

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

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Alexion Pharmaceuticals, Inc.



STATISTICAL ANALYSIS PLAN

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

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

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1. APPROVAL SIGNATURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this SAP.

Table 1: Abbreviations and acronyms

Abbreviation or acronym	Explanation
AE	Adverse event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ARR	Annualized Relapse Rate
AZA	Azathioprine
BMI	Body mass index
BP	Blood Pressure
BP (SF-36)	Bodily Pain (SF-36)
C5	Complement Protein 5
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel test
CRF	Case Report Form
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Extended Disability Status Scale
EOS	End of Study
EQ-5D	EuroQol 5 dimension health status
ET	Early Termination
FAS	Full Analysis Set
FS	Functional System
FSS	Functional System Scores
GH	General Health (SF-36)
ADA	Anti-Drug Antibody
HAI	Hauser Ambulation Index
HR	Heart Rate
HT	Reported Health Transition (SF-36)
ICF	Informed Consent Form
IP	Investigational Product
IST	Immunosuppressant Therapy
IV	Intravenous
IVIg	Intravenous immunoglobulin
IVMP	Intravenous methylprednisolone
IVRS	Interactive voice response system
kg	Kilograms

Abbreviation or acronym	Explanation
LETM	Longitudinally Extensive Transverse Myelitis
LOCF	Last Observation Carried Forward
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MH	Mental Health (SF-36)
MMF	Mycophenolate Mofetil
MMRM	Mixed Model for Repeated Measures
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NMO	Neuromyelitis Optica
NMO IgG	Neuromyelitis Optica antibody
NMOSD	Neuromyelitis Optica Spectrum Disorders
ON	Optic Neuritis
OSIS	Optic Spinal Impairment Score
PD	Pharmacodynamics
PE	Plasmapheresis Or Plasma Exchange
PF	Physical Function (SF-36)
PH	Proportional Hazards
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol Population
PT	Preferred Term (MedDRA)
PTSAEs	Pre-Treatment Serious Adverse Events
QOL	Quality of Life
RE	Role Emotional (SF-36)
RP	Role Physical (SF-36)
RR	Respiration rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS [®]	Statistical Analysis Software [®]
SBP	Systolic Blood Pressure
SF	Social Function (SF-36)
SF-36	Short Form Health Outcomes Survey (36 items)
SOC	System Organ Class (MedDRA)
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
VAS	Visual Analogue Scale

Abbreviation or acronym	Explanation
VS	Vital Signs
VT	Vitality (SF-36)
WHO ATC	World Health Organization Anatomical Therapeutic Chemical

4. DESCRIPTION OF THE PROTOCOL

Study ECU-NMO-301 is a Phase 3 randomized, double-blind, parallel-group, placebo-controlled, multi-center, multinational time-to-event trial to evaluate the safety and efficacy of eculizumab in patients with relapsing neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD) who are NMO-IgG seropositive. From here on, for the purposes of the protocol and this SAP, NMO will refer to both NMO and NMOSD. The Treating Physician is the PI or the Sub-Investigator for the study and will be responsible for the overall patient management including patient eligibility evaluation, supervision of the blinded IP administration, recording and treating of AEs and monitoring of safety assessment. At the time of a relapse, the Treating Physician will perform a complete neurologic exam and determine if a patient experiences an On-Trial Relapse and may treat the patient's relapse. The blinded EDSS Rater will be responsible for performing the EDSS assessments throughout the trial including at the time of a relapse. A total of approximately 132 eligible patients will be randomized 2:1 to eculizumab or placebo infusions. Patients may continue to receive a stable maintenance dose of protocol permitted supportive immunosuppressive therapies (ISTs) for relapse prevention, as defined by their Treating Physician, and must remain on that dose for the duration of the study or until the patient experiences a relapse. The study duration is estimated to take approximately 3-4 years including enrollment. Study duration for an individual patient, in this Time-to-Event trial, will vary depending on when the patient enters the trial and the patient's outcome. The study period for an individual patient will consist of: Screening Period, Study Period, End of Study Visit or Early Termination Visit and post treatment Follow-up Period (only for patients who withdraw from this study or do not enter the extension study). The End of Study Visit for an individual patient will take place when one of the following conditions is met, whichever comes first: (a) the patient experiences an On-Trial Relapse; or (b) the study ends by meeting 24 adjudicated On-Trial Relapse events in 24 patients. Patients may be provided the opportunity to participate in an extension trial (protocol ECU-NMO-302) to receive eculizumab after completion of the End of Study Visit.

The study objectives are as follows:

Primary Objective:

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

Secondary Objectives:

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

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

4.1. Changes from Analyses Specified in the Protocol

Applicable changes from protocol Version 6.0 are items 4, 5, 7, 11, 12, 14, 15 and 16 given below in Section 4.2 of this SAP. The analyses as specified in this SAP over-ride the protocol.

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

The following are changes to analyses as specified in the previous version of the SAP (version 4.0 dated February 18, 2016):

1. Updated the primary endpoint to time to first adjudicated On-Trial Relapse and the secondary endpoint of annualized relapse rate to adjudicated On-Trial annualized relapse rate to align with protocol version 6.0 dated July 1, 2016. Defined adjudicated On-Trial Relapse, On-Trial Relapse and adjudicated relapse in Section 5.1.1.
2. Clarified the definition of time at risk for relapse in Section 7.2.1 and updated calculations of time to first event and censoring time in Section 9.5.1. Patients will be censored at the end of the study or at the time of the next expected dose, whichever comes first. On-Trial ARR calculations were also updated with time in study period in Section 9.5.2.2.
3. Removed “Patients being randomized into wrong strata” as a major protocol deviation for the purposes of defining the PP population. This change was made because the randomization errors do not affect the clinical outcome in the study or misrepresent the intended population. The impact of stratification errors on analyses will be assessed through sensitivity analyses.
4. Defined relapse severity for no change or decrease in OSIS score and clarified the severity definition for transverse myelitis relapses based on the sensory subscale score in Section 5.1.4.1.
5. Clarified in Section 7 that the strata variable to be used for analyses will be based on four strata, stratifying first on EDSS, then on IST status, since small numbers of patients are expected in some cells of the strata.
6. Defined regions based on the sites with screened patients for the study in Section 7.1.1.
7. In Section 7.2.1, modified the sensitivity analyses for the primary endpoint due to the change in primary endpoint to time to first adjudicated On-Trial Relapse and to address stratification errors:
 - a. Added sensitivity analyses based on time to first On-Trial Relapse and time to first adjudicated relapse.
 - b. Added an un-stratified log-rank test as a sensitivity analysis for time to first adjudicated On-Trial Relapse and time to first On-Trial Relapse.

- c. Changed the covariates in the sensitivity analysis using a Cox proportional hazards regression model to include variables that may have a covariate effect on the primary endpoint: baseline EDSS dichotomized at the median, observed IST strata, and historical ARR.
 - d. Limited efficacy analyses on the Per Protocol Population to the primary endpoint and time to first On-Trial Relapse.
 - e. Removed sensitivity analyses including withdrawals due to AEs as relapse events, censoring relapses assessed after 48 hours, excluding patients without a follow-up assessment, and using IST strata defined as 1) naïve patients; 2) patients who previously had ISTs and are receiving an IST at the time of randomization; and 3) patients who previously had ISTs and are not receiving an IST.
 - f. Replaced the Cochran-Mantel-Haenszel test assessing eculizumab versus placebo treatment and patient evaluated within 48 hours (yes, no) with a summary of adjudication results and relapse evaluated within 48 hrs (yes, no) by treatment group for patients with On-Trial Relapses. No statistical testing will be performed as a patient may have more than one relapse.
8. Removed descriptive summaries by NMO and NMO spectrum disorder (NMOSD) as the definition of NMOSD has been revised over the course of this study.
 9. Removed summaries by IST subgroups expected to have small sample sizes and too few events and removed the Cox proportional hazards regression model with interaction terms which is likely not to converge due to few events.
 10. Clarified censoring time in light of the change to the primary endpoint and standardized missing data handling for the secondary/tertiary endpoints in Section 7.2.1.1.
 11. Changed the ordering of testing for the secondary endpoints in Section 7.2.2 to align with the order of interest from a clinical perspective in NMO: relapses, disability, ambulatory function, quality of life. This reduces the risk of a type II error if a more clinically important endpoint is set below another endpoint in the hierarchy for which the null hypothesis is not rejected.
 12. Since secondary and tertiary endpoints are mainly ordered categorical response variables, the analysis strategy as proposed in Koch, et al (Koch 1998) was applied in Sections 7.2.2 and 7.2.3. A non-parametric method which includes adjustment for covariables is specified for the primary evaluation of treatment effects for all randomized patients: A randomization-based nonparametric ANCOVA adjusted for baseline and stratified by randomization strata. Then statistical models are fit to describe the pattern and magnitude of treatment effects for the intended population: ANCOVA and mixed model for repeated measures (MMRM, Mallinckrodt 2008).
 13. Removed summary of visual acuity using the Snellen chart assessments by treatment group as the data are open-text and not numerical or categorical. By-patient listings of the data will still be produced by treatment group.
 14. Added Section 7.3.2.5 AEs and SAEs over time by SOC, PT for assessment of adverse events over time.

