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Statistical Analysis Plan

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenia Gravis

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Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN1210-MG-306

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenia Gravis

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1. APPROVAL SIGNATURES

PPD

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

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
AChR Ab	acetylcholine receptor antibody
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AZA	azathioprine
bpm	beats per minute
C5	complement component 5
CI	confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
cTTO	composite time trade-off
EC	exclusion criteria
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	European Quality of Life 5 dimension-5-level
FAS	full analysis set
FDA	Food and Drug Administration
gMG	generalized myasthenia gravis
HR	heart rate
IC	inclusion criteria
IST	immunosuppressive therapy
LLT	Lowest Level Term
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living
MGC	Myasthenia Gravis Composite scale
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-Intervention Status
MG-QOL15r	Revised 15 Component Myasthenia Gravis Quality of Life
MM	minimal manifestation
MMF	mycophenolate mofetil
MMRM	mixed-effect model for repeated measures
MNAR	missing not at random
Neuro-QOL	Neurological Quality of Life
oMG	ocular myasthenia gravis
OLE	Open-label Extension
OLES	Open-label Extension Set

Abbreviation or Acronym	Explanation
OLEES	Open-label Efficacy Extension Set
OR	Odds ratio
PY	patient years
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PKAS	PK analysis set
PPS	Per Protocol set
PTAE	pre-treatment adverse event
q8w	every 8 weeks
QMG	Quantitative Myasthenia Gravis score for disease severity
QoL	quality of life
QT	interval between the start of the Q-wave and the end of the T-wave in an ECG
QTc	corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	statistical analysis software®
SD	Standard deviation
SOC	System Organ Class
SS	Safety Set
TEAE	treatment-emergent adverse event
VAS	visual analogue scale
WHO-DD	World Health Organization Drug Dictionary

4. DESCRIPTION OF THE PROTOCOL

ALXN1210-MG-306 is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab for the treatment of adult patients with generalized myasthenia gravis (gMG). Approximately 160 eligible patients will be randomized 1:1 to 1 of 2 treatment groups: (1) ravulizumab infusion or (2) placebo infusion; randomization will be stratified by region (North America, Europe, Asia-Pacific, and Japan). There will be 3 periods in this study: a 4-week Screening Period, a 26-week Randomized-Controlled Period, and an Open-label Extension (OLE) Period of up to 2 years.

Patients being treated with an immunosuppressive therapy (IST) at the time of the Screening Visit may continue to receive ISTs throughout the Randomized-Controlled and OLE Periods. However, the dosage of IST must not be changed, and no new ISTs may be added during the Randomized-Controlled Period of the study, unless deemed by the Investigator to be medically necessary.

Throughout the study, rescue therapy (eg, high-dose corticosteroids, acute plasmapheresis/plasma exchange, or acute intravenous immunoglobulin) will be allowed if a patient experiences Clinical Deterioration, as defined by the study protocol. The rescue therapy for a particular patient will be at the discretion of the Investigator.

During the Randomized-Controlled Period, patients in the ravulizumab or placebo treatment groups will receive a weight-based loading dose of ravulizumab or placebo, respectively, on Day 1. At Week 2, patients will receive weight-based maintenance doses of ravulizumab or placebo, respectively, every 8 weeks (q8w) through the completion of the Randomized-Controlled Period.

After the 26-week Randomized-Controlled Period and assessments on Week 26 (Day 183), patients randomized to the placebo group will receive a blinded weight-based loading dose of ravulizumab and patients randomized to the ravulizumab group will receive a blinded flat dose of ravulizumab 900 mg to ensure maintenance of complete complement component (C5) inhibition until the next scheduled maintenance dose at Week 28 (Day 197). Starting at Week 28, all patients will begin open-label ravulizumab maintenance doses q8w.

The primary objective of this study is to assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile.

The secondary objectives of the study are the following:

- To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in the Quantitative Myasthenia Gravis (QMG) total score.
- To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in quality of life measures.
- To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on other efficacy endpoints.

4.1. Planned Analyses

A clinical study report (CSR) will be produced based on efficacy, safety, pharmacokinetic(s) (PK), pharmacodynamic(s) (PD), and immunogenicity data collected through the end of the 26-week Randomized-Controlled Period. For patients in the OLE at the time of database lock, long-term data will be included up to a data cutoff date which will occur when the last patient enrolled completes the Randomized-Controlled Period. Assessments to be included are: primary, and secondary endpoints, and clinical laboratory assessments up to Week 52 as well as adverse events (AEs), serious adverse events (SAEs), and concomitant medications up to the data cutoff. This SAP outlines only the analyses that are to be included in the CSR.

A final SAP/CSR to summarize long-term efficacy, safety, PK, PD, and immunogenicity parameters will be produced at study completion.

4.2. Changes From Analyses Specified in the Protocol

None.

4.3. Changes From Analyses Specified in the Previous Version of the SAP

Not applicable.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint(s)

The primary endpoint of the study is change from Baseline in MG-ADL total score at Week 26 of the Randomized-Controlled Period.

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of ADL in patients with myasthenia gravis (MG) (refer to Section 10.6 [Appendix 6] of the protocol). The 8 items of the MG-ADL questionnaire are derived from symptom-based components of the original 13-item QMG scale to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. In this functional status instrument, each response is graded 0 (normal) to 3 (most severe). The range of total MG-ADL score is between 0 to 24 (inclusive). Higher scores indicate worse symptoms. The recall period for MG-ADL is the preceding 7 days.

A 2-point reduction in MG-ADL total score is considered a clinically meaningful improvement (Muppidi, 2011). A ≥ 3-point improvement in MG-ADL total score from Baseline at Week 26 was selected as a robust clinically significant threshold for the secondary endpoint.

5.1.2. Secondary Endpoints

The secondary efficacy endpoints of the study (to be tested in a hierarchical manner) are:

1. Change from Baseline in QMG total score at Week 26.
2. Improvement of at least 5 points in the QMG total score from Baseline at Week 26.
3. Change from Baseline in the Revised 15 Component Myasthenia Gravis Quality of Life (MG-QOL15r) score at Week 26.
4. Change from Baseline in Neurological Quality of Life (Neuro-QOL) Fatigue score at Week 26.
5. Improvement of at least 3 points in the MG-ADL total score from Baseline at Week 26.

5.1.2.1. Quantitative Myasthenia Gravis Total Score

The QMG scoring system for disease severity provides an objective evaluation of muscle strength in MG based on quantitative testing of sentinel muscle groups. The scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item); each graded 0 to 3 (0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe) (refer to Section 10.7 [Appendix 7] of the protocol). The range of total QMG score is between 0 to 39 (inclusive), with higher scores indicating more severe disease. For patients taking cholinesterase inhibitors, the dose of the cholinesterase inhibitor will be withheld for at least 10 hours prior to the QMG evaluation.

A 3.5-point difference has been shown to correlate with clinically meaningful change (Zinman, 2007; Barth, 2011). A ≥ 5-point improvement in QMG total score from Baseline at Week 26 was selected as a robust clinically significant threshold for the secondary endpoint.

5.1.2.2. Revised Myasthenia Gravis Qualify of Life-15 Scale

The revised 15 Component Myasthenia Gravis Qualify of Life (MG-QOL15r) (refer to Section 10.10 [Appendix 10] of the protocol) is a health-related quality of life (QoL) evaluative instrument specific to patients with MG. The MG-QOL15r is designed to provide information about patients' perception of impairment and disability, determine the degree to which disease manifestations are tolerated, and to be administered and interpreted easily. The MG-QOL15r will be completed by the patient. The scoring system for each of the 15 items are: 0 = Not at all, 1 = Somewhat, and 2 = Very much. The MG-QOL15r total score ranges from 0 to 30 (inclusive). Higher scores indicate greater dissatisfaction with MG-related dysfunction.

5.1.2.3. Neuro-QOL Fatigue Scale

The Neuro-QOL Fatigue is a reliable and validated brief 19-item survey of fatigue, completed by the patient. The scoring system for each of the 19 items are: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always. The Neuro-QOL Fatigue total score ranges from 19 to 95 (inclusive). Higher scores indicate greater fatigue and greater impact of MG on activities (refer to Section 10.11 [Appendix 11] of the protocol).

5.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Change from Baseline in the Myasthenia Gravis Composite (MGC) score at Week 26.
- Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) at Week 26.
- Change from Baseline in European Quality of Life 5-dimension-5-level (EQ-5D-5L) at Week 26.
- Change from Baseline in MG-ADL subcomponent scores for the bulbar, limbs, respiratory, and ocular at Week 26.
- Change from Baseline in QMG subcomponent scores for the bulbar, limbs, respiratory, and ocular at Week 26.
- Incidence of hospitalizations/MG-related hospitalizations.
- Incidence of Clinical Deterioration/MG crisis.

5.1.3.1. Myasthenia Gravis Composite Scale

The Myasthenia Gravis Composite (MGC) scale is a validated assessment tool for measuring clinical status of patients with MG. The MGC assesses 10 important functional areas most frequently affected by MG and the scales are weighted for clinical significance that incorporates patient-reported outcomes (refer to Section 10.8 [Appendix 8] of the protocol). The range of total MGC score is 0 to 50 (inclusive), with lower scores indicating less disability and higher scores indicating greater disability. For patients taking cholinesterase inhibitors, the dose of the cholinesterase inhibitor will be withheld for at least 10 hours prior to the MGC evaluation.

5.1.3.2. Myasthenia Gravis Foundation of America Post-Intervention Status

The MG clinical state will be assessed using a modified version of the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) (Refer Section 10.13 [Appendix 13] of the protocol). Change in status categories of Improved, Unchanged, or Worse, as well as the minimal manifestation (MM) will be assessed by the Investigator or the same neurologist skilled in the evaluation of patients with MG throughout the study. The subscores of MM, ie, MM-0, MM-1, and MM-3, will not be used.

