worse outcome between the treatment arms and that the odds of a worse outcome are lower in the ravulizumab arm.

The change from baseline in the EDSS score will be categorized into clinically important worsening (no worsening, clinical worsening), as described in more detail in Appendix 9.5.6. This endpoint will be analyzed using a logistic regression model including treatment group, with baseline EDSS as a covariate.

Sensitivity analyses of clinically important worsening in EDSS score will be performed adjusting for propensity score strata in which the logistic regression model will include treatment group, with baseline EDSS as a covariate, and stratified according to propensity score strata. This analysis will also be performed adjusting for the Study ECU-NMO-301 observed randomization IST strata; baseline EDSS will be included as a covariate in the model and not in the stratification.

Table summaries and by-patient listings of the clinically important worsening in EDSS will be produced presenting results from the logistic regression model, and otherwise, as described for the clinically important change in HAI.

7.2.3. Exploratory Efficacy Endpoint Analyses

The exploratory efficacy endpoints include:

1. Optic Spinal Impairment Score (OSIS)
2. The change in visual acuity, color vision, and confrontational visual fields
3. Change from baseline in the SF-36 domain scales and summary scores
4. Change from baseline in the EQ-5D 5 dimensions of health
5. Medical resource utilization and health outcomes

Summaries and analyses of these endpoints will be presented for the FAS. Patient listings of the exploratory endpoint parameters will be produced for all patients in the FAS.

Relapse severity, using the OSIS scale will only be summarized for Optic Neuritis and Transverse Myelitis relapses based on the OSIS Visual Acuity, Motor and Sensory Scales. Results will be summarized by relapse number (eg, first; second; third), and across relapses, for adjudicated On-Trial Relapses. The worst severity observed over all relapse visits will be used. Should a patient have a relapse that includes more than one type of relapse or more than one relapse, the worst grade will be used to classify the overall severity of the relapse(s). For ON

relapses in one eye, the severity of the eye with the relapse will be presented; for bilateral ON relapses the worse severity will be used. See Appendix 9.5.7 for details.

Baseline is defined as the last available assessment prior to treatment for all patients regardless of their treatment group. Visual acuity, confrontational visual fields, and color vision, EQ-5D dimensions, and SF-36 scores and summary scales will be evaluated as the change from baseline to the 6-week post-relapse/EOPT time point (ie, for the placebo arm: 6 weeks post-relapse for the patients who have an On-Trial Relapse, or Study ECU-NMO-301 end of study (EOS) for patients who did not have a relapse; for the ravulizumab arm: the 6-week Post-relapse Visit for the first observed relapse for the patients who have an On-Trial Relapse or the EOPT Visit for patients who did not have a relapse).

The change from baseline in the visual acuity will be analyzed according to the eye with the greater worsening and will be conditional on patients with adequate eyesight at baseline to perform the test. Treatment groups will be compared using the ANCOVA of the ranks of the change from baseline, adjusted for the ranks of the baseline score of the corresponding eye.

Color vision will be evaluated among patients in the ravulizumab treatment group as the shift from baseline in color vision (no change from normal, or worsened), among patients with at least one eye with normal color vision. The shift is described in further detail in Appendix 9.5.12. The proportion of patients with a change from normal to worsened will be presented with exact 95% confidence limits.

Confrontational visual fields will be analyzed as the change from baseline in number of quadrants with deficits identified across both eyes and conditional on patients with adequate eyesight at baseline to perform the test in at least one eye. The analysis will be based on the Wilcoxon signed-rank test, among patients in the ravulizumab treatment group.

SF-36 scores will be derived as defined in Appendix 9.5.8. The change from baseline in SF-36 and the change from baseline in EQ-5D dimensions will be analyzed as described for the EQ-5D index score, using ANCOVA of the ranks of the change from baseline, adjusted for the ranks of the corresponding baseline score.

Summaries and analyses of the medical resource utilization and health outcomes are described in Section 7.2.7.

7.2.4. Other Efficacy Analyses

7.2.4.1. Relapse Types and Effect on Other Endpoints

For adjudicated On-Trial Relapse(s), summary tables of the types of relapses will be produced by treatment group. A by-patient listing of the relapses will be produced.

Changes from baseline and changes from the last assessment prior to an adjudicated On-Trial Relapse to each post-relapse time point will be summarized for EDSS, HAI, and visual acuity, color vision, and confrontational visual fields for each adjudicated On-Trial Relapse (eg, first; second; third relapse). These summaries will also be produced for the changes to each post-relapse time point relative to On-Trial relapses. Patient listings for the EDSS, HAI, visual acuity, color vision, and confrontational visual fields assessments will include the change from the last assessment prior to each On-Trial Relapse and from the last assessment prior to each adjudicated On-Trial Relapse.

On-Trial Relapses will also be evaluated summarizing the number and rate of relapses requiring hospitalization and the number and rate of acute treatments for relapses (ie, IV methylprednisolone, plasma exchange, and high-dose oral steroids) by treatment group. Rates will be compared across treatment groups using Poisson regression, with treatment group as a factor and the log of time as an offset variable.

7.2.5. Pharmacokinetic and Pharmacodynamic Analyses

Blood and cerebrospinal fluid (CSF) samples will be collected to evaluate the PK activity of ravulizumab over time. Descriptive statistics of ravulizumab concentration data will be presented for each scheduled sampling time point for which concentration data are available.

Blood and CSF samples will also be collected to evaluate the PD of ravulizumab over time: free complement component 5 (C5) in serum samples; and free C5 in CSF samples. Descriptive statistics will be presented for all ravulizumab PD endpoints at each sampling time for which the PD endpoint is available. The PD effects of ravulizumab will be evaluated by assessing the absolute values and changes and percentage changes from baseline in free C5 over time, as appropriate.

Summaries will be presented separately for PK and PD endpoints observed in blood and CSF samples. Patient listings of the PK/PD parameters will be produced.

7.2.6. Biomarker Assessments

A listing of serum and CSF anti-AQP4 antibody titers will be produced on available data. Summaries and analyses of biomarkers are outside the scope of this document.

7.2.7. Medical Resource Utilization and Health Outcomes

Descriptive statistics will be provided for the following:

- The number of days of hospitalizations for the 2 years prior to Screening (for all hospitalizations, and those related to NMOSD Relapse) and the ratio of the number of days of hospitalization in the 2-year period. Refer to Appendix 9.5.9 for details.
- The number of days of hospitalizations during the Study Period (for all hospitalizations, and for adjudicated On-Trial Relapses) and the ratio of the number of days of hospitalizations and days in the Study Period.

The following endpoints will be summarized by treatment group showing total counts, event rates as per patient-years of follow-up in the study period, and the number and percentage of patients:

- With surgeries, and other selected procedures (inpatient or outpatient)
- With any diagnostic or therapeutic test or procedures
- For each type of diagnostic and therapeutic tests and procedures, as coded by Medical Dictionary for Regulatory Activities (MedDRA; version 21.0 or higher) by System Organ Class (SOC) and Preferred Term.

