Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ECU-NMO-303

A Phase 2/3 Open-Label, Single-Arm Trial to Evaluate the Safety and Activity of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder

Author: [redacted]

Date: **19 October 2021**

Version: **1.0**

1. APPROVAL SIGNATURES

[redacted]

20-Oct-2021 | 09:53:24 EDT

Date dd Mmm yyyy

[redacted]

20-Oct-2021 | 09:54:37 EDT

Date dd Mmm yyyy

[redacted]

20-Oct-2021 | 09:54:35 EDT

Date dd Mmm yyyy

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

TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this Statistical Analysis Plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or acronym	Explanation
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
Anti-AQP4 Ab	anti-aquaporin-4 antibody
ARR	annualized relapse rate
BMI	body mass index
BP	blood pressure
C5	complement protein 5
CI	confidence interval
COVID-19	coronavirus disease of 2019
DMC	data monitoring committee
ECG	electrocardiogram
EDSS	Extended Disability Status Scale
EOPT	end of Primary Treatment Period
ET	Early Termination
EQ-5D VAS	European Quality of Life Health 5-item questionnaire visual analog scale
EQ-5D-Y	European Quality of Life Health 5-item questionnaire-Youth
FAS	Full Analysis Set
FSS	Functional System Score
HAI	Hauser Ambulation Index
HR	heart rate
HRQOL	health-related quality of life
ICF	informed consent form
IST	immunosuppressive therapy
IVIg	intravenous immunoglobulin
MRI	magnetic resonance imaging
NMOSD	neuromyelitis optica spectrum disorder
ON	optic neuritis
OSIS	Optic Spinal Impairment Score
PD	pharmacodynamics
PE	plasma exchange
PedsQL	Pediatric Quality of Life Inventory
PedsQL Parent Proxy	Pediatric Quality of Life Inventory Parent Proxy
PK	pharmacokinetics
PR	interval between the P wave and QRS complex
PT	Preferred Term
PTAE	pre-treatment adverse events
PTSAEs	pre-treatment serious adverse events

Table 1: Abbreviations and Acronyms

Abbreviation or acronym	Explanation
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
RR	respiration rate
RR interval	the time elapsed between two successive R-waves of the QRS
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SoA	schedule of activities
SOC	System Organ Class
TEAEs	treatment-emergent adverse events
TEAESIs	treatment-emergent adverse events of special interest
TESAEs	treatment-emergent serious adverse events
TM	transverse myelitis
UMN	upper motor neuron
VA	Visual Acuity
VF	Visual Field

4. DESCRIPTION OF THE PROTOCOL

The ECU-NMO-303 study is a Phase 2/3 open-label, single-arm study to evaluate the safety and efficacy of eculizumab in pediatric patients (aged 2 to < 18 years) with relapsing neuromyelitis optica spectrum disorder (NMOSD). A total of 12 eligible patients will be enrolled, with a minimum target of 10 evaluable patients. Of the 10 evaluable patients, at least 3 of the patients will be aged 2 to < 12 years at the time of enrollment, and at least 5 patients will be aged 12 to < 18 years at the time of enrollment.

There are 4 periods in this study: the Screening Period (1–6 weeks), the Primary Treatment Period (Day 1–Week 52/53), the Extension Treatment Period (104 weeks), and the Safety Follow-Up Period (8 weeks following the last dose of eculizumab). The Primary Treatment Period ends on Week 53 for patients who were enrolled in the 10 to < 20 kg weight cohort, because for this weight cohort, the maintenance dose, administered every 2 weeks, begins on Week 1; for all other weight cohorts the Primary Treatment Period will end at Week 52 because the maintenance dosing begins on even-numbered weeks. For weight-based dosing regimen, see protocol Section 6.1.

The study objectives and endpoints are as follows:

Objectives	Endpoints
Primary Treatment Period[a]: Primary: Efficacy	
• Evaluate the efficacy of eculizumab in relapsing pediatric patients with neuromyelitis optica spectrum disorder (NMOSD).	• The change from Baseline in the Annualized Relapse Rate (ARR) at 52/53 Weeks.[b] • Time to First Relapse.
Primary Treatment Period[a]: Secondary: Safety	
• Evaluate the safety and tolerability of eculizumab treatment in relapsing pediatric patients with NMOSD.	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events leading to study drug discontinuation. • Incidence of antidrug antibodies (ADA). • Changes from Baseline in vital signs, electrocardiogram (ECG) parameters, and clinical laboratory assessments. • Change from Baseline in both weight and height.
Primary Treatment Period[a]: Secondary: Efficacy	
• Evaluate the efficacy of eculizumab by additional efficacy measures including:	
• Disease-related disability	• Change from Baseline in Expanded Disability Status Scale (EDSS) score at 52/53 weeks in patients ≥ 5 years of age. • Change from Baseline in the Hauser Ambulatory Index (HAI) score at 52/53 weeks.

Objectives	Endpoints
• Quality of life	• Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) at 52/53 weeks in patients ≥ 5 years of age. • Change from Baseline in Pediatric Quality of Life Inventory Parent Proxy (PedsQL Parent Proxy) at 52/53 weeks in patients < 5 years of age.
• Change in ophthalmologic examination findings	• Change from Baseline in Visual Acuity (VA) as measured by the Snellen or LEA symbols Eye Chart examination at 52/53 weeks in all patients. • Change from Baseline in Confrontational Visual Fields (VF) as measured during ophthalmologic examination at 52/53 weeks in all patients. • Change from Baseline in color vision as measured during ophthalmologic examination at 52/53 weeks in all patients.
Primary Treatment Period[a]: Secondary: PK/PD	
• Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in relapsing pediatric patients with NMOSD.	• Changes in serum eculizumab concentration over time. • Changes in serum free complement protein 5 (C5) concentrations and in vitro hemolytic activity over time.
Primary Treatment Period[a]: Tertiary Efficacy Assessment	
• Evaluate the efficacy of eculizumab by additional efficacy measures including • Quality of life	• Change from Baseline in the European Quality of Life-5 Dimensions-Youth (EQ-5D-Y) score for patients ≥ 8 years of age and EQ-5D-Y Proxy score for patients aged between 5-7 years, at 52/53 weeks.
Extension Treatment Period[c]: Secondary Safety and Efficacy	
• Characterize long-term safety of eculizumab treatment in pediatric patients with NMOSD. • Characterize long-term efficacy of eculizumab treatment in pediatric patients with NMOSD.	• The safety and efficacy endpoints of the Primary Treatment Period will be evaluated during the Extension Treatment Period.

[a] Open-label eculizumab intravenous (IV) infusion, for a total of 52/53 weeks.
[b] Baseline ARR will be calculated using historical relapse data for each patient in the 2 year period prior to screening. For patients who start in weight cohort 10 to < 20 kg, the On-Trial one-year evaluation will occur on Week 53, an odd-numbered week, because maintenance dosing, which is administered every 2 weeks, begins on Week 1. For all other cohorts the On-Trial one-year evaluation will occur on Week 52, because maintenance dosing begins on an even-numbered week. Hence, the end of the Primary Treatment Period is designated as Week 52/53 throughout the protocol.
[c] After completing the Primary Treatment Period, patients will continue receiving open-label eculizumab in the Extension Treatment Period for 104 weeks.
Note: Statistical analysis of the primary endpoints will be limited to the change from Baseline to Week 52/53 On-Trial ARR. Time to first relapse results will be considered descriptive; therefore, no adjustments for

multiplicity will be made.