5.1.3.3. European Quality of Life 5-Dimension-5-Level

The EQ-5D-5L (refer to Section 10.9 [Appendix 9] of the protocol) is a self-assessed, health-related QoL questionnaire. It is a measure of health status consisting of two parts. The first part assesses health in five dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each level is rated on a scale that describes the degree of problems in that area (ie, I have no problems walking about, slight problems walking, moderate problems walking, severe problems walking, or unable to walk). This part of the EQ-5D-5L questionnaire provides a descriptive profile that can be used to generate a health state profile. For example, a patient in health state 12345 would have no problems with mobility, slight problems with self-care (washing or dressing), moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. The EQ-5D-5L health states can be represented by a single summary number (index value), which reflects how good or bad a health state is according to the preferences of the general population of a country/region. A health state index score will be calculated using US specific value set (Pickard, 2019). Refer to Section 9.4.3 for additional description and method of calculation.

The second part of the questionnaire consists of a visual analogue scale (VAS) on which the patient rates their perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health).

5.1.3.4. Myasthenia Gravis-Activities of Daily Living Subcomponent Scores

MG-ADL subcomponent scores for bulbar, limb, respiratory, and ocular function are derived from the MG-ADL items. Refer to Section 9.4.1 for the scoring method.

5.1.3.5. Quantitative Myasthenia Gravis Subcomponent Scores

Quantitative Myasthenia Gravis subcomponent scores for bulbar, limb, respiratory, and ocular muscle strength are derived from the QMG items. Refer to Section 9.4.2 for the scoring method.

5.1.3.6. Clinical Deterioration

Clinical Deterioration is defined as any of the following:

1. Patients who experience an MG Crisis, which is defined as weakness from MG that is severe enough to necessitate intubation or to delay extubation following surgery. The respiratory failure is due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness often accompanies the respiratory muscle weakness, or may be the predominant feature in some patients; or,

2. Change to a score of 3 or a 2-point worsening from Baseline on any 1 of the individual MG-ADL items other than double vision or eyelid droop, that in the investigator's assessment is associated with significant symptomatic worsening; or,
3. Administration of rescue therapy to a patient whose, in the opinion of the Investigator or Investigator-designated physician, health would be in jeopardy, if rescue therapy were not given (eg, emergent situations).

5.2. Safety

The safety and tolerability of ravulizumab compared with placebo will be evaluated by physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory assessments, the Columbia-Suicide Severity Rating Scale (C-SSRS) and incidence of AEs and SAEs.

5.2.1. Adverse Events (AEs)

An AE is defined as untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The severity of AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. Each CTCAE term is a Lowest Level Term (LLT) per Medical Dictionary for Regulatory Activities (MedDRA). Each LLT will be coded to a MedDRA Preferred Term:

- Grade 1: Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)
- Grade 2: Moderate (minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)
- Grade 3: Severe (severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL)
- Grade 4: Life-threatening (urgent intervention indicated)
- Grade 5: Fatal (death related to AE)

Adverse events are further defined in Protocol Section 10.3.

5.2.1.1. Adverse Events of Special Interest

Meningococcal infections will be collected as adverse events of special interest (AESI) for this Study.

5.2.2. Vital Signs and Pulse Oximetry

Vital signs and pulse oximetry will be measured at every visit and will include assessments of systolic and diastolic blood pressure (mmHg), temperature (°C or °F), oxygen saturation, and heart rate (HR) in beats per minute (bpm).

5.2.3. Laboratory Assessments

A central laboratory will be used to evaluate all laboratory assessments. Samples for analysis of serum pregnancy, hematology, clinical chemistry, coagulation, and urinalysis will be collected (Refer Appendix 2 of the protocol for a listing of all protocol required safety laboratory parameters).

5.2.4. Electrocardiograms (ECGs)

A single 12-lead ECG will be used to obtain HR and measures of PR, QRS, QT, and corrected QT (QTc) intervals. The QT interval will be corrected for HR using Fridericia's formula (QTcF).

5.2.5. Physical Examination

A physical examination will be performed assessing general appearance; skin; head, ear, eye, nose, throat; neck; lymph node; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal. An abbreviated physical examination will be performed consisting of a body system relevant examination based upon Investigator judgment and patient symptoms.

5.2.6. Suicidal Risk Monitoring

The Columbia-Suicide Severity Rating Scale (refer to Section 10.14 [Appendix 14] and Section 10.15 [Appendix 15] of the protocol) is a validated questionnaire used extensively across primary care, clinical practice, surveillance, research, and institutional settings to assess suicidal ideation and behavior. The C-SSRS will be administered and assessed at screening for both lifetime and past 1 year (12 months) and at study visits as outlined in the protocol schedule of assessments.

5.3. Pharmacokinetic/Pharmacodynamic/Immunogenicity

Assessments for PK/PD/immunogenicity are as follows:

- Change in serum ravulizumab concentration over time.
- Change in serum free C5 concentration over time.
- Incidence of antidrug antibodies (ADAs) over time.

5.4. Exploratory Biomarkers

Blood samples for acetylcholine receptor antibody (AChR Ab) will be collected at specified time points. The AChR Ab analysis will be conducted at a central laboratory.

Remaining samples from PK, PD, immunogenicity, and biomarker testing may be stored for future biomarker research. Analyses may be performed on biomarker variants thought to play a role in gMG activity/progression or treatment response to ravulizumab. These samples may also be used to develop methods, assays, prognostics, and/or companion diagnostics related to the study drug target, disease process, pathways associated with disease state, and/or mechanism of action of the study drug.

Samples may be stored for a maximum duration according to local regulations following the last patient's last visit for the study, at a facility selected by the sponsor, to enable further analyses.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

6.1. Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all randomized patients who received at least 1 dose of study drug. The primary population for assessment of efficacy during the Randomized-Controlled Period is the FAS. Patients will be compared for efficacy according to the treatment they were randomized to receive, regardless of the treatment received.

6.2. Per Protocol Set (PPS)

The Per Protocol Set (PPS) will consist of a subset of the FAS without any major protocol deviations during the Randomized-Controlled Period. The PPS will include all patients who meet all the following criteria:

- Missed 0 doses (scheduled and supplemental) of study drug during the 26 weeks of Randomized-Controlled Period
- Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy. Specifically,
    - Met following inclusion criteria (IC)
        - IC#2: Diagnosed with MG at least 6 months prior to the date of the Screening Visit
        - IC#3: Confirmed MG diagnosis as required per protocol
        - IC#4: MGFA Class II to IV
        - IC#6: Stable dose of MG treatment received per time periods specified by the protocol
    - Did not meet exclusion criteria (EC):
        - EC#1: Any active or untreated thymoma or history of thymic carcinoma or thymic malignancy
        - EC#2: History of thymectomy, thymomectomy, or any thymic surgery within the 12 months prior to screening
        - EC#8: Clinical features consistent with MG crisis/exacerbation or Clinical Deterioration during the screening period
        - EC#11: Prohibited medications within the time period specified in exclusion #11
        - EC#12: Previous treatment with a complement inhibitor
        - EC#13: Participation in another interventional treatment study or use of any experimental therapy within the time specified in exclusion #13

- Did not receive incorrect randomized treatment (ie, all patients who received their correctly assigned treatment)
- Did not take a cholinesterase inhibitor within 10 hours prior to the QMG and MGC tests at baseline and Week 26.
- Did not receive rescue medication on Day 1
- Did not have changes in background MG medication in accordance with Section 6.5.1 of the protocol
- Did not have unblinding of treatment allocation by the Investigator

Determination of any other applicable major protocol deviations potentially affecting efficacy will be made prior to database lock and study unblinding.

The primary and secondary endpoint analyses for the Randomized-Controlled Period will be performed on the PPS.

6.3. Safety Set

The Safety Set (SS) will consist of all patients who received at least 1 dose of study drug (ravulizumab or placebo). Patients will be compared for safety according to the treatment they actually received. For a patient to be analyzed according to the treatment they actually received and not according to the randomization schedule, they would have to receive that treatment for the entire duration of the Randomized-Controlled Period. Safety analyses for the Randomized-Controlled Period will be performed on the SS.

6.4. Other Sets

The randomized set will consist of all randomized patients grouped by randomized treatment group.

The PK Analysis Set (PKAS) will consist of all ravulizumab treated patients with at least 1 post-baseline PK concentration available.

The Ravulizumab Treated Set will consist of all patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the OLE.

The Open-label Extension Set (OLES) will consist of all patients who received at least 1 dose of ravulizumab starting from Week 26 onward and prior to the data cutoff date.

The Open-label Efficacy Extension Set (OLEES) will consist of a subset of the OLES who have completed Week 52 study visit or withdrew from the study prior to Week 52.

7. STATISTICAL ANALYSIS

All data collected in this study will be presented using summary tables, figures, and data listings. Summaries for the Randomized-Controlled Period will be presented by treatment group (ie, "Ravulizumab" and "Placebo") and overall. Additionally, efficacy and safety summaries for patients in the Ravulizumab Treatment Period up to the data cutoff date will be presented as detailed in the following sections by treatment sequence (ie, "Ravulizumab to Ravulizumab" and "Placebo to Ravulizumab"). For continuous variables, summary statistics will include number of observations (n), mean, SD, median, minimum, and maximum values. Frequencies and percentages will be calculated for categorical variables. For table and figure summaries, all data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report forms (eCRF) even if the assessment is outside of visit window.

Unless otherwise specified, data collected at an unscheduled visit will be included in by patient listings, but no assignment of the scheduled visit will be made for the purposes of summary tabulations. However, unscheduled study visits will be used in the calculation of baseline values.

All analyses will be performed using Statistical Analysis Software® (SAS®) release, version 4.7.3 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software.

The following table displays the analysis periods utilized in this SAP.

Table 2: Analysis Periods From Day 1 Through the Data Cutoff Date

Period	Time Window	Study Assessment	Exposure to Study Drug in Treatment Group	
			Ravulizumab to Ravulizumab Group	**Placebo to Ravulizumab Group**
1	First study drug administration until the Week 26 dose	Randomized-Controlled Period	Ravulizumab	Placebo
2	On/after the ravulizumab dose date/time at Week 26 to cutoff date	Open-label Extension Period	Ravulizumab	Ravulizumab
3	First ravulizumab infusion to cutoff date	Ravulizumab Treatment Period	Ravulizumab	Ravulizumab

7.1. Study Patients

7.1.1. Disposition of Patients

A summary of patient disposition will be presented by treatment group and overall and will include a summary of the number and percentage of patients screened, screen failed, randomized, and treated. The number and percentage of patients who completed the study through the end of the Randomized-Controlled Period or discontinued/withdrew from the study in the Randomized-Controlled Period, along with primary reason for discontinuation/withdrawal, will be summarized.