7.3. Safety Analyses

All safety analyses will be conducted on the Safety Set. All safety data will be presented in patient listings. No formal hypothesis testing is planned. Baseline is defined as the last available assessment prior to treatment for all patients regardless of their treatment group.

7.3.1. Study Duration, Treatment Compliance, and Exposure

Study duration, treatment duration, treatment compliance, and exposure will be summarized by treatment group for the Safety Set. Likewise, each patient's study duration, treatment duration, treatment compliance, and exposure will be summarized in patient listings.

Study duration will be calculated as the time in days from the first dose date of study drug until the date of discontinuation/completion from the Study (ie, Study duration (weeks) = the earlier of data cutoff date or discontinuation (or death) – First Dose Date + 1, all divided by 7). See Protocol Section 4.4 for the definition of the data cutoff date. Treatment duration will be calculated as the time in days from the first dose date of study drug until the last dose date of study drug (ie, Treatment duration (days) = Last Dose Date – First Dose Date + 1). The total number of patients with any missed infusions and the reasons for any missed infusions, including COVID-19 related reasons, will be presented; unscheduled infusions will be presented in a similar fashion.

Patients taking supplemental doses of study drug will be summarized in by-patient listings.

7.3.2. Adverse Events (AEs)

Adverse events are defined in Protocol Section 10.3.

AEs will be coded by primary SOC and Preferred Term using the MedDRA (version 21.0 or higher).

Adverse events of the ravulizumab arm will include any TEAEs reported with a start date on or prior to the earlier of the data cutoff date or the discontinuation (or death) date. To account for the few patients in the placebo group who may have been followed longer than patients in the ravulizumab arm at the time of analysis, TEAEs reported in the placebo group will only be included in summaries if the start day of the event is less than or equal to the longest study duration in the ravulizumab arm.

In addition to presenting frequencies and percentages of patients, TEAE rates based on 100 person-years of follow-up will be produced by treatment group where stated. Person-years of follow-up and additional details regarding AEs are outlined in Appendix 9.4.6.

A table and listing of PTAEs and PTSAEs will be produced. Both tabular outputs and listings will be created for TEAEs and TESAEs as described in this SAP. Study display tables and listings for AEs will be presented by treatment group, with details described below.

7.3.2.1. Overall Summary of Adverse Events

An overview of TEAEs will be presented showing the number of TEAEs, event rate, and number and percentage of patients who:

- Experienced any TEAE

- Discontinued study drug due to an AE
- Experienced an AE considered related to study drug
- Experienced an AE considered not related to study drug
- Experienced a mild, moderate, or severe TEAE.

These statistics will be prepared for all TEAEs and, separately, for TESAEs (except severity) and non-serious TEAEs. The number and percentage of patients who died, if applicable, will also be presented. These tables will be presented both including and excluding the coded PT for NMOSD.

Additional overall summary tables will be presented by age, gender, race, region, and for COVID-19 related AEs. For those patients diagnosed with COVID-19, an overall summary table of AEs experienced on or after as well as on or within 6 months after the first COVID-19 related AE will also be provided.

See Appendix 9.4 for definition of related TEAEs.

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

The number of TEAEs/TESAEs, the event rates, and the number and percentage of patients with events will be presented by SOC and PT and by PT alone. Patients are counted once in each SOC and PT. Percentages will be based on the total number of patients in the treatment group. SOCs will be listed alphabetically and PTs within each SOC will be listed in order of frequency of occurrence (%) based on Total Patients. Adverse event rates based on 100 person-years of follow-up will be produced for all TEAEs and all TESAEs by treatment group. Person-years of follow-up are defined in Appendix 9.4. These tables will be presented both including and excluding the coded PT for NMOSD.

Additional summary tables will be presented stratifying TEAEs and TESAEs by age, gender, race, and region. These tables will also be provided for COVID-19 related AEs; and for those patients diagnosed with COVID-19, summaries of AEs experienced on or after, as well as on or within 6 months after first COVID-19 related AE will also be provided.

The incidence of TEAEs leading to study drug discontinuation and the incidence of TEAEs leading to study discontinuation will be summarized.

The number of non-serious adverse events, event rates, and the number and percentage of patients with non-serious events will be presented by SOC and PT.

Detailed listings of patients who experience TEAEs, TESAEs, and related TEAEs will be presented. Detailed listings will include severity and relationship to treatment, as well as action taken regarding study treatment, other action taken, and patient outcome. A separate listing of patients who discontinued from the study due to a treatment-emergent AE will also be provided. A separate listing of patients who died during the study will also be provided.

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

Summaries of TEAEs by relationship (see Appendix 9.4) to treatment will be provided. Summary of TESAEs by relationship will also be provided.

Adverse event rates based on person-years of follow-up will be produced for all TEAEs/TESAEs by relationship to treatment and treatment group.

7.3.2.4. AEs and SAEs by SOC, PT, and Severity

Summaries of TEAEs by severity will be provided.

Adverse event rates based on person-years of follow-up will be produced for all TEAEs by severity and treatment group.

7.3.2.5. AEs and SAEs Over Time by SOC, PT

Summaries of TEAEs and TESAEs over time will be provided. The number and percentage of patients with each TEAE and each TESAE will be presented per 6-month time interval. The denominator per time interval will be the number of patients continuing in the study with study duration including all or part of the interval.

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

A listing of patient deaths and cause of death will be produced, if applicable.

Treatment-emergent adverse events of special interest (TEAESIs) will be summarized by treatment group in tabular form. There is only one AESI: Meningococcal Infections.

7.3.3. Other Safety

Other safety parameters will be presented for the ravulizumab treatment group alone. All data will be presented in listings.

7.3.3.1. Analyses for Laboratory Tests

Each laboratory parameter will be presented by visit. Changes from baseline as well as shift tables will be presented. All laboratory values will be classified as normal, below normal, or above normal based on normal ranges supplied by the central laboratory. Frequencies of abnormal values will be presented in tabular form.

7.3.3.2. Vital Signs

Vital signs (SBP and DBP), temperature, respiration rate (RR) and sitting or lying HR, and changes from baseline in vital signs will be summarized by visit.

Weight (kg) and the change from baseline will be summarized by visit.

Vital signs outliers: The number and percentage of subjects having observed any vital signs that satisfy any of the following conditions will be presented by time point:

- 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
- SBP < 90 mmHg; SBP > 140 mmHg; SBP > 160 mmHg
- Temperature < 36 degrees Celsius; Temperature > 38 degrees Celsius

- Weight ≥ 7% decrease from Baseline; Weight ≥ 7% increase from Baseline

7.3.3.3. Other Safety Parameters of Special Interest

Other safety parameters of special interest include certain adverse events mentioned in Section 7.3.2.6 as well as ECG data, and suicidal ideation and behavior. Listings of physical examinations will be produced. A by-patient listing of *Neisseria meningitidis* vaccinations will be produced showing the date of vaccinations for each patient. Pregnancy tests will be summarized in patient listings.