This Statistical Analysis Plan (SAP) describes the analyses of the Primary Treatment Period. Another SAP will be developed to describe the analyses that include the Extension Treatment Period prior to the completion of the entire study.

4.1. Changes from Analyses Specified in the Protocol

Not applicable

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

Not applicable

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint(s)

The primary efficacy endpoint is the change between the Baseline Annualized Relapse Rate (ARR) and the On-Trial ARR at 52/53 weeks. Baseline ARR will be calculated using historical relapse data for each patient in the 2-year period prior to screening for this study. Time to first On-Trial Relapse is a co-primary efficacy endpoint.

Note: For the purposes of the protocol and this SAP, the terms "relapse" and "attack" are synonymous. The definition of Historical Relapses and On-Trial Relapses are as follows.

Historical Relapse

Historical Relapses are the relapses that occurred prior to the Screening Visit, including the first NMOSD attack. For this protocol, Historical Relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or magnetic resonance imaging [MRI] findings or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of existing neurologic symptoms that required treatment. Treatment is defined as use of high-dose intravenous (IV) steroids, plasma exchange (PE), or intravenous immunoglobulin (IVIg). Events that occur within a 30-day interval are considered as 1 relapse.

On-Trial Relapse:

On-Trial Relapses are acute attacks 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 Investigator. 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 will not be considered an On-Trial Relapse. The relapse must be preceded by at least 30 days of clinical stability. The Investigator is not required to wait 24 hours prior to initiating treatment for the relapse.

All Investigator-Reported On-Trial Relapses will additionally be adjudicated by the Relapse Adjudication Committee (RAC) as part of a sensitivity analysis. The RAC, consisting of medical experts who have particular expertise in NMOSD, will conduct independent reviews for all relapse events identified by the Investigators. The RAC will decide by majority vote whether each Investigator-Reported On-Trial Relapse meets the objective criteria for an On-Trial Relapse. A relapse that is determined by both the Treating Physician and the RAC to meet the criteria of an On-Trial Relapse in this trial is classified as a positively adjudicated On-Trial Relapse. A separate 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.

During this trial, potential relapse events that occur may be evaluated by the Treating Physician and be determined by him/her to not meet the definition of an On-Trial Relapse. These events are

however also evaluated by the RAC. If this event is adjudicated positively as a relapse by the RAC, then it will be also included in the category of "positively adjudicated relapses". In other words, a positively 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.

Historical ARR, which will be called the Baseline ARR, for all patients will be calculated using Historical Relapse data for each patient in the 2-year period prior to screening for this study. The Investigator-reported On-Trial ARR for the Primary Treatment Period will be calculated for the time period from the first dose of eculizumab through Week 52/53 or Early Termination (ET) from the Primary Treatment Period. Details of Historical ARR and On-Trial ARR can be found in Appendix 9.5.1. All Investigator-Reported On-Trial Relapses will additionally be adjudicated by the RAC as part of a sensitivity analysis.

Time to First On-Trial Relapse will be measured in days, beginning at the time the patient's first dose of eculizumab is administered until the patient's first On-Trial Relapse is reported by the investigator. Time to first adjudicated On-Trial Relapse will be measured similarly based on patient's first adjudicated On-Trial Relapse.

5.1.2. Secondary Endpoints

The secondary efficacy endpoints for the study are:

- Change from Baseline in Expanded Disability Status Scale (EDSS) score at 52/53 weeks in patients ≥ 5 years of age
- Change from Baseline in the Hauser Ambulatory Index (HAI) score at 52/53 weeks
- Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) scores at 52/53 weeks in patients ≥ 5 years of age
- Change from Baseline in Pediatric Quality of Life Inventory Parent Proxy (PedsQL Parent Proxy) scores at 52/53 weeks in patients < 5 years of age
- Change from Baseline in Visual Acuity (VA) as measured by the Snellen or LEA symbols Eye Chart examination at 52/53 weeks in all patients
- Change from Baseline in Confrontational Visual Fields (VF) as measured during ophthalmologic examination at 52/53 weeks in all patients
- Change from Baseline in color vision as measured during ophthalmologic examination at 52/53 weeks in all patients

5.1.2.1. 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.

See Protocol Appendix 9 for the EDSS.

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). See Protocol Appendix 10 for the HAI.

5.1.2.3. Pediatric Quality of Life Inventory (PedsQL) and PedsQL Parent Proxy

PedsQL is a brief, standardized, generic assessment instrument that systematically assesses patients' and their parents' perceptions of health-related quality of life (HRQOL) in pediatric patients with chronic health conditions using pediatric cancer as an exemplary model. The PedsQL is based on a modular approach to measuring HRQOL and consists of a 15-item core measure of global HRQOL and 8 supplemental modules assessing specific symptom or treatment domains. The PedsQL was empirically derived from data collected from 291 pediatric cancer patients and their parents at various stages of treatment. Items are reverse scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQOL. The test is designed for self-completion in patients aged ≥ 5 years by respondents (with 3 age-appropriate PedsQL tests available for ages 5-7, 8-12, and 13-18 years old), and by a proxy in patients aged ≥ 2 to < 5 years. Attempts should be made to have the same proxy complete the evaluation at each visit. See Protocol Appendix 11 for the PedsQL.

5.1.2.4. Visual Acuity (VA)

VA is usually affected by optic neuritis (ON), progressing over a period of hours to days. Summaries and analyses of VA will be performed using the results from the EDSS Rater assessments. The assessment quantifies ability to read letters or symbols of varying sizes at a fixed distance in relation to the distance at which a patient with normal vision could read the same letters or symbols. The VA assessment is typically recorded as acuity ratio distance (for example, 6 meters or 20 feet), so for normal VA it would be recorded as 20/20 or 6/6. Sometimes this is entered as the denominator of the fraction (in US) or as a decimal (ex US).

5.1.2.5. Confrontational Visual Fields (VF)

The ophthalmological examination will evaluate confrontational VF. For each eye, the examiner will determine if there is VF deficit in each quadrant. It is critical for these assessments that the Baseline ophthalmologic status be known so that changes in the examination can be used to evaluate prior or ongoing ON. Central scotomas are common in patients experiencing ON; however, VF defects can present with a broad spectrum of patterns (Keltner, 1999). This assessment will be performed for all patients in this study.

5.1.2.6. Color Vision

Color vision will be assessed using Ishihara plates. This will be assessed in all patients in this study. Loss of color vision can be a marker of ON and is therefore an important assessment tool in NMOSD. Patients with 10 or more correctly identified Ishihara plates will be considered as

having normal color vision, and patients with 9 or less correctly identified will be considered as having abnormal color vision.