15. Section 7.3.2.6 has been updated to add details for the adverse events of special interest.
16. Added outlier definitions and summaries for vital signs (Section 7.3.3.2) and ECGs (Section 7.3.3.3.1).
17. Revised Section 9.5.3 to reflect that the QualityMetric Health Outcomes Scoring Software 5.0 will be used to derive the 8 domain scores and 2 component scores for the SF-36.
18. The SAS code in section 9.5.5 was updated to align with specified analysis methods as described in this SAP.
19. Administrative changes for accuracy, clarity and consistency.

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, relapses and attacks are synonymous.

Relapses (i.e. attacks) within 24 months prior to the Screening Visit and relapses on trial will be collected and analyzed. The definitions of Historical Relapses, On-Trial Relapses, and adjudicated On-Trial Relapses are as follows:

Historical Relapse:

Historical relapses are the relapses that occurred prior to the Screening Visit, including the first NMO attack. For the 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 an existing neurologic symptoms that required treatment. Treatment is defined as use of high-dose intravenous steroids, plasma exchange (PE) or IVIg. Events that occur within a 30-day interval are considered as one relapse. 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.

On-Trial Relapse:

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

On-Trial Relapses will be monitored throughout the trial. Patients will be educated on the potential signs and symptoms of NMO relapse. The Investigator or his/her designee will review, in detail, the signs and symptoms of a potential relapse with the patient at each visit. The patients will be instructed to contact the investigator at the first sign or symptom of a potential relapse. All potential relapses must be evaluated by both the EDSS Rater and the Treating Physician. Patients should be evaluated within 24 hours of notification of the investigator or the appropriate designee of any signs or symptoms suggestive of a potential relapse, and no later than 48 hours. The Treating Physician will make the decision as to whether the neurologic change is considered an On-Trial Relapse (based on On-Trial Relapse Definition) and treat the patient's relapse according to the Standardized On-Trial Relapse Treatment plan. Follow-up

visits to monitor the course of the relapse until stabilization will be made at the Treating Physician discretion, in addition to the assessment at the next scheduled visit.

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

Adjudicated On-Trial Relapse:

To obtain an independent assessment of all On-Trial Relapse events using objective and consistent clinical criteria, all relapses will be independently reviewed by an Adjudication Committee. The Committee, consisting of medical experts in neurology and/or neuroophthalmology, will conduct independent reviews for all relapse events identified by the Investigators. The Committee will decide by majority vote whether each Investigator-identified On-Trial Relapse meets the objective criteria for an adjudicated On-Trial Relapse. A separate Charter will document all adjudication criteria and procedures for this trial. Throughout this SAP, adjudicated On-Trial Relapse refers to an On-Trial Relapse that was positively adjudicated by the committee. An adjudicated relapse refers to a relapse that was positively adjudicated by the committee, regardless of whether it was confirmed as an On-Trial Relapse by the Treating Physician.

After the 6 week post-On-Trial Relapse evaluation, relapsed patients are finished with Study ECU-NMO-301. Qualifying patients will be offered enrollment in the extension study in which all patients receive eculizumab. Patients who do not continue into the extension study will need to return for a safety follow-up visit 8 weeks after the last IP dose.

5.1.2. Secondary Endpoints

The secondary efficacy endpoints as specified in the protocol include:

1. Change from baseline in Extended Disability Status Scale (EDSS) score at the end of study (EOS)
2. Adjudicated Annualized Relapse Rate
3. Change from baseline in EuroQoL (EQ-5D) at the EOS
4. Change from baseline in Modified Rankin Scale (mRS) score at the EOS
5. Change from baseline in Hauser Ambulatory Index (HAI) score at the EOS

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.

See the protocol appendix for the EDSS.

The blinded EDSS Rater will perform the Kurtzke neurological assessment to determine if the relapse is associated with changes in any of the Functional System Scores (FSS) or total EDSS score. The EDSS Rater will be responsible for performing the EDSS assessments throughout the trial.

5.1.2.2. EQ-5D

The EQ-5D is a generic, standardized patient self-administered instrument that provides a simple, descriptive profile and a single index value for health status. The EQ-5D comprises 5 dimensions of health: mobility, self-care, 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.

See the protocol appendix for the EQ-5D.

5.1.2.3. Modified Rankin Scale (mRS)

The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. The Treating Physician will administer the mRS.

The scale runs from 0-6, running from no disability to death.

0 - No symptoms.

1 - No significant disability. Able to carry out all usual activities, despite some symptoms.

2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3 - Moderate disability. Requires some help, but able to walk unassisted.

4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6 - Dead.

5.1.2.4. Hauser Ambulatory Index

The Hauser Ambulatory Index 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 worse (restricted to wheel chair; unable to transfer self independently). The Treating Physician or a designee is to administer the HAI.

See the protocol appendix for the Hauser Ambulatory Index.

5.1.2.5. Annualized Relapse Rate

Annualized relapse rate will be computed for each patient. A pre-treatment annualized relapse rate will be computed for each patient using the historical relapse data for that patient. An adjudicated On-Trial annualized relapse rate will be computed for each patient based on all adjudicated On-Trial Relapse events. An On-Trial annualized relapse rate will also be computed for each patient based on the On-Trial Relapses as determined by the Treating Physician observed in the trial for the patient.

See Section 9.5.2 of this SAP for the formulas for calculating annualized relapse rate.

5.1.3. Tertiary Endpoints

The tertiary efficacy endpoints for the study are:

1. Change from baseline in Hauser Ambulatory Index at the EOS in patients with abnormal baseline ambulatory function
2. Change from baseline in visual acuity at the EOS in all patients and in patients with abnormal baseline visual function
3. Change from baseline in the SF-36 at the EOS
4. Change from baseline in the EDSS Functional System Score (FSS) at the EOS

5.1.3.1. Hauser Ambulatory Index in Patients with Abnormal Baseline Ambulatory Function

Patients with abnormal ambulatory function are patients with a baseline Hauser value of 1 to 9 (i.e. a baseline value of 0 is considered normal).

5.1.3.2. Visual Assessment

Assessment of visual function includes the assessment of the optic disc, visual fields, the presence or absence of a scotoma and visual acuity. Both the treating physician and the EDSS Rater will assess vision. For the Treating Physician, visual acuity will be measured using the Snellen chart. For the blinded EDSS Rater, the assessment is recorded as part of the visual (optic) Functional System Score for the EDSS. The visual score on the FSS will be used for statistical analysis of changes in visual acuity.

The Visual Functional System Score is as follows:

- 0 = Normal

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

5.1.3.3. Visual Acuity in Patients with Abnormal Baseline Visual Function

Patients with abnormal visual acuity at baseline are patients with a baseline Kurtzke FSS for visual acuity of 1 to 6 at baseline (i.e. a baseline value of 0 is considered normal).

5.1.3.4. SF-36 Quality of Life

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

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

Scale	Number of Items	Definition of Scale
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 will be used in this study. See the protocol appendix for SF-36 questionnaire.

5.1.3.5. Kurtzke Functional System Score (FSS)

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

5.1.4. Other Efficacy Endpoints

5.1.4.1. Severity of a Relapse

Severity of relapse (major or minor) will be measured by the Opticospinal Impairment Score (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 Table 3 in the ECU-NMO-301 protocol.

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:

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 (MRC grade 5- or 4+) in affected limb(s)
- 3 = Moderate weakness (grade 3 or 4) in 1 or 2 UMN muscles in affected limb(s)
- 4 = Moderate weakness (grade 3 or 4) in 3 UMN muscles in affected limb(s)
- 5 = Severe weakness (grade 2) in 1 or more muscles in affected limb(s)
- 6 = Some plegic (grade 0 or 1) muscles in 1 or more limbs
- 7 = Plegia (grade 0 or 1) of all muscles in 1 or more limbs

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

5.2. Safety

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

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

5.2.1. Adverse Events (AEs)

Adverse Events are defined in Protocol Section 12.2.

For SAEs the reporting period to Alexion or Alexion Pharmacovigilance Delegate begins following the patient's signing of the Informed Consent Form (ICF) (providing consent to participate in the trial) and continues through 8 weeks after the last dose of study medication. There is no time limit for SAEs that are thought to be causally related.

For non-serious AE, the reporting period starts following first dose of IP and continues through the last study visit, including the safety Follow-Up Visit. AEs that are thought to be causally related are to be followed until the event or sequelae resolve or are determined to be medically stable.

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

- Pre-Treatment Serious Adverse Events (PTSAEs)
- Treatment-Emergent Adverse Events (TEAEs)
- Treatment-Emergent Serious Adverse Events (TESAEs)

PTSAEs are the serious AEs that occur between the signing of informed consent and first IP dose (i.e., eculizumab or placebo). TEAEs are AEs that onset on or after the first IP dose in the study. Likewise, TESAEs are SAEs that onset on or after the first IP dose in the study. A table and listing of PTSAEs will be produced. Both tabular outputs and listings will be created for TEAEs and TESAEs as described in this SAP.

