Study ALXN1210-MG-306 Objectives and Endpoints

Objectives	Endpoints
Primary	
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.	Change from Baseline in MG-ADL total score at Week 26 of the Randomized-Controlled Period.
Secondary	
• 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.	• Change from Baseline in QMG total score at Week 26.
• To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in quality of life measures.	• Change from Baseline in the Revised 15-Component Myasthenia Gravis Quality of Life (MG-QOL15r) score at Week 26. • Change from Baseline in Neuro-QOL Fatigue score at Week 26.
• To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on other efficacy endpoints.	• Improvement of at least 3 points in the MG-ADL total score from Baseline at Week 26. • Improvement of at least 5 points in the QMG total score from Baseline at Week 26.
Exploratory	
• To assess the efficacy of ravulizumab in the treatment of gMG based on other efficacy endpoints throughout the study.	• Change from Baseline in the Myasthenia Gravis Composite (MGC) score at Week 26. • Myasthenia Gravis Foundation of America (MGFA) Post-Intervention Status (PIS) at Week 26. • Change from Baseline in Euro Quality of Life (EQ-5D-5L) at Week 26. • Change from baseline in MG-ADL subcomponent scores (bulbar, limbs, respiratory, and ocular) at Week 26. • Change from baseline in QMG subcomponent scores (bulbar, limbs, respiratory, and ocular) at Week 26. • Incidence of hospitalizations/MG-related hospitalizations. • Incidence of Clinical Deterioration/MG crisis.
PK/PD/Immunogenicity	
• To evaluate the PK/PD and immunogenicity of ravulizumab in the treatment of gMG throughout the study.	• Change in serum ravulizumab concentration over time. • Change in serum free C5 concentration over time. • Incidence of treatment-emergent antidrug antibodies over time.
Safety	
To characterize the overall safety of ravulizumab in the treatment of gMG.	• Incidence of adverse events and serious adverse events over time. • Changes from Baseline in vital signs and laboratory assessments.

The above endpoints will be evaluated over time throughout the study.

Table 1: Schedule of Activities: Screening Through End of the Randomized-Controlled Period (Continued)

Period/Phase	Screening	Randomized-Controlled Period								Clinical Deterioration[1]
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET[2]**	
Study Day		**D1**	**D8**	**D15**	**D29**	**D71**	**D85**	**D127**	**D183**	
Window (day)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
Weeks	**-4 to -2 W**		**W1**	**W2**	**W4**	**W10**	**W12**	**W18**	**W26**	
Clinical Lab Tests[10]	X	X		X		X		X	X	X
Pregnancy Test [11]	X	X		X		X		X	X	
PK, Free C5[12]		B/P		T/P		T/P		T/P	T	X
ADA[13]		X				X		X	X	X
N meningitidis Vaccine[13]	X									
Patient Safety Information Card[14]		X	X	X	X	X	X	X	X	
Randomization[15]		X								
Study Drug Infusion[16]		X		X		X		X		

[1] Evaluation of Clinical Deterioration must be performed as soon as possible, within 48 hours of notification to the Investigator of symptom onset. If Clinical Deterioration occurs between scheduled visits, only the assessments for the Clinical Deterioration visit are needed. If Clinical Deterioration occurs on a scheduled visit, all scheduled assessments should be performed for that visit as well as for the evaluation of Clinical Deterioration. Additional evaluation visits may be scheduled at the discretion of the Investigator.

[2] If a patient withdraws early from the study during the Randomized-Controlled Period, an Early Termination Visit will be performed.

[3] MG history will include diagnosis date; initial MG clinical presentation (oMG or gMG); time to gMG, if initial clinical presentation was oMG; maximum MGFA classification since diagnosis; ventilatory support since diagnosis; dates of MG exacerbation or crisis since diagnosis and prior to Day 1; and any MG-related hospitalizations in 2 years prior to screening. MG-specific medication or therapy taken within 2 years prior to screening will be recorded.

[4] Refer to Section 4.2.4.

[5] Vital signs and pulse oximetry will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), pulse oximetry (oxygen saturation [SO_2]), heart rate (beats/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). On dosing days, vital signs will be taken before study drug administration and after the patient has been resting for at least 5 minutes.

[6] To be performed, if necessary, on the basis of the patient's health status and the clinical judgment of the Investigator.

[7] The MG-ADL is required to be performed first, followed by the QMG. The MG-activities of daily living (MG-ADL) assessment should be performed by a Properly Trained Clinical Evaluator (as defined in the study protocol), preferably the same evaluator, throughout the study. The recall period for MG-ADL is the preceding 7 days or since the last visit if the visit interval is less than 7 days.

[8] The QMG and MGC assessments should be performed by a Properly Trained Clinical Evaluator (as defined in the study protocol), preferably the same evaluator, throughout the study. If a patient is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the assessment.

[9] C-SSRS will be assessed for both lifetime and past 1 year (12 months).

[10] Clinical laboratory tests will be performed at the central laboratory.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab for the treatment in patients with gMG. Approximately 160 eligible patients will be stratified by region (North America, Europe, Asia-Pacific, and Japan) and randomized 1:1 to 1 of 2 treatment groups: (1) ravulizumab infusion or (2) placebo infusion. There will be 3 periods in this study: Screening Period, Randomized-Controlled Period, and an Open-Label Extension (OLE) Period.

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

Eight weeks after the final dose of study drug is administered, all enrolled patients will return for an End of Study (EOS) Visit (Visit 25) at Week 132 during which final study assessments will be conducted. If a patient withdraws from the study, or completes the study early (prior to Visit 24; Week 124), the patient will be encouraged to return for an Early Termination (ET)/EOS Visit, 8 weeks after the day the last dose of study drug was administered, during which final planned safety assessments will be conducted (see Section 4.5 for further details regarding end of study and study completion). Attempts should be made to follow all patients for safety for 8 weeks from the day the last dose of study drug is administered.

Patients who are being treated with an immunosuppressive therapy (IST) at the time of the Screening Visit may continue taking their baseline ISTs throughout the Randomized-Controlled and OLE Periods. However, the dosage of IST must not be changed and no new ISTs may be added or discontinued 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 corticosteroid, plasmapheresis (PP)/plasma exchange (PE), or intravenous immunoglobulin [IVIg]) will be allowed if a patient experiences Clinical Deterioration as defined in this protocol (Section 4.2.1). The rescue therapy used for a particular patient will be at the discretion of the Investigator.

The primary endpoint for this study will be measured at Week 26 (Day 183), irrespective of rescue therapy.

Including the 8-week safety follow-up, which begins after the last dose of study drug is administered, the overall study duration for an individual patient is estimated to take up to 132 weeks (from enrollment through the end of the Safety Follow-up). The period of active patient-participation is estimated to take up to 132 weeks (from enrollment through the EOS Visit). Schedules of Activities (SOA) for the Randomized-Controlled Period and the OLE Period are provided in Table 1 and Table 2, respectively.

4.1.1. Screening Period (2 - 4 Weeks Prior to Day 1)

At the screening visit, after obtaining informed consent, the patient will be screened for study eligibility through medical history review, demographic data, and laboratory assessments. The medical history review will include MG diagnosis date; initial MG clinical presentation (ocular MG [oMG] or gMG); time to gMG, if initial clinical presentation was oMG; maximum MGFA classification since diagnosis; ventilatory support since diagnosis; dates of MG exacerbation or crisis since diagnosis and prior to Day 1; and any MG-related hospitalizations in 2 years prior to screening. MG-specific medication or therapy (eg, thymectomy, ISTs including corticosteroids, IVIg, and PE/PP) within 2 years prior to screening will be recorded.

If all inclusion criteria and none of the exclusion criteria are met, patients will be vaccinated against *N meningitidis,* if not already vaccinated within the 3 years prior to their enrollment in the study. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

If a patient experiences a Clinical Deterioration or MG Crisis during the Screening Period, the Sponsor must be notified.