5.1.3. Tertiary Efficacy Endpoints

The tertiary efficacy endpoint for the study is:

Change from Baseline in the European Quality of Life-5 Dimensions-Youth (EQ-5D-Y) score for patients ≥ 8 years of age and EQ-5D-Y Proxy score for patients aged between 5 and 7 years, at 52/53 weeks

5.1.3.1. European Quality of Life-5 Dimensions-Youth (EQ-5D-Y) score and EQ-5D-Y Proxy score

The EQ-5D-Y is based on the EQ-5D and is designed for use in patients aged ≥ 4 to < 18 years. The EQ-5D-Y will be used in this study for self-completion in patients enrolled between the ages ≥ 8 to < 18 years by respondents, and by a proxy in patients enrolled between the ages ≥ 5 to < 8 years. Attempts should be made to have the same proxy complete the evaluation at each visit. Children < 5 years will not have EQ-5D-Y assessed in the study.

The EQ-5D-Y consists of 3 pages: the EQ-5D-Y descriptive system (page 2) and the European Quality of Life Health 5 dimension questionnaire visual analog scale (EQ-5D VAS) (page 3). The descriptive system comprises the same 5-component scale as the EQ-5D-5L, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, but uses child-friendly wording (ie, mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad, or unhappy). Each dimension has 3 levels and is rated on a scale that describes the degree of problems in that area: “no problems”, “some problems”, “a lot of problems” with Level 1 indicating the lowest degree of problems and Level 3 indicating the greatest degree of problems. Respondents are asked to indicate their health state by ticking (or placing a cross) in the box that best describes their health status.

The EQ-5D VAS is an overall health scale where the rater selects a number between 0-100 to describe the condition of their health, with 100 being ‘The best health you can imagine’ and 0 being ‘The worst health you can imagine’. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

See Protocol Appendices 7 and 8 for the EQ-5D-Y and EQ-5D-Y proxy.

5.1.4. Other Efficacy Endpoints

5.1.4.1. Optic Spinal Impairment Score (OSIS)

The Optic Spinal Impairment Score (OSIS) will be used as a scoring system for the severity of a relapse. The OSIS VA Subscale Scores will be used to categorize the severity of ON. The OSIS Motor Subscale Scores and Sensory Subscale Scores will be used to categorize the severity of transverse myelitis (TM). OSIS score will be assessed by the Investigator at the time of the relapse.

See Protocol Appendix 12 for the OSIS.

5.2. Safety

The safety of eculizumab will be assessed based on adverse events (AEs), serious adverse events (SAEs), and changes from baseline through the end of Primary Treatment Period (EOPT) in vital signs, routine clinical laboratory tests (eg, chemistry, hematology), physical examination, electrocardiogram (ECG) results, and pregnancy tests for female patients of childbearing potential.

An independent Data Monitoring Committee (DMC) will conduct interim monitoring of safety data. The DMC will have access to all safety data. The DMC may make recommendations to the Sponsor regarding safety issues, study conduct, and modifying, extending, or stopping the study.

In addition, the DMC will receive reports concerning patients who have discontinued. Notification of study discontinuation and reason for the discontinuation will be sent to the DMC according to the schedule defined in the Charter. The DMC will also review summaries of all relapses.

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

5.2.1. Adverse Events (AEs)

Adverse events are defined in Protocol Appendix 3.

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the last visit (Safety Follow-up Visit) of the Extension Period, as specified in the Schedule of Activities (SoA) (Protocol Section 1.2).

For the purposes of this SAP, 4 types of AEs will be noted:

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

PTAEs are the AEs that occur between the signing of ICF and first investigational product (IP) dose. PTSAEs are the serious AEs that occur between the signing of ICF and first IP dose. TEAEs are AEs with onset on or after the first IP dose in the study. Likewise, TESAEs are SAEs with onset on or after the first IP dose in the study.

5.2.2. Vital Signs

Temperature (°C or °F), respiratory rate (RR), heart rate (HR) (beats/minute), and systolic and diastolic blood pressure (BP) (mm Hg) will be assessed. Vital signs will be obtained after the patient has been supine or seated for at least 5 minutes. Ideally, each patient's BP should be measured using the same arm.

Body weight will be measured in pounds or kilograms. Height will be measured in inches or centimeters. Body mass index (BMI) will be calculated.

5.2.3. Laboratory Assessments

Blood samples for chemistry panel, complete blood count and differential, and serum pregnancy test, and urine samples for urinalysis and urine pregnancy test will be collected as outlined in the SoA (See Protocol Section 1.2).

Immunogenicity: Blood samples will be collected for evaluation for antidrug antibody (ADA) at specified time points to describe the presence or absence of an immune response to eculizumab.

5.2.4. Other Safety Assessments

5.2.4.1. Physical Examination

A physical examination will include assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, pulse, chest, heart, abdomen, extremities; musculoskeletal and general neurologic examination. A targeted physical examination consists of a body-system relevant examination based upon Investigator judgment and patient symptoms.

5.2.4.2. Electrocardiogram (ECG)

A single 12-lead ECG will be obtained as outlined in the SoA (see Protocol Section 1.2) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Whether the ECG is within normal limits and the clinical significance of abnormal results will be documented.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

6.1. Full Analysis Set (FAS)

The Full Analysis Set (FAS) includes all patients who have received at least 1 dose of eculizumab.

6.2. Safety Set

The Safety Set includes all patients who have received at least 1 dose of eculizumab.

6.3. Other Sets

6.3.1. Pharmacokinetics/Pharmacodynamics (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 eculizumab and who have evaluable PK/PD data.

7. STATISTICAL ANALYSIS

The primary analysis will be conducted when all patients have completed the 52/53-week Primary Treatment Period or discontinued prior to the completion of the Primary Treatment Period. This analysis will include all efficacy, safety, and PK/PD study data for regulatory submission purpose and will be the final analysis of the Primary Treatment Period.

Summary statistics will be computed and displayed by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of patients, mean, standard deviation (SD), 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. Estimates of changes in the efficacy endpoints will be accompanied by 2-sided 95% confidence intervals (CIs).

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, and number and percentage of enrolled and treated patients among all screened patients will be provided. A 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
- Patients who completed the Primary Treatment Period
- Patients who discontinued the Primary Treatment Period with reason for discontinuation
- Patients who continued to the Extension Treatment Period
- Patients who completed the Extension Treatment Period
- Patients who discontinued the Extension Treatment Period with reason for discontinuation
- Patients who completed the study
- Patients who discontinued the study with reason for discontinuation
- Patients in analysis datasets

A by-patient listing will be provided for patient disposition.

7.1.2. Protocol Deviations

The protocol deviations will be summarized in a table and a listing. Summaries will be presented overall and by important and not important deviations, and by prespecified deviation categories.

7.1.3. Demographics, Disease Characteristics, and History

Patient demographic and baseline characteristics will be summarized using the Safety Set. Summary statistics will be presented. No formal hypothesis testing will be performed. Baseline is defined as the last available assessment prior to the first dose of eculizumab.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age group at enrollment (2 to < 12 years or 12 to < 18 years)
- Age at first eculizumab dose (years)
- Sex
- Race and ethnicity
- Japanese patient
- Region
- Baseline weight
- Baseline weight cohort (≥ 40 kg, 30 to < 40 kg, 20 to < 30 kg, 10 to < 20 kg)
- Baseline height
- Baseline 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
- Core clinical characteristics used in NMOSD diagnosis
- 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)
- Historical ARR based on 2 years prior to Screening
- EDSS, HAI, PedsQL, PedsQL Parent Proxy, OSIS, VA, Confrontational VFs, color vision, EQ-5D-Y score, and EQ-5D-Y Proxy score 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 for the Safety Set. Likewise, Baseline physical examination information will be summarized for the Safety Set. 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 ARR in the 24 months prior to the Screening Visit will be summarized for patients in the Safety Set.