5.2.2. Vital Signs

Vital signs will be measured at every visit and will include assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and heart rate (HR). Vital signs will be

obtained after the patient has been supine or seated for at least 5 minutes. Ideally, each patient's BP should be measured using the same arm. Systolic and diastolic BPs will be documented in mmHg. Temperature will be obtained in degrees Celsius or Fahrenheit. HR will be documented in beats per minute.

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

5.2.3. Laboratory Assessments

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

Chemistry panel, complete blood count and urinalysis, hemolytic markers, renal function measures, and serum pregnancy test (see Appendix 8 of the protocol for details) will be prepared and shipped according to the instructions in the laboratory manual to the central laboratory. Samples will be analyzed at the central laboratory.

Immunogenicity: blood samples will be collected for evaluation for Anti-Drug Antibody at specified time points to describe the presence or absence of an immune response to eculizumab.

5.2.4. Other Safety Events of Special Interest

5.2.4.1. Physical Examination

A complete physical examination will be performed at Visit 1 (Screening), Visit 52 (Week 96), and at EOS visit or early termination (ET) visit. The complete physical examination will include assessments of the following organ/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, pulse, chest, heart, abdomen, extremities, musculoskeletal, and general neurological examination. For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff at these visits.

5.2.4.2. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be conducted at Visit 1, 30, 52 and at EOS visit or ET visit. The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and to determine the clinical significance of the results. These assessments will be indicated on the CRF.

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

The C-SSRS is a questionnaire used for suicide risk assessment developed by Kelly Posner, PhD, David Brent, MD, Chris Lucas, MD, Madelyn Gould, PhD, MPH, Barbara Stanley, PhD, Greg Brown, PhD, Prudence Fisher, PhD, Jaime Zelazny, NR, MPH, Ainsley Burke, PhD, Maria Oquendo, MD, and J. John Mann, MD. The C-SSRS is a measure of suicidal ideation and behavior. The C-SSRS will be performed by the Treating Physician or an appropriately trained designee. The Baseline/Screening C-SSRS will be performed at Baseline (Visit 2). The C-SSRS will also be performed at Visit 6 (Week 4), Visit 8 (Week 8), Visit 10 (Week 12), and every 12th-week visit thereafter through the EOS/ET Visit; at the week 6 Follow-Up Relapse

Evaluation Visit, and at the Safety Follow-up visit. Additional C-SSRS assessments are permitted, as needed. This is to ensure that patients who are experiencing suicidal ideation or behavior are properly recognized and adequately managed or referred for further evaluation.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

Efficacy analyses will be performed on the Full Analysis Set (FAS) population as well as the Per Protocol (PP) population. The safety analyses will be based on the Safety Set population. In some analyses, subgroups may be analyzed as indicated in this SAP.

6.1. Full Analysis Set (FAS)

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

6.2. Per Protocol (PP) Set

The Per-Protocol (PP) population is a subset of the Full Analysis Set population, excluding patients with major protocol deviations. The PP population will include all patients who:

- Have no major protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy,
- Patients who took at least 80% of the required treatment doses while they were in the double-blind study period (for patients who have relapses any dosing after the relapse will not be included in this calculation).

The PP population will be determined prior to database lock and unblinding. Key inclusion criteria are #2-6 and key exclusion criteria are 1, 2, and 4.

Major protocol deviations 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 Per-Protocol population will include the time period from the first study dose 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 the Per-Protocol population requirement.

6.3. Safety Set

Safety analyses will be performed on the Safety Set Population. The Safety Population includes all patients who receive at least 1 dose of study drug (eculizumab or placebo). Patients will be compared for safety according to the treatment they actually received.

Patients who have signed informed consent but are not treated in the study are not in the Safety Population. 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

PK/PD analyses will be performed on the PK/PD Analysis Set. This population includes patients with at least one PK or PD result. Details for the PK/PD Analysis Set can be found in a separate PK/PD analysis plan. A PK/PD analysis plan will be issued separately, in which details for the PK/PD analyses will be described.

7. STATISTICAL ANALYSIS

Summaries will be presented by treatment group. For continuous variables, summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum values. Frequencies and percentages will be calculated for categorical variables. Graphical displays will be produced, as appropriate.

Randomization was stratified using two variables: 1) EDSS score at randomization (Day 1) (≤ 2.0 , vs. ≥ 2.5 to ≤ 7); and 2) patients' prior supportive (i.e., for relapse prevention) IST and IST status at randomization (Day 1) (treatment naïve patients vs. patients continuing on the same IST(s) since last relapse vs. patients with changes in IST(s) since last relapse) (see Standard Protocol Definition in Section 7.4).

Since small numbers of patients are expected in some cells of the strata, it is planned to collapse into four strata for analyses using a hierarchical approach, stratifying first on EDSS, then on IST status. For this SAP, the randomization stratification variable refers to four strata based on randomization EDSS score and IST status, unless otherwise specified: (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.

Some patients were randomized using incorrect baseline information. For this SAP, observed stratification refers to strata based on the correct EDSS and IST status observed at baseline. Primary analyses will be as randomized, with some sensitivity analyses using observed strata (Ke 2017).

7.1. Study Patients

7.1.1. Disposition of Patients

A table summarizing the number of screened patients, number and percentage of screen failures, and number and percentage of randomized patients for all screened patients will be provided. A listing of each patient who failed screening with reason for screen failure will be produced.

Summaries of patient disposition will include all patients randomized. The following summaries will be generated:

- Patients who were randomized, treated, completed
 - Overall and by treatment group
 - By region (America (ARG, COL, USA), Europe (CZE, DEU, DNK, ESP, FRA, GBR, HRV, ITA, RUS, TUR), and Asia-Pacific (AUS, HKG, JPN, KOR, MYS, THA, TWN))
 - By site
- Patients who discontinued the study with reason for discontinuation
- Patients in analysis datasets and reason for exclusion from specific datasets

- Patients with inclusion/exclusion criteria violations

7.1.2. Protocol Deviations

The protocol deviations will be summarized in a table and a listing.

For the purposes of defining the PP population, major protocol deviations are:

- Not meeting all of the key inclusion/exclusion criteria.

Key inclusion criteria are

- Diagnosis of NMO as defined by 2006 Criteria by Wingerchuk et. al.(6) (Appendix 1 in the Protocol), or NMOSD as defined by 2007 Criteria by Wingerchuk et al (18) (Appendix 2 in the Protocol)
- NMO-IgG seropositive confirmed by a qualified laboratory
- Historical Relapse (as defined by the protocol) of at least 2 relapses in the last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to the screening
- EDSS score ≤ 7
- If a patient enters the trial receiving IST(s) for relapse prevention, the patient must be on a stable maintenance dose of IST(s), as defined by the Treating Physician, prior to screening and must remain on that dose for the duration of the study, unless the patient experiences a relapse

Key exclusion criteria are:

- Use of rituximab within 3 months prior to screening
- Use of mitoxantrone within 3 months prior to screening
- If a patient enters the trial receiving oral corticosteroid(s) with or without other IST(s), the daily corticosteroid dose must be no more than prednisone 20 mg/day (or equivalent) prior to screening and must remain on that dose for the duration of the study or until the patient experiences a relapse
- Patients who took less than 80% of the required treatment doses while they were in the Study Period
- Taking a prohibited medication during the double-blind treatment period (prior to an On-Trial Relapse, if applicable). The following medications are prohibited during the trial and will result in the patient being excluded from the PP population:
 - Concomitant use of rituximab with eculizumab is contraindicated
 - Use of mitoxantrone
 - Use of immunomodulatory therapies including: interferon beta-1b; interferon beta-1a, and glatiramer acetate
 - Other biologic agents such as tocilizumab
 - IVIg for relapse prevention

- PE for relapse prevention
- Change in dosing or addition of an IST during the treatment phase prior to the first relapse. 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 protocol deviation. High dose steroids of greater than 3 days will be considered a major protocol deviation.
- Any patient who had emergency unblinding by the investigator during the study
- Any other protocol deviation that would be considered to have a major effect on the assessment of efficacy. These will be determined by medical and statistical review of all protocol deviations prior to database lock and unblinding. This includes unforeseen changes in ISTs or dosing of ISTs.

7.1.3. Demographics, Disease Characteristics, and History

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

Demographic and baseline characteristics will also be summarized by treatment group and stratification variable for the FAS and PP populations.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (at First Dose Date)
- Sex
- Race and ethnicity
- Japanese Descent
- Region
- Baseline Weight
- Baseline Height
- Baseline BMI

7.1.3.2. Disease Characteristics

The following NMO disease characteristics will be summarized:

- Age at NMO Initial Clinical Presentation (years)
- Age at NMO / NMOSD Diagnosis (years)
- NMO Initial Clinical Presentation
- NMO Diagnosis

- Time from Initial Clinical Presentation to First Dose Date (years)
- Time from NMO Diagnosis to First Dose Date (years)
- Time from Initial Clinical Presentation to NMO Diagnosis (months)
- EDSS score at randomization (≤ 2.0 , vs ≥ 2.5 to ≤ 7)
- IST status at randomization (treatment naïve patients, vs. patients continuing on same IST(s) since last relapse vs. patients with changes in IST(s) since last relapse).
- IST Subgroup at baseline (See Section 7.2.1 of this SAP)
- EDSS, mRS and HAI scores at baseline

7.1.3.3. Medical / Surgical History and Baseline Physical Examination

Baseline medical history information, i.e., number (%) of patients who have a medical or surgical history will be summarized by treatment group for the following sets: FA, PP, and Safety. Likewise, Baseline Physical Examination information will be summarized by treatment group for the following sets: FA, PP, and Safety. By Patient Listings will be created for medical/surgical history and physical examinations.