4.1.2. Randomization

At the time of randomization, all patients will be reassessed for eligibility based on the study inclusion and exclusion criteria. All patients who are vaccinated, continue to meet all of the inclusion criteria and none of the exclusion criteria at Randomization [Day 1]), and have been cleared for randomization by the Investigator, will be randomized 1:1 to the ravulizumab group or the placebo group. Patients will be centrally randomized using interactive response technology (IRT). The randomization will be stratified by region (North America, Europe, Asia-Pacific, and Japan).

4.1.3. Randomized Controlled Period (26 Weeks)

Throughout the study, rescue therapy (eg, high-dose corticosteroid, PE/PP, or IVIg) will be allowed when a patient's health would be in jeopardy if rescue therapy was not administered (eg, emergent situations), or if a patient experiences Clinical Deterioration as defined in this protocol. The rescue therapy used for a particular patient will be at the discretion of the Investigator.

Patients must be informed of potential signs and symptoms of Clinical Deterioration or MG Crisis and instructed to contact the Investigator to be evaluated within 48 hours of notification of the Investigator of the symptom onset. At the evaluation visit, the Investigator or the Investigator's designee will perform the assessments as specified by this protocol. The Investigator or designee will determine whether or not the patient meets the definition of Clinical Deterioration as defined by this protocol in Section 4.2.1 and treat the patient accordingly.

The primary endpoint for this study will be measured at Week 26 (Day 183), irrespective of rescue therapy.

See the SOA for further details regarding visit procedures throughout the study (Section 1.3).

Clinical Evaluator training and certification for this protocol will take place either at the Investigator's Meeting or via the Sponsor's designated on-line training portal.

4.2.4. Responsibilities for Myasthenia Gravis Assessments

Responsibilities for MG assessments are listed in Table 3. Throughout the study, MG assessments should be performed at approximately the same time of day by a Properly Trained Clinical Evaluator, and preferably the same evaluator. The MG-ADL should always be performed first, followed by the QMG.

Table 3: Myasthenia Gravis Assessments and Responsibilities

Assessment	Evaluator
MG-ADL	Properly Trained Clinical Evaluator
QMG	Properly Trained Clinical Evaluator
MGC	Properly Trained Clinical Evaluator
MGC (MMT Components)	Investigator or Neurologist
MGFA-PIS (modified version)	Investigator or Neurologist
MGFA Classification	Investigator or Neurologist

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living Profile; MGC = Myasthenia Gravis Composite scale; MGFA = Myasthenia Gravis Foundation of America; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MMT = manual muscle test; QMG = Quantitative Myasthenia Gravis score for disease severity.

4.3. Scientific Rationale for Study Design

Published data support the MG-ADL profile as an established, sensitive, and objective assessment of treatment response over time in patients with gMG (Howard, 2017).

The safety parameters being evaluated are commonly used in clinical studies per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) guidance.

Placebo was selected as the control and patients will be allowed to continue stable therapy with standard of care therapy (ie, ISTs) throughout the course of the study, which thereby allows for comparison of the safety and efficacy of ravulizumab when administered in addition to the patient's standard of care treatment to current standard of care therapies in patients with gMG.

Given the heterogeneity of the disease and fluctuation in the severity of symptoms, there is no 1 international standard of care accepted, and targeted treatment with complement-inhibitor drugs, such as the recently introduced eculizumab, is not yet widely available to patients worldwide and is not yet considered standard of care for all patients with gMG. A placebo-controlled study allows for the evaluation of treatment effect and allows for a double-blind design; an important study condition to be maintained when considering endpoints that includes neurological scales, which are known to be especially prone to placebo effects. The placebo-controlled part of the study will be limited to 26 weeks, after which time all patients will transition to open-label treatment with ravulizumab for up to 2 years during the OLE Period. At all points throughout the study, physicians will be encouraged to prioritize patient safety, and if patients experience Clinical Deterioration, the full range of rescue therapies will be permitted.

4.4. Justification for Dose

The ravulizumab dosage regimen for this study (Table 4) was approved for the treatment of adult patients with PNH based on comprehensive modelling and simulation analyses of Phase 1 and 2 PK/PD data in healthy volunteers and PK/PD/efficacy (lactate dehydrogenase) and safety data in patients with PNH. This regimen is considered optimal for achieving immediate, complete, sustained inhibition of terminal complement activity within each dosing interval and for the entire treatment course in adult patients.

Table 4: Ravulizumab Weight-Based Dosing

Weight (kg)	Loading Dose (mg)	Maintenance Dose (mg) (administered q8w)
≥ 40 to < 60	2400	3000
≥ 60 to < 100	2700	3300
≥ 100	3000	3600

Abbreviation: q8w = every 8 weeks.

Consistent with approved eculizumab labeling for treating adult and pediatric patients with aHUS and adult patients with gMG, supplemental dosing of ravulizumab in the amount of 50% (rounded up if not in integral of 300 mg due to vial configuration) will be given in the setting of concomitant PE/PP rescue therapy. For adult patients with gMG, supplemental dosing of ravulizumab (in the amount of 600 mg) will be given in the setting of concomitant IVIg rescue therapy. The 600 mg supplemental ravulizumab dose has been selected based on PK simulations considering the published data describing the impact of co-administration of IVIg on eculizumab PK/PD (Fitzpatrick, 2011) (see Table 7 and Table 8).

Supplemental study drug (or placebo) dosing is required if PE/PP or IVIg rescue therapy is provided on non-dosing days; no supplemental study drug (or placebo) dosing is required if PE/PP or IVIg infusion is provided on a dosing day, but it must occur prior to study drug administration. If PE/PP or IVIg is administered on scheduled dosing visits, regular dosing will be started within 60 minutes after the completion of PE/PP or IVIg. If PE/PP or IVIg is administered on non-scheduled dosing visits, for patients receiving PE/PP: supplemental dose administration will be started within 4 hours after the PE/PP session is completed; for patients receiving IVIg: supplemental dose administration will be started within 4 hours after the last continuous session(s) of IVIg is completed (see Section 6.5.1.4).

The favorable benefit/risk profiles of ravulizumab from the Phase 3 studies in patients with PNH have confirmed immediate (after the first dose or loading dose), complete (free C5 < 0.5 µg/mL) and sustained (throughout entire active treatment course) terminal complement inhibition under the above investigated dosage regimen. Based on the totality of PK, PD, ADA, efficacy, and safety data obtained from the ravulizumab development program, the above body weight-based dosage regimen for treating adult patients with PNH may also be beneficial in treating patients with gMG.

After the 26-Week Randomized-Controlled Period and assessments on Day 183 (Week 26), patients in the placebo group will receive a blinded loading dose of ravulizumab and patients in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg; the 900-mg dose was chosen to ensure maintenance of complete C5 inhibition until the next scheduled maintenance

6.4. Concomitant Therapy

Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria (Section 5.2) and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the patient takes or undergoes within 28 days prior to the start of screening until the first dose of study drug, will be recorded in the patient's eCRF. In addition, history of meningococcal vaccination must be collected for the 3 years prior to first dose of study drug. MG-specific medication or therapy (eg, thymectomy, ISTs including corticosteroids, IVIg, and PE/PP) within 2 years prior to screening will be recorded.

All medication use and procedures undertaken during the study will be recorded in the patient's source document/medical chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and any other current medications. Concomitant medications will be recorded from the first infusion of study drug through 8 weeks after the patient's last dose of study drug. Any changes in concomitant medications also will be recorded in the patient's source document/medical chart and eCRF. Any concomitant medication deemed necessary for the patient's standard of care during the study, or for the treatment of any AE, along with any other medications, other than those listed as prohibited medications in Section 6.5.1.5 may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the patient's source document/medical chart and eCRF.