A table summarizing the above information by the stratification factor 'region' will be provided. The regions will be: North America, Europe, Asia-Pacific, and Japan.

The number and percentage of patients in each analysis set will be tabulated. The number and percentage of patients not meeting specific inclusion or exclusion criterion will be summarized.

An additional summary of patient disposition for patients who entered the OLE Period prior to the data cutoff date will be presented by treatment sequence and overall. This summary will be performed on the OLES and will include the number and percentage of patients who entered the OLE Period and are continuing at the time of the data cutoff. The number and percentage of patients who discontinued/withdrew from the study along with the reasons for discontinuation from OLE period will be summarized. A similar summary will be performed for the OLEES.

A listing of disposition data by patient will be provided. A listing of patients who did not meet the inclusion criteria or met the exclusion criteria will also be provided.

7.1.2. Protocol Deviations

All important protocol deviations will be listed for all patients in the FAS. The number and percentage of patients with important protocol deviations will be summarized by treatment group and overall using the FAS. A by-patient listing of important protocol deviations will be provided.

7.1.3. Demographics, Disease Characteristics, and History

All demographic and baseline characteristics information will be summarized using the FAS, SS, OLES, and OLEES. No statistical test will be performed for homogeneity among treatment groups. Summary statistics will be presented by treatment group and overall. Demographic and baseline characteristics including MG disease characteristics will also be summarized by treatment group and region. By-patient listings of demographic information, MG disease characteristics, MG medical history, and medical/surgical history will be provided.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Sex
- Race and Ethnicity utilizing designations for race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Other) and two designations for ethnicity (Hispanic or Latino; and Not Hispanic or Latino) as characterized in Section IV of the Food and Drug Administration (FDA) guidance titled ‘Collection of Race and ethnicity data in clinical trials’
- Age (years) at First Infusion: descriptive statistics (n, mean, SD, minimum, and maximum) and frequency of patients in the following categories: ≤65 years, > 65 years
- Baseline Weight: descriptive statistics (n, mean, median, SD, minimum, and maximum) and frequency of patients in the following categories: ≥ 40 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg
- Baseline Height
- Baseline Body Mass Index
- Region randomization stratification

7.1.3.2. Disease Characteristics

The following disease characteristics will be summarized.

- Age (years) at MG diagnosis
- Years from MG diagnosis to informed consent
- Type of first MG clinical presentation: ocular MG (oMG) or generalized MG (gMG)
- Time to gMG, if the first presentation was oMG (months)
- Maximum MGFA clinical classification prior to screening
- Baseline MGFA clinical classification
- Ventilator support at any time prior to Screening
- History of MG exacerbation and MG crisis (number of patients with exacerbations or crisis, and total number of exacerbations or crisis overall and per 100 patient-years) and whether any MG medication was taken.
- All cause hospitalization and hospitalizations due to MG in the 2 years prior to screening and per 100 patient-years; duration and need for ventilator support during the hospitalization.

7.1.3.3. Medical/Surgical History and Baseline Physical Examination

Medical history will be classified by System Organ Class (SOC) and Preferred Term using the latest available version of MedDRA and will be reported by treatment group and overall for the SS. Likewise, baseline physical examination information will be summarized for the SS.

7.1.4. Prior and Concomitant Medications / Therapies

Prior and concomitant MG and non-MG medications during the Randomized-Controlled Period as well as all meningococcal vaccinations, will be summarized separately using the SS. In addition, concomitant MG and non-MG medications during the OLE Period will be summarized using the OLES, and OLEES. Prior non-MG medications include all medications taken within 28 days prior to informed consent and up to the first dose of study drug administration. Prior MG medications include all medications taken within 2 years prior to informed consent and up to the first dose of study drug administration. The MG medications taken more than 2 years prior to informed consent will be presented in by-patient listings along with all other MG medications. Prior meningococcal vaccinations include all vaccinations administered within 3 years of the first dose study drug administration. Concomitant medications during the Randomized-Controlled Period are defined as medications received by the patients on/after first study infusion through Week 26 (ie, prior to the first study infusion in the OLE Period). Concomitant medications during the OLE Period are defined as medications received by the patients on/after first study infusion in the OLE Period.

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version in use by Alexion at the time of the analysis. Medication summaries by treatment group and overall (ie, number [%] of patients using prior and concomitant medications), will be presented by WHO-DRUG Anatomical Therapeutic Chemical (ATC) Level 3 and by WHO-DRUG generic name. Medications will be ordered by most prevalent WHO ATC based on total

patients reporting any medication in that drug class. Then, by most prevalent generic name based on total patients reporting any medication in that drug class/generic name. Similar summaries will be provided for patients experiencing clinical deterioration.

Concomitant non-MG medications used by 5% of patients or more will be provided.

Immunosuppressive therapy use (0, 1, 2, etc.) within 2 years prior to informed consent and up to the first dose of study drug administration as well as at baseline will be presented by treatment group. Any IST dose at baseline will be presented by treatment group for the following ISTs: Corticosteroid, azathioprine (AZA), and mycophenolate mofetil (MMF).

Changes in concomitant MG medications during the Randomized-Controlled Period as well as the reason, will be summarized by treatment group and for patients experiencing clinical deterioration. Concomitant prohibited medication summaries by treatment group will be presented.

The MG therapy status during the Randomized-Controlled Period will be summarized by treatment group and visit. Similar summaries will be provided for patients experiencing clinical deterioration during the Randomized-Controlled Period.

Non-pharmacologic therapies and procedures will be classified by SOC and Preferred Term and will be reported by treatment group and overall for the SS.

7.2. Efficacy Analyses

The FAS will be the primary population used for the analyses of all efficacy endpoints for the Randomized-Controlled Period. Sensitivity analyses of the primary and secondary efficacy endpoints will also be conducted using the PPS. The Randomized-Controlled Period Baseline is defined as the last available assessment value prior to first study drug infusion. In general, the baseline assessment will be the Day 1 assessment. For QMG and MGC, in the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG and MGC tests, the Screening Visit assessment will be used as Baseline. If cholinesterase inhibitor was not withheld for at least 10 hours for these visits, the Day 1 assessment will be used as Baseline.

Efficacy analyses of MG-ADL and QMG total scores will be performed on the OLEES as specified in Section 7.2.4. The OLE Baseline is defined as the last available assessment prior to first study drug administered in the OLE Period. In general, the OLE Baseline assessment will be the Day 183 assessment. In the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG test, the prior visit assessment will be used as baseline.

7.2.1. Primary Analysis

The primary endpoint is change from Baseline in MG-ADL total score at Week 26 of the Randomized-Controlled Period.

Change from Baseline in MG-ADL total score at Week 26 will be analyzed using a mixed-effect model for repeated measures (MMRM; [Mallinckrodt 2001, 2004]). The model will include the MG-ADL change from Baseline score at each prespecified time point (Weeks 1, 2, 4, 10, 12, 18, and 26) as the response variable, fixed categorical effects of treatment, study visit and treatment-by-study visit interaction, the randomization stratification variable region; as well as fixed covariate of baseline MG-ADL total score. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each patient. 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: first order autoregressive, compound symmetry, and Toeplitz method. A difference in treatment effect between the ravulizumab and placebo treatment groups along with a 2-sided 95% confidence interval (CI) and p-value will be calculated. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. Missing data will not be imputed for the primary analysis. Similar summaries will be presented for the other Randomized-Controlled Period study visits.

Absolute levels and the change in MG-ADL total score will be summarized by treatment group and visit.

7.2.1.1. Handling of Dropouts or Missing Data

Missing data for primary, secondary, and tertiary endpoints at Week 26 analyses will be handled as indicated for the specific analyses.

Baseline is defined as the last available assessment prior to first study drug infusion for all patients. If the Day 1 assessment is missing, the last Screening assessment will be used as the Baseline assessment.

7.2.1.2. Subgroup Analysis

Summaries of primary and secondary endpoints during the Randomized-Controlled Period will be produced for the following subgroups by treatment group: Region, gender, race, age at first study drug infusion (18 to 65 years and > 65 years), IST use at baseline (corticosteroid, corticosteroid + IST, none), years from diagnosis to informed consent (≤ median, >median), MGFA (II, III, and IV), and baseline body weight categories (≥ 40 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg). If the number of patients for a given subgroup category is less than 10, then the category maybe collapsed with another category.

7.2.1.3. Multicenter Studies

Based on the small number of randomized patients expected at each study site in this multinational study, center will not be used as an explanatory factor in the efficacy analyses.

7.2.1.4. Hypothesis Testing and Significance Level

Primary Hypothesis

The primary hypothesis for this study is that ravulizumab is superior to placebo in improving MG-ADL total score at Week 26.

The treatment effect based on the primary endpoint will be estimated by the difference in means between the ravulizumab group and the placebo group in the change from Baseline in MG-ADL total score at Week 26 irrespective of rescue therapy. A lower value of the corresponding estimate will indicate a beneficial treatment effect.

Secondary Hypotheses

The following secondary hypotheses will be included in step-wise multiplicity adjustment (provided the null hypothesis for primary endpoint is rejected)

1. Ravulizumab is superior to placebo in improvement of QMG total score at Week 26.
2. Ravulizumab is superior to placebo in QMG 5-point response (≥ 5-point improvement from baseline in QMG total score) at Week 26.
3. Ravulizumab is superior to placebo in improvement of the MG-QOL15r total score at Week 26.
4. Ravulizumab is superior to placebo in improvement of Neuro-QOL Fatigue total score at Week 26.
5. Ravulizumab is superior to placebo in MG-ADL 3-point response (≥ 3-point improvement from baseline in MG-ADL total score) at Week 26.

The study is designed to control the overall 2-sided Type I error of $\alpha = 0.05$. The primary null hypothesis will be tested first at $\alpha=0.05$. If statistically significant, 5 secondary hypotheses will be tested for superiority using a closed-testing procedure with the following order:

1. Change from Baseline in QMG total score at Week 26
2. Proportion of patients with improvement of at least 5 points in the QMG total score from baseline at Week 26
3. Change from Baseline in MG-QOL15r at Week 26

4. Change from Baseline in Neuro-QOL Fatigue at Week 26

5. Proportion of patients with improvement of at least 3 points in the MG-ADL total score from baseline at Week 26

The testing will proceed from (#1) to (#5), and if statistical significance is not achieved (p-value >0.05), then subsequent endpoints will not be considered statistically significant. Estimates and CIs will be computed for all these secondary endpoints regardless of the outcome of the closed testing procedure.