History of prior NMO relapses including a summary of the type of relapses and the annualized relapse rate in the 24 months prior to the screening visit for this study will be summarized by treatment group. Likewise, the History of prior NMO relapses including a summary of the type of relapse and the annualized relapse rate in the 24 months prior to the screening visit for this study will be summarized by treatment group and stratification variable for the patients in the FAS and PP populations.

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 study treatment. Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD 2018MAR or higher). Summaries will be performed on the Safety set.

Prior and concomitant medications will be summarized by treatment group. The number (%) 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 agents:

- The choice of IST agents is at the discretion of the Treating Physician with the exception of the disallowed medications. Standard recommended dosing should be used for the chosen IST. Use of corticosteroids is permitted, however to assure

balance between treatment groups with respect to steroid dosing, the total daily dose should not exceed prednisone 20 mg per day or equivalent.

- Immunosuppressive agents, such as corticosteroid, AZA, MMF, methotrexate, tacrolimus, cyclosporine or cyclophosphamide either in combination or as mono-therapy are permitted.
- If a patient enters the trial receiving IST(s) for relapse prevention, the patient must have been on a stable maintenance dose of these IST(s), as defined by their Treating Physician, prior to the Screening Visit and must remain on that dose for the duration of the study. No new IST(s) or switch to another IST is permitted during the trial unless the patient experiences a relapse. After a relapse there are no restrictions on medication adjustments or changes.
- If a patient enters the trial receiving steroids either as mono-therapy or in combination with another IST, the daily steroid dose cannot be more than prednisone 20 mg daily (or equivalent). The patient must remain on that dose for the duration of the trial unless the patient experiences a relapse.
- The IST(s) and its dosing regimen for a particular patient must remain stable during the trial. If changes in the dose or dosing regimen are considered, due to a known toxicity or side effects associated with the given immunosuppressive agent, the Sponsor should be notified of the change.

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 will be summarized by treatment group. Listings of supportive ISTs will be produced. Changes in ISTs during the study will be summarized.

The following medications are prohibited during the trial:

- Concomitant use of rituximab or tocilizumab with eculizumab is contraindicated
- Use of mitoxantrone
- Use of immunomodulatory therapies including: interferon beta-1b; interferon beta-1a, and glatiramer acetate
- Use of IVIg for relapse prevention
- Use of PE for relapse prevention

If prohibited medications are used by patients in this study, then a listing of those patients, their treatment group, and their prohibited medications will be produced.

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

Non-drug therapies and procedures prior to study treatment and during the study will be summarized by system organ class and preferred term for each treatment group using counts and percentages. By-patient listings of Non-Drug Therapies and Procedures will be produced by treatment group. Summaries will be performed on the Safety set.

7.2. Efficacy Analyses

Efficacy analyses will be performed on the Full Analysis Set (FAS) population. The primary efficacy analysis of time to first adjudicated On-Trial relapse as well as the sensitivity analysis of time to first On-Trial relapse as determined by the Treating Physician will also be performed on the Per Protocol (PP) population. Baseline is defined as the last available assessment prior to treatment for all patients regardless of treatment group.

Patients who experience an On-Trial Relapse as determined by the Treating Physician may enter the extension trial after completion of the Week 6 Relapse Evaluation Visit. Thus, the Week 6 Relapse Evaluation Visit also serves as the EOS Visit for patients experiencing an On-Trial Relapse.

The EOS Visit will be completed when one of the following conditions is met, whichever comes first: (a) the patient experiences a relapse as described above; or (b) the trial ends by meeting 24 adjudicated On-Trial Relapse events in 24 patients; or (c) the patient withdrawals from the study.

7.2.1. Primary Analysis

The primary efficacy endpoint is time to first adjudicated On-Trial Relapse. The trial will be considered to have met its primary efficacy objective if a statistically significant difference (i.e. $p\text{-value} \leq 0.05$) is observed between the eculizumab treatment group and placebo group. The comparison of the treatment groups for the primary endpoint will use a log-rank test including strata for the randomization stratification variable. Confidence intervals and p-values will be presented. Hazard ratio and risk reduction from a stratified Cox proportional hazards model will be summarized. A sensitivity analysis will be performed on time to first On-Trial Relapse as determined by the Treating Physician using the same stratified log-rank test. These analyses will be performed for the FAS and PP populations.

An un-stratified log-rank test will be performed as a sensitivity analysis for the primary endpoint and for the time to first On-Trial Relapse as determined by the Treating Physician for the FAS population.

In addition, a sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator, baseline EDSS dichotomized at the median, historical ARR, and the observed IST strata for the FAS population. This sensitivity analysis will also be performed on the time to first On-Trial Relapse.

A sensitivity analysis will also be performed on time to first adjudicated relapse as determined by the committee using the stratified log-rank test for the FAS population.

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

The time at risk for relapse will be defined as the time from first dose to the end of study period: the last dose plus 16 days (or last dose plus 9 days if in induction period) or the last date observed in the study, whichever comes first. A censoring indicator will be equal to 1 if the patient did not experience relapse (was censored) during this time, and 0 if the patient experienced a relapse. See Section 9.5.1 for calculations.

A descriptive summary of adjudicated On-Trial Relapses by region, age group (≥ 45 vs < 45), gender, and race will be produced. In addition, the following subgroups will be used for data summary purposes based on anticipated IST and steroid usage standard of care. Additional combinations of IST subgroups maybe summarized depending on the distribution of ISTs used by patients during the study.

- Use of steroids alone
- Use of Azathioprine*
- Use of Mycophenolate Mofetil*
- No IST usage
- Historical Usage of Rituximab

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

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

1. Summary of the number of patients by treatment group (eculizumab versus placebo)
2. Summary of the number and percentage of patients with adjudicated On-Trial Relapses by treatment group
3. Estimated proportion of subjects relapse-free at 48 weeks (Kaplan-Meier estimate)
4. Summary of the total number of adjudicated On-Trial Relapses by treatment group
5. Summary of the total patient-years in study period by treatment group
6. Summary of the adjudicated On-Trial Annualized Relapse Rate by treatment group
7. Kaplan-Meier curves for the time to first adjudicated On-Trial Relapse by treatment group

No formal statistical tests are planned for these subgroup summaries of treatment response. All subgroups will also be summarized for On-Trial Relapses.

In order to account for relapses that are not evaluated according to the protocol (i.e., within 48 hours of the reporting of sign and symptoms of a possible relapse), a summary of adjudication results will be produced by treatment group and relapse evaluated within 48 hrs (yes, no) for patients with On-Trial Relapses. Summaries of the severity of the On-Trial Relapses versus patient evaluated within 48 hours (yes, no) by treatment group will also be produced.

7.2.1.1. Handling of Dropouts or Missing Data

In this time to first relapse study, all FAS and PP patients would either have experienced an adjudicated On-Trial Relapse or would have ended participation in the study 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 to the end of study period: the last dose plus 16 days (or last dose plus 9 days if in induction period) or the last date observed in the study, whichever comes first. See Section 9.5.1 for calculations. A censoring indicator will be equal to 1 if the patient did not experience relapse (was censored), and 0 if the patient experienced a relapse. Reasons for censoring will be summarized by treatment group.

Missing data for the primary analysis of EDSS, EQ-5D, mRS, HAI, and visual acuity (Kurtzke FSS) at the EOS (i.e. 6 week post-relapse for the patients who have relapses or EOS for patients who do not have relapses) will be handled as follows: If the assessment 6 weeks after the first relapse is missing or if a non-relapse patient is missing the EOS score, 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 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 Section 9.5.3.7.

7.2.1.2. Subgroup Analysis

Some efficacy analyses will involve subgroups of the FAS populations. These subgroup analyses include

- A descriptive summary of adjudicated On-Trial and On-Trial Relapses by region, age, gender, and race will be produced. Kaplan-Meier curves for both treatment groups will be produced. Likewise, Kaplan-Meier curves for each treatment group within strata will be produced.
- Descriptive summaries of adjudicated On-Trial and On-Trial Relapses by treatment group will be produced for IST subgroups. Kaplan Meier curves for the time to relapse by treatment group will be produced for IST subgroups.
- Change from baseline in HAI at the EOS Visit in patients with abnormal baseline ambulatory function. Patients with abnormal ambulatory function are patients with a baseline HAI value of 1 to 9 (i.e. a baseline value of 0 is considered normal).
- Change from baseline in visual acuity at the EOS Visit in patients with abnormal baseline visual function. Patients with abnormal visual acuity at baseline are patients with a baseline Kurtzke FSS for visual acuity of 1 to 6 at baseline (i.e., a baseline value of 0 is considered normal).
- The assessment of the severity and type of relapses will be conducted in the subgroups of patients who had On-Trial Relapses by treatment group.