6.5. Study Drug Compliance

Study drug will be administered in a controlled setting under the supervision of the Investigator or designee, thereby ensuring compliance with study drug administration.

6.5.1. Allowed Medications

6.5.1.1. Palliative and Supportive Care

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

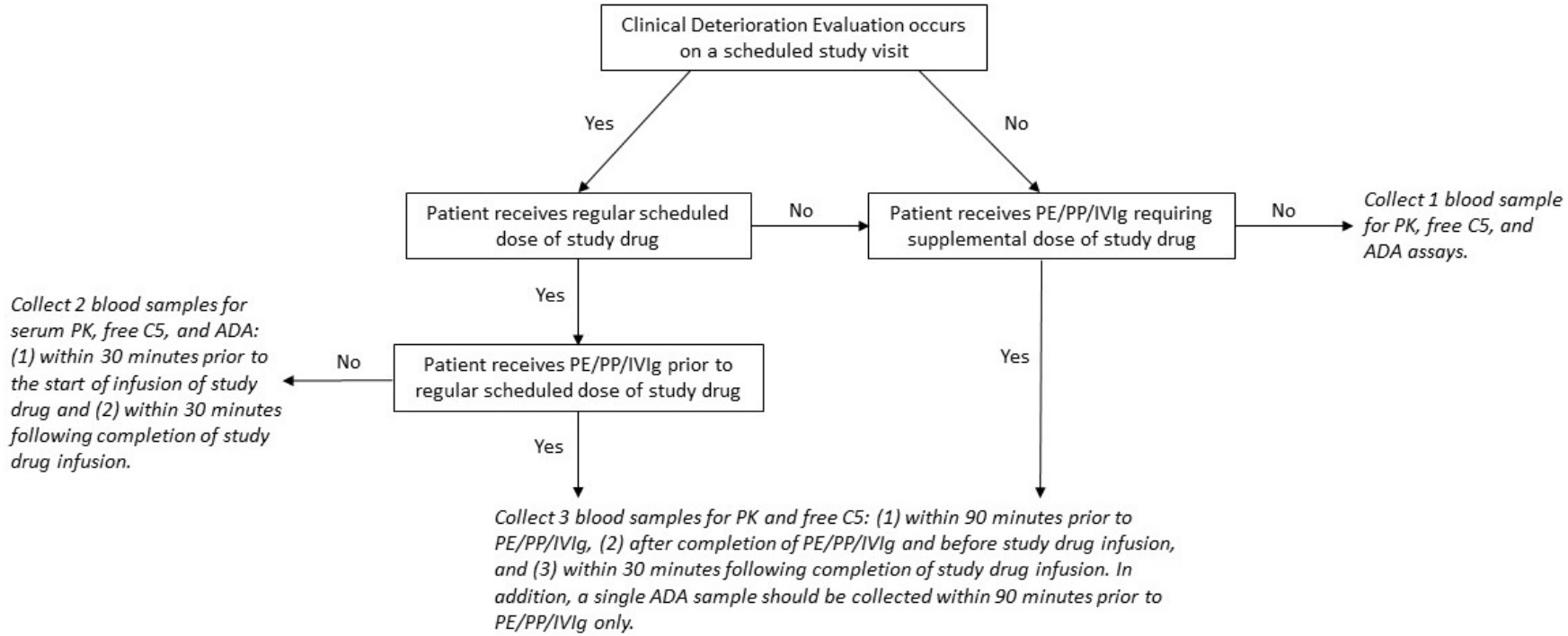
The medications described in the following sections are allowed under certain circumstances and restrictions.

6.5.1.2. Cholinesterase Inhibitors

For patients who enter the study receiving a cholinesterase inhibitor at screening, the dose and schedule of their cholinesterase inhibitor should be maintained stable throughout the entire Randomized-Controlled and OLE Periods, unless there is compelling medical need. Increases in cholinesterase therapy that are required as a result of intercurrent illness or other medical cause of deterioration are permitted, but dosing should be returned to dosing levels at study entry as soon as feasible and the Sponsor should be notified of the change.

1. Cholinesterase inhibitor treatment must be withheld for at least 10 hours prior to administration of the QMG and MGC tests.
2. If a decrease in cholinesterase inhibitor is considered based on clinical evaluation, Sponsor approval must be obtained prior to the change in dose.

Figure 2: PK/PD/ADA Sampling for Clinical Deterioration



Abbreviations: ADA = antidrug antibody; IVIg = intravenous immunoglobulin; PD = pharmacodynamic(s); PE = plasma exchange; PK = pharmacokinetic(s); PP = plasmapheresis

administered and interpreted easily (Burns, 2016). The MG-QOL15r will be completed by the patient. Higher scores indicate greater extent of and dissatisfaction with MG-related dysfunction.

8.1.8. Neurological Quality of Life Fatigue

The Neuro-QOL Fatigue is a reliable and validated brief 19-item survey of fatigue, completed by the patient (Cella, 2010). Higher scores indicate greater fatigue and greater impact of MG on activities (Section 10.11 [Appendix 11]).

8.1.9. Myasthenia Gravis Foundation of America Clinical Classification

The MGFA Clinical Classification will be assessed on Day 1 (Section 10.12 [Appendix 12]).

8.1.10. Myasthenia Gravis Foundation of America Post-Intervention Status

The MG clinical state will be assessed using a modified version of the MGFA-PIS (Section 10.13 [Appendix 13]). Change in status categories of Improved, Unchanged, or Worse, as well as the minimal manifestation (MM) will be assessed and recorded at the time points indicated in the SoA (Section 1.3) 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 in this protocol.

8.2. Safety Assessments

8.2.1. Physical Examination

A physical examination will include assessments of the following body systems: 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 consists of a body-system relevant examination based upon Investigator judgment and patient symptoms. For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff.

8.2.2. Vital Signs and Pulse Oximetry

Vital signs and pulse oximetry will be measured at every visit and will include assessments of systolic and diastolic BP (mmHg), temperature (°C or °F), SO_2, and HR (beats per minute). Vital signs will be obtained after the patient has been supine or seated for at least 5 minutes. Ideally, each patient's BP should be measured using the same arm.

8.2.3. Electrocardiogram

Single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (Section 1.3) using an ECG machine to obtain HR and measures of PR, QRS, QT, and QTc intervals. QT interval will be corrected for heart rate using Fridericia's formula (QTcF). Patients must be supine for approximately 5 - 10 minutes before ECG collection and remain supine but awake during ECG collection.

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be indicated on the eCRF.

8.2.4. Clinical Safety Laboratory Assessments

Laboratory assessments will be tested at a central laboratory facility. Any clinically significant abnormal results should be followed until resolution or stabilization.

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Clinically significant abnormal laboratory findings associated with the underlying disease are not considered AEs unless they are judged by the Investigator to be more severe than expected for the patient's condition.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

8.2.4.1. Urinalysis and Urine Chemistry

Urine samples will be analyzed for the parameters listed in Section 10.2 (Appendix 2). A microscopic examination of urine samples will be performed if the results of the macroscopic analysis are abnormal.

8.2.4.2. Virus Serology

Human immunodeficiency virus testing for HIV-1 and HIV-2 is required of all patients prior to enrollment. Patients who are HIV positive will not be enrolled.

8.2.4.3. Immunogenicity Assessments

Blood samples will be collected to test for presence of ADAs to ravulizumab in serum prior to study drug administration. Further characterization of antibody responses may be conducted as appropriate, including ADA titer, binding and neutralizing antibodies, PK/PD, safety, and activity of ravulizumab. Antibodies to ravulizumab will be evaluated in serum samples collected from all patients according to the SoA (Section 1.3). Serum samples will be screened for antibodies binding to ravulizumab and the titer of confirmed positive samples will be reported. The detection and characterization of antibodies to ravulizumab will be performed using a validated assay by or under the supervision of the Sponsor.