7.3.3.3.1. Electrocardiograms (ECG)

The ECG results will be summarized by visit. Listings of ECG results will be produced. Descriptive statistics by visit will be presented for each ECG parameter (including HR, PR duration, QRS duration, QT duration, RR duration, and QT interval corrected using Fridericia's formula [QTcF]) value and for change from baseline. ECG outliers for QTc categories (≥ 450 and ≤ 480, > 480 to ≤ 500, and > 500 msec and changes from baseline > 30 and ≤ 60 msec and > 60 msec) will be presented.

The number and percentage of subjects having observed QT, QTcF that satisfy any of the following conditions will be presented by time point

- < 450 msec
- 450 to ≤ 480 msec
- > 480 to ≤ 500 msec
- > 500 msec

The number and percentage of subjects having changes from baseline for QT, QTcF that satisfy any of the following conditions will be presented by time point

- ≤ 0 msec
- > 0 to ≤ 30 msec
- > 30 to ≤ 60 msec
- > 60 msec

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

The number and percentage of patients with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent based on the C-SSRS during the Treatment Period will be summarized for the ravulizumab treatment group. Treatment-emergent suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be based on available assessments after Day 1. In this summary, 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 events at least once during the Treatment Period will be summarized for the ravulizumab group. 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 for the ravulizumab group.

Two shift tabulations from baseline for the C-SSRS will be produced during the Treatment Period. The baseline C-SSRS assessment includes both (A) lifetime assessment (for both the suicidal behavior and for the suicidal ideation sections) and (B) recent assessment: 1 year prior to study start for the suicidal behavior section, and 1 month prior to the study start for the suicidal ideation section. A separate shift tabulation will be produced using each of these two baselines. The three groupings for the shift tables 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 is counted in one cell only for each of the two tabulations. Patients with both suicidal ideation and suicidal behavior are included in the suicidal behavior category for the particular tabulation.

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

7.3.3.3.3. Immunogenicity

For assessment of immunogenicity, the presence of confirmed positive antidrug antibodies (ADAs) will be summarized. A by-patient listing showing ADA results over time will include positive/negative ADA, and for confirmed positive ADA, the ADA titer and presence of neutralizing antibodies.

7.4. Interim Analysis

The primary analysis will be conducted when all patients have completed the Primary Treatment Period. This analysis will include all efficacy, safety, PK/PD and immunogenicity study data for regulatory submission purposes and will be the final analysis of the Primary Treatment Period. This analysis will not be considered an interim analysis. Interim analyses that include data collected during the Long-Term Extension Period may be performed to support submission requirements.

8. REFERENCES

Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011 May;46(3):399-424.

D'Agostino RD. Tutorial in Biostatistics Propensity Score Methods for Bias Reduction in the Comparison of a Treatment to a Non-Randomized Control Group. StatMed. 1998; 17:2265-2281

Ishihara S. Ishihara Guide. The series of plates designed as a test for color deficiency 38 plates Edition. Kanehara Trading Inc., Tokyo, Japan. [cited 2020 Apr 06] Available from: https://cdn.shopify.com/s/files/1/0282/4578/6729/files/730019Guide.pdf

Heinze G, Schemper M. A Solution to the problem of monotone likelihood in Cox regression. Biometrics. 2001;57:114-119.

Koch GG, Tangen CM, Jung J-W, Amara IA. Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. StatMed. 1998;17:1863-1892.

OPTUM® PRO CoRE 1.5 Smart Measurement® System User's Guide. Optum Incorporated, Johnston, RI; 2019.

Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. Pharmacoepidemiol Drug Saf. 2005;14;465-476.

Szende A, Oppe M, Devlin N, editors. EQ-5D value sets: Inventory, comparative review and user guide. Dordrecht: Springer; 2007.

VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167(4):268-274, doi:10.7326/M16-2607.

Wingerchuk DM, Banwell F, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015(85):177-189.

Xie, J, Liu, C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Statistics in Medicine. 2005; 24:3089–3110.

9. APPENDICES

9.1. Protocol Schedule of Events

Refer to the protocol for a schedule of events.

9.2. Changes from Analyses Specified in the Previous Version of the SAP

See Section 4.2.

9.3. Sample Size, Power, and Randomization

This is an open-label, external placebo-controlled study to evaluate ravulizumab in NMOSD patients with the primary endpoint of time to first adjudicated On-Trial Relapse. The placebo treatment arm in Study ECU-NMO-301 will serve as the external control.

The sample size and power calculation assumptions for this study using the primary endpoint, time to first relapse, are as follows:

- Log-rank test for comparison of ravulizumab to placebo
- 47 patients in the placebo treatment group
- Power 90%
- Two-sided 5% level of significance
- Drop-out rate 2-10%
- Relapse-free rate of 92% for the ravulizumab arm at 12 months
- Relapse-free rate of 63% for the placebo arm at 12 months

With these assumptions, a maximum sample size of approximately 55 patients in the ravulizumab treatment group provides at least 90% power to detect a treatment difference in time to first positively adjudicated relapse.

This study is not a randomized study.

9.4. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

9.4.1. Age

Age will be presented as the number of years between date of birth and the reference date. The following ages may be computed, with reference dates indicated:

Table 3: Age and Reference Date

Age	Reference Date
• Age at Enrollment	• Date of Signing ICF
• Age at Disease Onset	• Date of Initial Clinical Presentation
• Age at First Infusion	• Date of First Infusion

Abbreviation: ICF = informed consent form

For all dates (except adverse event and medication start 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 month 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.

9.4.2. Disease Duration

NMOSD disease duration will be presented as the number of years between the date of first infusion and the date of initial clinical presentation (ie, INT [(Date of first infusion – Date of initial clinical presentation + 1)/365.25]). For 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 month 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.

9.4.3. Definition of Baseline Values

Baseline is defined as the last available assessment prior to or on the day of first study drug treatment for all patients regardless of their treatment group.

Baseline BMI (kg/m^2) = (Baseline weight in kg)/(Baseline height in meters)^2

9.4.4. Change from Baseline

Change from baseline will be calculated as

Change from baseline = Assessment value – Baseline assessment value.

9.4.5. QTcF Calculations

The Fridericia formula, QTcF, is as follows:

QTcF = QT interval / (60/HR)^ (1/3), where HR is heart rate.

9.4.6. Adverse Events

The analysis of Adverse events is described in detail in Section 7.3.2.

Treatment-emergent AEs are events with start dates and start times on or after the date and time of the first study drug dose (placebo or ravulizumab). If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to 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 study drug dose, then the AE is treatment emergent; else,

- If the start year is the same as the year of the first study drug 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 day of an AE reported in a patient in the placebo arm is greater than the longest duration of Primary Treatment Period in the ravulizumab arm, then the AE will not be summarized.