Under this prespecified closed testing procedure, no adjustment of the Type I error is required.

Hypotheses Related to Exploratory Efficacy Objectives

The exploratory hypotheses are as follows:

1. Ravulizumab is superior to placebo in improvement of MGC total score at Week 26.

2. Ravulizumab is superior to placebo in MGFA-PIS at Week 26.

3. Ravulizumab is superior to placebo in improvement of EQ-5D-5L index score at Week 26.

4. Ravulizumab is superior to placebo in improvement of MG-ADL subcomponent scores (bulbar, limbs, respiratory, and ocular) at Week 26.

5. Ravulizumab is superior to placebo in improvement of QMG subcomponent scores (bulbar, limbs, respiratory, and ocular) at Week 26.

6. Ravulizumab is superior to placebo in reducing incidence of hospitalizations/MG-related hospitalizations.

7. Ravulizumab is superior to placebo in reducing incidence of Clinical Deterioration/MG crisis.

7.2.1.5. Sensitivity Analyses

The following sensitivity analyses will be produced for the primary endpoint of change in MG-ADL to Week 26:

- Placebo-based sensitivity analysis:

  The placebo-based sensitivity analysis will consider the missing not at random (MNAR) mechanism for the missing data, where it will be assumed that unobserved outcomes for patients who discontinue early from ravulizumab will follow the trajectory of outcomes similar to the one in the placebo group, taking into account observed values prior to discontinuation (Ratitch, 2014). Patients discontinuing early from placebo will be assumed to have unobserved outcomes similar to placebo patients who remain on their randomized treatment. The assumption that the efficacy profiles of dropouts after discontinuation of ravulizumab are similar to those of patients in the placebo group provides an estimate of efficacy attributable to patients in the ravulizumab group if received through the time point of interest, while limiting efficacy after early discontinuation to that of the placebo group. Refer to Section 9.4.5 for additional description.

- Tipping point sensitivity analysis:

  An additional sensitivity analysis will be performed based on the delta-adjusted stress testing method (tipping point analysis). This approach assumes that patients who discontinue from ravulizumab treatment experience worsening, defined by a prespecified adjustment (delta) in the primary efficacy endpoint compared with the observed efficacy score of patients that continue the study to next visit (Ratitch, 2014). Since a negative change in MG-ADL total score indicates improvement, the prespecified value of delta will be a non-negative quantity. For each value of delta, the treatment effect will be determined, and the value of delta for which the nominal 2-sided p-value crosses 0.05, will be considered as the 'tipping point' in the sense that the positive conclusion drawn from the primary analysis is reversed when patients who drop out are assumed to experience this fixed worsening after the discontinuation visit. After such a tipping point is determined, clinical judgment will be applied as to the plausibility of the assumptions underlying this tipping point. This methodology is expected to inform what it would take to overturn study conclusions based on varying assumptions about missing data. A value of delta as zero will be considered equivalent to the primary analysis. Refer to Section 9.4.6 for additional description.

- The primary endpoint analyses ignoring the randomization strata will be performed.
- The primary endpoint analyses will be performed including rescue received during the Randomized-Controlled Period (Yes/No) in the model.

7.2.2. Secondary Analyses

Secondary endpoints will be tested in a hierarchical manner for superiority following the order described in Section 7.2.1.4

Point estimates and CIs will be computed for all secondary efficacy endpoints for descriptive purposes, regardless of whether a lack of significance of a test precludes assessment of subsequent tests.

Change from Baseline to Week 26 in QMG total score, MG-QOL15r score, and Neuro-QOL Fatigue score will be analyzed using MMRM as described for the primary endpoint in Section 7.2.1.

The secondary endpoints of at least 3-point improvement in MG-ADL from baseline to Week 26 irrespective of rescue therapy (and at least 5-point improvement in QMG total score) will be analyzed using a mixed effect repeated measures model. The MG-ADL 3-point (and QMG 5-point) response at post dosing visits during the Randomized-Controlled Period will be used as the response variable and fixed categorical effects of treatment, study visit and treatment-by-study visit interaction, and the randomization stratification variable region, as well as fixed covariate of baseline MG-ADL total score as a continuous variable (and QMG total score) will be included in the model as explanatory variables. The treatment effect will be evaluated via contrast for the treatment-by-visit term at Week 26. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each patient. If this analysis fails to converge, a first-order autoregressive structure in which the highest correlation assumed between visits that are closest in time will be used. Odds ratios (ORs) of

treatment effect (ravulizumab group compared to placebo) along with a 2-sided 95% CIs and p-values will be calculated. An estimate of OR > 1 will indicate a beneficial treatment effect. Similar summaries will be presented for the other Randomized-Controlled Period study visits and for various point reductions in MG-ADL (eg, at least 2, 3, etc.) and in QMG (eg, at least 3, 4, etc.).

Additional summaries of the proportion of patients with various point reductions in the MG-ADL total score from baseline to Week 26 irrespective of rescue therapy will be produced by treatment group. Similarly, summaries of the proportion of patients with various point reductions in the QMG total score from baseline to Week 26 will be produced by treatment group. These summaries will additionally be generated for patients who received any rescue therapy during the Randomized-Controlled Period, those who did not receive any rescue therapy, and classifying patients who received rescue as non-responders from the time rescue therapy was administered.

7.2.3. Exploratory Analyses

Absolute scores and changes from Baseline in MGC, EQ-5D-5L VAS and health state index scores, and MG-ADL and QMG subcomponent scores, will be summarized by treatment group and visit. The MG-ADL and QMG subcomponent scores will be analyzed for all patients and for patients with abnormal subcomponent scores at baseline. The same approach using MMRM as described for the primary analysis of MG-ADL will be employed.

A summary of the MGFA-PIS will be presented by treatment group and visit showing the number and percentage of patients in each category (ie, improved and achieved minimal manifestation, improved and did not achieve minimal manifestation, unchanged, and worsened). The treatment effect corresponding to the MGFA-PIS endpoint will be estimated by the proportional OR of the cumulative proportions over the ordinal categories (starting from the best outcome) of this endpoint in the ravulizumab group compared with the placebo group at Week 26, irrespective of rescue therapy. An estimate of OR > 1 will indicate a beneficial treatment effect. A logistic regression of the cumulative odds (cumulated over the categories starting from best outcome) will be performed using treatment as fixed categorical effect and adjusting for region. Note: the above categories might be collapsed if the model does not converge. If the assumption of proportional odds is rejected, a different approach will be considered.

The number of patients hospitalized, reason for admission, and duration will be summarized by treatment group. Hospitalization/MG-related hospitalizations (yes/no) maybe be analyzed using a logistic regression model with treatment group and the randomization stratification variable region, provided there are enough hospitalizations/MG-related hospitalizations to perform the analysis. The treatment effect will be estimated by the OR in the ravulizumab group compared with the placebo group. An estimate of OR < 1 will indicate a beneficial treatment effect. Additionally, the number of hospitalizations/MG-related hospitalization (0, 1, 2, and ≥ 3) irrespective of rescue therapy will be summarized. The incidence of hospitalization/MG-related hospitalization per 100-patient years (PY) of exposure irrespective of rescue therapy, may be analyzed using a Poisson regression repeated measures model if there are enough hospitalizations/MG-related hospitalization to perform this analysis. The model will include the following terms: treatment group and the randomization stratification variable region. The log of

time in the study will be used as the offset variable. The treatment effect will be estimated by the Incidence rate ratio in the ravulizumab group compared to the placebo group.

The number of patients with clinical deterioration/MG crisis over 26 weeks irrespective of rescue therapy, will be summarized by treatment group. The same approaches as described for hospitalization/MG-related hospitalization will be employed for clinical deterioration/MG crisis.

The number of patients admitted to a rehabilitation center or hospice and duration during the Randomized-Controlled Period will be summarized by treatment group.

7.2.4. Other Efficacy Analyses

The following describes the analyses to be performed for patients in the OLEES.

Change from Randomized-Controlled Period Baseline in MG-ADL total score through Week 52 for patients in the "Ravulizumab to Ravulizumab" will be performed on the OLEES and analyzed using MMRM. The model will include MG-ADL total score change from Baseline as the response variable, fixed categorical effects of study visit and the randomization stratification variable region; as well as fixed covariate of baseline MG-ADL total score. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each patient. 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: first order autoregressive, compound symmetry, and Toeplitz method. A 2-sided 95% CI will be calculated. Similarly, change from the OLE Period Baseline in MG-ADL total score through Week 52 will be performed on the OLEES and analyzed using MMRM for each treatment sequence. A similar analysis will be conducted for the other secondary endpoints QMG total score, MG-QOL15r, and Neuro-QOL Fatigue score.

Absolute levels and change from Randomized-Controlled Period Baseline and OLE Period Baseline in MG-ADL and QMG total scores will be summarized by visit for each treatment sequence.

The proportion of patients with various point reductions (eg at least 2, 3, etc.) in the MG-ADL total score from Randomized-Controlled Period Baseline through Week 52 for patients in the "Ravulizumab to Ravulizumab" arm will be produced. Two-sided 95% CIs will be calculated. Similarly, the proportion of patients with various point reductions in the MG-ADL total score from the OLE Period Baseline through Week 52 will be produced by treatment sequence. Similar summaries will be provided for QMG with various point reductions (eg, at least 3, 4, etc.).

7.2.5. Pharmacokinetic and Pharmacodynamic Analyses

Graphs of mean serum concentration-time profiles during the Randomized-Controlled Period will be constructed. Graphs of serum concentration-time profiles for individual patients may also be provided. Descriptive statistics will be calculated for serum concentration data at each sampling time during the Randomized-Controlled Period, as appropriate.

Pharmacodynamic analyses during the Randomized-Controlled Period will be performed for all patients who receive at least 1 dose of ravulizumab and who have evaluable PD data.

Descriptive statistics will be presented for all ravulizumab PD endpoints at each sampling time during the Randomized-Controlled Period. The PD effects of ravulizumab administered intravenously will be evaluated by assessing the absolute values, changes and percentage changes from baseline in free C5 serum concentrations over time, as appropriate.