Detailed instructions on the procedure for collecting, processing, storing, and shipping serum samples for immunogenicity analysis will be provided in the laboratory manual.

8.2.5. Suicidal Risk Monitoring

8.2.5.1. Columbia-Suicidal Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS; Section 10.14 [Appendix 14] and Section 10.15 [Appendix 15]) is a validated questionnaire used extensively across primary care, clinical practice, surveillance, research, and institutional settings to assess suicidal ideation and behavior (Posner, 2011). The C-SSRS will be administered by the Investigator or a properly

trained designee. The C-SSRS will be assessed for both lifetime and past 1 year (12 months) as specified in the SoA (Section 1.3). The C-SSRS is being implemented to ensure that patients who are experiencing suicidal ideation or behavior are properly recognized and adequately managed.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported to the Investigator or qualified designee by the patient (or when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator or qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following up events that are serious, considered related to the study drug or study procedures; or that caused the patient to discontinue the study drug (Section 7).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3 (Appendix 3).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs will be collected from the signing of the ICF until 8 weeks after the last dose of study drug is administered.

Medical occurrences that begin before the start of study drug but after obtaining informed consent must be recorded in the AE case report form (CRF) as AEs and not in the Medical History/Current Medical Conditions CRF.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the Sponsor within 24 hours of awareness.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, regardless of whether or not the event is related to the study drug, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- The Investigator must notify the Sponsor of an SAE within 24 hours of the first awareness of the event.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- The Council for International Organizations of Medical Sciences (CIOMS) or MedWatch reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) (Section 10.3 [Appendix 3]) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. Alexion procedures for the reporting of SUSARs are in accordance with United States Title 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries, as well as IRBs/IECs where applicable.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and acknowledge the report and notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5. Pregnancy

Contraception guidance that must be followed for the study duration is detailed in Section 10.4 (Appendix 4).

For patients of childbearing potential, a serum pregnancy test (ie, beta-human chorionic gonadotropin) will be performed at Screening and at the EOS/ET. Urine pregnancy tests will be performed at all other required time points, as indicated in the SoA (Section 1.3). A negative pregnancy test is required prior to administering ravulizumab to patients of childbearing potential.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and should be reported as described in Section 10.3 (Appendix 3).

8.3.6. Vaccine and Antibiotic Prophylaxis

As with any terminal complement antagonist, the use of ravulizumab increases the patient's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within the 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes. Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement-inhibitors (eg, eculizumab).

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given per official guidance and local practice on the appropriate use of antibacterial agents. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the patients during the course of the study, patients will be provided a safety card to carry with them at all times. Additional discussion and explanation of the potential risks, signs, and symptoms will occur at each visit as part of the review of the patient safety card as described in the SoA (Section 1.3). Vaccination(s) for *N meningitidis* will be recorded on the patient's eCRF.

8.3.7. Study Drug Administration Reactions

8.3.7.1. Local and Systemic Reactions

Infusion-site reactions are those localized to the site of IV study drug administration and may include those such as erythema, pruritus, and bruising. Infusion-associated reactions are those which are systemic in nature and which may be immune or nonimmune-mediated generally occurring within hours of study drug administration. Immune-mediated reactions may include allergic reactions (eg, anaphylaxis), while nonimmune-mediated reactions are nonspecific (eg, headache, dizziness, nausea). Monitoring for these reactions will be conducted as part of routine safety assessments for this study.

8.3.7.2. Infusion-Associated Reactions

Infusion-associated reactions are defined as systemic AEs (eg, fever, chills, flushing, alterations in HR and BP, dyspnea, nausea, vomiting, diarrhea, and generalized skin rashes) occurring during or within 24 hours of the start of IV infusion that are assessed by the Investigator to be possibly, probably, or definitely related to the study drug.

8.4. Adverse Events of Special Interest

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

8.5. Pharmacokinetics

Blood samples will be obtained to assess pre- and post-treatment serum ravulizumab concentrations at the time points and within the windows indicated in the SoA (Section 1.3). Samples obtained outside of the allotted windows will be considered protocol deviations. Unused samples may be retained for a period of up to 5 years to perform additional assessments as necessary.

Additional details on sample collection, including blood volume requirements, are provided in the laboratory manual.

8.6. Pharmacodynamics

Blood samples will be obtained to assess pre- and post-treatment serum free C5 at the time points and within the windows indicated in the SoA Section 1.3). Samples obtained outside of the allotted windows will be considered protocol deviations. Unused samples may be retained for a period of up to 5 years to perform additional assessments as necessary.

Additional details on sample collection, including blood volume requirements, are provided in the laboratory manual.

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Blood samples for the assessment of AChR auto-Abs will be obtained at the time points indicated in the SoA (Section 1.3).

Additional details on sample collection, including blood volume requirements, are provided in the laboratory manual.

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.

8.9. Healthcare Resource Utilization

Healthcare resource utilization data, associated with medical encounters, will be collected by the Investigator or designee for all patients throughout the study. Data will be recorded in the eCRF.

The data collected may be used to conduct exploratory economic analyses and will include:

- Whether patients were admitted to a hospital, rehabilitation center, or hospice
- Whether the primary reason for admission was related to MG (yes/no)
- Duration of hospitalization (admission and discharge dates)

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.

9.2. Sample Size Determination

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%. Assumptions related to statistical power calculations are based on Study ECU-MG-301. Details are provided in Section 10.16 (Appendix 16).

9.3. Populations for Analyses

For purposes of analysis, the following analysis sets are defined in Table 9.

Table 9: Study ALXN1210-MG-306: Analysis Sets

Population	Description
Randomized set	All randomized patients grouped by randomized treatment group (for reporting disposition, demographics, and baseline characteristics).
PK Analysis Set (PKAS)	All ravulizumab treated patients with at least1 post-baseline PK concentration available.
Full analysis set (FAS)	All randomized patients who received at least 1 dose of study drug grouped by randomized treatment group (for reporting efficacy data).
Per protocol set (PPS)	Subset of FAS without any major protocol deviations[1] during Randomized-Controlled Period grouped by randomized treatment group (for reporting key efficacy data).
Safety set (SS)	All patients who received at least 1 dose of study drug grouped by treatment actually received (for reporting exposure and safety data). 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 Randomized-Controlled Period.
Open-label extension set	All patients who received at least 1 dose of ravulizumab starting from Week 26 onward (for reporting all data from the OLE Period).

[1] Determination of applicable major protocol deviations for this purpose will be made prior to database lock and study unblinding.

9.4. Statistical Analyses

9.4.1. Enrollment and Disposition

The number of patients screened, screen failures, and randomized patients will be presented. Enrollment information will be presented grouped by stratification factor and treatment group. Number of patients discontinued along with reasons from Randomized-Controlled Period, OLE Period, and the overall study will be summarized.

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 ($p \leq 0.05$), then subsequent endpoints will not be considered to be statistically significant. Estimates and confidence intervals will be computed for all these secondary endpoints regardless of the outcome of the closed testing procedure.

9.4.5.5. Per Protocol Analyses for Primary and Secondary Endpoints

Supplemental per protocol analyses for primary and secondary endpoints will be performed based on per protocol set (PPS) in the same manner as done for FAS.

9.4.6. Safety Analyses

The safety and tolerability of ravulizumab will be assessed based on adverse events, clinical laboratory findings, vital sign findings, and ECG abnormalities. Safety analyses will be performed on the Safety Population and OLE set based on the study period under consideration.