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 on or after first study treatment. Medications will be coded using the World Health Organization Drug Dictionary (WHO Drug Dictionary version March 2021 or higher). Summaries will be presented for the Safety Set.

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.

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

The following medications are allowed under certain circumstances and restrictions.

Immunosuppressive Therapy (IST) Agents:

- The choice of immunosuppressive therapy (IST) agents is at the discretion of the Investigator with the exception of disallowed medications (see Protocol Section 6.6.2). Standard recommended dosing should be used for the chosen IST. Use of corticosteroids is permitted; however, the total daily dose must not exceed 0.5 mg/kg/day of prednisone or equivalent and in no case may the dose exceed 20 mg/day.
- Patients who enter the study receiving supportive IST(s) (eg, corticosteroid, azathioprine [AZA], mycophenolate mofetil [MMF], methotrexate [MTX], tacrolimus [TAC], cyclosporine A [CsA], or cyclosporine [CYC]) for the prevention of relapse, either in combination or monotherapy, must be on a stable dosing regimen of adequate duration prior to Screening. See Protocol Section 6.6.1.2 for details. The patient must remain on that dose regimen during the Screening Period and for the Primary Treatment Period (52/53 weeks). During the Primary Treatment Period, the patient's IST dose may be adjusted on the basis of weight/body-surface/age to account for the child's growth. No other adjustment in IST dosage and no new ISTs will be permitted, unless the patient experiences a relapse or a safety event, and a change in IST dose would be deemed necessary by the Investigator to guarantee the patient's safety.

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, at Baseline, and during the Primary Treatment Period will be summarized. Listings of supportive ISTs will be produced. Changes in ISTs during the Primary Treatment Period will be summarized.

Treatment of On-Trial Relapse

During this study, the treatment of relapse is at the discretion of the Investigator.

For patients with On-Trial Relapses, the use of ISTs, plasmapheresis and PE will be summarized and listings will be produced. Investigational procedures for On-Trial Relapses will be summarized for patients with On-Trial Relapses. Listings of investigational procedures for On-Trial Relapses will be produced for patients with On-Trial Relapses.

The following medications and therapies, except when used in the treatment of On-Trial Relapse or when permitted by the Investigator and Sponsor, if applicable, are prohibited during the study:

- Mitoxantrone
- Rituximab or other biologicals that may affect immune system functioning, such as tocilizumab
- IVIg for relapse prevention
- PE for relapse prevention
- Use of immunomodulatory therapies including: interferon beta-1b, interferon beta-1a, glatiramer acetate, natalizumab, alemtuzumab, and fingolimod.

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.

Non-pharmacologic therapies and procedures prior to study treatment and during the study will be summarized by System Organ Class (SOC) and Preferred Term (PT) using counts and percentages. By-patient listings of non-pharmacologic therapies and procedures will be produced. Summaries will be presented for the Safety Set.

7.1.5. Summary of Study Visit Impacted by Coronavirus Disease of 2019 (COVID-19)

The number and percentage of patients who had at least one study visit that was altered to accommodate coronavirus disease of 2019 (COVID-19) restrictions, reasons for these modified study visits, and the number and percentage of patients who missed at least one study visit and reasons may be summarized on the Safety Set, if applicable.

7.2. Efficacy Analyses

Efficacy analyses will be performed on the FAS. Baseline is defined as the last available assessment prior to the first dose of eculizumab.

7.2.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the change from baseline in the patient-level ARR at 52/53 weeks. Baseline ARR for all patients will be calculated using Historical Relapse data for each patient in the 2-year period prior to screening for this study. On-Trial ARR as reported by the Investigator will be calculated using the time period from the first dose of eculizumab through Week 52/53 or ET from the Primary Treatment Period (see Appendix 9.5.1 for more details). The study will be considered to have met its primary efficacy endpoint if a statistically significant p-value (< 0.05) is observed for the change in ARR between the Baseline ARR and the On-Trial ARR in favor of eculizumab treatment using the Wilcoxon signed rank test. The patient-level ARR will also be summarized using mean, median, SD, minimum, and maximum. The number of On-Trial Relapses, number of patient-years in the Primary Treatment Period, and

the study-level ARR (and exact 95% CI based on Poisson distribution) will be summarized descriptively. A plot showing the time in Primary Treatment Period and when relapses occur will be produced for patients with On-Trial Relapse.

If no On-Trial Relapse is observed during the Primary Treatment Period, the patient-level On-Trial ARR and study-level On-Trial ARR will be 0. Change in ARR between the Baseline ARR and the On-Trial ARR will be estimated and the Wilcoxon signed rank test will be performed.

If there are patients who missed 2 or more infusions consecutively due to COVID-19-related reasons, the time period for the calculation of On-Trial ARR will exclude the time period when the patient missed eculizumab infusion, to account for the impact of the pandemic. Any relapse occurring during this period will not be included in the calculation of On-Trial ARR and will be presented in listings. See Appendix 9.5.1 for more details. A sensitivity analysis will be performed in which all On-Trial relapses are included in the calculation of On-Trial ARR irrespective of the impact of the pandemic.

Time to first On-Trial Relapse is a co-primary efficacy endpoint. The time to first On-Trial Relapse and the percentage of patients who are relapse-free while on eculizumab treatment in the Primary Treatment Period along with 95% CIs based on complementary log-log transformation will be computed using the Kaplan-Meier method. Time to first On-Trial Relapse results will be considered descriptive; therefore, no adjustment for multiplicity will be made. Definitions of the time to first event and the censoring times are provided in Appendix 9.5.2.

If there are patients who missed 2 or more doses consecutively due to COVID-19-related reasons, the time period for the analysis of time to first On-Trial Relapse is truncated to account for the impact of the pandemic. See Appendix 9.5.2 for more details. Any relapse after the end of the truncated Primary Treatment Period will be presented in listings. A sensitivity analysis will be performed in which all On-Trial relapses are included in the analysis of time to first On-Trial Relapse irrespective of the impact of the pandemic.

Sensitivity Analyses of the Primary Efficacy Endpoint:

A sensitivity analysis will be performed for the change in patient-level ARR between the Baseline ARR and the adjudicated On-Trial ARR in a similar manner. Change in ARR will be summarized and results from the Wilcoxon signed rank test will be presented.

The percentage of patients who are relapse-free while on eculizumab treatment in the Primary Treatment Period along with 95% CIs will also be computed using the Kaplan-Meier method for the adjudicated On-Trial Relapses.

7.2.1.1. Handling of Dropouts or Missing Data

In this study, all FAS patients would either have experienced an On-Trial Relapse or would have ended participation in the Primary Treatment Period without an On-Trial relapse. The patients who do not have On-Trial Relapses will have patient-level ARR as 0, and will be censored and will have a censor time that is based on the patient's time from first dose to the end of the Primary Treatment Period date, as described in Appendix 9.5.1. A censoring indicator will be equal to 1 if the patient did not experience an On-Trial Relapse (was censored), and 0 if the patient experienced an On-Trial Relapse. Reasons for censoring will be summarized.