All other AEs are considered Pre-treatment adverse events (PTAEs).

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

In Study ALXN1210-NMO-307, the AE relationship is collected as two categories: related and not related. In Study ECU-NMO-301, the AE relationships are collected as 5 categories; therefore, for the placebo treatment group related AEs are defined as possible, probable or definitely related; and unrelated AEs are defined as unlikely or not related. AEs with missing relationship to study treatment will be assumed to be related to study treatment.

Person-years of follow-up is defined as:

> Person-years of follow-up = (Last Study Date – First Dose Date + 1)/365.25; the last study date in the ravulizumab treatment group will be the earlier of the data cutoff date and date of discontinuation; and the last study date in the placebo group will be the date of the last study date in Study ECU-NMO-301. The person-years of follow-up in the placebo group will not exceed the maximum person-years of follow-up in the ravulizumab treatment group.

Total person-years of follow-up for a particular treatment group based on the Safety Set is the sum of the person-years of follow-up for all the patients in the particular treatment group.

Adverse event rates based on 100 person-years of follow-up for a particular Preferred Term and treatment group will be calculated as the number of events for the particular adverse event in the particular treatment group times 100 (years) divided by the total person-years of follow-up for that particular treatment group.

9.5. Additional Details on Statistical Methods

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

In this study, FAS and PPS patients have experienced an adjudicated On-Trial Relapse during the Primary Treatment Period, or have ended the Primary Treatment Period without an adjudicated On-Trial Relapse, or both. The patients who do not have an adjudicated On-Trial Relapse during the Study Period will be censored at the last known date during the Primary Treatment Period (see below). In addition, those patients who, for COVID-19 related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether will be censored at the time of the missed dose, if the missed or delayed

dose occurred before the EOPT Visit or the 6-week Post-relapse Visit. A censoring indicator will be equal to 1 if the patient did not experience a relapse (was censored), and 0 if the patient experienced a relapse.

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

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

For patients in the ravulizumab treatment group without an adjudicated On-Trial Relapse during the Study Period, the censoring time (in days) is defined as:

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

where EOPT Date is the minimum non-missing value of the following dates: the data cutoff date (as defined by the 3 scenarios described in Protocol Section 4.4), 35 days after a dose was expected but not administered due to COVID-19 related reasons, the Last Dose Date + 63 days (or 16 days, if the last dose was a Day 1 dose), and the final disposition date (eg, Safety Follow-up date) for patients who have left the study before the data cutoff date. Relapses observed after the EOPT date will not be included in the primary analysis; for the sensitivity analysis in which patients are not censored due to the missed or delayed dose for COVID-19 related reasons, that aspect of the censoring rule will not be applied.

For patients in the placebo treatment group 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 the minimum non-missing value of the following dates: First dosing date plus the longest follow-up time in the ravulizumab treatment group, Last Dose Date + 16 days (or + 9 days if in induction phase) and the last date observed in ECU-NMO-301. Note: Patients in the placebo treatment group who were followed longer than the longest censoring time or time to first relapse observed in the ravulizumab treatment group, will be censored at that time (ie, first dosing date plus the longest follow-up time in the ravulizumab treatment group). Any relapses that had been observed among patients in the placebo group after this time will not be included in the primary analysis.

9.5.2. Annualized Relapse Rate Calculations

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

Detailed information on relapses within the 24 months prior to Screening must be assessed by the Investigator to determine if they meet the criteria for the Historical Relapse definition as specified in Protocol Section 8.2.3.1. For patients that have a relapse during any Screening Period and get rescreened and treated in the study, any relapses during the prior Screening Periods will be counted as historical relapses in the assessment of historical annualized relapse rate.

To allow for the 30-day window of counting distinct relapses, the historical annualized relapse rate 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 Screening Visit. Historical relapse time will be 25 months for NMOSD patients with disease greater than 25 months from the date of the 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.

9.5.2.2. Adjudicated On-Trial Annualized Relapse Rate (ARR[Adjudicated])

The adjudicated On-Trial annualized relapse rate will be calculated for the ravulizumab treatment group as:

$$ARR_{(Adjudicated)} = \frac{Number\ of\ adjudicated\ relapses\ in\ the\ study\ period}{Sum\ of\ Time\ in\ study\ period \text{ across patients } in\ the\ ravulizumab\ treatment\ group}$$

The number of relapses in the Study Period is the total number of relapses across all patients from the start of study treatment (first dose date) to the end date of the patient's Primary Treatment Period, excluding the time from 36 days after a dose that was missed or delayed due to COVID-19 related reasons (ie, excluding from 36 days after the missed dose until the day before the next dose). The End of Primary Treatment Period (EOPT) Date is the minimum non-missing value of the following dates: the data cutoff date (as defined by the 3 scenarios described in Protocol Section 4.4), the Last Dose Date + 63 days (or 14 days, if the last dose was a Day 1 dose), and the final disposition date (eg, Safety Follow-up date) for patients who have left the study before the data cutoff date, excluding the time from 36 days after a dose that was missed or delayed due to COVID-19 related reasons until the day before the next dose. Relapses observed after the EOPT date will not be included in the analysis. The $ARR_{(Adjudicated)}$ will be 0 for patients with no adjudicated On-Trial Relapses during the Study Period. A sensitivity analysis will exclude the time in which the patient had a COVID-19 infection (ie, the start to the end date of the adverse event indicating COVID-19 infection).

The adjudicated On-Trial ARR will also be calculated for each patient in the ravulizumab arm using the number of adjudicated On-Trial Relapses in the Study Period experienced by the patient divided by the time in the Study Period for that patient.

9.5.2.3. Time in Study Period

The time in Study Period (in years) is as follows for patients in the ravulizumab treatment group:

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

where EOPT Date is the minimum non-missing value of the following dates: the data cutoff date (as defined by the 3 scenarios described in Protocol Section 4.4), the Last Dose Date + 63 days (or 14 days, if the last dose was a Day 1 dose), and the final disposition date (eg, Safety Follow-up date) for patients who have left the study before the data cutoff date. In the sensitivity analysis of the ARR in which the time period more closely reflects that of the placebo treatment group and in the analysis of hospitalization rates and acute treatment rates, the EOPT Date will be the minimum of the EOPT Date and 6 weeks after the first On-Trial Relapse. If a patient missed a dose due to COVID-19, the time from 36 days after a dose that was missed or delayed

due to COVID-19 related reasons until the day before the next dose will be subtracted from the Time in Study Period in both the main and the sensitivity analysis.

For patients in the placebo treatment group the time in Study Period (in years) is

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

where EOS Date is the minimum non-missing value of the following dates: Last Dose Date + 16 days (or + 9 days if in induction phase) and the last date observed in Study ECU-NMO-301. Patients in the placebo treatment group who were followed longer than the longest time observed in the ravulizumab treatment group, will have a time in study period equal to the time of the longest time observed in the ravulizumab treatment group.