9.4.6.1. Analysis of Adverse Events

Analysis and reporting for AEs will be based on treatment-emergent adverse events (TEAEs), including treatment-emergent serious adverse events (TESAEs) defined as an AE with onset on or after first dose of ravulizumab in the Randomized-Controlled Period. Treatment-emergent AEs and TESAEs will be summarized by MedDRA SOC and Preferred Term, by severity, and by relationship to the study drug. Patient-years adjusted event rates will be generated to characterize long-term safety profile.

9.4.6.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements and Electrocardiogram Parameters

Laboratory measurements as well as their changes from Baseline at each visit and shift from baseline, if applicable, will be summarized descriptively. ECG, vital sign, and pulse oximetry findings will also be summarized using descriptive analyses.

9.4.6.3. Other Safety Analyses

The number and percentage of patients in each of the C-SSRS categories and shift analyses will be produced. Results from pregnancy tests will be summarized.

9.4.6.4. Analysis of Pharmacokinetics and Pharmacodynamics

Individual serum concentration data for all patients who receive at least 1 dose of ravulizumab and who have evaluable PK data will be used to derive PK parameters for ravulizumab.

Pharmacokinetic parameters such as peak and trough serum ravulizumab concentrations will be reported and summarized.

Graphs of mean serum concentration-time profiles 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, as appropriate. Population-PK will be performed with this data but will be described in a separate report.

Pharmacodynamic analyses 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 (Section 1.3). The PD effects of ravulizumab administered IV will be evaluated by assessing the absolute values and changes from baseline in free C5 serum concentrations over time, as appropriate. Assessments of ravulizumab PK/PD relationships may be explored using data from this study or in combination with data from other studies.

9.4.6.5. Analysis of Immunogenicity

The presence of ADAs in serum ravulizumab will be assessed over the duration of the study. Immunogenicity results will be analyzed by summarizing the number and percentage of patients who develop detectable ADA. The association of ADA with ravulizumab concentration, PD parameters, efficacy, and TEAEs may be evaluated.

9.4.6.6. Analysis of Exploratory Biomarkers

Acetylcholine receptor antibody titer levels as well as their changes from Baseline at each visit will be summarized descriptively.

9.5. Interim Analyses

No interim analysis is planned for Study ALXN1210-MG-306 during the Randomized-Controlled Period. The primary analysis will be conducted when the last patient completes the Randomized-Controlled Period, the database is locked, and the study randomization schedule is unblinded. Periodic analysis and reporting will be performed during the OLE Period based on regulatory requirement. Final analysis and reporting will be conducted at the conclusion of the study.

9.6. Data Monitoring Committee

No independent Data Monitoring Committee is planned for Study ALXN1210-MG-306.

10.3.2. Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
• **Results in persistent disability/incapacity** The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
1. Is a congenital anomaly/birth defect
2. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

10.3.3. Suspected Unexpected Serious Adverse Reactions

Suspected Unexpected Serious Adverse Reactions Definition
Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to study drug or procedure. The US 21CFR312.32 and EU Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs where applicable.

10.3.4. Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion or designee in lieu of completion of the AE/SAE report. If applicable, additional information such as relevant medical records, should be submitted with a signed SAE cover page to Alexion Global Pharmacovigilance (GPV) via ClinicalSAE@alexion.com or via Facsimile: + 1.203.439.9347. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before sending to GPV.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Event Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017. Each CTCAE term is a Lowest Level Term (LLT) per 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)

Any change in the severity of an AE should be documented based on specific guidelines in the eCRF Completion Guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met specific criteria for an SAE as described above.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related (unrelated)
  - Related: Temporal relationship to the study drug. Other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain the event; the event corresponds with the known pharmaceutical profile; improvement on discontinuation; reappearance on rechallenge.

Adverse Event Recording

- The Investigator will use clinical judgment to determine the relationship to the study drug.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.

Adverse Event and Serious Adverse Event Recording

- The expectedness and reporting criteria of an SAE will be determined by the Sponsor, based on the Reference Safety Document. The Investigator will also consult the IB in his/her assessment.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Alexion or designee. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Alexion GPV.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion or designee with a copy of any postmortem findings including histopathology, if available.
- The site will enter new or updated SAE data into the electronic system as soon as it becomes available, but no later than 24 hours. The Investigator will submit any updated SAE data to the GPV within 24 hours of awareness of the information.

10.3.5. Reporting of Serious Adverse Events

Serious Adverse Event Reporting to Alexion or Designee via the RAVE Safety Gateway

All SAEs must be reported to Alexion GPV within 24 hours of the Investigator or site staff awareness. These timelines for reporting SAE information to the Sponsor need to be followed for the initial SAE report and for all follow-up SAE information.

The Investigator or designee must record the SAE data in the eCRF and verify the accuracy of the information with corresponding source documents. The SAE report should be submitted electronically via the RAVE Safety Gateway.

In the event that either the electronic data capture (EDC) or the RAVE Safety Gateway is unavailable at the site(s), the SAE must be reported on the paper SAE Contingency Form accompanied by an Investigator signed cover page. Facsimile transmission or email may be used in the event of electronic submission failure.

For all SAEs, the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed below
  - Causality of the SAE(s)
  - Treatment of/intervention for the SAE(s)
  - Outcome of the SAE(s)
  - Supporting medical records and laboratory/diagnostic information
- The primary mechanism for reporting an SAE to Alexion or designee will be the RAVE Safety Gateway.
- If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE reporting via facsimile or email. Facsimile transmission or email may be used in the event of electronic submission failure.
  Email: clinicalsae@alexion.com
  Facsimile: + 1.203.439.9347

Serious Adverse Event Reporting to Alexion or Designee via the RAVE Safety Gateway
• As soon as the EDC becomes available, the data should be entered in the eCRF and forwarded to Alexion GPV via the RAVE Safety Gateway. • When further information becomes available, the eCRF should be updated with the new information and an updated SAE report should be submitted to Alexion GPV via the RAVE Safety Gateway. • After the study is completed at a given site, the EDC will be taken offline to prevent the entry of new data or changes to existing data. • If a site identifies a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form to Alexion GPV.
SAE Reporting to Alexion or Designee via Paper Contingency Case Report Form
• If applicable, additional information such as relevant medical records should be submitted to Alexion GPV via the email address or facsimile number noted above. • All paper forms and follow-up information submitted to the Sponsor outside of the RAVE Safety Gateway (eg, discharge summary) should be kept in the appropriate section of the study file.

Clinical Criteria for Diagnosing Anaphylaxis:

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
(1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following: a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
(2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
(3) Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Systolic BP of less than 90 mmHg or greater than 30% decrease from that patient's baseline

Abbreviations: BP = blood pressure; PEF = peak expiratory flow.
Source: Sampson, 2006

10.7. Appendix 7: Quantitative Myasthenia Gravis Score for Disease Severity

To be completed by Study Site

Study Number: ALXN1210-MG-306 Subject ID: _____

Date Completed: _____ Time Completed: _____

Was any Anticholinesterase Medication taken **within 10 hours** of assessment?

☐ No ☐ Yes; If yes, please record please record time of last dose: _____

☐ N/A (patient is not on acetylcholinesterase therapy)

QMG form

Test Item	None	Mild	Moderate	Severe	Score	
Grade	**0**	**1**	**2**	**3**	Raw	Scale
Double vision on lateral gaze Right or left (circle one), secs	61	11-60	1-10	Spontaneous		
Ptosis (upward gaze)	61	11-60	1-10	Spontaneous		
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete		
Swallowing 4 oz water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)		
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9		
Right arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9		
Left arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9		
Forced Vital Capacity	≥ 80	65-79	50-64	<50		
Rt- hand grip, kg Men Women	 ≥ 45 ≥ 30	 15-44 10-29	 5-14 5-9	 0-4 0-4		
Lt- hand grip, kg Men Women	 ≥ 35 ≥ 25	 15-34 10-24	 5-14 5-9	 0-4 0-4		
Head lifted (45 degrees supine), seconds	120	30-119	1-29	0		
Right leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0		
Left leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0		
				TOTAL QMG SCORE :		

Evaluator Signature:	Date:

QMG - United States/English – Original version
QMG_AU2.0_eng-UBorl.docx

Appendix 9: Euro Quality of Life Questionnaire (Continued)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

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 of 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.