7.2.6. Exploratory Biomarker Analyses

Exploratory biomarker analyses will be included in a separate standalone report. A listing of AChR Ab will be provided.

7.3. Safety Analyses

All safety analysis through the Randomized-Controlled Period will be conducted on the SS. All safety analyses for patients during the Ravulizumab Treated Period will be conducted on the ravulizumab treated set. Baseline is defined as the last available assessment prior to first study drug infusion.

7.3.1. Study Duration, Treatment Compliance, and Exposure

Summary statistics (mean, standard deviation [SD], median, minimum, and maximum) through the Randomized-Controlled Period will be produced by treatment group for the following using the FAS and SS:

- Duration of study participation calculated as the time in days from the signing of informed consent until the date of completion/discontinuation (or death) from the Randomized-Controlled Period/Week 26 (ie, study duration = date of completion of Randomized-Controlled Period/discontinuation [or death]-date of informed consent + 1)
- Total time on study treatment (days) calculated as the time in days from first study drug infusion date until the date of completion/discontinuation (or death) from the Randomized-Controlled Period (ie, treatment duration = date of completion of Randomized-Controlled Period /discontinuation [or death] - first study drug infusion date + 1).
- Total dose administered and total infusion volume
- Number of infusions
- Number of loading doses and maintenance doses per patient
- Number of supplemental doses per patient
- Total number of patients with an infusion interruption and total number of infusions interrupted. Similar summaries of infusion interruptions will be provided for loading, maintenance, and supplemental infusions.
- Total number of patients with an infusion interruption due to an AE and total number of infusions interrupted. Similar summaries of infusion interruptions will be provided for loading, maintenance, and supplemental infusions.

The frequency and percentage of patients who had a percentage of drug compliance range by increments of 10% (ie, ≥ 90% to ≤ 100%, ≥ 80% to < 90%, etc) during the Randomized-Controlled-Period will also be included. This will be calculated as follows:

Percent compliance = Total number of infusions taken from Day 1 to end of Randomized-Controlled Period (excluding Day 183 infusion) / Total number of expected infusions to end of Randomized-Controlled Period (excluding Day 183 infusion)

Additionally, the following summaries by treatment sequence will be presented for patients in Ravulizumab Treatment Period using the ravulizumab treated set. The exposure to placebo will not be re-summarized. Only exposure to ravulizumab up to data cutoff date will be summarized:

- Duration of study participation calculated as the time in days from the signing of informed consent until the date of data cutoff date/discontinuation (or death) from the OLE period (ie, study duration = date of data cutoff date/discontinuation [or death] -date of informed consent + 1)
- Total time on ravulizumab (days) calculated as the time in days from first ravulizumab infusion date until data cutoff date/discontinuation (or death) (ie, treatment duration = data cutoff date/discontinuation - first ravulizumab infusion date + 1).
- Total patient-years of exposure (years) to ravulizumab
- Number of ravulizumab infusions from first ravulizumab infusion to data cutoff date
- Total number of patients with ravulizumab infusion interruption from first ravulizumab infusion to data cutoff date as well as total number of ravulizumab infusions interrupted.
- Total number of patients with ravulizumab infusion interruption due to an AE from first ravulizumab infusion to data cutoff date as well as total number of ravulizumab infusions interrupted.

The frequency and percentage of patients who had a percentage of drug compliance range by increments of 10% (ie, ≥ 90% to ≤ 100%, ≥ 80% to < 90%, etc) through data cutoff will also be included. This will be calculated as follows:

Percent compliance = Total number of ravulizumab infusions taken from first ravulizumab infusion to data cutoff date / Total number of expected ravulizumab infusions to data cutoff date

By-patient listings will be produced for study duration, treatment compliance, and exposure.

7.3.2. Adverse Events (AEs)

Adverse Events through the Randomized-Controlled Period will be classified by SOC and Preferred Term using the latest available version of MedDRA and will be reported by treatment group and overall. The AEs will be determined as occurring prior to treatment (pre-treatment) or as on or after first treatment (treatment-emergent) as described in Section 9.3. Analyses of pre-treatment adverse events (PTAEs) and treatment-emergent adverse events (TEAEs) through the Randomized-Controlled Period (Week 26/Day 183) will be tabulated and presented separately. Patients having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity/relationship tables, the patient's highest grade/most related event within a category will be counted. Percentages will be based on the number of treated patients in the SS within a treatment group and overall. Tables will be sorted

by descending frequency of SOC and by descending frequency of Preferred Term within SOC based on the ravulizumab arm. The rate of TEAE adjusted by patient-year (PY) of exposure, defined in Section 9.3 will be displayed together with the number of events.

All TEAEs during the Ravulizumab Treatment Period will be tabulated and presented by treatment sequence and overall using the ravulizumab treated set. Percentages will be based on the number of treated patients in the ravulizumab treated set within a treatment sequence and overall.

Listings will be provided for all TEAEs and PTAEs for the SS.

AEs will include the displays described in the following sub-sections.

7.3.2.1. Overall Summary of Adverse Events

Overall summary tables of TEAEs during the Randomized-Controlled Period and for patients in the Ravulizumab Treatment period will be presented using summary statistics (n, %). The number of events and rate per 100 PY (n, rate) and number of patients with events (n, %) will be displayed for the following events subcategories:

- Total number of TEAEs and patients with TEAEs
- Related TEAEs
- Not related TEAEs
- Grade 1 TEAEs
- Grade 2 TEAEs
- Grade 3 TEAEs
- Grade 4 TEAEs
- Grade 5 TEAEs

The number and percentage of patients who have any TEAE leading to study treatment discontinuation or who died on study will be presented.

These statistics will be prepared separately for SAEs with the exception of severity grading. Additional summary tables stratifying AEs occurring throughout the Randomized-Controlled Period by gender, race, region, age at first study drug infusion (18 to 65 years and > 65 years), IST use at baseline (corticosteroid, corticosteroid + IST, none), MGFA (II, III, and IV), and baseline body weight categories (≥ 40 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg) will be provided.

For patients in the ravulizumab treated set, the above overall summaries of TEAEs will be presented by treatment sequence and time intervals during the Ravulizumab Treatment Period (0 to 6 months (ie, first ravulizumab dose to Week 26 ravulizumab dose), >6 to 12 months; > 12 to 18 months, and 0 to cutoff).

7.3.2.2. Adverse Events and Serious Adverse Events by System Organ Class and Preferred Term

The number of AEs and the number and percentage of patients with events during the Randomized-Controlled Period will be presented by SOC and Preferred Term. Patients are counted once in each SOC and Preferred Term. Percentages will be based on the total number of treated patients in the treatment group. Additional summary tables of TEAEs by SOC and Preferred Term occurring in 2% or more of patients as well as stratifying AEs by gender, race, region, age at first study drug infusion, IST use at baseline, MGFA, and baseline body weight categories will also be provided. All SAEs will be summarized similarly.

In addition, for patients in the ravulizumab treated set, TEAEs by SOC and Preferred Term will be presented by treatment sequence and time intervals during the Ravulizumab Treatment Period.

7.3.2.3. Adverse Events and Serious Adverse Events by System Organ Class, Preferred Term, and Relationship

The number of AEs and the number and percentage of patients with events will be presented by SOC and Preferred Term as described above by relationship (related, not related). If a patient has more than one occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. All SAEs will be summarized similarly.

In addition, for patients in the ravulizumab treated set, TEAEs by SOC and Preferred Term by relationship will be presented by treatment sequence during the Ravulizumab Treatment Period.

7.3.2.4. Adverse Events and Serious Adverse Events by System Organ Class, Preferred Term, and Severity

The number of AEs and the number and percentage of patients with events will be presented by SOC and Preferred Term as described above by severity (Grade 1-5). If a patient has more than 1 occurrence of an AE, the most severe occurrence will be used in the summary table.

In addition, for patients in the ravulizumab treated set, TEAEs by SOC and Preferred Term by severity will be presented by treatment sequence during the Ravulizumab Treatment Period.

7.3.2.5. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

A listing of patient deaths will be produced. Meningococcal infections, the AESIs, will be included in the TEAE summaries by SOC and Preferred Term.

7.3.3. Other Safety

7.3.3.1. Analyses for Laboratory Tests

Absolute values and changes from baseline in central laboratory parameter (continuous variables) will be summarized descriptively at each visit, by treatment group. Baseline is defined as the last available assessment value prior to the first study drug infusion. Shift tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high based on normal range values. For purposes of analyses, laboratory results based upon standardized units will be used. Box plots will be presented for the following central laboratory

parameters by visit: aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, glucose, hematocrit, hemoglobin, lymphocytes neutrophils, leukocytes, and platelets.

For patients in the ravulizumab treated set, absolute values and changes from baseline in central laboratory parameter (continuous variables) will be summarized descriptively at each visit, by treatment sequence. Baseline is defined as the last assessment prior to first dose of ravulizumab.

All central laboratory data will be presented in by-patient listings.

7.3.3.2. Vital Signs, Pulse Oximetry, and Physical Examination

Absolute values and changes from baseline in vital signs (blood pressure [systolic and diastolic], HR, respiratory rate, and temperature) and pulse oximetry will be summarized descriptively at each visit during the Randomized-Controlled Period, by treatment group. Baseline is defined as the last available assessment value prior to the first study drug infusion. A listing of vital signs will be presented.

Absolutes values and changes from baseline in weight will be summarized by visit and treatment group. A listing of weight will be produced.

The number and percentage of patients with at least 1 post-treatment vital sign measurement meeting any of the following criteria will be summarized by treatment group:

- Systolic blood pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic blood pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Heart rate: <60 bpm, >100 bpm
- Body weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
- Temperature: >38.0°C, <36.0°C
- Respiratory rate: <12 breaths/min, > 20 breaths/min

Adverse changes from baseline in physical examination findings will be classified as AEs and analyzed accordingly.

7.3.3.3. Electrocardiogram (ECG)

Descriptive statistics by visit and treatment group will be presented for each ECG parameter (including PR, QRS, QT, and QTcF) values and for change from baseline values. An outlier analysis will be performed that will summarize the frequency and percentage of patients who meet any of the following outlier criteria:

- QT, QTcF interval >450 msec
- QT, QTcF interval >480 msec
- QT, QTcF interval >500 msec
- QT, QTcF interval increases from baseline >30 msec
- QT, QTcF interval increases from baseline > 60 msec

A listing of ECG results will be presented.