9.5.3. Propensity Score Calculation

This is an open-label, external placebo-controlled study to evaluate ravulizumab in NMOSD patients with the primary endpoint of time to first adjudicated On-Trial Relapse. The placebo treatment arm in Study ECU-NMO-301 will serve as the external control.

"The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. The propensity score allows one to design and analyze a non-randomized study so that it mimics some of the particular characteristics of a randomized controlled study. In particular, the propensity score is a balancing score: conditional on the propensity score, the distribution of observed baseline covariates will be similar between treated and untreated subjects." (Austin, 2011).

Propensity scores will be created to represent the probability of being in the ravulizumab arm as compared to the placebo arm. The probability of being in the ravulizumab arm will be modelled through logistic regression using baseline covariates as predictors (D'Agostino, 1998). The baseline covariates will represent variables that may enroll into the ravulizumab arm at a different rate than had been enrolled in the placebo arm and are considered potentially important prognostic factors (Seeger, 2005). These variables include:

- Region (Americas, Europe, Asia-Pacific)
- Gender
- Age at first dose (continuous)
- Background IST (yes/no)
- Baseline EDSS (continuous)
- Historical ARR the 24 months prior to Screening

The propensity scores are the predicted probability from the logistic regression model of a patient being in the ravulizumab treatment group vs the placebo group; baseline characteristics listed above will be included as predictors in this model from which a propensity score for each patient will be derived. Patients will then be grouped into two strata based on the propensity score: patients with scores above or below (≤) the median.

To observe the effects of the propensity score stratification, a table showing descriptive statistics of the propensity score and each baseline covariate included in the model will be provided by strata and treatment group.

Furthermore, stabilized inverse probability of treatment weights (sIPTW) will be used in a weighted analysis of the primary endpoint. The IPTW is the weight defined as the inverse of the probability of being in the treatment group to which the patient was assigned. If a few patients have large weights, the resulting weighted estimator may have a large variance. In order to reduce the variance, these weights are stabilized by multiplying the IPTW by the marginal probability of receiving the given treatment.

$$sIPTWr = \left(\frac{Nr}{N}\right) * \left(\frac{1}{Propensity\ Score}\right)$$

$$sIPTWp = \left(\frac{Np}{N}\right) * \left(\frac{1}{1 - Propensity\ Score}\right)$$

where Nr is the number of patients in the ravulizumab group, Np is the number of patients in the placebo group, and N is the total number of patients. Weights higher than 10 will be trimmed to 10.

To assess the balance in baseline characteristics, a table showing descriptive statistics of each baseline covariate included in the model using the weighted observations will be provided by treatment group.

The SAS procedure, PSMATCH, will be used to calculate the propensity scores, the strata, and the sIPTW.

9.5.4. HAI Clinically Important Change

HAI clinically important change will be defined as follows:

HAI Clinically Important Change	Baseline Value	Change to Meet Definition
Clinical Worsening	0	At least 2 points increase
	1+	At least 1 point increase
Clinical Improvement	2+	At least 1 point decrease
Stable	0	0 or 1 point increase
	1	0 or 1 point decrease
	2+	0 change

9.5.5. EQ-5D Calculations

The EQ-5D-3L version 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 United States time trade-off (US TTO) method (Szende, 2007). The calculation is illustrated in the table below:

US TTO Value Set		**Example: The Value for Health State 21232**	
Full health (11111)	1	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

9.5.6. EDSS Clinically Important Worsening

EDSS clinically important worsening will be defined as follows:

Baseline Value	**Clinical Worsening**
0	At least 2 point increase
1 to 5	At least 1 point increase
> 5	At least 0.5 point increase

Patients with non-missing change who do not meet the definition of worsening, will be evaluated as no worsening (improvement or no change).

9.5.7. OSIS

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.

Optic Neuritis Relapses:

The OSIS Visual Acuity (V_A) Scale is as follows:

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

Severity of ON:

Severity of ON will be based on the eye experiencing the ON. If both eyes experience ON, then ON will be calculated for each eye and the severity of major will be assigned to the relapse if at least one eye had major severity and minor will be assigned otherwise.

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

Transverse Myelitis 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 points in any of the Treating Physician assessments below will be classified as a major relapse. Otherwise, the relapse will be considered minor severity.

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

9.5.8. SF-36 Calculations

The SF-36 is a self-administered questionnaire designed to assess generic health-related quality of life (HRQoL) in healthy and ill adult populations. Eight health domain scores (PF, SF, RP, BP, GH, MH, RE, and VT) and two component scores (PCS and MCS) will be calculated for further statistical analysis of the SF-36 data.

The SF-36v2 Health Survey with the standard (4-week) recall period was used in this study. The OPTUM PRO CoRE 1.5 Smart Measurement System will be used to derive the 8 domain scores and 2 component scores. The algorithms used by the software to the score the data are described below (excerpted from the User's Guide).

9.5.8.1. Data Cleaning and Item Recoding

First, the data are checked for out-of-range values. Out-of-range values are any values that are outside the range of acceptable item response values for the SF-36v2 Health Survey. Out-of-range values will be converted to missing values. Next, ten items (BP01, BP02, GH01, GH03, GH05, VT01, VT02, SF01, MH03, MH05) are reverse scored. Reverse scoring of these items is required so that a higher item response value indicates better health for all SF-36v2 Health Survey items and summary measures.

9.5.8.2. Item Recalibration

For most of the SF-36v2 Health Survey items, research to date offers good support for the assumption of a linear relationship between the item scores and the underlying health concept defined by their scales. However, empirical work has shown that two items, items GH01 and BP01, require recalibration to satisfy this important scaling assumption. The Bodily Pain (BP) scale requires additional scoring rules because the items offer both different numbers and different content of response choices and administration of item BP02 depended upon the response to an item like item BP01 in past studies. The recommended scoring for item GH01 and the Bodily Pain items will be used.

9.5.8.3. Computation of Raw Scores

After recoding and recalibrating the required item values, a raw score is computed for each scale. This score is the simple algebraic sum of the final values for all items in that scale.

9.5.8.4. Transformation of Raw Scale Score to 0-100 Scores

The next step involves transforming each raw scale score to a 0-100 scale.

This transformation converts the lowest and highest possible scores to zero and 100, respectively. Scores between these values represent the percentage of the total possible score achieved.

9.5.8.5. Transformation of 0-100 Scores to T-score Based Scores

The first step in T-score based scoring consists of standardizing each SF-36v2 Health Survey scale using a z-score transformation. A z-score indicates how far a score deviates from the mean in standard deviation units. The z-score for each scale is computed by subtracting the mean 0-100 score observed in the 2009 general US population from each SF-36v2 Health Survey scale score (0-100) scale and dividing the difference by the corresponding scale standard deviation observed in the 2009 general US population. The means and standard deviations utilized are dependent upon the recall period option chosen by the user, based on the SF-36v2 Health Survey form used to collect the data being scored.