Table 11: List of Abbreviations and Definitions of Terms (Continued)

GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
GPV	Global Pharmacovigilance
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
IST	immunosuppressant therapy
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
mAb	monoclonal antibody
MAC	membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living profile
MGC	Myasthenia Gravis Composite score
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-Intervention Status
MG-QoL15r	Revised Myasthenia Gravis Quality of Life 15-item scale
MM	minimal manifestation
MMF	mycophenolate mofetil
MMRM	Mixed-effects Model with Repeated Measures
MNAR	Missing Not At Random
MTX	methotrexate
N meningitidis	*Neisseria meningitidis*
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Neuro-QOL	Neurological Quality of Life
NMJ	neuromuscular junction

Overall Design:

This 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 patients with gMG. Approximately 160 eligible patients will be stratified by region (North America, Europe, Asia-Pacific, and Japan) and randomized 1:1 to 1 of 2 treatment groups: (1) ravulizumab infusion or (2) placebo infusion. There will be 3 periods in this study: Screening Period, Randomized-Controlled Period, and an Open-Label Extension (OLE) Period.

Eight weeks after the final dose of study drug is administered, all enrolled patients will return for an End of Study (EOS) Visit (Visit 25) at Week 132, during which final study assessments will be conducted. If a patient withdraws from the study or completes the study early because ravulizumab has become registered or approved (in accordance with country-specific regulations) prior to Visit 24, the patient will be encouraged to return for an Early Termination Visit, 8 weeks after the last dose of study drug was administered, during which final planned safety assessments will be conducted. Attempts should be made to follow all patients for safety for 8 weeks following the patient's last dose of study drug.

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, plasmapheresis/plasma exchange, or intravenous immunoglobulin) will be allowed if a patient experiences Clinical Deterioration, as defined by the study protocol. The rescue therapy used for a particular patient will be at the discretion of the Investigator.

The primary endpoint for this study will be measured at Week 26. Endpoints will be measured and analyzed irrespective of rescue therapy. For those patients who complete the study, as defined in the protocol, the EOS Visit is defined as patient's last visit in the (up to) 2-year OLE Period. Including the 8-week safety follow-up, which begins after the patient's last dose of study drug is administered, the overall study-duration for an individual patient is estimated to take up to 132 weeks (from enrollment through the end of the Safety Follow-up). The period of active patient-participation is estimated to take up to 132 weeks (from enrollment through the EOS Visit).

Number of Patients:

Patients will be screened until enough patients have been enrolled to achieve an estimated total of 160 patients, with approximately 80 patients per group.

Intervention Groups and Duration:

At the time of randomization, all patients will be reassessed for eligibility based on the study inclusion and exclusion criteria. All patients who meet the inclusion criteria and none of the exclusion criteria, have been vaccinated against *Neisseria meningitidis,* within the timeframe specified in the inclusion criteria, and have been cleared for randomization by the Investigator will be randomized 1:1 to 1 of 2 treatment groups: (1) ravulizumab infusion or (2) placebo

Table 1: Schedule of Activities: Screening Through End of the Randomized-Controlled Period (Continued)

[11] Pregnancy tests must be performed on all patients of child-bearing potential at the specified time points. Serum pregnancy test will be performed at Screening and Day 183/ET; urine pregnancy tests will be performed locally at all other required time points. A negative urine test result performed locally is required prior to administering ravulizumab to patients of childbearing potential at the indicated visits. Additional pregnancy tests (urine or serum) may also be performed at any visit at the Investigator's discretion.

[12] Baseline (B) and trough (T) blood samples for serum PK, free C5 (PD), and ADA will be collected predose (within 30 minutes prior to the start of infusion of study drug). Peak (P) blood samples for serum PK/PD samples are to be taken within the 30 minutes following completion of study drug infusion. The T samples may be drawn through the venous access created for the dose infusion, prior to administration of the dose. The P samples will be drawn from the patient's opposite, noninfused arm. On Day 183 (Week 26), the T sample is considered a Randomized-Controlled Period assessment and the P sample is considered an Extension Period assessment. All collection times will be recorded in eCRF. In the event of Clinical Deterioration, blood samples for serum PK/PD and ADA analyses will be collected if supplemental dosing is provided (see Section 8.1.2).

[13] To reduce the risk of meningococcal infection (*N meningitidis*), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

[14] Patients will be given a Patient Safety Information Card prior to the first dose of study drug. At each visit throughout the study, the study staff will ensure that the patient has the Patient Safety Information Card.

[15] All patients that continue to meet all inclusion criteria and none of the exclusion criteria and have been cleared for randomization by the Investigator will be centrally randomized through interactive response technology (IRT).

[16] Study drug will be administered intravenously via infusion after completion of all other tests and procedures, excluding the peak blood sampling for PK/PD, free C5, and ADA.

Abbreviations: AChR Ab = acetylcholine receptor antibody; ADA = antidrug antibody; B = baseline sample; C5 = complement component 5; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; EQ-5D-5L=Euro Quality of Life; ET = Early Termination; HIV = Human Immunodeficiency Virus; MG = Myasthenia Gravis; MG-ADL = Myasthenia gravis Activities of Daily Living profile; MGC = Myasthenia gravis Composite score; MGFA = Myasthenia Gravis Foundation of America; MGFA-PIS = MGFA-Post-Intervention Status; *N meningitidis = Neisseria meningitidis;* P = peak sample; PK/PD = pharmacokinetic(s)/pharmacodynamic(s); QMG = Quantitative Myasthenia Gravis score for disease severity; QoL = quality of life; T = trough sample; W = week(s).

4.1.4. Open-Label Extension Period

After the 26-Week Randomized-Controlled Period and assessments on Day 183 (Week 26), patients in the placebo group will receive a blinded loading dose of ravulizumab and patients in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg; the 900-mg dose was chosen to ensure maintenance of complete 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 OLE Period for each patient will commence when the patient receives a dose of ravulizumab on Week 26 (Day 183) and will continue for up to 2 years or until the product is registered or approved (in accordance with country-specific regulations), whichever occurs first.

4.2. Standard Protocol Definitions

4.2.1. Clinical Deterioration

For this protocol, 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. Significant symptomatic worsening to a score of 3 or a 2-point worsening from Baseline on any one of the individual MG-Activities of Daily Living (MG-ADL) items other than double vision or eyelid droop; 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).

4.2.2. Unscheduled Visits

Under exceptional circumstances, additional (unscheduled) visits outside the specified visits are permitted at the discretion of the Investigator. Procedures, tests, and assessments will be performed at the discretion of the Investigator and efforts will be made to map the corresponding data to the appropriate visit as described in the electronic case report form (eCRF) completion guidelines and training materials.

4.2.3. Properly Trained Clinical Evaluator

Properly Trained Clinical Evaluators are study staff that have been certified in administering the MG-ADL, QMG, and Myasthenia Gravis Composite (MGC) assessments. Only Properly Trained Clinical Evaluators may administer these assessments. A Properly Trained Clinical Evaluator may be a neurologist, physical therapist, or other study team member delegated by the Investigator. Only the Investigator or a neurologist may perform the manual muscle test (MMT), components of the MGC, the Myasthenia Gravis Foundation of America-Post-Interventional Status (MGFA-PIS), and Myasthenia Gravis Foundation of America (MGFA) Classification.

dose at Week 28 (Day 197). Starting at Week 28 (Day 197), all patients will begin open-label ravulizumab maintenance doses q8w.