7.2.1.3. Multicenter Studies

Since a small number of patients are anticipated at each center, the study will be randomized across centers and not within centers. As such, center will not be used as a covariate in the efficacy analyses.

7.2.1.4. Hypothesis Testing and Significance Level

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

7.2.1.5. Sensitivity Analyses

Table 5 in section 9.5.6 summarizes sensitivity analyses for the primary endpoint as described above. Additional sensitivity summaries based on subgroups will be made to summarize relapses by treatment group.

Sensitivity analyses for the secondary efficacy endpoints are described in Section 7.2.2 for each endpoint and are also summarized in Table 5.

7.2.2. Secondary Analyses

Baseline is defined as the last available assessment prior to treatment for all patients regardless of their treatment group. Hypothesis testing comparing eculizumab treatment with placebo treatment for the secondary efficacy analyses will be performed using a closed testing procedure with the following rank order:

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

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

The comparison of the two treatment groups for the secondary endpoint, adjudicated On-Trial annualized relapse rate, will use Poisson regression analysis. Treatment group, the randomization stratification variable, and historical annualized relapse rate will be covariates in the model, and the log of time in the study will be used as the offset variable.

A sensitivity analysis will be performed for ARR using all On-Trial Relapses as determined by the Treating Physician in a Poisson regression analysis with treatment group, the randomization stratification variable, and historical ARR as covariates in the model, and the log of time in the trial will be used as the offset variable. See Section 9.5.2 for calculations of annualized relapse rates.

The primary analysis for the change from baseline in EDSS score to the EOS (i.e. 6 week post-relapse for the patients who have relapses or EOS for patients who do not have relapses) will be a randomization-based nonparametric ANCOVA adjusted for baseline EDSS and stratified by randomization IST strata (Zink 2012). Missing data will be handled as described in Section 7.2.1.1. A sensitivity analysis for the change from baseline in EDSS score to the EOS will be an ANCOVA with treatment group, baseline EDSS, and randomization IST strata as covariates.

Change from baseline in EDSS score will also be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach (i.e. a mixed model). The model will include fixed categorical effects for observed IST strata, treatment group, and study visit, and a continuous fixed covariate for baseline EDSS score. All post-baseline EDSS scores at the scheduled visits will be included in the models; patients without any post-baseline scores will not be included. An unstructured covariance structure will be used to model the within patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion (AIC): first-order autoregressive, compound symmetry, and Toeplitz. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The parameter estimates for the covariates and their associated p-values will be provided and treatment comparisons will be based on the treatment main effect.

In addition, sensitivity analyses for the change from Baseline in EDSS will include an analysis over year 1 using a mixed model for repeated measures with baseline EDSS score, observed IST strata, treatment group indicator, study visit and study visit by treatment group interaction as covariates. All post-baseline EDSS scores at the scheduled visits up to week 48 will be included in the models; patients without any post-baseline scores will not be included.

The change from baseline in EDSS parameter will be statistically analyzed at each visit using a restricted maximum likelihood (REML)-based repeated measures approach (i.e. a mixed model). An unstructured covariance structure will be used to model the within patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion (AIC): first-order autoregressive, compound symmetry, and Toeplitz. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The estimation of change from baseline on defined weeks along with 95% confidence intervals and p-values will be provided, as will the parameter estimates for the covariates and their associated p-values.

Table summaries and by-patient listings of the EDSS assessments and changes from baseline in EDSS will be produced. The distribution of EDSS scores over time will also be summarized.

Changes from baseline to the EOS (i.e. 6 week post-relapse for the patients who have relapses or EOS for patients who do not have relapses) in mRS, HAI, EQ-5D VAS, and EQ-5D index score will be analyzed in a similar manner as changes in EDSS score. A randomization-based nonparametric ANCOVA adjusted for baseline score and stratified by the randomization stratification variable will be used. Sensitivity analyses will include an ANCOVA with treatment group, baseline score, and randomization stratification variable as covariates, as well as a mixed model for repeated measures including all post-baseline scores at the scheduled visits with baseline score, observed stratification variable, treatment group indicator, study visit as covariates, and a mixed model for repeated measures including all post-baseline scores at the scheduled visits over year 1 with baseline score, observed stratification variable, treatment group

indicator, study visit and study visit by treatment group interaction as covariates. Table summaries and by-patient listings of the assessments and changes from baseline in the assessments will be produced. The distributions of mRS and HAI scores over time will also be summarized.

The health profiles of the patients based on the EQ-5D will be presented in tabular form by treatment group over the visit assessments. These health profiles will present the frequency and the proportion of reported problems for each EQ-5D level (i.e. no problem, some problems, and extreme problems) for each dimension (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). A by-patient listing will be produced for the EQ- 5D index scores using US TTO and VAS scores, and will include visit and change from baseline.

7.2.3. Tertiary Analyses

The tertiary efficacy endpoints include:

1. Change from baseline in ambulatory function as measured by HAI at EOS Visit in patients with abnormal baseline ambulatory function
2. Change from baseline in visual function as measured by visual acuity at EOS Visit in all patients and patients with abnormal baseline visual function
3. Change from baseline in the SF-36 at EOS
4. Change from baseline in the Kurtzke FSS (other than visual acuity) at EOS Visit

Changes from baseline in visual acuity will be analyzed in a similar manner as changes in mRS, HAI, EQ-5D VAS, and EQ-5D index scores described in Section 7.2.2 using the Kurtzke FSS visual acuity assessment. Baseline value and the randomization or observed stratification variable will be used in the analyses for this endpoint. Table summaries and by-patient listings of visual acuity assessments and changes from baseline in the visual acuity will be produced. Changes from baseline in the HAI and visual acuity for patients who were abnormal at baseline will be analyzed in a similar manner to the secondary endpoint analyses described for HAI in Section 7.2.2. Visual acuity using the Snellen chart assessments will be summarized in by-patient listings.

Change from baseline in SF-36 QOL endpoints will be analyzed in a similar manner to the secondary endpoint analyses described for mRS, HAI, EQ-5D VAS, and EQ-5D index scores described in Section 7.2.2. The 8 health domain scores transformed to the 0-100 scale (PF, SF, RP, BP, GH, MH, RE and VT) and the two norm-based composite scores, PCS and MCS, will be analyzed. Details for calculating the 8 health domain scores and composite scores are given in Section 9.5.3 of this SAP. The Health Transition (HT) based on item 2 of the SF-36 will be listed by visit and by treatment group.

Changes from baseline in the Kurtzke FSS will be analyzed in a similar manner to the secondary endpoint analyses described for the mRS, HAI, EQ-5D VAS, and EQ-5D index scores described in Section 7.2.2.

Patient listings of the tertiary endpoint parameters will be produced.

7.2.4. Other Efficacy Analyses

7.2.4.1. Severity of a Relapse

For adjudicated On-Trial Relapse(s) and for On-Trial Relapse(s), summary tables of the types of relapses and the severity of the relapses will be produced by treatment group. A by-patient listing of the relapses will be produced. The severity of a relapse will be determined using the OSIS scale. The determination of the severity of a relapse is defined in Section 5.1.5.1 of this SAP.

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. The worst severity observed over all relapse visits will be used. In the event that a patient has a relapse that includes more than one type of relapse, the worst grade will be used to classify the overall severity of the relapse.

Changes from baseline to all of the study collected time-points after a relapse will be summarized for EDSS, HAI, and visual acuity for the first adjudicated On-Trial Relapse and for the first On-Trial Relapse. Changes from the last assessment prior to the relapse to all study collected time-points after a relapse will also be summarized for EDSS, HAI, and visual acuity. Patient listings for the EDSS, HAI, and visual acuity assessments before and after a relapse will be created for the patients with relapses.

On-Trial Relapses will also be assessed by summarizing the number and rate of relapses requiring hospitalization and the number and rate of treatments for relapses by treatment group.

7.2.5. Pharmacokinetic and Pharmacodynamic Analyses

Blood samples will be collected at specified time points to study the concentration of eculizumab versus time. PK parameters such as maximum concentration as well as trough and peak eculizumab concentration during the induction and maintenance treatment phases will be reported. Clearance and terminal half-life will be estimated. Details will be described in a separate PK/PD analysis plan.

Cerebrospinal fluid (CSF) samples for PK/PD analyses will also be collected at specified time points for patients who consent to these assessments. Details for PK/PD analyses related to CSF samples will be described in a separate PK/PD analysis plan.

Blood samples for PD analysis will be collected at specified time points to assess pre- and post-treatment serum hemolytic activity and therefore C5 complement activity inhibition. Free C5 concentration will be measured.