The next step of the T-score based scoring is to linearly transform each SF-36v2 Health Survey z-score to have a mean score of 50 and a standard deviation of 10. This is done by multiplying each SF-36v2 Health Survey z-score by 10 and adding the resulting product to 50. These are referred to as 'norm-based' scores. The norm-based scores will be used for the 8 domain scores.

9.5.8.6. Scoring the SF-36v2 Health Survey Component Summary Measures

The first step in scoring the component summary measures consists of standardizing each SF-36v2 Health Survey scale using a z-score transformation as described previously. The z-score for each scale is computed by subtracting the mean 0-100 score observed in the 2009 general US population from each SF-36v2 Health Survey scale score (0-100) scale and dividing the difference by the corresponding scale standard deviation observed in the 2009 general US population. The means and standard deviations utilized are dependent upon the recall period option chosen by the user, based on the SF-36v2 Health Survey form used to collect the data being scored.

After a z-score has been computed for each SF-36v2 Health Survey scale, the second step involves computation of aggregate scores for the physical and mental summaries using weights (factor score coefficients) derived from the 1990 general US population. These are the same weights as those used to score PCS and MCS from the SF-36 Health Survey. An aggregate physical score is computed by multiplying the z-score of each SF-36v2 Health Survey scale by its associated physical factor score coefficient and summing the eight products. If any of the scale scores are missing, then the aggregate physical score is not computed. An aggregate mental score is computed by multiplying the z-score of each SF-36v2 Health Survey scale by its associated mental factor score coefficient and summing the eight products. If any of the scale scores are missing, then the aggregate mental score is not computed.

The third step involves transforming the aggregate physical and mental summary scores to the T-score based (50, 10) scoring. This is done by multiplying each aggregate summary score obtained from Step 2 by 10 and adding the resulting product to 50.

9.5.8.7. Imputation of Missing Items

The maximum data recovery option will be used for missing data estimation. This results in the application of algorithms that compute a scale score for those respondents who have answered at

least one item that represents that construct. For the PF scale, item parameters obtained through item response theory (IRT) methods are used to estimate a missing value on an item based upon a respondent's responses to answered items. For the seven remaining scales, a person-specific estimate based on the mean response to the answered items on the scale is used to estimate a missing value. Additionally, a PCS and MCS score is calculated for those respondents who have calculated scores on at least seven of the eight SF-36v2 Health Survey scales. However, PCS is not estimated if the PF scale is missing, and MCS is not estimated if the MH scale is missing.

9.5.9. Hospitalizations Prior to Screening

The number of days of hospitalization in the 2-years prior to Screening and the ratio of the number of days of hospitalization in that window will be calculated based on a 2-year window, for patients with initial presentation of NMOSD more than 2 years prior to Screening. For patients whose initial presentation of NMOSD occurred less than 2 years prior to Screening, the number of days of hospitalizations and the ratio number of days of hospitalization will be calculated relative to the time of initial presentation.

9.5.10. SAS Code for Efficacy Analyses

9.5.10.1. SAS Code for the Primary Efficacy Endpoint

The primary efficacy endpoint is time to first adjudicated On-Trial Relapse. The comparison of the treatment groups for the primary endpoint will use the log-rank test. The basic SAS code for this log-rank test is:

```
proc lifetest data = ADTTE;
        time aval*cnsr(1);
        strata trt01p;
run;
```

where trt01p is a variable that indicates the patient's treatment group, aval is a variable for the patient's time in Study Period at time of relapse or censoring, cnsr is the censoring variable (1= no event (censored), 0= event).

The hazard ratio and risk reduction will be estimated from a Cox proportional hazards (PH) model. The basic SAS code for this analysis is:

```
proc phreg data = ADTTE;
    class trt01p;
    model aval*cnsr(1) = trt01p {/Firth risklimits=PL};
    hazardratio trt01p;
run;
```

where trt01p is a variable that indicates the patient's treatment group, aval is a variable for the patient's time in Study Period at time of relapse or censoring, cnsr is the censoring variable (1 = no event (censored), 0= event). Firth's adjustment with profile likelihood confidence limits

(Heinze, 2001), noted above as optional, will be applied if no relapses were observed in a treatment arm.

A sensitivity analysis of the comparison of the treatment groups for the primary endpoint will use a log-rank test including strata for the propensity score strata. The basic SAS code for this log-rank analysis is:

```
proc lifetest data = ADTTE;
        time aval*cnsr(1);
        strata propstrat  / group=trt01p;
run;
```

where trt01p is a variable that indicates the patient's treatment group, aval is a variable for the patient's time in Study Period at time of relapse or censoring, cnsr is the censoring variable (1 = no event (censored), 0= event), propstrat is the propensity score stratification variable with two strata. This code will also be used in the sensitivity analysis stratifying on Study ECU-NMO-301 randomization strata, by replacing the propstrat variable above with the randomization strata variable.

The hazard ratio and risk reduction will be estimated from a stratified Cox proportional hazards (PH) model. The basic SAS code for this analysis is:

```
proc phreg data = ADTTE;
    class trt01p propstrat;
    model aval*cnsr(1) = trt01p {/Firth risklimits=PL};
    strata propstrat;
    hazardratio trt01p;
run;
```

where trt01p is a variable that indicates the patient's treatment group, aval is a variable for the patient's time in Study Period at time of relapse or censoring, cnsr is the censoring variable (1 = no event (censored), 0= event), propstrat is the propensity score stratification variable with two strata. This code will also be used in the sensitivity analysis stratifying on Study ECU-NMO-301 randomization strata, by replacing the propstrat variable above with the randomization strata variable. Firth's adjustment with profile likelihood confidence limits (Heinze, 2001), noted above as optional, will be applied if no relapses were observed in a treatment arm or treatment arm within a stratum.

Another sensitivity analysis of the comparison of the treatment groups for the primary endpoint will use a weighted log-rank test, using sIPTW weights described in Appendix 9.5.3. The basic SAS code for this log-rank analysis is:

```
proc lifetest data = ADTTE;
        time aval*cnsr(1);
```

```
    strata trt01p;
    weight sIPTW;
run;
```

where trt01p is a variable that indicates the patient's treatment group, aval is a variable for the patient's time in Study Period at time of relapse or censoring, cnsr is the censoring variable (1 = no event (censored), 0= event), sIPTW is a variable representing the sIPTW weight.

The hazard ratio and risk reduction will be estimated from a weighted Cox PH model. The basic SAS code for this analysis is:

```
proc phreg data = ADTTE;
  class trt01p;
  model aval*cnsr(1) = trt01p {/Firth risklimits=PL};
  weight sIPTW;
  hazardratio trt01p;
run;
```

where trt01p is a variable that indicates the patient's treatment group, aval is a variable for the patient's time in Study Period at time of relapse or censoring, cnsr is the censoring variable (1 = no event (censored), 0= event), sIPTW is a variable representing the sIPTW weight. Firth's adjustment with profile likelihood confidence limits (Heinze, 2001), noted above as optional, will be applied if no relapses were observed in a treatment arm.