7.3.3.4. Immunogenicity

The number and percentage of patients developing confirmed positive ADAs, and anti-drug neutralizing antibodies, where applicable, will be summarized by treatment group and visit.

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

The following categories are C-SSRS categories and have binary responses (yes/no):

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
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 is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined as follows:

Suicidal Ideation (1-5): A yes answer to any one of the five suicidal ideation questions (categories 1-5) on the C-SSRS

Suicidal Behavior (6-10): A yes answer to any one of the five suicidal behavior questions (categories 6-10) on the C-SSRS

Suicidal ideation or behavior: A yes answer to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

For each of the 3 composite endpoints as well as the self-injurious behavior without suicidal intent, the number and percentage of patients who experience an event at baseline and at least once during the treatment period will be summarized by treatment group. The Baseline C-SSRS assessment includes both (A) Lifetime assessment (for both the suicidal ideation and for the suicidal behavior categories) and (B) 1 year prior to treatment.

A shift tabulation from baseline will be produced by treatment group during the randomized-controlled period. A separate shift tabulation will be produced using each of these 2 baselines against the 3 composite endpoints. The 3 groupings for the shift tables are: (a) No suicidal ideation or behavior, (b) composite endpoint of Suicidal Ideation, and (c) composite endpoint of Suicidal Behavior. Each patient is counted in one cell only for each of the 2 tabulations. Patients with both Suicidal Ideation and Suicidal Behavior are included in the Suicidal Behavior category for the particular tabulation.

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. Sample Size, Power, and Randomization

Approximately 160 patients will be randomly assigned to ravulizumab and placebo in a 1:1 ratio (ravulizumab:placebo) stratified by region (North America, Europe, Asia-Pacific, and Japan) to ensure at least 90% nominal power to reject the null hypotheses of no treatment difference for the primary and secondary endpoints based on 2-sided Type I error (α) = 5%. The power calculations were based on the longitudinal change from baseline in MG-ADL total score observed in REGAIN (Study ECU-MG-301). The treatment effect (difference between the eculizumab and the placebo arms in mean change (95% CI) from baseline to Week 6 for MG-ADL) was estimated to be -1.9 (-3.27, -0.55) and the estimated common SD was 3.7. Based on these parameter estimates and the assumption that Study ALXN1210-MG-306 will provide similar results, a total of N = 160 patients is required to ensure at least 90% power to reject the null hypothesis of no treatment effect for MG-ADL at the Type I error rate = 5% (2-sided) based on a t-statistic for 2 independent samples. A simulation-based approach was also adopted to independently verify the sample size calculation in which a large number of virtual datasets were generated with a total of 160 patients (equally distributed between 2 arms) each having a longitudinal profile of change in MG-ADL and baseline MG-ADL score generated according to the treatment-specific variance-covariance structure obtained from REGAIN database. The empirical power was calculated by the proportion of times these virtual trials rejected the null hypothesis based on the MMRM model described above.

9.3. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

Age

Age will be presented as the number of years between date of birth and the reference date. The following ages (in years) may be computed using the formula (reference date – date of birth) + 1/365.25, with reference dates indicated as follows:

Table 3: Age and Reference Date

AGE	REFERENCE DATE
• Age at enrollment	• Date of signing ICF
• Age at MG diagnosis	• Date of MG diagnosis
• Age at first infusion	• Date of first infusion

Abbreviations: ICF = informed consent form; MG = myasthenia gravis

For all dates, in cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing 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

The MG disease duration will be presented as the number of years between the date of first infusion and the date of the first MG diagnosis (ie, INT [(Date of first infusion – Date of MG diagnosis + 1)/365.25] or a similar formula using months and years or years only in the event of partial dates for first symptoms)

Definition of Baseline Values

The Randomized-Controlled Period Baseline The Randomized-Controlled Period Baseline is defined as the last available assessment value prior to first study drug infusion. In general, the baseline assessment will be the Day 1 assessment. For QMG and MGC, in the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG and MGC tests, the Screening Visit assessment will be used as Baseline. If cholinesterase inhibitor was not withheld for at least 10 hours for these visits, the Day 1 assessment will be used as Baseline.

The OLE Baseline is defined as the last available assessment prior to first study drug administered in the OLE Period. In general, the OLE Baseline assessment will be the Day 183 assessment. In the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG test, the prior visit assessment will be used as baseline.

Change From Baseline

Change in values from baseline will be calculated as follows.

Change in Value = (subsequent value – baseline value), given that both the baseline value and subsequent value are non-missing.

Adverse Events

Treatment-emergent adverse events (TEAEs) are events with start dates and start times on or after first dose of study drug administration. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

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

All other AEs are considered PTAEs.

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

The rate of AEs adjusted by PY of exposure is defined as "number of events per 100 patient-years." Total PY will be summed across all individual PY of exposure. The PY of exposure is calculated as (Week 26 completion date or discontinuation/death date)-(first study drug infusion date) + 1 for the Randomized-Controlled Period and as (Data cutoff date or discontinuation/death date)-(first ravulizumab infusion date) + 1 for the Ravulizumab Treated Period.

9.4. Additional Details on Statistical Methods

9.4.1. Myasthenia Gravis-Activities of Daily Living Subcomponent Scores

The MG-ADL subcomponent scores for the bulbar, limbs, respiratory, and ocular are derived from the MG-ADL items. The following illustrates the scoring procedure:

MG-ADL Subcomponent	Score
Bulbar	Sum of talking, chewing, swallowing
Limbs	Sum of impairment of ability to brush teeth or comb hair and impairment of ability to arise from a chair
Respiratory	Breathing
Ocular	Sum of double vision and eyelid droop

9.4.2. Quantitative Myasthenia Gravis Score for Disease Severity Subcomponent Scores

The QMG subcomponent scores for the bulbar, limbs, respiratory, and ocular are derived from the QMG items. The following illustrates the scoring procedure:

QMG Subcomponent	Score
Bulbar	Sum of the items of swallowing and speech
Limbs	Sum of right arm outstretched, left arm outstretched, right hand grip, left hand grip, head lift, right leg outstretched, and left leg outstretched
Respiratory	Forced vital capacity
Ocular	Sum of the items of double vision, ptosis, and facial muscles

9.4.3. European Quality of Life 5 dimension-5-level Health State Index Calculations

The responses to the five EQ-5D dimensions can be converted into a single number called an index value. The EQ-5D-5L health state index scores is derived by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by subtracting the appropriate weights for each dimension level of health state from 1. The EQ- 5D-5L index scores for this study will be obtained using the US composite time trade-off (cTTO) method. The calculation is illustrated in Table 4 below:

Table 4: EQ-5D-5L US Composite Time Trade-off (cTTO) Value Set

US TTO		Example: the value for health state 21354
Full health (11111)		Full Health=1
Mobility level 2	-0.096	-0.096
Mobility level 3	-0.122	
Mobility level 4	-0.237	
Mobility level 5	-0.322	
Self-Care level 2	-0.089	0
Self-Care level 3	-0.107	
Self-Care level 4	-0.220	
Self-Care level 5	-0.261	
Usual Activity level 2	-0.068	
Usual Activity level 3	-0.101	-0.101
Usual Activity level 4	-0.255	
Usual Activity level 5	-0.255	
Pain/Discomfort level 2	-0.06	
Pain/Discomfort level 3	-0.098	
Pain/Discomfort level 4	-0.318	
Pain/Discomfort level 5	-0.414	-0.414
Anxiety/Depression level 2	-0.057	
Anxiety/Depression level 3	-0.123	
Anxiety/Depression level 4	-0.299	-0.299
Anxiety/Depression level 5	-0.321	
Health State Index Score		=1-0.096+0-0.101-0.414-0.299=0.090

9.4.4. SAS Code for Repeated Measures Mixed Model Analysis

The main analysis method for the primary endpoint of change from baseline to Week 26 in MG-ADL and many of the secondary and tertiary endpoints involve mixed model repeated measures analysis. The basic SAS® code for change in MG-ADL is given by:

```
proc mixed data=ADEFF method=reml;

class subjid trt01pn avisitn region;

model chg= trt01pn  avisitn trt01pn*avisitn base region/ddfm=kr solution;

repeated avisitn/type=un subject=subjid;

lsmeans trt01pn *avisitn/cl diff;
```

where subjid is the patient identifier variable, trt01pn is the randomized treatment group, avisitn is the visit variable, base is the MG-ADL value at baseline, chg is the change from baseline in MG-ADL, and region is the randomization stratification variable.

9.4.5. SAS Code for Placebo-based Sensitivity Analysis

A sensitivity analysis for the change from baseline in MG-ADL at Week 26 will be analyzed using the MMRM model as specified for the primary analysis. For patients who discontinued treatment, responses after treatment discontinuation, for both groups, will be imputed with multiple imputation methodology (SAS PROC MI) based on the response for placebo treated patients. Markov Chain Monte Carlo (MCMC) imputation method will be used to fill in the intermittent missing values under the assumption of missing at random (MAR) and generate a monotone pattern (1000 imputations will be generated). Subsequently, multiple imputation will be performed at each visit sequentially, using a regression method obtained only from placebo treated patients with terms for baseline MG-ADL total score at baseline and the randomization stratification variable region. After obtaining complete data sets for each visit, these complete data sets will be analyzed using MMRM analysis, and inferences from each complete data set will be combined to obtain an overall test statistic for treatment effect. Below is some sample code:

Markov Chain Monte Carlo (MCMC) imputation method:

```
proc mi data=ADEFF out=monotone seed=123 nimpute=1000;
by trt01pn;
mcmc impute=monotone;
var base region1 region2 region3 Week1 - Week26;
```

where trt01pn is the randomized treatment group, base is the MG-ADL value at baseline, Week 1 – Week 26 are the change from baseline in MG-ADL at the particular visit, and region1,2,3 are 3 dummy variables based on the randomization stratification region.