The population PK analysis of eculizumab in NMO patients will be performed to assess the concentration of eculizumab versus time. PK parameters such as maximum concentration as well as trough and peak eculizumab concentration during the induction and maintenance treatment phases will be reported. Clearance and terminal half-life will be estimated. PD analysis will be performed to assess pre- and post-treatment serum hemolytic activity and therefore C5 complement activity inhibition. Free C5 concentration will be summarized. The potential exposure response analyses for selected efficacy and safety endpoints may also be performed based on the outcomes of exploratory data visualization.

Details for PK/PD analyses and potential exposure response analyses will be described in a separate PK/PD analysis plan. Serum and CSF free C5 and percentage of baseline, serum and CSF Eculizumab concentrations, and percent hemolysis will be summarized by Treatment Group and Visit/Time Point.

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

7.2.6. Biomarker Assessments

Serum NMO-IgG Antibody samples will be collected at Screening, Baseline, Relapse evaluation visits, and at other study visits as outlined in the protocol Schedule of Assessments. Only patients with documented positive test for the AQP4 autoantibody (also called NMO-IgG) obtained prior to or during the screening will be included in the study. Only validated diagnostic tests performed by a qualified laboratory are acceptable. Sample analysis will be conducted at the Mayo Clinic laboratory. Cerebrospinal fluid (CSF) samples for NMO-IgG antibody level will also be collected at specified time points for patients who consent to having these assessments.

Shifts from baseline in serum and CSF NMO-IgG antibody titer level will be summarized by treatment group and visit. Shifts from baseline in serum and CSF NMO-IgG antibody titer levels to relapse evaluation visits will also be produced. A listing of serum and CSF NMO-IgG antibody titers will be produced.

7.3. Safety Analyses

All safety analyses will be conducted on the Safety Set (treatment actually received). All safety data will be provided, by treatment group, 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 FAS, PP, and Safety populations. 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 (i.e. Study duration (days) = Date of discontinuation/completion (or death) – First Dose Date + 1)). 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 (i.e. treatment duration (days) = Last Dose Date – First Dose Date + 1).

If a patient undergoes plasmapheresis or plasma exchange (PE) for an On-Trial Relapse during the Treatment Period, a supplemental dose of IP, 2 vials (equivalent to 600 mg of eculizumab) should be administered after each PE, preferably within 1-2 hours. If PE is administered on day of regularly scheduled IP administration, patients will receive the regularly scheduled number of vials after each PE, preferably within 1-2 hours. In addition patients are to continue protocol specified dosing until the 6 week post-attack assessment. Patients taking supplemental doses of IP will be summarized in by-patient listings.

7.3.2. Adverse Events (AEs)

Adverse Events are defined in Protocol Section 12.2.

In Study ECU-NMO-301, for SAEs the reporting period to Alexion or Alexion Pharmacovigilance Delegate begins following the patient's signing of the ICF (providing consent to participate in the trial) and continues through 8 weeks after the last dose of study medication. For non-serious AE, the reporting period starts following first dose of IP and continues through the last study visit. AEs that are thought to be causally related are to be followed until event or sequelae resolve or are determined to be medically stable.

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

- Pre-Treatment Serious Adverse Events (PTSAEs)
- Treatment-Emergent Adverse Events (TEAEs)
- Treatment-Emergent Serious Adverse Events (TESAEs)

PTSAEs are the serious AEs that occur between the signing of informed consent and first IP dose (i.e. eculizumab or placebo). TEAEs are AEs that onset on or after the first IP dose in the study. Likewise, TESAEs are SAEs that onset on or after the first IP dose in the study. A table and listing of 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 are described below; additional details regarding AEs are outlined in Section 9.4.

AEs will be coded by primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (version 21.0 or higher).

7.3.2.1. Overall Summary of Adverse Events

All TEAEs will be presented using summary statistics (n, %). The number of Events (n) and number of patients with events (n, %) will be shown for the following event subcategories:

Table 3: Treatment-Emergent Adverse Events (TEAEs)

Relationship	Severity
Related AEs	Mild AEs
Not Related AEs	Moderate AEs
	Severe AEs

Additionally, the number and percentage of patients who withdrew from the study due to an AE or who died on study will be presented. These statistics will be prepared for all TEAEs and, separately, for SAEs (except severity). See Section 9.4 for definition of related TEAEs.

An overall summary table of TEAE information will be presented that will summarize the frequency and percentage of patients who:

- Experienced any AE,
- Discontinued due to an AE,

- Died (if applicable),
- Experienced a related AE,
- Experience a serious AE,
- Experienced a severe AE

Additional overall summary tables by age, gender, race and region will also be provided.

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

The number of TEAEs/TEAEs 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 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 Section 9.4.

Additional summary tables stratifying TEAEs and TESAEs by age, gender, race and region will also be provided.

The number of non-serious adverse events 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. The incidence of AEs leading to study discontinuation will be summarized. 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 section 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 TSAEs over time will be provided. The denominator per time interval will be the number of patients continuing in the trial 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. The following provides a list of AESI:

- Infections:
 - Meningococcal Infections
 - Aspergillus Infections
 - Other Serious Infections
- Sepsis
- Infusion Reactions
- Serious Cutaneous Adverse Reactions
- Cardiac Disorders
- Angioedema

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

7.3.3. Other Safety

7.3.3.1. Analyses for Laboratory Tests

Descriptive statistics by visit and treatment group will be presented for each laboratory parameter. 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. All data will be presented in listings.

7.3.3.2. Vital Signs

Vital signs (systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and sitting or lying heart rate (HR)), and changes from baseline in vital signs will be summarized by visit and by treatment group. Listings of vital signs will be produced.

Weight will be summarized by visit and treatment group. Changes in weight will be summarized by visit and treatment group. Listings of weight will be produced.

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

- DBP <50 mmHg; DBP >90 mmHg; DBP >100mmHg
- 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 suicide ideation and behavior. Physical examinations will be summarized by treatment group and visit. Listings of physical examinations will be produced. Immunogenicity as measured by Anti-Drug Antibody will be summarized in tabular form by treatment group and presented in by-patient listing. A by-patient listing of N. meningitides vaccinations will be produced showing the date of vaccinations for each patient by treatment group. Pregnancy tests will be summarized in patient listings.

7.3.3.3.1. Electrocardiograms (ECG)

The ECG results will be summarized by treatment group and visit. Listings of ECG results will be produced. Descriptive statistics by visit will be presented for each ECG parameter (including ventricular rate, PR duration, QRS duration, QT duration, RR duration, QTcB, and 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 by treatment group.

The number and percentage of subjects having observed QT, QTcB or QTcF that satisfy any of the following conditions will be presented by treatment and 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, QTcB, or QTcF that satisfy any of the following conditions will be presented by treatment and 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 Columbia-Suicide Severity Rating Scale (C-SSRS) during the treatment period will be summarized by treatment group. Treatment-emergent Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent will be based on Visits 6, 8, 10, and every 12th weeks thereafter through EOS/ET; at the week 6 Relapse Evaluation Visit, and/or at the Safety Follow-up visit. 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 by treatment 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 by treatment group.

Two shift tabulations from baseline for the C-SSRS will be produced by treatment group 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.

7.4. Interim Analysis

Not applicable.

8. REFERENCES

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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 a randomized double-blind placebo controlled study to evaluate eculizumab in NMO patients with a primary endpoint of time to first adjudicated On-Trial Relapse. As such, the study is based on observing relapse events. Based on the power calculations, a total of 24 relapse events in 24 individual patients are to be observed.

Approximately 132 NMO patients will be randomized in a 2:1 (eculizumab: Placebo) ratio. Therefore, approximately 88 NMO patients will be randomized to eculizumab and approximately 44 NMO patients will be randomized to Placebo. Randomized patients who discontinue after initiation of treatment will not be replaced.

This is a randomized, placebo-controlled trial to evaluate eculizumab in NMO patients. The sample size and power calculation assumptions for this time to first event study are as follows:

- Log-rank test for comparison of eculizumab to placebo
- 2:1 randomization (eculizumab:placebo)
- Power 90%
- Two-sided 5% level of significance
- Drop-out rate 10%
- Accrual period of approximately 21 months
- Relapse-free rate of 80% for the eculizumab arm at 12 months
- Hazard ratio of 0.24 (-log hazard ratio = 1.41) which corresponds to a relapse-free rate of 40% for the placebo arm at 12 months

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

All patients who are vaccinated and cleared for randomization by their Principal Investigator (PI) or Sub-Investigator and by the Sponsor will be randomized on Day 1 on a 2:1 basis to the Eculizumab Arm or the Placebo Arm. The randomization will be across centers. The randomization stratification will include two variables: 1) EDSS score at Day 1 (≤ 2.0 , vs ≥ 2.5 to

≤ 7); and 2) IST status at randomization for relapse prevention (treatment naïve patients, on the same IST(s) since the last relapse and with changes in IST(s) since last relapse).

Patients will be centrally randomized via IVRS Almac clinical service based randomization application.

9.4. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

Age

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

Table 4: Age and reference date

AGE	REFERENCE DATE
• Age at Enrollment	• Date of Signing ICF
• Age at Randomization	• Date of Randomization
• Age at Disease Onset	• Date of Initial Clinical Presentation
• Age at First Infusion	• Date of First Infusion

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.