9.5.10.2. SAS Code for the Secondary/Exploratory Efficacy Endpoints

9.5.10.2.1. Poisson Regression Analysis

The analysis of the adjudicated On-Trial ARR will involve Poisson Regression analysis. The basic SAS code for that analysis is given by:

```
  proc genmod data = ADEFF;
  model aval = base_mean / dist = poisson link = log offset = logtime;
  estimate 'Mean' intercept 1 / exp;
  where trt01p='Ravulizumab';
run;
```

where aval is the number of relapses in the Study Period, base_mean is the annualized relapse rate at baseline (ie, historical ARR within the 24 months prior to Screening) centered on the mean baseline of the ravulizumab arm, and logtime is the log of the time in years the patient is in the study period.

The above code provides the 95% CI of the estimated adjudicated On-Trial ARR and the mean (mu) and standard error (sigma) on the log scale to test the hypothesis that the estimated adjudicated On-Trial ARR is equal to 0.25. This will be calculated as follows:

```
pValueboth = sdf('normal', abs(mu/sigma)) + cdf('normal',-abs(mu/sigma));
```

where sdf is the survival density function and calculates the upper area of the tail and cdf is the cumulative density function specifying the normal distribution and calculates the lower area of the tail, both based on the normal distribution.

A p-value ≤0.05 and estimated adjudicated On-Trial ARR < 0.25 is a statistically significant result in favor of ravulizumab.

9.5.10.2.2. Partial Proportional Odds Analysis

The analysis of clinically important differences in HAI will use a partial proportional odds model. The basic SAS code for that analysis is given by

```
proc logistic data=both order=internal;
    class trt01p (param=ref ref='Placebo');
    model clindiff = trt01p base /unequalslopes={base, if non-proportional};
run;
```

where trt01p is the treatment group, clindiff is the clinical important difference endpoint with 3 categories, and base is the baseline HAI score.

A sensitivity analysis will include the propensity score stratification variable with two strata as a covariate in the model as follows:

```
proc logistic data=both order=internal;
    class trt01p (param=ref ref='Placebo');
    model clindiff = trt01p base propstrat /unequalslopes={base propstrat, if non-proportional};
run;
```

where trt01p is the treatment group, clindiff is the clinical important difference endpoint with 3 categories, base is the baseline HAI score and propstrat is the propensity score stratification variable with two strata. This code will also be used in the sensitivity analysis stratifying on Study ECU-NMO-301 observed randomization strata, by replacing the propstrat variable above with the observed randomization strata variable.

9.5.10.2.3. ANCOVA of the Ranks of Change from Baseline

The primary analysis of the EQ-5D index and the EQ-5D VAS scores and some exploratory endpoints is an ANCOVA of the ranks of the change from baseline, adjusted for baseline.

The basic SAS code for that analysis is given by

```
proc rank data=eq5dadsl out=ranks ties=mean;
        var chg base;
        ranks chg_rank base_rank;
        where fasfl = 'Y';
run;
proc glm data=ranks;
```

```
        class trt01p;
        model chg_rank = base_rank trt01p /solution;
run;
```

where chg is the change from baseline, base is the value at baseline, and trt01p is the treatment group.

A sensitivity analysis will include the propensity score stratification variable with two strata as a covariate in the model as follows:

```
proc glm data=ranks;
        class trt01p pstrfas;
        model chg_rank = base_rank trt01p pstrfas/solution;
run;
```

9.5.10.2.4. Logistic Regression Analysis

The analysis of clinically important worsening in EDSS will use a logistic regression model. The basic SAS code for that analysis is given by

```
proc logistic data=both order=internal;
        class trt01p (param=ref ref='Placebo');
        model clinworse = trt01p base;
run;
```

where trt01p is the treatment group, clinworse is the clinical important worsening endpoint with 2 categories, and base is the baseline EDSS score.

A sensitivity analysis of clinically important worsening in EDSS will be a stratified logistic regression including propstrat as the propensity score stratification variable with two strata as follows:

```
proc logistic data=both order=internal;
        class trt01p (param=ref ref='Placebo') propstrat;
        model clinworse = trt01p base;
        strata propstrat;
run;
```

where trt01p is the treatment group, clinworse is the clinical important worsening endpoint with 2 categories, base is the baseline EDSS score, and propstrat is the propensity score stratification variable. This code will also be used in the sensitivity analysis stratifying on Study ECU-NMO-301 randomization strata, by replacing the propstrat variable above with the observed randomization IST strata variable.

9.5.10.3. SAS Code for Propensity Score Strata and sIPTW

The code for the propensity score strata is as follows:

```
proc psmatch data=adsl2 region=allobs;
        class trt01p sex noistfl Americas asiapac;
        psmodel trt01p(Treated='Ravulizumab')= aage Americas asiapac sex bledss noistfl
arrhs24;
        strata nstrata=2 key=total stratumwgt=total;
        output out(obs=all)=Outps_strat;
run;
```

The code for determining the sIPTWs using propensity scores is as follows:

```
proc psmatch data=adsl2 region=allobs;
        class  trt01p sex noistfl americas asiapac;
        psmodel trt01p(Treated='Ravulizumab')= aage americas asiapac sex bledss noistfl
arrhs24;
        psweight weight=atewgt(STABILIZE=YES) nlargestwgt=10;
        output out(obs=all)=OutEx1 weight=_ATEWgt_;
run;
```

9.5.11. E-Value Calculation

Vanderweele, 2017 describe the E-value as "the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the treatment and the outcome, conditional on the measured covariates, to fully explain away a specific treatment-outcome association." The E-value will be calculated as proposed by Vanderweele, 2017, using the following formula:

$$\text{E-Value} = RR^* + \text{sqrt}\{RR^* \times (RR^*-1)\}$$

where RR is an estimate of the risk ratio of association between treatment and outcome, and RR* is the inverse of RR. To estimate the RR from the Cox proportional hazards model the hazard ratio (HR) will be transformed as follows to provide an estimate of the RR:

$$RR \approx (1-0.5^{\text{sqrt}(HR)})/(1-0.5^{\text{sqrt}(1/HR)})$$

9.5.12. Color Vision

Ishihara Plates will be used to determine normal/abnormal color vision as described in Section 5.1.3. Color vision will be evaluated as the shift from baseline and described for patients with normal color vision in at least one eye, with shifts defined as follows:

Shift in Color Vision	Definition
1: Worsened	In either eye: • Change from normal to abnormal; or • Change from normal to not performed due to vision loss
0: No Change	• If the above criteria for worsening were not met.

9.6. Details of the Study ECU-NMO-301 Per Protocol Definition

The Per Protocol Definition described in Section 6.2 and Section 7.1.2, is very similar to what was used in Study ECU-NMO-301 with differences stemming from differences in design; for example, in Study ECU-NMO-301, patients whose treatment had to be unblinded were excluded from the PPS.