Missing data in secondary and tertiary efficacy endpoints will not be imputed.

7.2.1.2. Subgroup Analysis

Summaries of the primary efficacy endpoints by age subgroups (age at enrollment 2 to < 12 years and 12 to < 18 years) will be produced. Results will be descriptive.

Some efficacy analyses will involve subgroups of the FAS:

- The assessment of EDSS will be conducted in patients ≥ 5 years of age
- The assessment of PedsQL will be conducted in patients ≥ 5 years of age
- The assessment of PedsQL Parent Proxy will be conducted in patients < 5 years of age
- The assessment of EQ-5D-Y will be conducted in patients ≥ 8 years of age
- The assessment of EQ-5D-Y Proxy score will be conducted in patients aged between 5-7 years

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

Change in ARR between the Baseline ARR and the On-Trial ARR will be evaluated using the 2-sided Wilcoxon signed rank test at the 0.05 level of significance.

7.2.1.5. Sensitivity Analyses

Sensitivity analyses for the primary endpoints are described above in Section 7.2.1.

7.2.2. Secondary Efficacy Endpoint Analyses

Results of secondary efficacy endpoints will be descriptive. No formal statistical test will be performed.

Changes from Baseline for the EDSS score will be summarized at the Week 52/53 Visit as well as over the applicable study visits during the Primary Treatment Period. Summaries will include 95% CIs of the mean and median. The distribution of EDSS scores over time will also be summarized. By-patient listings of the EDSS scores will be produced.

Changes from Baseline at the Week 52/53 Visit as well as over the applicable study visits during the Primary Treatment Period in HAI score, Self-Reported PedsQL, and Parent Proxy PedsQL will be analyzed in a similar manner as changes in the EDSS score. Table summaries and by-patient listings of the assessments will be produced. The distribution of HAI scores over time will be summarized.

VA will be summarized as the number and percentage of patients in each of the following categories for each eye at the Week 52/53 Visit as well as over the applicable study visits during the Primary Treatment Period. Shifts from Baseline to each study visit will be presented.

- VA 20/20 – 20/29

- VA 20/30 – 20/59
- VA 20/60 – 20/100
- VA 20/101 – 20/200
- VA < 20/200

Confrontational VFs will be summarized as the number and percentage of patients with number of deficits (0, 1, 2, 3, 4) identified in each eye among patients with adequate eye-sight to perform the assessment, at the Week 52/53 Visit as well as over the applicable study visits during the Primary Treatment Period. Shifts from Baseline to each study visit will be presented.

Color vision will be summarized as the number and percentage of patients with normal or abnormal color vision in each eye among patients with adequate eye-sight to perform the assessment, at the Week 52/53 Visit as well as over time in a similar manner as described for confrontational VFs.

7.2.3. Tertiary Efficacy Endpoint Analyses

The tertiary efficacy endpoint for the study is:

- Change from Baseline in the EQ-5D-Y/EQ-5D-Y Proxy score at 52/53 weeks.

Results of tertiary efficacy endpoints will be descriptive. No formal statistical test will be performed.

Changes from Baseline in EQ-5D-Y VAS/EQ-5D-Y VAS Proxy score at the Week 52/53 Visit as well as over the applicable study visits during the Primary Treatment Period will be analyzed in a similar manner as changes in the EDSS score. Table summaries and by-patient listings of the assessments will be produced. The number and percentage of patients in each level (“no problems”, “some problems”, “a lot of problems”) will be presented by dimension at the Week 52/53 Visit as well as over the applicable study visits during the Primary Treatment Period. Shifts from Baseline to each study visit will be presented.

7.2.4. Other Efficacy Analyses

7.2.4.1. Relapse Severity and Types

For On-Trial Relapse(s), a by-patient listing of the relapses will be produced. Relapse severity, using the OSIS scale will be presented for ON and TM relapses based on the OSIS VA, motor, and sensory scales for 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, 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. Relapse severity will be presented at relapse level and patient level. See Appendix 9.5.4 for details.

The types of relapses will be presented for On-Trial Relapse(s) in a listing.

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, PE, and high-dose oral steroids). Use of IVIg will be summarized but not analyzed.

7.2.5. Pharmacokinetic and Pharmacodynamic Analyses

Blood samples will be collected to evaluate the PK activity of eculizumab over time. Individual serum concentration data will be used to derive PK parameters for eculizumab. Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration time profiles for individual patients may also be generated. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics (mean, SD, median, minimum, maximum) will be calculated for serum concentration data at each sampling time, as appropriate.

Blood samples will also be collected to evaluate the PD of eculizumab over time. Descriptive statistics will be presented for all eculizumab PD endpoints at each sampling time. Box plots of free complement protein 5 (C5) values over time will be constructed. The PD effects of eculizumab will be evaluated by assessing the absolute values and changes and percentage changes from baseline in free C5 and in vitro hemolytic activity over time, as appropriate.

The population PK analysis and PD analysis may be performed according to a separate analysis plan and the results presented separately from the main Clinical Study Report.

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

7.2.6. Biomarker Assessments

Serum anti-aquaporin-4 antibody (Anti-AQP4 Ab) samples will be collected at Screening, relapse evaluation visits, and at other study visits as specified in the SoA (Protocol Section 1.2). Shifts from baseline in serum Anti-AQP4 Ab titer level will be summarized by visit on available data. A listing of serum Anti-AQP4 Ab titers will be produced on available data.

7.2.7. Medical Resource Utilization

The number of days of hospitalization will be summarized by relationship to NMOSD. A listing will be produced to summarize hospitalization and medical resource utilization.

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 test is planned. Baseline is defined as the last available assessment prior to treatment.

7.3.1. Study Duration, Treatment Compliance, and Exposure

Study duration, treatment duration, treatment compliance, and exposure will be summarized 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 date of signing ICF until the date of completion/discontinuation from the Primary Treatment Period (ie, Study duration [weeks] = date of completion/discontinuation [or death] from the Primary Treatment Period – date of signing ICF + 1, all divided by 7). 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 in the Primary Treatment

Period (ie, treatment duration [days] = Last Dose Date – First Dose Date + 1). See Appendix 9.5.3 for more details.

Patients with missed scheduled infusion and the reasons for any missed infusions, including COVID-19-related reasons, may be presented in a listing if applicable. Unscheduled infusions may be presented in a similar fashion if applicable.

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

7.3.2. Adverse Events (AEs)

AEs are defined in Protocol Section 10.3. TEAEs are defined in Section 5.2.1.

AEs will be coded by primary SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) (version 23.1 or higher).

In addition to presenting frequencies and percentages of patients, AE rates based on 100 patient-years of follow-up will be produced where stated. Patient-years of follow-up and additional details regarding AEs are outlined in Appendix 9.4.6.

A 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.

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 group at enrollment.

See Appendix 9.4.6 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 treated patients. SOCs will be listed alphabetically and PTs within each SOC will be listed in order of frequency of occurrence (percentage). AE rates based on 100 patient-years of follow-up will be produced for all TEAEs and all TESAEs. Patient-years of follow-up are defined in Appendix 9.4.6. These tables will be presented both including and excluding the coded PT for NMOSD.