The following is a partial SAS code for the placebo-based pattern imputation at Week X:

```
proc mi data=monotone out=outmi seed=123 nimpute=1;
by _imputation_;
 class trt01pn region;
var base region Week1 - Week26;
 monotone reg(/details);
mnar model (Week X/modelobs=(trt01pn=”0”))
run;
```

Once multiple completed data sets are generated, the same method, MMRM, used for the primary analysis, is then used to analyze each imputed data set separately (Refer to Section 9.4.4 for SAS code), and inferences from each complete dataset will be combined to obtain an overall test statistic using proc mianalyze:

```
proc mianalyze data=diff2;
by avisitn;
modeleffects estimate;
```

```
stderr stderr;
```

9.4.6. SAS Code for Tipping Point Sensitivity Analysis

The following illustrates the sensitivity analysis for the primary endpoint of change from Baseline to Week 26 in MG-ADL with the tipping-point approach where a search is conducted for a tipping point that reverses the study conclusion from being favorable to ravulizumab to being unfavorable. For the tipping point sensitivity analysis, the missing data mechanism for the missing change from baseline values at Week 26 will be considered to be MNAR. Markov Chain Monte Carlo (MCMC) imputation method will be used to fill in the intermittent missing values under the assumption of MAR and generate a monotone pattern (1000 imputations will be generated). Subsequently imputations are performed for missing change observations at every visit sequentially for the ravulizumab treated patients assuming not the full treatment effect, but the treatment effect minus a shift parameter delta. The adjustment will be applied to the first unobserved outcome from ravulizumab. After obtaining complete data sets for multiple shift parameters, the complete data sets will be used in the MMRM analysis, and inferences from each complete dataset will be combined using SAS PROC MIANALYZE to obtain an overall test statistic for each shift value. Multiple shift parameters will be tested until the inference concludes that statistical significance disappears. The following is a partial SAS code for the multiple imputation analysis for a specified shift parameter at Week X:

```
proc mi data=monotone out=outmi seed=123 nimpute=1;
by _imputation_;
  class trt01pn Region;
  monotone method=reg ;
  var trt01pn region base Week 1 - Week26;
  mnar adjust (Week X /shift=delta adjustobs=(trt01pn='Ravulizumab'));
```

where trt01pn is the randomized treatment group, base is the MG-ADL value at baseline, Week 1 – Week 26 are the change from baseline in MG-ADL at the particular visit, and region is the randomization stratification.

The 1000 imputed data sets are then analyzed using MMRM (Refer Section 9.4.4 for SAS code) and PROC MIANALYZE procedure will be used to generate valid statistical inferences about these parameters.

9.4.7. SAS Code for Mixed Effect Repeated Measures Model

The analysis of secondary endpoints of at least 3-point improvement in MG-ADL and at least 5-point improvement in QMG will involve fitting a mixed effect repeated measures model. The basic SAS code for that analysis is given by:

```
proc glimmix data=adeff    method = rmpl;
  class usubjid trt01pn avisitn region ;
  model crit2fn =  trt01pn avisitn trt01pn*avisitn region/ dist = binomial link = logit;
      random avisitn / subject = usubjid residual type = un;
```

```
lsmeans trt01pn*avisitn/ilink diffs oddsratio cl;
```

9.4.8. SAS Code for Proportional Odds Model

The analysis of MGFA-PIS at Week 26 will involve fitting the proportional Odds model with proc logistic. The basic SAS code for that analysis is given by:

```
proc logistic data=adeff descending;
  class trt01pn region;
  model aval=trt01pn region;
  oddsratio trt01pn;
```

9.4.9. SAS Code for Poisson Regression

The analysis of incidence of hospitalization/MG-related hospitalization and clinical deterioration/MG crisis will involve Poisson regression analysis. The basic SAS code for that analysis is given by:

```
proc genmod;
 class tr01pg1n region;
 model count = tr01pg1n region/ type3 dist=poisson scale=pearson offset=logpy;
estimate "log Ravuvs Placebo" trt01pn 1 -1 /exp;
 lsmeans trt01pn/ilink exp cl;
run;
```

where trt01pn is the randomized treatment group, count is the number of hospitalization (or MG hospitalization/Clinical deterioration/MG crisis), region is the randomization stratification variable.

Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN ADDENDUM

PROTOCOL NUMBER: ALXN1210-MG-306

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenia Gravis

Author: PPD

Date: 3 December 2020

Version: V1.0, Final

1. APPROVAL SIGNATURES

PPD

Date dd Mmm yyyy

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
AE	Adverse event
C5	Complement component 5
COVID-19	Coronavirus Disease 2019
eCRF	Electronic case report form
FAS	Full analysis set
FVC	Force vital capacity
IVIg	Intravenous immunoglobulin
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living
MMRM	Mixed-effect model for repeated measures
MNAR	Missing not at random
OLE	Open-label Extension
OLES	Open-label Extension Set
PD	Pharmacodynamic(s)
PE	Plasma exchange
PK	Pharmacokinetic(s)
PP	Plasmapheresis
PPS	Per Protocol set
PT	Preferred term
QMG	Quantitative Myasthenia Gravis score for disease severity
RCP	Randomized-Controlled Period
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Safety Set

4. STATISTICAL ANALYSIS PLAN ADDENDUM

The Statistical Analysis Plan (SAP) Addendum details the changes and/or additional analyses required to address the impact of Coronavirus Disease 2019 (COVID-19) on the planned analyses as described in the Final SAP Version 1.0 dated 6 April 2020. In general, the study objectives for this study have not changed and the interest remains in a treatment effect that is not confounded by pandemic-related disruptions. Additionally, the originally planned statistical methodology as specified in Section 7.2 of SAP V1.0 has not changed. Section 4.2 below details the changes from the analyses specified in SAP V1.0.

4.1. Changes From Analyses Specified in the Protocol

None.

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

Changes from analyses specified in the final SAP Version 1.0 dated 6 April 2020 include the following:

1. The planned analyses of long-term safety and efficacy data for patients in the Open-Label Extension (OLE) at the time of database lock is updated from Section 4.1 of SAP V1.0 to restrict the scope of safety analyses in the OLE to patients who completed or would have completed Week 52 assessments as of the data cutoff date, which is based on when the last patient enrolled completes the Randomized Controlled Period. This will align the follow up time for both safety and efficacy. Details of the assessments to be summarized up to Week 52 for these patients as well as for discontinued patients who would have reached Week 52 by the data cutoff date had they remained on study are provided in Version 1.0 of the SAP and include at a minimum the following: disposition, study drug exposure, primary and secondary endpoints, and clinical laboratory assessments as well as adverse events (AEs), serious adverse events (SAEs), and concomitant medications.

   Based on this, the definition of the Open-Label Extension Set (OLES) will be updated from Section 6.4 of SAP V1.0 to consist of all patients who received at least 1 dose of ravulizumab starting from Week 26 and who have completed Week 52 study visit or who would have completed Week 52 by the data cutoff date but withdrew from the study. This analysis set will also replace the Open-Label Efficacy Extension Set for all analyses specified in SAP V1.0.

2. A modified Full Analysis Set (mFAS) will be added and will consist of a subset of the Full Analysis Set (FAS) excluding patients who were impacted by COVID-19 during the Randomized-Controlled Period (RCP) as follows:
   a. Patients who had a COVID-19 related adverse event during the RCP
   b. Patients who missed 2 consecutive scheduled doses of study drug during the RCP due to COVID-19-related disruptions

c. Patients who terminated early during the RCP due to COVID-19 related disruptions
d. Patients who received concomitant treatments for COVID-19 during the RCP that could be used as MG medication

3. The originally planned statistical analyses as specified in Section 7.2 of SAP V1.0 will be utilized for statistical inference of all primary and secondary endpoints as well as the exploratory endpoints that are analyzed using mixed-effect model for repeated measure (MMRM). Patients impacted by the following pandemic related intercurrent events will be handled using the hypothetical strategy as follows:

   a. Efficacy assessments for patients who had COVID-19 related SAE will be excluded from the planned analysis from date of the event up to 2 weeks from resolution of the SAE.

   b. Efficacy assessments for patients who had a change in their MG concomitant treatment due to COVID-19 will be excluded from the planned analysis until the dose returns to baseline levels.

   c. Efficacy assessments for patients who missed 1 dose of study drug due to COVID-19-related disruptions will not be excluded from the planned analysis with the following exceptions:

      - If the efficacy assessment took place more than 16 weeks from the last administration of study drug, then it will be excluded.
      - For patients randomized to placebo who missed the loading dose at Week 26, efficacy assessments will be excluded up to 7 days from reinitiating study drug administration.

   d. Efficacy assessments for patients who missed 2 or more sequential doses of study drug due to COVID-19 will be excluded from the planned analysis up to 2 weeks from reinitiating study drug administration.

   e. The tipping point sensitivity analyses specified in Section 7.2.1.5 of SAP V1.0 will tip missing data due to pandemic-unrelated missing data but will use standard missing at random (MAR) imputations for pandemic-related missing data. Similarly, the placebo-based sensitivity analysis will limit efficacy after early discontinuation due to pandemic-unrelated missing data in the ravulizumab group to that of the placebo group but will use standard MAR imputations for pandemic-related missing data.

4. Calculation of drug compliance during the RCP as specified in Section 7.3.1 of the SAP will be modified from being based on number of scheduled doses given out of number of expected scheduled doses, to reflecting percentage of time during the RCP that the patient is considered to have complete terminal complement inhibition ie 100%-sum (percentage of time non-compliant with scheduled doses). Non-compliance time will be calculated for any consecutively missed scheduled dose(s) as shown in Table 2. Negative non-compliance, which might occur for discontinued patients, will be set to 0.

Table 2: Non-Compliance Calculations for Patients in the Randomized-Controlled Period

First Scheduled Dose Missed	Non-Compliance Calculations[a]
Any except Day 15	[(Minimum (Day of dose re-initiation relative to Day 1 or 183[b] or Day of discontinuation) – (target day of last dose given relative to Day 1+56+14))/183]*100
Day 15	[(Minimum (Day of dose re-initiation relative to Day 1 or 183[b] or day of discontinuation) – (target day of last dose given relative to Day 1 + 14 + 14=29))/183]*100

[a] The initial 56 and 14 days in the calculations reference the dose coverage of the last dose given. The second 14 days is added to take into account the potential for dosing visits occurring within 2 weeks of an expected visit to be entered under the regularly scheduled visit.