Patients in the placebo treatment group, who were excluded from the Study ECU-NMO-301 PPS are as follows:

Study ECU-NMO-301 Patient ID		Reason for Exclusion
[redacted]		Change in IST
		Key I/E Eligibility Violation
		Emergency Unblinding

These patients will be excluded from the PPS in these analyses as well.

DocuSign

Certificate Of Completion

Envelope Id: 5F2450164AF14A2682FF4EBF58591B37
Status: Completed
Subject: Please DocuSign: ALXN1210-NMO-307-SAPv3_20210709_final_clean.docx
Source Envelope:
Document Pages: 60
Signatures: 3
Envelope Originator:
Certificate Pages: 2
Initials: 0
[redacted]
AutoNav: Enabled
100 College Street,
EnvelopeId Stamping: Disabled
New Haven, CT 06510
Time Zone: (UTC-05:00) Eastern Time (US & Canada)
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
09-Jul-2021 | 13:07
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Alexion Pharmaceuticals, Inc. Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 09-Jul-2021 | 13:13 Viewed: 09-Jul-2021 | 13:21 Signed: 09-Jul-2021 | 13:25
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Alexion Pharmaceuticals, Inc. (Regulated) Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 09-Jul-2021 | 13:13 Viewed: 09-Jul-2021 | 13:14 Signed: 09-Jul-2021 | 13:15
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
[redacted] [redacted] [redacted] Alexion Pharmaceuticals, Inc. - Qualified (Regulated) Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 09-Jul-2021 | 13:13 Viewed: 09-Jul-2021 | 13:15 Signed: 09-Jul-2021 | 13:15
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	09-Jul-2021 | 13:13
Certified Delivered	Security Checked	09-Jul-2021 | 13:15
Signing Complete	Security Checked	09-Jul-2021 | 13:15
Completed	Security Checked	09-Jul-2021 | 13:25
Payment Events	**Status**	**Timestamps**

Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN ADDENDUM

PROTOCOL NUMBER: ALXN1210-NMO-307

A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)

Author: [redacted]

Date: 25 Jul 2020

Version: V1.0, Final

1. APPROVAL SIGNATURES

[redacted]

26-Jul-2022 | 09:16:34 EDT

Date dd Mmm yyyy

[redacted]

26-Jul-2022 | 09:15:26 EDT

Date dd Mmm yyyy

[redacted]

25-Jul-2022 | 18:51:19 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 Addendum to the Statistical Analysis Plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
AE	Adverse event
ARR	Annualized relapse rate
ADA	Antidrug antibody
C5	Complement component 5
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
C-SSRS	Columbia-suicide severity rating scale
FUP	Follow-up
NMOSD	Neuromyelitis Optica Spectrum Disorder
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software®
SMR	Standardized Mortality Ratio

4. STATISTICAL ANALYSIS PLAN ADDENDUM

This Statistical Analysis Plan (SAP) is an addendum to the ALXN1210-NMO-307 SAP version 3.0, dated 09 July 2021.

This analysis will provide supplemental results to the analyses of the Primary Treatment Period (data-cut of 15 March 2022). The data-cut date for the upcoming analysis will be 15 July 2022, with the exception of pharmacokinetic (PK), pharmacodynamic (PD), antidrug antibodies (ADA) and central laboratory data which have a cut date of 15 June 2022.

Analyses for the following endpoints are described in SAP version 3 (09 July 2021), with limited modifications described in Section 4.2 . The selected endpoints for the upcoming analyses include the following:

1. Study Patients
    - Disposition of patients
    - Protocol deviations
    - Concomitant medications/therapies, including changes in ISTs among patients permitted to change.
2. Efficacy Analyses
    - Time to first adjudicated on-trial relapse
        - The survival analysis methods specified in SAP Section 7.2.1 are used for time to first adjudicated on-trial relapse. Sensitivity analyses will include:
            - Not censoring at missed or delayed dose due to COVID-19 pandemic
            - Stratified analysis by propensity score
            - Weighted analysis using the stabilized inverse probability treatment weights
            - Stratified analysis by the study ECU-NMO-301 observed randomization stratification variable
            - Adjusting for time since most recent relapse prior to day 1
        - Summary of patients by censoring reasons
        - Summary of adjudicated on-trial relapse requiring hospitalization or acute treatments for relapses
        - Assessment of severity and type of relapses in the subgroup of patients who had one or more adjudicated on-trial relapses
    - Time to first on-trial relapse
        - This endpoint will be analyzed using the same statistical analysis methods as time to first adjudicated on-trial relapse, which is specified in SAP section 7.2.1.
        - Summary statistics will be provided for the follow assessments:

        - On-trial relapses requiring hospitalization or acute treatments for relapses
        - Assessment of severity and type of relapses in the subgroup of patients who had one or more on-trial relapses
    - Adjudicated on-trial ARR
        - This endpoint will be analyzed using the same statistical analysis methods specified in SAP section 7.2.2. However, in the event of 0 relapses, statistical testing will use the method indicated in Section 4.2 of this addendum.
        - Sensitivity analyses will include:
            - Not censoring at missed or delayed dose due to COVID-19 pandemic
            - Analyses comparing to the placebo group
            - By treatment group, adjusting for propensity score strata
            - By treatment group, adjusting for observed study ECU-NMO-301 randomization strata
    - Other endpoints: PK and PD endpoints including Ravulizumab concentrations and free component 5 (C5) in serum, and ADA.
3. Safety Endpoints

   Safety endpoints include AEs, laboratory parameters (shift tables only), and C-SSRS.

   Study duration and treatment duration will also be provided.

4.1. Changes from Analyses Specified in the Protocol

None.

4.2. Changes from Analyses Specified in the Previous Version of the SAP

The statistical methodology will be the same as specified in the final SAP version 3.0 dated 09 July 2022, with the following exceptions:

1. Selected analyses and summaries will be provided (eg, analyses for the selected endpoints will not be repeated using the Per Protocol Set).
2. For the analysis of the adjudicated on-trial ARR, an exact method will be applied as the primary analysis if 0 adjudicated on-trial relapses are observed.

   The p-value is derived using the poisson distribution, the follow-up time, and the number of relapses to compare to the null hypothesis of a 0.25 ARR. The exact method of the upper limit of the 95% CI, used the Chi-square distribution as described by Ulm (Ulm, 1990). The SAS code for the p-value is as follows:

   ```
   x=poisson(0.25*FUP, count);
   ```

where FUP is the person-years of time in the Study Period, 0.25*FUP is the mean count under the null hypothesis, count is the observed number of relapses, and x is the probability of having observed count given the mean count under the null hypothesis.

3. For AE tables summaries will be provided for the ravulizumab arm only.

5. REFERENCES

Ulm K. A Brief Original Contribution: A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). American Journal of Epidemiology. 1990; Vol. 131, No. 2: 373-375.

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