Additional summary tables will be presented by SOC, PT, and age group at enrollment.

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 and TESAEs 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 TEAE will also be provided.

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

Summaries of TEAEs by relationship to treatment will be provided. Summary of TESAEs by relationship will also be provided.

AE rates based on patient-years of follow-up will be produced for all TEAEs/TESAEs by relationship to treatment.

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

Summaries of TEAEs by severity will be provided.

AE rates based on patient-years of follow-up will be produced for all TEAEs by severity.

7.3.2.5. 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 in tabular form. The following provides a list of adverse events of special interest (AESI):

- Infections:
  - Meningococcal infections
  - Aspergillus infections
  - Other serious infections
- Sepsis
- Infusion reactions
- Angioedema

TEAESIs will be summarized by SOC/PT, by PT alone and by relationship.

7.3.3. Other Safety

Listings will be produced for all other safety parameters.

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.

7.3.3.2. Vital Signs

Vital signs (systolic and diastolic BP, temperature, respiration rate [RR] and HR), and changes from baseline in vital signs will be summarized by visit.

Weight and the change from baseline will be summarized by visit. Height and BMI will be summarized in a similar manner.

7.3.3.3. Other Safety Parameters of Special Interest

Other safety parameters of special interest include certain AEs mentioned in Section 7.3.2.5 as well as ECG data. Listings of physical examinations will be produced. A by-patient listing of *Neisseria meningitidis* vaccinations will be produced showing the date, type, and dose information of vaccinations. *Haemophilus influenzae* vaccination and *Streptococcus pneumoniae* vaccination will be summarized in patient listings. Pregnancy tests will be summarized in patient listings.

7.3.3.3.1. Electrocardiograms (ECG)

The ECG results will be summarized by visit. Descriptive statistics by visit will be presented for each ECG parameter (including HR, PR duration, QRS duration, QT duration, RR interval, and QT interval, Fridericia Correction [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 patients 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 patients 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. Immunogenicity

For assessment of immunogenicity, the presence of confirmed positive ADAs will be summarized by visit. The number of patients with any positive post-baseline ADA 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 52/53-week Primary Treatment Period or discontinued prior to the completion of the Primary Treatment Period. This analysis will include all efficacy, safety, and PK/PD study data of the Primary Treatment Period for regulatory submission purpose 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 Extension Treatment Period may be performed at the discretion of the Sponsor.

8. REFERENCES

Keltner JL, Johnson CA, Spurr JO, Beck RW. Comparison of central and peripheral visual field properties in the Optic Neuritis Treatment Trial. Am J Ophthalmol. 1999;128(5):543-553.

9. APPENDICES

9.1. Protocol Schedule of Events

Refer to the protocol for a SoA (see Protocol Section 1.2).

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

Not applicable

9.3. Sample Size, Power, and Randomization

Approximately 12 patients will be enrolled to achieve the minimum of 10 evaluable patients. Of the 10 evaluable patients, at least 3 of the patients will be aged 2 to < 12 years at the time of enrollment, and at least 5 patients will be aged 12 to < 18 years at the time of enrollment.

In this pediatric study, patients will act as their own controls. As such the Historical ARR, which will be called the Baseline ARR, will be compared with the ARR of the patient while on eculizumab during the Primary Treatment Period. A sample size of 12 patients (10 evaluable patients) will provide approximately 85% power to detect a statistically significant treatment effect of eculizumab to reduce the ARR, assuming a 2-sided significance level of 0.05, by the Wilcoxon signed rank test, and a dropout rate of 15%. The sample size calculation also assumes a Baseline ARR of at least 1 relapse/year. Likewise, the sample size calculation also assumes an eculizumab-treated ARR of 0.082 relapse/year with a SD of the difference in relapse rates of 0.8 relapses/year, based on the ECU-NMO-301 study, which was a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the safety and efficacy of eculizumab in patients aged ≥ 18 years with Anti-AQP4 Ab-positive NMOSD.

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 2: Age and Reference Date

Age	Reference Date
• Age at first dose	• Date of first eculizumab dose
• Age at enrollment	• Date of signing informed consent form
• Age at NMOSD initial clinical presentation	• Date of NMOSD initial clinical presentation
• Age at NMOSD diagnosis	• Date of NMOSD diagnosis

For all dates (except AE 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, integer [(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.

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 / (RR interval)^ (1/3)

RR interval is calculated as:

RR interval = 60*1000/HR

9.4.6. Adverse Events

The analysis of AEs is described in detail in Section 7.3.2.

TEAEs are events with start dates and start times on or after the date and time of the first study drug dose. 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.

All other AEs are considered PTAEs.

Patient percentages are based on the total number of treated patients.

The AE relationship is collected as two categories: related and not related.

Patient-years of follow-up is defined as:

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

where the Last study date is the date of completion or discontinuation from the Primary Treatment Period. Total patient-years of follow-up based on the Safety Set is the sum of the patient-years of follow-up for all the patients in the Safety Set.

Adverse event rates based on 100 patient-years of follow-up will be calculated as the number of events times 100 (years) divided by the total patient-years of follow-up.

9.5. Additional Details on Statistical Methods

9.5.1. Annualized Relapse Rate Calculations

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

For patients that have a relapse during any Screening Period and get re-screened and treated in the trial, 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 ARR will be calculated for each patient as:

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

Historical relapse time will be based on data 25 months prior to the date of the Screening Visit. Historical relapse time will be 25 months for NMOSD patients with disease duration 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.

9.5.1.2. On-Trial Annualized Relapse Rate

The patient-level On-Trial ARR for the Primary Treatment Period will be calculated as:

$$ARR_{(On-Trial)} = \frac{Number\ of\ On-Trial\ relapses\ in\ Primary\ Treatment\ Period}{Time\ in\ Primary\ Treatment\ Period}$$

and the adjudicated On-Trial ARR for the Primary Treatment Period will be calculated as:

$$ARR_{(Adjudicated)} = \frac{Number\ of\ adjudicated\ On-Trial\ relapses\ in\ Primary\ Treatment\ Period}{Time\ in\ Primary\ Treatment\ Period}$$

for the time period from the first dose of eculizumab through Week 52/53 or ET from the Primary Treatment Period.

The EOPT date will be determined by the last date in the Primary Treatment Period, or the last dose date in the Primary Treatment Period + 16 days (or + 9 days if in induction phase), whichever occurs first. The time in Primary Treatment Period (in years) for the purposes of calculating ARR is as follows:

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

If there are patients who missed 2 or more infusions consecutively due to COVID-19-related reasons, in the primary analysis, the time period for the calculation of On-Trial ARR will exclude the time when the patient missed eculizumab infusion, to account for the impact of the pandemic. Let the Last Pre-COVID-19 Dose Period Date be the last dose date prior to missing 2 or more infusions consecutively due to COVID-19-related reasons + 16 days (or + 9 days if in induction phase). Let the First Post-COVID-19 Dose Date be the date of first dose patient received post the COVID-19 interruption of study drug treatment. The time in Primary Treatment Period (in years) for these patients for calculating ARR is as follows:

$$\begin{aligned} &Time\ in\ Primary\ Treatment\ Period \\ &\quad = (Last\ Pre-COVID-19\ Dose\ Period\ Date - First\ Dose\ Date \\ &\quad + \ EOPT\ Date - First\ Post-COVID-19\ Dose\ Date + 2)/365.25 \end{aligned}$$

If there are patients who missed 2 or more doses consecutively due to COVID-19-related reasons and did not restart study drug treatment before study discontinuation, the time in Primary Treatment Period (in years) for these patients for calculating ARR is as follows:

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

In sensitivity analysis, the time period is not adjusted and all On-Trial relapses will be included in the calculation of On-Trial ARR.