The proposed q8w dosage regimen will facilitate studying a range of PK drug exposures useful in assessing ravulizumab exposure-response relationships in patients with gMG. Safety and tolerability of ravulizumab have been established over a wide range of PK exposures, including those expected under the proposed gMG dosage regimens, in healthy volunteers and patients.

4.5. End of Study Definition

A patient is considered to have completed the study if:

- The patient has completed all periods of the study including the last visit of the OLE Period, or
- In the event the study is completed early, the patient has completed all applicable periods of the study including the EOS visit
- The patient completes the study early (and completes the EOS Visit) because the study drug has become registered or approved (in accordance with country-specific regulations)

Measurement of the primary endpoints will be complete after the last visit of the last patient in the Randomized-Controlled Period. The EOS is defined as the date of the last visit of the last patient in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last patient in the study globally. The study completion date corresponds to the last visit when the final patient in the study is examined or received an intervention for the primary or secondary endpoints and AEs.

6.5.1.3. Immunosuppressive Agents

The following immunosuppressive agents are allowed during the study: corticosteroid, AZA, MMF, MTX, TAC, CYC, or CY. The immunosuppressive agent(s) and its appropriate dose level to be used for an individual patient will be at the discretion of the treating physician/Investigator.

1. Corticosteroid: for patients who enter the study receiving oral corticosteroid, eg, prednisone, the dose/schedule may not be changed during the entire double-blind study period (ie, the Randomized-Controlled Period). If a decrease or taper in steroid dose is considered during the Randomized-Controlled Period based on clinical evaluation, Sponsor approval must be obtained prior to the change in order for the patient to remain on study. If the dose level subsequently must be increased, the dose level increase cannot be above the dose level reported at the baseline (at the start of randomized treatment).
2. High-dose steroid should be reserved for patients that experience Clinical Deterioration as defined by this protocol. Every effort should be made to notify the Sponsor within 24 hours of administration should a patient require rescue therapy for Clinical Deterioration.
3. AZA, MMF, MTX, TAC, CYC, or CY: for patients who enter the study receiving above mentioned immunosuppressive agents, the dosing regimen of the immunosuppressive agent may not be changed during the entire Randomized-Controlled Period. If a change in the dosing regimen is considered due to known toxicity or side effects associated with the given immunosuppressive agent, Sponsor approval must be obtained prior to the dose change. A different immunosuppressive agent cannot be added or substituted during the 26-week Randomized-Controlled Period.

6.5.1.4. Plasma Exchange/Plasmapheresis/Intravenous Immunoglobulin

Use of PE/PP or IVIg (acute use only) will be allowed for patients who experience a Clinical Deterioration as defined by this protocol. The rescue therapy used for a particular patient will be at the discretion of the Investigator. Every effort should be made to notify the Sponsor within 24 hours should a patient require rescue therapy.

Supplemental study drug (or placebo) dosing is required if PE/PP or IVIg rescue therapy is provided on nondosing days; if PE/PP or IVIg infusion is provided on a dosing day, it must occur prior to study drug administration.

1. If PE/PP or IVIg is administered on nonscheduled dosing visits:
    a. Patients receiving PE/PP: supplemental dose administration will be started within 4 hours after the PE/PP session is completed (Table 7)
    b. Patients receiving IVIg: supplemental dose administration will be started within 4 hours after the last continuous session(s) of IVIg is completed (Table 8)
2. If PE/PP or IVIg is administered on scheduled dosing visits:
    a. Regular dosing will be started within 4 hours after the completion of PE/PP or IVIg
3. No gap is required between a supplemental dose and the regular scheduled dose.

8.1.3. Myasthenia Gravis Activities of Daily Living Profile

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of ADL in patients with MG (Section 10.6 [Appendix 6]). The 8 items of the MG-ADL questionnaire were 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 0 - 24. The recall period for MG-ADL is the preceding 7 days. The MG-ADL profile should be administered by a properly trained evaluator. For consistency, the same evaluator should administer the questionnaire throughout the study.

8.1.4. Quantitative Myasthenia Gravis Score

The QMG 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, with 3 being the most severe (Section 10.7 [Appendix 7]). The range of total QMG score is 0 - 39. The QMG scoring system is considered to be an objective evaluation of therapy for MG and is based on quantitative testing of sentinel muscle groups. The MGFA task force has recommended that the QMG score be used in prospective studies of therapy for MG (Benatar, 2012).

8.1.5. Myasthenia Gravis Composite Score

The MGC is a validated assessment tool for measuring clinical status of patients with MG. The range of total MGC score is 0 - 50. 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 (Burns, 2010) (Section 10.8 [Appendix 8]).

8.1.6. Euro Quality of Life 5D-5L

The Euro Quality of Life-5L (EQ-5D-5L) (Section 10.9 [Appendix 9]) is a self-assessed, health-related QoL questionnaire. The scale measures QoL on a 5-component scale 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, moderate problems, severe problems, or unable to walk). This tool also has an overall health scale where the rater selects a number between 1 - 100 to describe the condition of their health, 100 being the best imaginable. Convergent validity was demonstrated by a correlation between EQ-5D-5L and the dimensions of World Health Organization 5 Well Being questionnaires, ($r = 0.43$, $p < 0.001$) (Janssen, 2013). The EQ-5D-5L approach is reliable, average test-retest reliability using interclass coefficients with mean of 0.78 and 0.73 (Brooks, 1996; Chaudhury, 2006).

8.1.7. Revised Myasthenia Gravis Qualify of Life-15 Scale

The revised Myasthenia Gravis Qualify of Life 15-item scale (MG-QOL15r) (Section 10.10 [Appendix 10]) is a health-related QoL evaluative instrument specific to patients with MG. The MG-QOL15r was designed to provide information about patients' perception of impairment and disability, determine the degree to which disease manifestations are tolerated, and to be

9. STATISTICAL CONSIDERATIONS

Statistical methods described in this section will be further elaborated in a separate SAP. The SAP will be developed and finalized before database lock. The analyses will be performed using the SAS® statistical software system Version 9.4 or later. Statistical analyses will include tabulations of summary data, inferential analyses, by-patient listings and figures. Inference from efficacy analyses will be based on 2-sided Type I error (α) = 5%. Summary statistics for continuous variables will minimally include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented.

The baseline value for analysis and reporting will be based on the last nonmissing measurement on or prior to the first dose of study drug. The treatment groups for analysis and reporting will be based on the conventions outlined in Table 9. A 'Total' group will be formed to report demographics, baseline characteristics and other prestudy information such as prestudy SAEs, medical history, or prior medications. Details for imputation of efficacy data will be described in the SAP. Missing safety data will not be imputed.

A clinical study report (CSR) will be produced based on efficacy, safety, PK, PD, and immunogenicity data collected though the end of the 26-week Randomized-Controlled Period. A final CSR to summarize long-term efficacy, safety, PK, PD, and immunogenicity parameters will be produced at study completion.

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary hypothesis for this study is that ravulizumab is superior to placebo in improvement of 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 placebo group in the change from Baseline in MG-ADL total score at Week 26 irrespective of rescue therapy[1]. A lower value of the corresponding estimate will indicate a beneficial treatment effect.

9.1.2. Secondary Hypotheses

The following secondary hypotheses will be included in study-wise multiplicity adjustment (provided the null hypothesis for primary endpoint is rejected) (Section 9.4.5.4):

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.

[1] Rescue therapy includes high-dose corticosteroids, PE/PP or IVIg. It will be allowed when a patient's health is in jeopardy, if rescue therapy was not administered (eg, emergent situations), or if a patient experiences Clinical Deterioration

9.4.2. Demographics, Baseline Characteristics, Inclusion and Exclusion Criteria, and Protocol Deviations

All demographic information and baseline characteristics will be reported by treatment group and overall. No statistical test will be performed for homogeneity among treatment groups.