[b] 183 days is used for patients who did not reinitiate study drug in the randomized-controlled period by data cutoff date

5. Calculation of ravulizumab drug compliance for patients in the ravulizumab treatment Period (including OLE) using the ravulizumab treated set, will be modified from being based on the number of scheduled ravulizumab doses given out of the number of expected scheduled ravulizumab doses to reflecting percentage of time during the ravulizumab treatment period that the patient is therapeutically dosed ie 100%-sum (percentage of time non-compliant with scheduled ravulizumab doses). Non-compliance time will be calculated for any consecutively missed scheduled dose(s) as shown in Table 3. Negative non-compliance, which might occur for discontinued patients, will be set to 0:

Table 3: Non-Compliance Calculations for Patients in the Ravulizumab Treatment Period

First Scheduled Ravulizumab Dose Missed	Non-Compliance Calculations[a]
Ravulizumab to Ravulizumab	
Any except Day 15 or Day 197	[(Minimum (Day of dose re-initiation relative to Day 1 or 365[b] or day of discontinuation) – (target day of last dose given relative to Day 1+56+14))/365]*100
Day 15 or Day 197	[(Minimum (Day of dose re-initiation relative to Day 1 or 365[c] or day of discontinuation) – (target day of last dose given relative to Day 1 + 14 + 14))/365]*100
Placebo to Ravulizumab	

First Scheduled Ravulizumab Dose Missed	Non-Compliance Calculations[a]
Any except Day 183 or Day 197	[(Minimum (Day of dose re-initiation relative to Day 1 or 365[d] or day of discontinuation) – (target day of last ravu dose given relative to Day 1))+56+14)/183]*100
Day 183	[(Minimum (Day of dose re-initiation relative to Day 1 or 365[e] or day of discontinuation) – 183)/183]*100
Day 197	[(Minimum (Day of dose re-initiation relative to Day 1 or 365[f] or day of discontinuation) – (target day of last ravu dose given)+14+14))/183]*100

[a] The initial 56 and 14 days in the calculations reference the dose coverage of the last dose given. The second 14 days is added to take into account the potential for dosing visits occurring within 2 weeks of an expected visit to be entered under the regularly scheduled visit.

[b] 365 days is used for patients who did not reinitiate study drug in the OLE by data cutoff date

6. Section 7 of the SAP V1.0 specifies that data collected at an unscheduled visit will be included in by-patient listings, but assignment of the scheduled visit will not be made for the purposes of summary tabulations with the exception of calculation of baseline values. This is updated to utilize the window algorithm specified below to allow the use of unscheduled postbaseline visits, if available, to replace missing scheduled visits, and this update is not intended to reassign all visits. Assessments collected for clinical deterioration will not be utilized. Assessments conducted at early termination visits will be similarly assigned.

   For all postbaseline by-visit assessments, the number of days from baseline will be calculated using the following formula: (date of assessment) - (date of first study treatment) + 1. This number of days will be used to assign analysis visit for a missed visit/assessment. This may not always correspond to the electronic case report form (eCRF) visit.

   For all visits, the lower bound and the upper bound for the analysis visit windows are defined as the midpoints of the target date of scheduled visits. If the date of assessment falls in between the lower bound and the upper bound for a visit as defined in the protocol schedule of assessment, then it will be assigned to that visit. If the interval separating 2 scheduled visits is an even number of days, that middle day will be included in the lower bound of the next visit window. For example, for an assessment with a scheduled visit Day 127, and a prior scheduled visit Day of 85 and subsequent scheduled visit Day of 183, the window will start at 106 days from baseline and will go to 154 days from baseline.

   If only one record is within an analysis visit window, the data from that record will be used for the missed visit/ assessment in the analysis. If more than one record is within the same analysis visit window, the record closest to the midpoint of the interval will be used

for the missed visit/assessment. If two records are "tied" before and after the middle of the interval, the earlier record will be used in the analysis.

The following additional sensitivity and supplementary analyses will be included to assess the impact of the pandemic disruption on the trial and to address pandemic-related data missingness:

1. The summary of patient disposition specified in Section 7.1.1 of the SAP V1.0 will include COVID-19 related screen failure reasons and COVID-19 related discontinuations/withdrawals from both the Randomized-Controlled Period and the OLE Period.
2. Descriptive statistics of demographic, baseline disease characteristics as specified in Section 7.1.3 of the SAP V1.0, and the change from baseline in Myasthenia Gravis-Activities of Daily Living (MG-ADL) during the RCP, will be provided by enrollment period as follows: before March 2020, March 2020-August 2020, and after September 2020. Similarly, a summary table of treatment emergent adverse events during the RCP by System Organ Class (SOC) and Preferred Term (PT) stratified by enrollment period will be provided.
3. A summary of the number and percentage of patients with pre-treatment and treatment emergent known Exposure to COVID-19 during the RCP will be provided by treatment group using the Safety Set (SS).
4. A summary of COVID-19 related important protocol deviations during the RCP will be provided. A by-patient listing of all protocol deviations will be provided.
5. A summary of the number and percentage of patients who missed a study visit and/or who had a modified study visit during the RCP along with the reasons (COVID-19 related/not), will be provided by treatment group and by visit using the FAS. For patients who had a modified study visit, the method for the different assessments will be summarized. Similar summaries will be provided for patients in the OLES.
6. For the secondary endpoint change from baseline to Week 26 in Quantitative Myasthenia Gravis (QMG), an additional analysis will be performed after using a multiple imputation approach and using a regression method to impute Forced Vital Capacity (FVC) for patients whose other sentinel muscle groups were evaluated. This will be followed by calculating QMG total scores and analyzed using MMRM. In addition, an analysis of the 5-point improvement in the recalculated QMG total score from Baseline to Week 26 will be performed utilizing mixed effect repeated measures model.
7. The primary and secondary endpoint analyses will be repeated using the mFAS. Similarly, a summary table of treatment emergent adverse events (TEAE) by SOC and PT will be conducted on the mFAS.
8. To assess the impact of change in endpoint ascertainment, descriptive statistics of the primary endpoint of change from baseline in MG-ADL by visits during the RCP and by method of assessment (in clinic versus alternative method), will be provided by pooled treatment arms using the FAS.
9. A summary table of TEAEs during the RCP by SOC and Preferred Term will be provided for patients who were diagnosed with COVID-19 using the SS.

10. The following summaries will be added to the summaries specified in Section 7.3.1 of the SAP V1.0 using the FAS and SS: the total number and percentage of patients with any missed doses per schedule of assessment during the RCP, the reason and the total number of missed doses (1, 2, 3, 4 or more), will be provided. Similarly, the total number of patients with any unscheduled infusions during the RCP, the reason and the total number of unscheduled doses (1, 2, 3, 4 or more) will be provided. Similar summaries will be provided for patients in the ravulizumab Treatment Period using the ravulizumab treated set.

The following include additional clarifications and analyses to SAP V1.0.

- The first criterion for inclusion into the PPS in Section 6.2 of SAP V1.0 is clarified as follows:

  During the RCP, missed 0 doses per protocol schedule of assessment. Patients with a clinical deterioration per protocol during the RCP who receive rescue therapy (IVIg/PP/PE) should have received at least 1 supplemental dose at the conclusion of rescue therapy.

- The summary of actual values, change from baseline, and percentage change from baseline in serum free C5 concentrations as detailed in Section 7.2.5 of the SAP V1.0 will be modified to exclude Day 1 free C5 samples considered biologically implausible. The exclusions will be corroborated with the paired PK data.

- A summary of infusion reactions during the RCP will be summarized by preferred term and by treatment group using the SS.

- The proportion of patients with a $\geq$ 2-point reduction in MG-ADL regardless of rescue therapy for at least 4 consecutive visits during the first 10 weeks, will be summarized by treatment group. The same summary classifying patients who received rescue therapy as non-responders will be produced.

Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN ADDENDUM 2

PROTOCOL NUMBER: ALXN1210-MG-306

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenia Gravis

Author: PPD

Date: 10 June 2021

Version: V1.0, Final

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
FAS	Full analysis set
IST	immunosuppressant therapy
IVIg	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living
PE	plasma exchange
PP	plasmapheresis
QMG	Quantitative Myasthenia Gravis score for disease severity
SAP	statistical analysis plan
SMQ (N)	standard MedDRA queries (narrow)
SS	safety set

4. STATISTICAL ANALYSIS PLAN ADDENDUM

This Statistical Analysis Plan (SAP) Addendum 2 V1.0 details in Section 4.2 the changes and/or additional analyses from the SAP V1.0 dated 06 April 2020 and the SAP addendum V1.0 dated 03 December 2020.

4.1. Changes from Analyses Specified in the Protocol

None.

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

Changes and/or additional analyses from those specified in the final SAP V1.0 dated 6 April 2020 and the SAP addendum V1.0 dated 03 December 2020 include the following:

1. Additional summaries of myasthenia gravis (MG) therapies will be provided using the safety set (SS) as follows:

    a. Number and percentage of patients with 0, 1, 2 or more of immunosuppressant therapy (IST) or intravenous immunoglobulin (IVIg)/ Plasmapheresis (PP)/ Plasma exchange (PE) within 2 years prior to Screening visit will be provided. ISTs include corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus, or rituximab.

    b. Number and percentage of patients with 0, 1, 2 or more ISTs within 2 years prior to Screening visit will be provided.

    c. Number and percentage of patients with 0, 1, 2 or more ISTs at first dose of study drug will be provided. Please note that use of rituximab is not allowed within 6 months prior to Screening.

2. The additional MG therapy categories in # 1 will be added to the list of subgroups for primary and secondary endpoint table analyses using the FAS as specified in the final SAP V1.0 dated 6 April 2020 Section 7.2.1.2.

3. For the secondary endpoints of at least 3-point improvement in Myasthenia Gravis-Activities of Daily Living (MG-ADL) and at least 5-point improvement in Quantitative Myasthenia Gravis score for disease severity (QMG) from baseline to Week 26, the following other covariance structures may be utilized in the mixed-effect model for repeated measures if a convergence issue occurs with the proposed unstructured covariance and first auto-regressive structures: compound symmetry and Toeplitz method.

4. A summary of treatment emergent adverse events during the Randomized-Controlled Period utilizing standard Medical Dictionary for Regulatory Activities (MedDRA) query

(narrow) (SMQ[N]) of hypersensitivity will be summarized by preferred term and by treatment group using the SS. This summary will replace the infusion related reaction summary described in SAP addendum V1.0.

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