The study-level ARR will be calculated as

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

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

$$ARR_{(Adjudicated)} = \frac{Total\ Number\ of\ adjudicated\ On-Trial\ relapses\ in\ Primary\ Treatment\ Period\ across\ patients}{Sum\ of\ the\ Time\ in\ Primary\ Treatment\ Period\ across\ patients}$$

The 95% CI of the ARR will be calculated using a Poisson regression model of the number of relapses and the offset parameter will be the log of the time in the Primary Treatment Period.

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

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

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

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

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

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

where EOPT Date is defined in the ARR calculation (Appendix 9.5.1.2).

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

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

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

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

If there are patients who missed 2 or more doses consecutively due to COVID-19-related reasons, in the primary analysis, the time period for the analysis of time to first On-Trial Relapse and time to first adjudicated On-Trial Relapse is truncated to account for the impact of the pandemic. For patients without an On-Trial Relapse prior to COVID-19 interruption of study drug treatment, the censoring time (in days) is defined as:

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

where Last Pre-COVID-19 Dose Period Date is defined in Appendix 9.5.1. For patients without an adjudicated On-Trial Relapse, the censoring time is defined in a similar manner. In sensitivity analysis, no adjustment is made to the censoring time and all On-Trial Relapse or adjudicated On-Trial Relapse are included in the analysis.

9.5.3. Treatment Duration

Treatment duration will be calculated as follows:

Treatment duration (days) = Last Dose Date - First Dose Date + 1

9.5.4. Optic Spinal Impairment Score (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 plegia (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

9.5.5. SAS Code for Efficacy Analyses

9.5.5.1. SAS Code for the Primary Efficacy Endpoint

The SAS code for testing change in patient-level ARR between the baseline ARR and the On-Trial ARR at 52/53 weeks using the 2-sided Wilcoxon signed rank test is given by:

```
proc univariate data=adeff;
    var arrdiff;
    ods output TestsForLocation=TestsForLocation;
run;
```

where arrdiff is change in ARR between the baseline ARR and the On-Trial ARR.

The SAS code for estimating the 95% CI of mean change in patient-level ARR is given by:

```
proc ttest data=adeff;
    paired aval1*aval2;
    ods output ConfLimits=ConfLimits;
run;
```

where aval1 is the baseline ARR and aval2 is the On-Trial ARR at 52/53 weeks.

The analysis of the study-level On-Trial ARR will involve Poisson Regression analysis. The basic SAS code for estimating the 95% CI of On-Trial ARR is given by:

```
proc genmod data= ADEFF;
    model aval= / link=log dist=poisson offset=logtime ;
    exact intercept / estimate cltype=exact alpha=0.05;
run;
```

where aval is the number of relapses in the Primary Treatment Period, and logtime is the log of the time in years the patient is in the Primary Treatment Period.

In the event that no On-Trial Relapse is observed, the upper CI will be 3.7/patient-years, where 3.7 is the upper limit of the Poisson distribution, capturing 97.5% of the distribution.

Time to first On-Trial Relapse is a co-primary efficacy endpoint. The basic SAS code for estimating the percentage of patients who are relapse-free while on eculizumab treatment in the Primary Treatment Period is:

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

where aval is a variable for the patient's time in the Primary Treatment Period at time of relapse or censoring, cnsr is the censoring variable (1 = no event (censored), 0= event).

9.5.5.2. SAS Code for the Secondary/Tertiary Efficacy Endpoint

The SAS code for estimating the changes from baseline for the EDSS score over the applicable study visits during the Primary Treatment Period is given by:

```
proc univariate data =adedss CIPCTLDF ;
        var chg;
run;
```

where chg is the change from baseline in EDSS score at each study visit.

The SAS code for estimating the 95% CI of mean change in EDSS score is given by:

```
proc ttest data=adedss;
    paired aval*base;
    ods output ConfLimits=ConfLimits;
run;
```

where base is the EDSS score at baseline and aval is the EDSS score at each study visit.

Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN ADDENDUM

PROTOCOL NUMBER: ECU-NMO-303

A Phase 2/3 Open-Label, Single-Arm Trial to Evaluate the Safety and Activity of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder

Author: [redacted]

Date: 15 Sep 2023

Version: 1.0, Final

1. APPROVAL SIGNATURES

[redacted]

18-Sep-2023

Date dd Mmm yyyy

[redacted]

19-Sep-2023

Date dd Mmm yyyy

[redacted]

18-Sep-2023

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
AESI	adverse event of special interest
ADA	antidrug antibody
ARR	annualized relapse rate
C5	complement component 5
CTCAE	Common Terminology Criteria for Adverse Events
PedsQL	Pediatric Quality of Life Inventory
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAEs	treatment-emergent adverse events
VA	visual acuity
VAS	visual analog scale
VF	visual fields

4. STATISTICAL ANALYSIS PLAN ADDENDUM

This SAP is an addendum to the ECU-NMO-303 SAP Version 1.0, dated 19 October 2021. This study is being terminated by the sponsor, as only 5 of 12 patients were enrolled, with 2 having discontinued prior to completing the primary treatment period and 3 having completed the primary treatment period and transitioning to another pediatric study (ALXN1210-NMO-317).

This analysis will provide final analysis results after the last patient discontinues this study.

4.1. Changes from Analyses Specified in the Protocol

Only selected summaries of those specified in Protocol Amendment 2 (03 May 2021) will be performed for the purpose of this terminated study.

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

The statistical analysis will follow the SAP Version 1.0, dated 19 October 2021, but will be limited to the endpoints described below, unless otherwise specified.

Listings for all endpoints will be provided as described in SAP Version 1.0.