Disease Duration

NMO disease duration will be presented as the number of years between the date of first infusion and the date of initial clinical presentation (i.e. $\text{INT}[(\text{Date of first infusion} - \text{Date of initial clinical presentation} + 1)/365.25]$). 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.

Definition of Baseline Values

During the Treatment Period, 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.

$$\text{Baseline BMI (kg/m}^2\text{)} = (\text{Baseline weight (in kg)})/(\text{Baseline Height in meters})^2$$

Change from Baseline

Change from baseline will be calculated as

$$\text{Change of Baseline} = \text{Assessment Value} - \text{Baseline Assessment Value.}$$

QTcB and QTcF Calculations

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

$$\text{QTcB} = \text{QT interval} / \text{sqrt(RR)}$$

The Fridericia formula, QTcF, is as follows:

$$QTcF = QT \text{ interval} / (RR)^{(1/3)}$$

Adverse Events

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

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first study drug dose (placebo or eculizumab). 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 Pre-Treatment Adverse Events (PTAEs).

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

Related AEs are defined as possible, probable or definitely related. Unrelated AEs are defined as unlikely or not related. AEs with missing relationship to study treatment will be assumed as related to study treatment.

Person-years of follow-up is defined as:

$$\text{Person-years of follow-up} = (\text{Last study date} - \text{First Dose date} + 1)/365.25$$

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.

Patient Populations / Immunosuppressant Therapy Status

There are 3 patient populations for this study defined by prior supportive treatment with immunosuppressive agents used for relapse prevention.

Treatment Naïve Patients

For the purpose of this protocol, treatment naïve patients are defined as those who have received either no IST or only corticosteroids.

Patients continuing on the same IST(s) since the last relapse

This includes patients with dose adjustment with the same IST(s) since the last relapse.

Patients with changes in IST(s) since last relapse

This includes patients who switched IST(s) [e.g. AZA to MMF], added IST, or withdrew any IST treatment.

9.5. Additional details on Statistical Methods

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

In this time to first relapse study, all FAS and PP patients would either have experienced an (adjudicated) On-Trial Relapse or would have ended participation in the study period without an (adjudicated) On-Trial Relapse. The patients who do not have (adjudicated) On-Trial Relapses during the study period will be censored at the last known date during the EOS Date (see below). 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:

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

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

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

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 Last Study Date.

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

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

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

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

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 Last Study Date.

9.5.2. Annualized Relapse Rate Calculations

9.5.2.1. Historical Annualized Relapse Rate ($ARR_{\text{historical}}$)

Detailed information on relapses within last 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 by the protocol.

Historical Relapses are the relapses that occurred prior to screening visit (i.e., the last screening visit for the patient). For this protocol, the Historical Relapse is defined as new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or MRI findings or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of an existing neurologic symptoms required treatment. Treatment is defined as use of high-dose intravenous steroids, plasma exchange (PE) or IVIg. 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 annualized relapse rate will be calculated for each patient as:

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

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 NMO 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. On-Trial Annualized Relapse Rate ($ARR_{(\text{On-Trial})}$)

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

For each patient, the adjudicated On-Trial annualized relapse rate will be calculated as:

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

and the On-Trial annualized relapse rate as determined by the Treating Physician will be calculated as:

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

The number of relapses in the study period is the number of relapses from the start of study treatment (first dose date) to the end of the study period for the patient. The end of study (EOS) period will be determined by the last dose date + 16 days (or +9 days if in induction phase) or the last day in NMO301, whichever occurs first. For patients who entered Study ECU-NMO-302 during the additional relapse follow-up visits, the EOS will be one day before the first study dose in Study ECU-NMO-302. The time in study period (in years) for the purposes of calculating ARR is as follows:

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

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 Last Study Date.

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

9.5.3. SF-36 Calculations

The SF-36 is a self-administered questionnaire designed to assess generic health-related quality of life 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 trial. The QualityMetric Health Outcomes Scoring Software 5.0 will be used to derive the 8 domain scores and 2 component scores. The algorithms used by the software to score the data are described below (excerpted from the User's Guide).

9.5.3.1. 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.

9.5.3.2. 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.

9.5.3.3. 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.

9.5.3.4. 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.

9.5.3.5. 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 U.S. 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 U.S. 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.

9.5.3.6. 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 U.S. 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 U.S. 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 U.S. 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.

9.5.3.7. 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 whom have answered at least one item that represents that construct. For the PF scale, item parameters obtained through 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 whom 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.

9.5.4. 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 (i.e. state 11111). EQ- 5D index scores for this study will be obtained using the US TTO method. The calculation is illustrated in the table below:

US TTO value set		Example: the value for health state 21232	
Full health (11111)	1	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:

$D1 = (\text{Number of States} \neq 1) - 1$

$I2 = (\text{Number of States} = 2) - 1$

$I3 = (\text{Number of States} = 3) - 1$

9.5.5. SAS Code for Efficacy Analyses

9.5.5.1. 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 a log-rank test including strata for the randomization stratification variable. The basic SAS code for this log-rank analysis is:

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

where trt01p is a variable that indicates the patient's randomized 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), strat is the randomization stratification variable with four strata. This same basic log-rank test SAS code will be used in the sensitivity analyses for time to first On-Trial Relapse as determined by the Treating Physician and time to first adjudicated relapse.

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 strat;
  model aval*cnsr(1) = trt01p;
  strata strat;
  hazardratio trt01p;
run;
```

An un-stratified log-rank test will be performed as a sensitivity analysis for time to first adjudicated On-Trial Relapse and time to first On-Trial Relapse. The basic SAS code for this analysis is:

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

SAS Code for a sensitivity comparison of the primary endpoint will use a Cox proportional hazards regression model with treatment group indicator, baseline EDSS dichotomized at median, historical ARR and observed IST strata:

```
proc phreg data = ADTTE;
  class trt01p edss_i ist_i;
  model aval*cnsr(1)=trt01p edss_i ist_i arrhist;
  hazardratio trt01p;
run;
```

where edss_i is baseline EDSS dichomized at the median, ist_i is observed IST strata, and arrhist is the historical ARR.

9.5.5.2. SAS Code for the Secondary/Tertiary Efficacy Endpoint

9.5.5.2.1. Randomization-based nonparametric ANCOVA

The primary analysis for the secondary and tertiary endpoints is a randomization-based nonparametric ANCOVA adjusted for baseline and stratified by the randomization stratification variable. The SAS/IML macro NParCov3 (Zink 2012) will be used for this analysis. The following macro call will be used:

```
%NParCov3(OUTCOMES=chg, COVARS=base, TRTGRPS=trt01pn, STRATA=strat,
HYPOTH=NULL, TRANSFORM=NONE, COMBINE=FIRST, C=1, DSNIN=ataeos,
DSNOUT=outdat);
```

where chg is the change from baseline at the EOS, base is the value at baseline, trt01pn is the numeric randomized treatment group, strat is the randomization stratification variable with four strata, dataeos is the input data set and outdat is the prefix for the output data sets. Note: For EDSS change from baseline, the strata will be randomized IST strata.

9.5.5.2.2. ANCOVA

Sensitivity analyses for the secondary and tertiary endpoints involve ANCOVA. The basic SAS code for such an analysis is given by:

```
proc glm data=ADEFF;  
  class strat trt01p;  
  model chg = base strat trt01p / solution;  
  lsmeans trt01p / cl diff stderr;  
quit;
```

9.5.5.2.3. Repeated Measures Mixed Model Analysis

Sensitivity analyses for the secondary and tertiary endpoints involve a mixed model for repeated measures analysis with treatment comparisons based on the main treatment effect. The basic SAS code for such an analysis is given by:

```
proc mixed data = ADEFF method = reml;  
  class subjid trt01p avisit strat;  
  model chg = trt01p avisit base strat / ddfm = kr solution;  
  repeated avisit / type=un subject=subjid;  
  where 1 < avisitn;  
run;
```

where subjid is the patient variable, trt01p is the randomized treatment group, avisit is the visit variable (0 representing the baseline visit), base is the value at baseline, chg is the change from baseline at a particular visit, and strat is the observed stratification variable with four strata. Note: For EDSS change from baseline, the strata will be observed IST strata.

Additional sensitivity analyses for the secondary and tertiary endpoints involve a mixed model for repeated measures analysis over year 1 using the full multivariate approach with treatment by time interaction. The basic SAS code for such an analysis is given by:

```
proc mixed data = ADEFF method = reml;  
  class subjid trt01p avisit strat;  
  model chg = trt01p avisit trt01p*avisit base strat / ddfm = kr solution;  
  repeated avisit / type=un subject=subjid;  
  lsmeans trt01p*avisit / cl diff;  
  where 1 < avisitn ≤ 28;
```

run;

where subjid is the patient variable, trt01p is the randomized treatment group, avisit is the visit variable (0 representing the baseline visit), base is the value at baseline, chg is the change from baseline for the parameter at a particular visit, and strat is the observed stratification variable with four strata. Note: For the change from baseline in EDSS score, the baseline for EDSS will be a covariate in the analysis along with the observed IST strata.

9.5.5.2.4. Poisson Regression Analysis

The analysis of the annualized relapse rate will involve Poisson Regression analysis. The basic SAS code for that analysis is given by:

```
proc genmod data = ADEFF;
    class trt01p strat;
    model aval = trt01p strat base / dist = poisson link = log offset = logtime type3;
    lsmeans trt01p / cl diff exp;
```

run;

where trt01p is the randomized treatment group, aval is the number of relapses in the study period, base is the annualized relapse rate at baseline (i.e. historical ARR), strat is the randomization stratification variable with four strata, and logtime is the log of the time in years that the patient is in the study.

9.5.6. Summary of Primary and Sensitivity Analyses

Table 5: Planned analyses

Endpoint	Primary Analysis	Sensitivity Analyses
Primary: Time to first adjudicated On-Trial Relapse	<ul style="list-style-type: none"> • Stratified log-rank: CI/p-value <ul style="list-style-type: none"> ○ Stratified Cox model: Hazard ratio/risk reduction ○ FAS population 	<ul style="list-style-type: none"> • Primary endpoint using stratified log-rank on PP population • Time to first On-Trial Relapse using stratified log-rank, FAS and PP • Primary endpoint and Time to first On-Trial Relapse using un-stratified log-rank, FAS • Primary endpoint and Time to first On-Trial Relapse using Cox PH model with treatment group, baseline EDSS dichotomized at the median, historical ARR, region, and observed IST strata as covariates, FAS

		<ul style="list-style-type: none"> • Time to first adjudicated relapse using stratified log-rank test, FAS
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Endpoint	Primary Analysis	Sensitivity Analyses
	All analyses of secondary endpoints performed on FAS	
Secondary #1: Adjudicated On-Trial ARR	<ul style="list-style-type: none"> • Poisson regression with treatment group, historical ARR, and randomization strata as covariates 	<ul style="list-style-type: none"> • On-Trial ARR using Poisson regression with treatment group, historical ARR, and randomization strata as covariates
Secondary #2: Change from Baseline in EDSS score at the EOS	<ul style="list-style-type: none"> • Randomization-based nonparametric ANCOVA adjusted for baseline EDSS and stratified by randomization IST strata <ul style="list-style-type: none"> ○ With data imputation as described 	<ul style="list-style-type: none"> • Change from Baseline in EDSS score at EOS using an ANCOVA adjusted for baseline EDSS and randomization IST strata • Change from Baseline in EDSS score at all scheduled visits using a mixed model for repeated measures with baseline EDSS score, observed IST strata, treatment group, and study visit as covariates • Change from Baseline in EDSS score at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline EDSS score, observed IST strata, treatment group, study visit, and study visit by treatment interaction as covariates
Secondary #3: Change from Baseline in mRS score at EOS	<ul style="list-style-type: none"> • Randomization-based nonparametric ANCOVA adjusted for baseline mRS and stratified by randomization strata <ul style="list-style-type: none"> ○ With data imputation as described 	<ul style="list-style-type: none"> • Change from Baseline in mRS score at EOS using an ANCOVA adjusted for baseline mRS and randomization strata • Change from Baseline in mRS score at all scheduled

		<p>visits using a mixed model for repeated measures with baseline mRS score, observed strata, treatment group, and study visit as covariates</p> <ul style="list-style-type: none">• Change from Baseline in mRS score at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline mRS score, observed strata, treatment group, study visit, and study visit by treatment interaction as covariates
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<p>Secondary #4: Change from Baseline in HAI score at EOS</p>	<ul style="list-style-type: none"> • Randomization-based nonparametric ANCOVA adjusted for baseline HAI and stratified by randomization strata <ul style="list-style-type: none"> ○ With data imputation as described 	<ul style="list-style-type: none"> • Change from Baseline in HAI score at EOS using an ANCOVA adjusted for baseline HAI and randomization strata • Change from Baseline in HAI score at all scheduled visits using a mixed model for repeated measures with baseline HAI score, observed strata, treatment group, and study visit as covariates • Change from Baseline in HAI score at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline HAI score, observed strata, treatment group, study visit, and study visit by treatment interaction as covariates
<p>Secondary #5a: Change from Baseline in EQ-5D VAS score at EOS</p>	<ul style="list-style-type: none"> • Randomization-based nonparametric ANCOVA adjusted for baseline EQ-5D VAS and stratified by randomization strata <ul style="list-style-type: none"> ○ With data imputation as described 	<ul style="list-style-type: none"> • Change from Baseline in EQ-5D VAS score at EOS using an ANCOVA adjusted for baseline EQ-5D VAS and randomization strata • Change from Baseline in EQ-5D VAS score at all scheduled visits using a mixed model for repeated measures with baseline EQ-5D VAS score, observed strata, treatment group, and study visit as covariates • Change from Baseline in EQ-5D VAS score at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline EQ-5D VAS score, observed strata, treatment group, study visit, and study visit by treatment interaction as covariates

<p>Secondary #5b: Change from Baseline in EQ-5D Index score at EOS</p>	<ul style="list-style-type: none"> • Randomization-based nonparametric ANCOVA adjusted for baseline EQ-5D Index and stratified by randomization strata <ul style="list-style-type: none"> ○ With data imputation as described 	<ul style="list-style-type: none"> • Change from Baseline in EQ-5D Index score at EOS using an ANCOVA adjusted for baseline EQ-5D Index and randomization strata • Change from Baseline in EQ-5D Index score at all scheduled visits using a mixed model for repeated measures with baseline EQ-5D Index score, observed strata, treatment group, and study visit as covariates • Change from Baseline in EQ-5D Index score at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline EQ-5D Index score, observed strata, treatment group, study visit, and study visit by treatment interaction as covariates
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Endpoint	Primary Analysis	Sensitivity Analyses
	<p>All analyses of tertiary endpoints performed on FAS</p>	
<p>Tertiary #1: Change from Baseline in HAI at EOS in patients with abnormal baseline</p>	<ul style="list-style-type: none"> • Randomization-based nonparametric ANCOVA adjusted for baseline HAI and stratified by randomization strata <ul style="list-style-type: none"> ○ With data imputation as described 	<ul style="list-style-type: none"> • Change from Baseline in HAI score at EOS in patients with abnormal baseline using an ANCOVA adjusted for baseline HAI and randomization strata • Change from Baseline in HAI score in patients with abnormal baseline at all scheduled visits using a mixed model for repeated measures with baseline HAI score, observed strata, treatment group, and study visit as covariates

		<ul style="list-style-type: none"> • Change from Baseline in HAI score in patients with abnormal baseline at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline HAI score, observed strata, treatment group, study visit, and study visit by treatment interaction as covariates
<p>Tertiary #2: Change from Baseline in Visual KFSS at EOS in all patients and in patients with abnormal baseline</p>	<ul style="list-style-type: none"> • Randomization-based nonparametric ANCOVA adjusted for baseline Visual KFSS and stratified by randomization strata <ul style="list-style-type: none"> ○ With data imputation as described 	<ul style="list-style-type: none"> • Change from Baseline in Visual KFSS at EOS in all patients and in patients with abnormal baseline using an ANCOVA adjusted for baseline Visual KFSS and randomization strata • Change from Baseline in Visual KFSS score in all patients and in patients with abnormal baseline at all scheduled visits using a mixed model for repeated measures with baseline Visual KFSS score, observed strata, treatment group, and study visit as covariates • Change from Baseline in Visual KFSS in all patients and in patients with abnormal baseline at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline Visual KFSS score, observed strata, treatment group, study visit, and study visit by treatment interaction as covariates
<p>Tertiary #3: Change from Baseline in SF-</p>	<ul style="list-style-type: none"> • Randomization-based nonparametric ANCOVA adjusted for baseline SF-36 	<ul style="list-style-type: none"> • Change from Baseline in SF-36 score at EOS using an ANCOVA adjusted for

<p>36 at EOS</p>	<p>and stratified by randomization strata</p> <ul style="list-style-type: none"> ○ With data imputation as described 	<p>baseline SF-36 and randomization strata</p> <ul style="list-style-type: none"> ● Change from Baseline in SF-36 score at all scheduled visits using a mixed model for repeated measures with baseline SF-36 score, observed strata, treatment group, and study visit as covariates ● Change from Baseline in SF-36 score at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline SF-36 score, observed strata, treatment group, study visit, and study visit by treatment interaction as covariates
<p>Tertiary #4: Change from Baseline in Kurtzke FSS (Brainstem, Pyramidal, Cerebellar, Sensory, Bowel/Bladder, Cerebral) at EOS</p>	<ul style="list-style-type: none"> ● Randomization-based nonparametric ANCOVA adjusted for baseline KFSS and stratified by randomization strata <ul style="list-style-type: none"> ○ With data imputation as described 	<ul style="list-style-type: none"> ● Change from Baseline in KFSS score at EOS using an ANCOVA adjusted for baseline KFSS and randomization strata ● Change from Baseline in KFSS score at all scheduled visits using a mixed model for repeated measures with baseline KFSS score, observed strata, treatment group, and study visit as covariates ● Change from Baseline in KFSS score at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline KFSS score, observed strata, treatment group, study visit, and study visit by treatment interaction as covariates