The number and percentage of patients not meeting specific inclusion or exclusion criterion will be summarized. Similar summary will be provided for major protocol deviations based on prespecified categories.

9.4.3. Medical/Surgical History, Physical Examination, and Myasthenia Gravis History

The medical and surgical history will be summarized by the Medical Dictionary for Regulatory (MedDRA) Activities, Version 20.1, or later by System Organ Class (SOC) and Preferred Term. Myasthenia gravis and abnormal physical examination will also be summarized.

9.4.4. Prior and Concomitant Medications

For analysis and reporting purpose, any medication started prior to first dose of study drug will be considered as prior medication; and medications that started on or after the first dose of study drug will be considered as concomitant medications. All prior and concomitant medications including MG-specific medications and rescue therapy during the study, if any, will be summarized.

9.4.5. Efficacy Analyses

9.4.5.1. Primary Efficacy Analysis

The Mixed-effects Model with Repeated Measures (MMRM) will be used for the primary efficacy endpoint (change from Baseline in MG-ADL total score at Week 26) using all available longitudinal data (either complete or partial) regardless of whether patients received a rescue therapy[2]. Missing data will not be imputed for the primary analysis. The model will include the MG-ADL change from Baseline score at each prespecified time point as the response variable, fixed categorical effects of treatment, study visit and treatment-by-study visit interaction, region; as well as fixed covariate of baseline MG-ADL total score. 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. Other covariance structures will be implemented if a convergence issue occurs (details to be provided in SAP). The Kenward-Rogers method will be used to estimate the denominator degrees of freedom.

[2] Rescue therapy includes high-dose corticosteroids, PE/PP or IVIg. It will be allowed when a patient's health is in jeopardy, if rescue therapy was not administered (eg, emergent situations), or if a patient experiences Clinical Deterioration

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH-GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The IRB/IEC and relevant regulatory authority must be notified of any significant amendment to the protocol, as applicable. Necessary approvals must be given before changes are implemented.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Contraception Guidance

Before receiving study drug, female patients who consider themselves to be postmenopausal must provide evidence of menopause based on a combination of amenorrhea for at least 1 year and increased serum follicle-stimulating hormone level (> 30 IU/L).

Patients of childbearing potential must use a highly effective or acceptable method of contraception (as defined below) starting at Screening and continuing for at least 8 months after the last dose of study drug.

Highly effective contraceptive methods include:

1. Hormonal contraception associated with inhibition of ovulation
2. Intrauterine device
3. Intrauterine hormone-releasing system
4. Bilateral tubal occlusion
5. Vasectomized partner provided that the partner is the patient's sole sexual partner
6. Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment; reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient

Acceptable contraceptive methods include:

7. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

The above-listed method(s) of contraception chosen for an individual patient can be determined by the Investigator with consideration for the patient's medical history and concomitant medications.

Patients with a spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use double barrier contraception (male condom plus appropriate barrier method for the female partner) while on treatment and for at least 8 months after the last dose of study drug. Double barrier contraception is required even with documented medical assessment of surgical success of a vasectomy.

Male patients must not donate sperm and female patients must not donate ova while on treatment and for at least 8 months after the last dose of study drug.

10.4.2. Pregnancy Testing

Patients of childbearing potential should only be included after a menstrual period and a negative highly sensitive serum pregnancy test.

Additional pregnancy testing should be performed per the time points specified in the SoA (Section 1.3).

10.6. Appendix 6: Myasthenia Gravis Activities of Daily Living Profile

To be completed by Study Site

Study Number: ALXN1210-MG-306 Subject ID: _____ Date Completed: _____

MG Activities of Daily Living (MG-ADL) profile

Grade	0	1	2	3	Score (0,1,2 or 3)
1. Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				MG-ADL score total (items 1-8)	**=**

Evaluator Signature:	Date:

MG-ADL - United States/English
MGADL_AU1.1_eng-USorl.docx

10.8. Appendix 8: Myasthenia Gravis Composite Scale

To be completed by Study Site

Study Number: **ALXN1210-MG-306** Subject ID: _____

Date Completed: _____ Time Completed: _____

MG Composite Scale

					Results
Ptosis, upward gaze (physician examination)	> 45 seconds = 0	11 – 45 seconds = 1	1 – 10 seconds = 2	Immediate = 3	Obtain results from QMG:
Double vision on lateral gaze, left or right (physician examination)	> 45 seconds = 0	11 – 45 seconds = 1	1 – 10 seconds = 3	Immediate = 4	Obtain results from QMG:
Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moderate weakness (can be forced open easily) = 1	Severe weakness (unable to keep eyes closed) = 2	Obtain results from QMG:
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6	Obtain results from MG-ADL:
Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6	Obtain results from MG-ADL:
Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing e.g. necessitating changes in diet = 5	Gastric tube = 6	Obtain results from MG-ADL:
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9	Obtain results from MG-ADL:
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e. ~50% weak, +/- 15%) = 3	Severe weakness = 4	
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e. ~50% weak, +/- 15%) = 4	Severe weakness = 5	
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e. ~50% weak, +/- 15%) = 4	Severe weakness = 5	

Please note that "moderate weakness" for neck and limb items should be construed as weakness that equals roughly 50% +/- 15% of expected normal strength. Any weakness milder than that would be "mild" and any weakness more severe than that would be classified as "severe".

Total Score _____

Evaluator Signature should be the signature of the individual (PI or Neurologist) completing the following assessments: Neck flexion or extension, Shoulder abduction and Hip flexion .Note: If individual transcribing items from MG-ADL and QMG (items 1-7) differs from evaluator, ensure individual appropriately initials here: _____

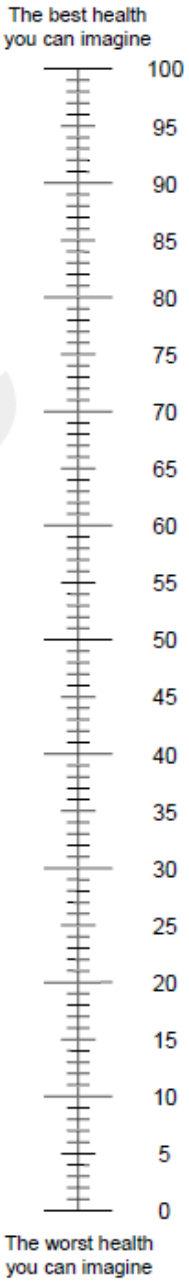
Evaluator Signature:	Date:

Permission granted for use from Ted Burns, MD, University of Virginia.

Appendix 9: Euro Quality of Life Questionnaire (Continued)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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10.17. Appendix 17: Abbreviations

Table 11: List of Abbreviations and Definitions of Terms

AChR	acetylcholine receptor
AChR Ab	acetylcholine receptor antibody
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
Alexion	Alexion Pharmaceuticals, Inc.; the Sponsor
AST	aspartate aminotransferase
AZA	azathioprine
BP	blood pressure
BUN	blood urea nitrogen
C5	complement component 5
C5b-9	terminal complement complex
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
CFR	Code of Federal Regulations
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CY	cyclophosphamide
CYC	cyclosporine
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EQ-5D-5L	Euro Quality of Life
ET	Early Termination
EU	European Union
FDA	(US) Food and Drug Administration

Table 11: List of Abbreviations and Definitions of Terms (Continued)

OLE	Open-Label Extension
oMG	ocular myasthenia gravis
PD	pharmacodynamic(s)
PE	plasma exchange
PIS	post-intervention status
PP	plasmapheresis
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PPS	Per protocol set
Q2W	every 2 weeks
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
SC	subcutaneous
SO_2	oxygen saturation
SoA	Schedule of Activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TAC	tacrolimus
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event