1. Study patients
   - Summary of patient disposition in the Safety Set
   - Summaries of demographic characteristics and baseline neuromyelitis optica spectrum disorder disease characteristics using the Safety Set
2. Efficacy analyses
   a. Primary efficacy endpoint analyses
   - The primary efficacy endpoint is the change from Baseline in the patient-level annualized relapse rate (ARR) at 52/53 weeks.
   - The primary analysis methods specified in SAP Version 1.0, Section 7.2.1 will be used for the change from Baseline in the patient-level ARR at 52/53 weeks, with one exception – the Wilcoxon signed rank test will not be presented due to the reduced sample size. Using this approach, the change from Baseline in patient-level ARR during the study period, including both the Primary Treatment Period and Extension Treatment Period, will also be analyzed.
   - Time to first on-trial relapse during the Primary Treatment Period will be summarized as described in SAP Version 1.0, Section 7.2.1. Additionally, time to first on-trial relapse during the study period, including both the Primary Treatment Period and the Extension Treatment Period, will be analyzed similarly.

   b. Secondary efficacy endpoint analyses
   - Change from Baseline in Expanded Disability Status Scale score at 52/53 weeks in patients ≥ 5 years of age
   - Change from Baseline in the Hauser Ambulatory Index score at 52/53 weeks

- Change from Baseline in Self-Reported Pediatric Quality of Life Inventory (PedsQL) scores at 52/53 weeks in patients ≥ 5 years of age
- Change from Baseline in PedsQL Parent Proxy scores at 52/53 weeks in patients < 5 years of age
- Change from Baseline in visual acuity (VA) as measured by the Snellen or LEA symbols Eye Chart examination at 52/53 weeks
- Change from Baseline in confrontational visual fields (VF) as measured during ophthalmologic examination at 52/53 weeks
- Change from Baseline in color vision as measured during ophthalmologic examination at 52/53 weeks

  SAP Version 1.0, Section 7.2.1.1 Handling of Dropouts or Missing Data indicates that missing data for secondary and tertiary endpoints will not be imputed. However, with fewer patients completing the Primary Treatment Period than planned, a supplementary analysis will be performed in which the last observed value will be carried forward to account for patients who did not complete the assessment at 52/53 weeks.

  The secondary efficacy endpoints will be summarized descriptively over the applicable scheduled visits using the statistical analysis methods specified in SAP Version 1.0, Sections 7.2.2 and 7.2.3. Using this approach, the change from Baseline to the end of the Primary Treatment Period will also be summarized.

  For VA, the shift, from Baseline will be summarized according to the eye with the greater worsening at the end of the Primary Treatment Period and will be conditional on patients with adequate eye-sight (acuity ratio >0.1) at baseline to perform the test. In addition, the number and percentage of patients in each of the categories specified in SAP Version 1.0, Section 7.2.2, will be presented for each eye at the end of Primary Treatment Period as well as over scheduled visits during the study period, including both primary and extension treatment periods. The shift from Baseline in the eye with the greater worsening is an update to SAP Version 1.0.

  For confrontational VF, the number and percentage of patients with a number of quadrants with deficits identified across both eyes (0-8) and conditional on patients with adequate eyesight at baseline to perform the test in at least one eye will be summarized as a shift from baseline to the end of primary treatment period as well as over scheduled visits, including both the Primary Treatment Period and the Extension Treatment Period. Summaries will be performed on a patient-basis, rather than for each eye, a change from SAP Version 1.0, Section 7.2.2. In addition, the confrontational VF will not be limited to patients with adequate eyesight to perform the test in at least one eye, as the test can be performed in eyes with poor visual acuity.

  Color vision will be evaluated as the change from Baseline (no change from normal or worsened) among patients with at least one eye with normal color vision. Color vision is considered as worsened if in either eye, it changes from normal to abnormal, or it changes from normal to not performed due to vision loss. Otherwise, color vision

is considered as no change. The proportion of patients with a change from normal to worsening at the end of Primary Treatment Period will be presented. In addition, the number and percentage of patients with normal or abnormal color visions at the end of the Primary Treatment Period as well as over scheduled visits will be summarized for each eye. The shift from Baseline to the end of the Primary Treatment Period from normal color vision to no change from normal or worsened is an update to SAP Version 1.0. Using both eyes in the endpoint is also an update to the SAP Version 1.0, ensuring that the analysis is performed at the patient-level.

c. Tertiary efficacy endpoint analyses

- The change from Baseline in the EQ-5D-Y Visual Analog Scale (VAS)/EQ-5D-Y VAS Proxy score will be summarized for patients ≥ 8 years of age and patients between 5 and 7 years of age separately at the end of the Primary Treatment Period and over the scheduled visits, including both the Primary Treatment Period and the Extension Treatment Period. Summaries will include 95% CIs of the mean and median. The number and percentage of patients in each level by dimension will be presented as well, while shifts from baseline will not be presented. If there is only 1 patient in any of the age subgroups, the summary will not be performed, a change from SAP Version 1.0. Clarification of the by age group analysis and the rule limiting analyses to age subgroups with at least 2 patients is an update to SAP Version 1.0.

d. Pharmacokinetic and pharmacodynamic analyses

- Summaries of serum eculizumab concentration, serum free complement component 5 (C5), and in vitro hemolytic activity assessment over time

  Tables and figures of mean (± SD) serum eculizumab concentrations over time in both the linear scale and semi-log scale, and for each patient, a figure of serum eculizumab concentration over time will be provided. For serum free C5 and hemolytic activity, tables and figures of mean (± SD) of absolute values over time, and figures of mean (± SD) of changes and percentage changes from baseline over time will be provided. Box plots will not be provided, a change from SAP Version 1.0.

3. Safety analyses will be summarized as described in Sections 7.3. of SAP Version 1.0 for the following:

   - Summary of study duration, treatment duration, treatment compliance, and exposure during the study period
   - Overall summary of all treatment-emergent adverse events (TEAEs). Severity will be presented grades as defined by CTCAE Version 5, rather than as mild, moderate, or severe, a change from SAP Version 1.0.
   - Summary of TEAEs by System Organ Class (SOC) and Preferred Term (PT)

     The following summaries are added

     – Summary of PT in descending order of frequency
     – Summary of SOC in descending order of frequency

SOC will be listed in order of frequency of occurrence (percentage), a change from SAP Version 1.0, in which SOC was planned to be presented alphabetically.

Given that the number of patients is smaller than originally planned, AE summaries will not be performed by age subgroup.

- Summaries of TEAEs by SOC and PT by relationship with treatment and by severity.
- Summaries of adverse events of special interest (AESI) will not be presented, given the limited number of such events; instead, a listing of AESI will be produced. This constitutes a change to SAP Version 1.0.
- Summary tables of laboratory parameters, vital signs, electrocardiogram parameters, and antidrug antibodies.

  The following definitions represent changes to SAP Version 1.0.

  - The summaries of antidrug antibodies (ADAs) incidence over the duration of the study, including the following response categories:
    - ADA negative: An ADA-negative signal in the ADA assay at all timepoints
    - ADA positive: An ADA-positive signal in the ADA assay at any timepoint

  - ADA-positive study participants may also be categorized as follows:
    - Pre-existing immunoreactivity: An ADA-positive response with either of the following two conditions met:
      - ADA-positive response at baseline with all post-first dose ADA results negative,

        OR

      - ADA-positive response at baseline with all post-first dose ADA responses less than 4-fold over the baseline titer level.
    - Treatment-emergent ADA responses: An ADA-positive response post-first dose when baseline results are negative or missing.
    - Treatment-boosted ADA responses: An ADA-positive response post first dose that is ≥ 4-fold over the baseline titer level when the baseline result is positive.
    - Persistent: ADA responses with 2 or more consecutive ADA-positive samples separated by at least a 16-week period, with no ADA-negative samples in between, irrespective of missing samples.
    - Indeterminate: ADA-positive sample only at the last collected sample.
    - Transient: ADA response that is neither a persistent nor an indeterminate response.
- Biomarker Assessments and Medical Resource Utilization will not be summarized, both changes from SAP Version 1.0.

5. REFERENCES

NA